



IOVANCE
BIOTHERAPEUTICS

ANNUAL
REPORT
2022

DEAR SHAREHOLDERS:

2022 was a pivotal year for lovance. We took several important steps towards achieving our mission to be the global leader in innovating, developing and delivering tumor infiltrating lymphocyte (TIL) therapy for patients with cancer.

Throughout the year, we continued to prioritize our biologics license application (BLA) submission for lifileucel on behalf of patients with advanced melanoma who progress on or after anti-PD-1 therapy. There are currently no U.S. Food and Drug Administration (FDA)-approved treatment options in this setting. Our rolling BLA submission, which we initiated in August 2022, was successfully completed in March 2023. As we await FDA acceptance of our BLA for review, we believe in the strength of our clinical data, manufacturing capabilities and ability to address a significant unmet need for people with metastatic melanoma. While we continue our transition to a commercial company, we are also expanding our pre-commercial and manufacturing readiness activities to support the launch of lifileucel.

Beyond our progress with our first BLA, we continue to develop our deep immuno-oncology pipeline. Throughout 2022 and into 2023, we are executing six active clinical trials and have presented clinical data for lovance TIL therapy in multiple solid tumor types and treatment settings. We reported and presented the clinical results from our C-144-01 trial, which is the basis for our BLA submission for lifileucel. We also initiated our first phase 3 study, TILVANCE-301, in the frontline melanoma treatment setting. We believe that our growing set of clinical data continue to demonstrate the potential for lovance TIL therapy to become the next paradigm-shifting treatment regimen for solid tumors.

Looking toward our next generation approaches to optimize TIL therapy, we hit a key innovation milestone by treating the first patient in our first-in-human study of our first genetically modified lovance TIL therapy, IOV-4001.

As part of our strategy to streamline and improve access to the TIL treatment regimen, we entered into a strategic transaction with Clinigen in January of 2023 to acquire worldwide rights to Proleukin®, an interleukin-2 (IL-2) product. Proleukin® has currently approved indications and, importantly, is also used to promote T-cell activity following TIL infusion. The strong strategic fit and rationale for this transaction include immediate and future revenue and full control of the IL-2 supply chain and logistics surrounding TIL therapy. As a result, we expect to lower clinical trial expenses and future cost of goods for lifileucel. The closing of the transaction is subject to required regulatory approvals and clearances and other customary closing conditions.

lovance TIL therapy (lifileucel) in Advanced (Unresectable or Metastatic) Melanoma

Our multi-pronged strategy in advanced melanoma is to address several unresectable or metastatic melanoma patient populations with significant unmet need. In post-anti-PD-1 advanced melanoma, the C-144-01 trial is the basis for our BLA submission as well as the largest single clinical study ever conducted for a cell therapy in melanoma. We presented positive data from C-144-01 Cohorts 2 and 4 to the medical community for the first time at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in November 2022, and published results from the study in the Journal of Immunotherapy of Cancer (JITC) in December.

We strongly believe that the strength of the clinical data from the C-144-01 trial as well as positive regulatory interactions and feedback support approval. During 2022, we aligned with FDA on the potency assay matrix for lifileucel in melanoma and held a successful pre-BLA meeting where FDA provided favorable feedback on the clinical efficacy data from Cohorts 2 and 4, including duration of follow up and that the clinical and safety dataset was sufficient for a BLA review. In the fourth quarter, we also reached agreement with FDA for our TILVANCE-301 Phase 3 trial to serve as a registrational trial in frontline advanced melanoma as well as a confirmatory study supporting full approval of lifileucel in post-anti-PD-1 advanced melanoma. We expect TILVANCE-301 to be well underway at the time of potential approval in this first indication.

The frontline melanoma opportunity for lifileucel is supported by positive results from Cohort 1A in our IOV-COM-202 trial of lifileucel in combination with pembrolizumab in immune checkpoint inhibitor (ICI) naïve advanced melanoma and extensive prior results from the National Cancer Institute (NCI) for TIL monotherapy in anti-PD-1 naïve melanoma patients. We look forward to advancing our frontline melanoma strategy throughout 2023, including site activation and enrollment in TILVANCE-301.

TIL Manufacturing and lovance Cell Therapy Center (iCTC)

Our manufacturing success rate is above 90% for more than 600 patients treated with lovance TIL therapy to date. Our iCTC facility is expected to supply most commercial TIL therapies upon approval, with contract manufacturers to provide additional flexibility to optimally balance capacity and patient demand. To ensure the iCTC and our contract manufacturer's facility are well-prepared for launch, we are engaged in rigorous efforts to support successful FDA pre-approval inspections during the BLA review process. Our manufacturing teams are also focused on scaling up our internal capabilities to ensure sufficient capacity at launch.

As we look to establish TIL as the next paradigm-shifting class of cancer therapy and plan for future capacity, we have existing infrastructure at iCTC to supply TIL products for more than 2,000 patients, with flexibility to build out additional shell space to supply products for more than 5,000 patients annually from this facility. Longer-term, our vision is to build capacity for more than 10,000 patients annually by adding new facilities as well as streamlining and automating manufacturing and testing processes.

Toward Commercialization

The lovance team has made steady progress with our commercial launch preparations for lifileucel. In addition, we are preparing for a smooth transfer and integration of Proleukin® upon the close of our planned acquisition. We are fortunate to have cross functional team members with prior Proleukin® leadership experience who are leading and developing our end-to-end integration processes.

To onboard our authorized treatment centers (ATCs) to be ready for the launch of lifileucel, our cross functional teams continue to partner with ATCs to develop new workflows that are unique to TIL therapy while leveraging workflows within existing cell therapy service lines at these ATCs. Each ATC receives targeted support, and we will coordinate just-in-time training to ensure launch readiness for multi-disciplinary teams to administer the lifileucel treatment regimen upon FDA approval. For initial launch, we aim to on-board at least 40 ATCs, with a longer-term goal to have enough sites so that most patients in the U.S. can be within a few hours' drive to an ATC offering lifileucel TIL therapy.

To further support ATCs, our lovanceCares™ program remains on track for launch to deliver a best-in-class cell ordering and patient support system that assists our patients, physicians and ATCs at every step of the process. In addition, our reimbursement strategies are focused on securing coding, coverage and payment to ensure patients have appropriate and timely access to lifileucel, with continued engagement with the key national and regional payers.

TIL Therapy in Non-Small Cell Lung and Cervical Cancers

Throughout 2022, we continued to progress our non-small cell lung cancer (NSCLC) and cervical cancer programs at lovance. Six cohorts across three lovance-sponsored NSCLC studies are investigating multiple treatment regimens in various populations at various stages of disease. In January of 2023, we shared initial positive topline data from Cohort 3A of the IOV-COM-202 trial, which we plan to highlight in detail at an upcoming medical meeting. Based on these positive Cohort 3A results, we plan to meet with FDA in 2023 to discuss our data and a potential registration path for lifileucel in patients with advanced NSCLC who are naïve to ICI treatment. In more advanced NSCLC patients, our IOV-LUN-202 phase 2 clinical trial is investigating LN-145 monotherapy in patients who have received prior anti-PD-1 and chemotherapy, in combination or sequentially, with an option for pre-progression tumor harvest. IOV-LUN-202, which is potentially registrational, continued to enroll patients throughout 2022 and continues enrollment this year.

We are also pleased to be moving forward with our registrational strategy for lifileucel in cervical cancer, which we updated in 2022 based on FDA feedback following a shift in the treatment landscape. In our ongoing C-145-04 trial, we expanded Cohort 2 to enroll additional patients with cervical cancer who have progressed after chemotherapy and anti-PD-1 therapy. Cohort 2 is intended to be pivotal to support regulatory approval, and we look forward to continuing Cohort 2 enrollment during 2023.

Next Generation TIL Therapies

To optimize the next generation of TIL therapies, we are developing genetically modified TIL therapies that utilize the gene-editing TALEN® technology licensed from Collectis, S.A. to inactivate single or multiple immune checkpoint proteins that inhibit antitumor response. IOV-4001 is our first genetically modified, PD-1 inactivated TIL therapy candidate. In the third quarter of 2022, we treated the first patient with IOV-4001 in our first-in-human IOV-GM1-201 trial in patients with previously treated advanced melanoma or NSCLC. Additional programs using the TALEN® technology are expected to enter clinical development in 2024. Other research and preclinical studies are exploring additional approaches to increase TIL potency including the selection of CD39/69 double negative TILs and enhancements such as tethered cytokines. As part of our strategy to optimize the TIL treatment regimen, we also continue IND-enabling studies for our novel IL-2 analog, IOV-3001.

Organizational Growth

In 2022, our employee population grew by 58% as we prepare to transition to a commercial stage company. We have more than 500 lovance employees who collectively represent a breadth and depth of experience in developing and commercializing cell and gene therapy. We believe the quality of our people is a testament to the potential of our lovance TIL therapy in solid tumors and our ability to maintain leadership within the field.

We are also committed to building and supporting a diverse workforce with a deep bench of talent and a strong corporate culture. We believe we have strong gender and ethnic diversity across our management team and overall organization. As of April 2023, women account for over 54% of the total number of manager-level or above positions and represent 55% of our total employees. Racially diverse employees (self-identifying as Black or African American, Hispanic or Latino, Asian, or two or more races) make up approximately 42% of the management-level team and 49% of our total workforce.

We remain committed to our vision of pioneering a transformational approach to cure cancer by harnessing the human immune system's ability to recognize and destroy diverse cancer cells in each patient. I am grateful for our dedicated employees, clinical investigators, collaboration partners, shareholders, and most importantly, the patients with cancer and their families who motivate us every single day.



Frederick G. Vogt, PhD, JD
Interim CEO, President, and General Counsel

GLOBAL LEADER IN INNOVATING, DEVELOPING AND DELIVERING TIL THERAPIES

Iovance Biotherapeutics is pioneering a transformational approach to treating cancer by harnessing the ability of the human immune system to recognize and attack diverse cancer cells in each patient. We are committed to continuous innovation in cell therapy, including gene-edited cell therapy, that we hope will be a promising option for patients with cancer.



IOVANCE IMMUNO-ONCOLOGY PIPELINE

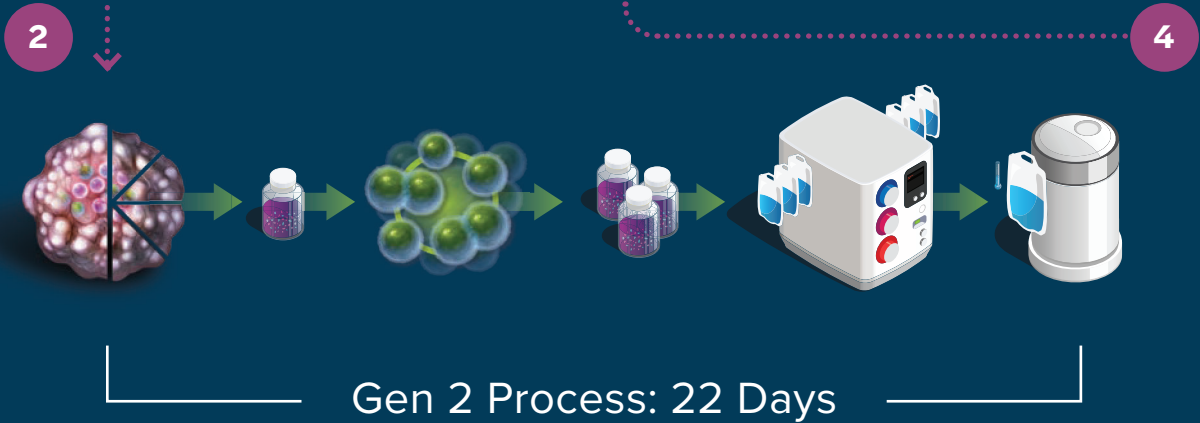
	PRODUCT CANDIDATE	INDICATION(S)	PHASE 1	PHASE 2	PIVOTAL
Advanced Melanoma (Metastatic or Unresectable)	TIL (Lifileucel/LN-144)	Post-anti-PD-1	C-144-01, Cohorts 2 & 4	Rolling BLA Submitted, ODD, RMAT	
	Lifileucel + pembro	Frontline	TILVANCE-301 Phase 3	Confirmatory, FTD	
	Lifileucel + pembro	Anti-PD-1 naïve	IOV-COM-202, Cohort 1A		
<i>Next Generation</i>	PD-1 Inactivated TIL (IOV-4001)	Post-anti-PD-1	IOV-GM1-201, Cohort 1		
Metastatic NSCLC	LN-145	2L post-chemo & post-anti-PD-1	IOV-LUN-202, Cohorts 1 & 2		
	LN-145 + pembro	Anti-PD-1 naïve	IOV-COM-202, Cohort 3A		
	LN-145	2-4L incl. post-anti-PD-1	IOV-COM-202, Cohort 3B*		
	LN-145 + ipi/nivo	Post-anti-PD-1	IOV-COM-202, Cohort 3C		
	<i>Next Generation</i>	LN-145 Gen 3 + core biopsy	2L post-chemo & post-anti-PD-1	IOV-LUN-202, Cohort 3	
	PD-1 Inactivated TIL (IOV-4001)	2-4L incl. post-anti-PD-1	IOV-GM1-201, Cohort 2		
Cervical	Lifileucel	Post-chemo & post-anti-PD-1	C-145-04, Cohort 2		BTD, ODD
	LN-145 + pembro	1L chemo and anti-PD-1 naïve	C-145-04, Cohort 3*		

*Enrollment complete
Abbreviations: 1L=first line; 2L=second line; 4L=fourth line; BTD=Breakthrough Therapy Designation; FTD=Fast Track Designation; ipi/nivo=ipilimumab/nivolumab; NSCLC=non-small cell lung cancer; ODD=Orphan Drug Designation; PD-1=programmed cell death protein-1; RMAT=Regenerative Medicines Advanced Therapy; TIL=tumor infiltrating lymphocytes

IOVANCE STREAMLINED 22-DAY GMP MANUFACTURING PROCESS



- 1 Patient Intake
- 2 Tumor Sample Procurement
- 3 Non-myeloablative Lymphodepletion
- 4 TIL Infusion
- 5 IL-2 Infusions
- 6 Recovery/Discharge



IOVANCE is committed to developing commercially available, broadly accessible cell therapies for people with cancer.

Our T-cell-based immunotherapy technology platforms are potentially applicable to many solid tumor types and blood cancers. Each platform is focused on leveraging patient-specific cells to recognize and attack diverse cancer cells that are unique to each patient.

Our lead TIL technology platform has enabled us to treat more than 600 patients using a scalable, 22-day process and other novel processes to manufacture personalized TIL therapies. With clinical data in melanoma, non-small cell lung, cervical and head and neck cancers, we believe that TIL therapy may become the next paradigm-shifting class of cancer treatment.



APRIL 2023 ENVIRONMENTAL, SOCIAL AND GOVERNANCE (ESG) SNAPSHOT

54%

OF MANAGER-LEVEL
OR ABOVE POSITIONS
ARE WOMEN

55%

OF TOTAL EMPLOYEES
ARE WOMEN

49%

OF EMPLOYEES SELF-
IDENTIFY AS BLACK OR
AFRICAN AMERICAN,
HISPANIC OR LATINO,
ASIAN, OR BEING 2+ RACES

IOVANCE'S COMMITMENT TO ESG:

Maintain stringent standards
for environmental stewardship

Set and achieved all
workplace safety goals

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2022

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transaction period from _____ to _____

Commission file number: 001-36860

IOVANCE BIOTHERAPEUTICS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction of
Incorporation or Organization)

75-3254381
(I.R.S. Employer
Identification No.)

825 Industrial Road, Suite 400, San Carlos, California
(Address of Principal Executive Offices)

94070
(Zip Code)

(650) 260-7120

(Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

<u>Title of Each Class</u>	<u>Trading Symbol(s)</u>	<u>Name Of Each Exchange On Which Registered</u>
Common Stock, \$ 0.000041666 Par Value per Share	IOVA	The Nasdaq Global Market

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer
Non-accelerated filer

Accelerated filer
Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report.

If the securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements.

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b).

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

Securities registered pursuant to Section 12(b) of the Act:

<u>Title of each class</u>	<u>Trading Symbol(s)</u>	<u>Name of each exchange on which registered</u>
Common stock, par value \$0.000041666 per value	IOVA	The Nasdaq Stock Market, LLC

The aggregate market value of the registrant's common stock held by non-affiliates on June 30, 2022, the last business day of the registrant's most recently completed second fiscal quarter, was approximately \$1.6 billion. Shares of common stock held by directors and executive officers and any ten percent or greater stockholders and their respective affiliates have been excluded from this calculation, because such stockholders may be deemed to be "affiliates" of the Registrant. This is not necessarily determinative of affiliate status of other purposes. As of February 21, 2023, there were 224,238,882 shares of the registrant's common stock outstanding.

Documents Incorporated By Reference

Portions of registrant's proxy statement relating to registrant's 2023 Annual Meeting of Stockholders (the "Proxy Statement") to be filed with the Securities and Exchange Commission pursuant to Regulation 14A, not later than 120 days after the close of the registrant's fiscal year, are incorporated by reference in Part III of this Annual Report on Form 10-K. Except with respect to information specifically incorporated by reference in this Annual Report on Form 10-K, the Proxy Statement is not deemed to be filed as part of this Annual Report on Form 10-K.

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Forward-Looking Statements and Market Data

This Annual Report on Form 10-K contains forward-looking statements that are based on management's beliefs and assumptions and on information currently available to management. All statements other than statements of historical facts contained in this report are forward-looking statements. In some cases, you can identify forward-looking statements by the following words: "may," "will," "might," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "aim," "potential," "continue," "ongoing," "goal," "forecast," "guidance," "outlook," or the negative of these terms or other similar expressions, although not all forward-looking statements contain these words.

These statements involve risks, uncertainties and other factors that may cause actual results, levels of activity, performance, or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this report, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the success, cost, enrollment, and timing of our clinical trials;
- the success, cost and timing of our product development activities;
- the ability of us or our third-party contract manufacturers to continue to manufacture tumor infiltrating lymphocytes, or TIL, in accordance with our selected process;
- our ability to design, construct and staff our own manufacturing facility on a timely basis and within the estimated expenses;
- the success of competing therapies that are or may become available;
- regulatory developments in the United States of America, or U.S., and foreign countries;
- the timing of and our ability to obtain and maintain U.S. Food and Drug Administration, or the FDA, or other regulatory authority approval of, or other action with respect to, our product candidates;
- our ability to attract and retain key scientific or management personnel;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- the ability and willingness of our third-party research institution collaborators to continue research and development activities relating to our product candidates;
- the potential of our other research and development and strategic collaborations;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our manufacturing methods and product candidates;
- our plans to research, develop and commercialize our product candidates;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- fluctuations in the trading price of our common stock; and
- our use of cash and other resources.

Actual results may differ from those set forth in this Annual Report on Form 10-K due to the risks and uncertainties inherent in our business, including, without limitation: the FDA may not agree with our interpretation of the results of its clinical trials; later developments with the FDA that may be inconsistent with already completed FDA meetings; the preliminary clinical results, including efficacy and safety results, from ongoing Phase 2 and Phase 3 clinical trials may not be reflected in the final analyses of these clinical trials including new cohorts within these clinical trials; the results obtained in our ongoing clinical trials, such as the studies and clinical trials referred to in this Annual Report on Form 10-K, may not be indicative of results obtained in future clinical trials or supportive of product approval; regulatory authorities may potentially delay the timing of FDA or other regulatory authority approval of, or other action with respect to, our product candidates, specifically, our description of FDA interactions are subject to FDA's interpretation, as well as FDA's authority to request new or additional information; we may not be able to obtain or maintain FDA or other regulatory authority approval of its product candidates; our ability to address FDA or other regulatory authority requirements relating to our clinical programs and registrational plans, such requirements including, but not limited to, clinical and safety requirements as well as manufacturing and control requirements; risks related to our accelerated FDA review designations; our ability to obtain and maintain intellectual property rights relating to our product pipeline; and the acceptance by the market of our product candidates and their potential reimbursement by payors, if approved.

We caution you that the risks, uncertainties, and other factors referenced above may not contain all the risks, uncertainties and other factors that are important to you. In addition, we cannot guarantee future results, level of activity, performance, or achievements. Any forward-looking statement made by us in this Annual Report on Form 10-K speaks only as of the date of this Annual Report on Form 10-K or as of the date on which it is made. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether because of new information, future events or otherwise, after the date of this Annual Report on Form 10-K.

Unless the context requires otherwise, in this report the terms "Iovance," the "Company," "we," "us" and "our" refer to Iovance Biotherapeutics, Inc.

PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company pioneering a transformational approach to treating cancer by harnessing the human immune system's ability to recognize and destroy diverse cancer cells using therapies personalized for each patient. We are preparing for potential U.S. regulatory approval and commercialization of the first autologous T-cell therapy to address a solid tumor cancer. Our mission is to be the global leader in innovating, developing and delivering tumor infiltrating lymphocyte, or TIL, therapies for patients with solid tumor cancers. Our autologous TIL therapy platform uses a centralized, scalable and proprietary 22-day manufacturing process to grow polyclonal T-cells unique to each patient and yields a cryopreserved, individualized therapy. We have applied multiple TIL therapy modalities in clinical trials in solid tumors, including TIL monotherapies for patients with later stage disease who have progressed on or after standard of care, as well as TIL combinations with standard of care therapies in patients who are earlier in their disease, to potentially improve outcomes compared to current standard(s) of care.

Our lead product candidate, lifileucel, is being developed in advanced, or metastatic or unresectable, melanoma as well as in other indications. Lifileucel was investigated in two consecutive cohorts in a clinical trial of advanced melanoma patients post-anti-PD-1 therapy, including in a prospectively defined pivotal cohort. These patients had progressed on or after standard of care therapy, which is immune checkpoint inhibitors, or ICIs, and, targeted BRAF/MEK inhibitor therapy where appropriate. Based on the positive results of these cohorts, we initiated a rolling Biologics License Application, or BLA, submission to the U.S. Food and Drug Administration, or FDA, for lifileucel in August 2022. We expect to complete this rolling BLA submission in the first quarter of 2023. Our Phase 3 clinical trial of lifileucel in combination with pembrolizumab, TILVANCE-301, is intended to be registrational in frontline advanced melanoma and serve as a confirmatory clinical trial to support full approval of lifileucel monotherapy in post-anti-PD-1 melanoma.

We are also pursuing registrational strategies for lifileucel in advanced cervical cancer and for our TIL therapy, LN-145, in metastatic non-small cell lung cancer, or NSCLC. To continuously innovate and maintain our global leadership within the field, we are investigating next generation approaches to optimize TIL products, manufacturing processes and treatment regimens, including a first-in-human clinical trial of our lead genetically modified TIL therapy, IOV-4001. We are also exploring a 16-day manufacturing

process, tumor tissue procurement via core biopsy, additional genetically modified TIL therapies including multiple immune checkpoint gene edits and cytokine-tethered TIL therapies, and a novel interleukin-2, or IL-2, analog, designated IOV-3001, as potential avenues to improve manufacturing timelines, sample collection and supportive treatments involved in the overall TIL therapy process and treatment regimen.

Highlights of our current development pipeline are presented in the figure below:

Iovance Solid Tumor Pipeline Highlights

	PRODUCT CANDIDATE	INDICATION(S)	PHASE 1	PHASE 2	PIVOTAL
Advanced Melanoma (Metastatic or Unresectable)	Lifileucel + pembro	Frontline	TILVANCE-301 Phase 3		Confirmatory, FTD
	TIL (Lifileuce/ LN-144)	Post-anti-PD-1	C-144-01, Cohorts 2 & 4		Rolling BLA In Progress, RMAT
	Lifileucel + pembro	Anti-PD-1 naïve	IOV-COM-202, Cohort 1A		
<i>Next Generation</i>	PD-1 Inactivated TIL (IOV-4001)	Post-anti-PD-1	IOV-GM1-201, Cohort 1		
Metastatic NSCLC	LN-145	2L post-chemo & post-anti-PD-1	IOV-LUN-202, Cohorts 1 & 2		
	LN-145 + pembro	Anti-PD-1 naïve	IOV-COM-202, Cohort 3A		
	LN-145	2-4L incl. post-anti-PD-1	IOV-COM-202, Cohort 3B*		
	LN-145 + ipi/nivo	Post-anti-PD-1	IOV-COM-202, Cohort 3C		
	<i>Next Generation</i>	LN-145 Gen 3 + core biopsy	2L post-chemo & post-anti-PD-1	IOV-LUN-202 Cohort 3	
	PD-1 Inactivated TIL (IOV-4001)	2-4L incl. post-anti-PD-1	IOV-GM1-201, Cohort 2		
Cervical	Lifileucel	Post-chemo & post-anti-PD-1	C-145-04, Cohort 2		BTD, ODD
	LN-145 + pembro	1L – chemo and anti-PD-1 naïve	C-145-04, Cohort 3*		

Platform Technologies and Manufacturing

Our T-cell-based immunotherapy technology platforms are potentially applicable to many solid tumor types and blood cancers. Each platform is focused on leveraging patient-specific cells to recognize and attack diverse cancer cells that are unique to each patient. Unlike cell therapies that act on a single or small number of shared antigen targets common to certain tumors, our polyclonal T-cells are personalized therapies designed to target a variety of neoantigens that are unique to the patient or tumor. The majority of solid tumor immune targets are patient-specific, with fewer than 1% shared among patients. TIL therapy is our lead T-cell-based immunotherapy platform in multiple advanced solid tumor cancers. For blood cancers, our peripheral blood lymphocyte, or PBL, therapy platform is based on polyclonal T-cells that are collected from a patient’s blood sample, and then amplified and reinvigorated.

TIL Clinical Development in Advanced, Metastatic or Unresectable Solid Tumor Cancers

Building on the prior TIL therapy clinical trials conducted at single academic centers, including the National Cancer Institute, or NCI, we have investigated TIL therapy in global, multi-center Phase 2 clinical trials in advanced melanoma, cervical cancer, NSCLC, and head and neck squamous cell carcinoma, or HNSCC. Additional information about our clinical trials is summarized below.

In post-anti-PD-1 advanced melanoma, we are investigating lifileucel in our C-144-01 clinical trial that supports our BLA submission and potential approval of lifileucel in advanced post-anti-PD-1 melanoma.

In frontline advanced melanoma patients who are naïve to anti-PD-1 therapy, we are investigating lifileucel in combination with pembrolizumab in the IOV-COM-202 clinical trial and the Phase 3 TILVANCE-301 clinical trial. TILVANCE-301 is a randomized Phase 3 clinical trial intended to support registration in advanced frontline melanoma as well as to serve as a confirmatory trial for full approval in advanced post-anti-PD-1 melanoma.

We are also executing a registrational strategy for lifileucel in advanced cervical cancer. C-145-04 is a multicenter Phase 2 clinical trial that is currently enrolling a pivotal cohort to support a BLA in cervical cancer following progression on or after chemotherapy and pembrolizumab.

In NSCLC, we are investigating our TIL therapy, LN-145, in two clinical trials in several NSCLC patient populations with significant unmet need. IOV-LUN-202 is a clinical trial of LN-145 in advanced NSCLC patients who have progressed following chemotherapy and anti-PD-1 therapy. IOV-COM-202 also includes cohorts of NSCLC patients treated with LN-145 monotherapy and combination therapy.

Our first genetically modified, PD-1 inactivated TIL therapy, IOV-4001, entered a first-in-human Phase 1/2 clinical trial, IOV-GM1-201, in 2022 in patients with previously treated advanced melanoma and NSCLC. IOV-4001 utilizes the gene-editing TALEN® technology, licensed from Collectis S.A., or Collectis, to inactivate the gene coding for the programmed cell death protein-1, or PD-1.

Beyond our Iovance-sponsored clinical trials, we have academic collaborations with leading cancer research centers to investigate TIL therapy, including next-generation processes and technologies, in other cancers and treatment settings.

Next-Generation Therapeutic and Manufacturing Approaches

Our current next-generation technology platforms are designed to optimize TIL therapy across four key initiatives: genetic modification, potency, manufacturing process and treatment regimens. More information on our next-generation approaches is included in the Next-Generation Product Candidates section of this Annual Report on Form 10-K.

Intellectual Property

We have established a leading intellectual property portfolio developed internally and licensed from third parties. We currently own more than 60 U.S. patents related to TIL therapy, including patents directed to compositions and methods of treatment and manufacturing in a broad range of cancers. Pending patent applications and granted patents cover the fields of TIL therapy, marrow infiltrating lymphocytes, or MIL therapy, and PBL therapy. We also license rights to a broad range of technologies related to our platforms. More details on our intellectual property portfolio are included within this Annual Report on Form 10-K.

Corporate Strategy

Be the global leader in innovating, developing and delivering TIL therapy

Our mission is to be the global leader in innovating, developing and delivering TIL therapy for patients with cancer. We are pioneering this transformational approach to cure cancer by harnessing the human immune system's ability to recognize and destroy diverse cancer cells in each patient. We are committed to continuous innovation in developing TIL cell therapy and optimizing the TIL treatment regimen that may extend and improve life for patients with cancer.

Obtain regulatory approval and successfully commercialize our lead product candidate lifileucel for the treatment of post-anti-PD-1 advanced melanoma

Our top priority is to expedite the regulatory approval and commercialization of our lead product candidate, lifileucel, for the treatment of patients with post-anti-PD-1 advanced melanoma. We initiated a rolling BLA for lifileucel in post-anti-PD-1 advanced melanoma in August 2022 and plan to complete the BLA submission in the first quarter of 2023.

Our medical affairs team is in the field educating key opinion leaders, or KOLs, and presenting and publishing our clinical results. Our U.S. commercial leadership team is preparing to launch lifileucel in 2023, if approved. We have experienced marketing, payer access and distribution teams, and we are building a specialty oncology sales force for launch. More than half the team has prior cell therapy experience.

The five primary areas of our pre-launch efforts include:

- onboarding of authorized treatment centers, or ATCs, with the goal of 40 ATCs for commercial launch;

- collaboration with healthcare professionals, or HCPs, who will be handling or administering our product;
- operational excellence in launch execution, commercial manufacturing and delivery of therapy;
- communication with payors about the value of lifileucel; and
- establishment of a cross-functional, patient-centric organization.

Prepare for commercial manufacturing to meet forecasted demand

We believe that we are the only company in the U.S. to have a centralized, demonstrated, and commercially viable TIL manufacturing process. To date more than 600 patients have been treated with Iovance TIL therapy manufactured using our proprietary processes, by contract manufacturing organizations, or CMOs, and by us at our own manufacturing facility, the Iovance Cell Therapy Center, or *iCTC*.

The *iCTC* is currently manufacturing TIL for our ongoing clinical trials and preparing to provide commercial supply upon potential BLA approval. We began construction of the *iCTC* in 2019, in Philadelphia, Pennsylvania, in order to control manufacturing capacity, product quality, manage logistics around supply and delivery, implement process improvement and realize potential cost efficiencies for TIL therapies that we may develop or commercialize. We intend to carefully manage our cost structure, and reduce the long-term cost of manufacturing our products, although there can be no assurance that we will be able to reduce our manufacturing costs to commercially attractive levels. We are building capacity to treat thousands of cancer patients annually, with flexibility to expand within existing shell space and an option to build on an adjacent lot to support future growth. We expect *iCTC* to supply most of our commercial TIL therapies at launch, with CMOs to supplement our internal manufacturing capacity under various manufacturing services agreements, or MSAs. Details of related agreements are provided in the Research, Development, Manufacturing and License agreements section of this Annual Report on Form 10-K.

Continue to improve our TIL manufacturing processes and technology

In 2018, we first utilized our TIL manufacturing process known as Gen 2, which reduced TIL manufacturing time from 5-6 weeks to 22 days while producing a cryopreserved TIL product for ease of administration and handling. We intend to establish Gen 2 as a viable commercial manufacturing process for our initial TIL therapies. Gen 2 was utilized in all patients in both Cohorts 2 and 4 of our C-144-01 clinical trial and is the manufacturing process for registration and the BLA submission for lifileucel. Gen 2 is also being utilized in most of our ongoing TIL clinical development programs. We also continue to develop and evaluate potential future TIL manufacturing processes, including our 16-day Gen 3 process, as well as processes for genetically modified and other next generation TIL products.

Advance and expand our pipeline of polyclonal T-cell therapies

We seek to collaborate with government, academic research institutions, and corporate partners to improve TIL manufacturing, and to develop and explore next generation approaches as well as TIL therapies for new indications. We have a Cooperative Research and Development Agreement, or CRADA, with the National Institutes of Health, or NIH, and the National Cancer Institute, or NCI. We also have ongoing licensing agreements and collaborations with H. Lee Moffitt Cancer Center, or Moffitt, The University of Texas M.D. Anderson Cancer Center, or MDACC, Yale University, The Ohio State University, Cellectis, Novartis Pharma AG, or Novartis, Melanoma Institute Australia, or MIA, and Beth-Israel Deaconess Medical Center, or BIDMC. A description of some of these collaborations and related agreements is provided in the Collaborations for New Tumor Types and Treatment Settings section of this Annual Report on Form 10-K.

Iovance-Sponsored Clinical Trials

TIL Therapy in Advanced Solid Tumor Cancers

Lifileucel for Advanced Melanoma

Melanoma is a common type of skin cancer, accounting for an estimated 99,780 patients diagnosed and 7,650 deaths in 2022 in the U.S. according to the Surveillance, Epidemiology and End Results program, or SEER, program. We are developing lifileucel to treat advanced melanoma. Our Phase 2 clinical trial, C-144-01, is a prospective, clinical trial evaluating lifileucel in advanced melanoma patients who have progressed on or after prior anti-PD-1 therapy and if BRAF mutant, after BRAF or BRAF/MEK inhibitor therapy. There are no FDA approved therapies in this treatment setting for advanced melanoma after anti-PD-1 therapy.

Based on the unmet need in post-anti-PD-1 advanced melanoma, as well as initial clinical data, lifileucel received a Regenerative Medicine Advanced Therapy, or RMAT, designation from the FDA in 2018.

In the C-144-01 trial, our Generation 1, or Gen 1, manufacturing process with non-cryopreserved product was used in Cohort 1, which was closed to enrollment in 2017. Our Gen 2 process with cryopreserved product was used in subsequent patients enrolled in both Cohorts 2 and 4. Cohort 2 was closed to enrollment in late 2018. Cohort 3 is an optional retreatment cohort.

Cohort 4, a pivotal cohort, was added in 2019, following an end of Phase 2, or EOP2, meeting held with the FDA in the third quarter of 2018 and completed dosing in January 2020. Cohort 4 built on the Cohort 2 results in the same patient population and used the same eligibility criteria, treatment and manufacturing process. Cohort 4 was designed to evaluate objective response rate, or ORR, read by an independent review committee, or IRC, using RECIST v1.1 as the prospectively defined primary endpoint.

The results from Cohort 2, including ORR as assessed by investigator, were presented at several medical meetings since 2018 and published in the Journal of Clinical Oncology in May 2021. We reported durable responses across a wide age range of metastatic melanoma patients, among those who have received prior anti-CTLA-4 and BRAF targeted treatments, regardless of BRAF mutation status, and in patients with PD-L1 high and low status. In May 2022, we announced topline IRC read data from the C-144-01 clinical trial from Cohort 4, which met the primary endpoint, ORR, of the clinical trial. In addition, we reported updated data from Cohort 2 and pooled Cohorts 2 and 4.

We presented additional data from C-144-01 Cohorts 2 and 4 at the Society for Immunotherapy of Cancer, or SITC, Annual Meeting in November 2022. The SITC 2022 presentation included pooled efficacy data read by IRC and safety data from 153 patients with advanced melanoma, including 66 patients enrolled in Cohort 2 and 87 patients enrolled in Cohort 4, with a median study follow up of 36.5 months and a data cutoff date of July 15, 2022. Across both cohorts, patients had received a median of 3 lines of prior therapy, including anti-PD-1 therapy in 100% of patients and anti-CTLA-4 therapy in 81.7% of patients, with prior combination anti-PD-1 and anti-CTLA-4 therapy received in 53.6% of patients. Baseline disease characteristics were generally similar between Cohorts 2 and 4. However, Cohort 4 patients showed both a higher disease burden and a higher proportion of patients with elevated lactate dehydrogenase, or LDH, a well-known negative prognostic factor in melanoma. The ORR assessed by an IRC using RECIST v1.1 was 31.4%, with 9 complete responses and 39 partial responses. The median time from lifileucel infusion to best response was 1.5 months, and responses deepened over time. Median duration of response, or mDOR, was not reached as estimated by Kaplan-Meier, or KM, method. Responses lasted for 24 months or greater in 41.7% of responders, including 47.8% of responders in Cohort 2 and 36.0% of responders in Cohort 4. Median overall survival, or mOS, had not been reached in patients who achieved a response at first assessment at 6 weeks, and mOS in all patients was 13.9 months. The treatment-related adverse event, or TEAE, profile was generally consistent with the underlying advanced disease and the safety profile of the lymphodepletion and IL-2 regimens. In December 2022, we published additional detail from C-144-01 in the Journal for Immuno Therapy of Cancer, or JITC.

Based on results from the C-144-01 clinical trial, we held a pre-BLA meeting with the FDA in July 2022 and initiated a rolling BLA for lifileucel in metastatic melanoma in August 2022. The BLA submission includes C-144-01 data from pivotal Cohort 4 and supportive Cohort 2. We plan to complete the rolling BLA submission in the first quarter of 2023.

We are also pursuing a registrational path for lifileucel in combination with pembrolizumab in frontline advanced melanoma. Our strategy is based on clinical results from Cohort 1A of the IOV-COM-202 clinical trial that support the combination, as well as prior published NCI data for TIL monotherapy in anti-PD-1 naïve melanoma patients. We reported initial results and updates from ongoing Cohort 1A of the IOV-COM-202 clinical trial at the American Society of Clinical Oncology, or ASCO, annual meeting in June 2021, SITC in November 2021. The Cohort 1A results to date have demonstrated that lifileucel can be safely combined with pembrolizumab. At our most recent medical meeting oral presentation at SITC, in November 2021, updated results from 10 patients demonstrated ORR of 60%. Six out of the 10 patients had a confirmed objective response, including three complete responses and three partial responses. The TEAE profile was consistent with the underlying advanced disease and the known adverse event profiles of pembrolizumab, lymphodepletion, and IL-2 regimens.

In an April 2022 corporate announcement, we provided updated data that demonstrated a 67% ORR in 12 patients in Cohort 1A. Eight patients had a confirmed objective response per RECIST v1.1, including three complete responses and five partial responses. Six of the eight responders had ongoing response at the time of the last data cut, and five responders had a duration of response of more than one year. In a January 2023 corporate press release, we disclosed that updated efficacy and safety results from nearly 20 patients treated in Cohort 1A remain consistent with previously reported Cohort 1A data and continue to support our strategy in frontline advanced melanoma.

During the fourth quarter of 2022, we reached agreement with the FDA and began start up activities for a Phase 3 multicenter, open-label, randomized, parallel group, treatment clinical trial, TILVANCE-301, in frontline advanced melanoma. The TILVANCE-301 trial, or NCT05727904, will randomize 670 patients to investigate lifileucel in combination with pembrolizumab in the experimental arm compared with pembrolizumab monotherapy in the control arm. The clinical trial will enroll participants with unresectable or metastatic melanoma who have had no prior therapy for metastatic disease. Previous adjuvant/neoadjuvant therapy with a single line of BRAF-targeted therapy, PD-1 inhibitor, or CTLA-4 inhibitor is allowed, if completed at least 6 months before progression to metastatic disease. In the experimental arm, a tumor sample is resected from each patient for lifileucel manufacturing. Patients receive pembrolizumab prior to and after the lifileucel regimen, every 6 weeks until disease progression. In the control arm, pembrolizumab monotherapy is given every 6 weeks until disease progression, with an optional crossover period to lifileucel monotherapy upon confirmed progressive disease verified by a blinded independent review committee, or BIRC, and if patients meet eligibility criteria. The FDA agreed to dual primary endpoints of ORR to support accelerated approval and progression free survival, or PFS, to support full approval of lifileucel in frontline advanced melanoma. TILVANCE-301 is also designed to serve as a confirmatory clinical trial to support full approval of lifileucel in post-anti-PD-1 advanced melanoma. The dual primary endpoints will be verified by BIRC using RECIST v1.1.

Lifileucel for Cervical Cancer

According to estimates from the SEER program, in 2022 approximately 14,100 women would be diagnosed with cervical cancer and approximately 4,280 cervical cancer-related deaths would occur in the U.S.

We are developing lifileucel alone and in combination with pembrolizumab for the treatment of advanced, unresectable or metastatic, cervical cancer. Lifileucel for advanced cervical cancer was formerly known as LN-145. C-145-04 is an ongoing Phase 2, multicenter pivotal clinical trial. In March 2019, the protocol for this clinical trial was amended to modify the primary endpoint of from ORR by investigator to ORR based on IRC assessment. Initial results from the C-145-04 clinical trial were reported at ASCO in June 2019.

In anticipation of a changing landscape, we amended the protocol for the C-145-04 clinical trial in November 2019 from a single cohort design into a multicohort study. Cohort 1 was defined to include patients who had progressed during or after systemic chemotherapy excluding ICI. Cohort 2 was newly added to include patients who have progressed during or after treatment with anti-PD-1/-L1 checkpoint inhibitor in addition to systemic chemotherapy. Cohort 3 was added to enroll patients who had not received prior systemic therapy to investigate lifileucel in combination with pembrolizumab. Cohort 3 results from 14 initial patients were included as part of an oral presentation at SITC in November 2021. The ORR was 57.1 % with eight out of 14 patients achieving an objective response, including one complete response, six partial responses and one unconfirmed partial response. The TEAE profile was consistent with the underlying advanced disease and the known adverse event profiles of pembrolizumab, lymphodepletion, and IL-2 regimens.

In the C-145-04 trial, we completed enrollment of Cohort 1 in 2020, Cohort 2 in 2021 and Cohort 3 in 2022. During 2022, following the FDA discussions and feedback on a registration strategy to address the shift in standard of care following the FDA approval of pembrolizumab in the frontline cervical cancer setting, we reopened Cohort 2 to enroll additional patients and to be a pivotal cohort to support a BLA for cervical cancer following progression on chemotherapy and pembrolizumab. We expect to continue enrollment in Cohort 2 in 2023.

LN-145 for Advanced, or Metastatic or Unresectable NSCLC

According to SEER program estimates, approximately 236,740 people would be diagnosed with lung and bronchus cancers, and approximately 130,180 deaths would occur related to these cancers in the U.S. in 2022.

We are developing our TIL therapy LN-145 alone and in combination with approved therapies to treat advanced NSCLC in the IOV-LUN-202 and IOV-COM-202 clinical trials. IOV-LUN-202 is investigating LN-145 monotherapy in patients with metastatic NSCLC who previously received approved systemic therapy of combined or sequential ICI and chemotherapy in three cohorts. The programmed death-ligand 1, or PD-L1, tumor proportion score, or TPS, in patients at the time they started frontline therapy was less than one percent or unknown in patients in Cohort 1 and greater than or equal to one percent in patients in Cohort 2. In Cohort 3, we are exploring treatment with TIL that is extracted from core biopsy and manufactured using our Gen 3 process.

In June 2021, the first patient was treated in the IOV-LUN-202 clinical trial. In a poster on IOV-LUN-202 at the American Association for Cancer Research, or AACR, Annual Meeting in April 2022, we featured protocol updates including changes to eligibility criteria, and the option for pre-progression tumor harvest, to broaden enrollment in reflection of the unmet need in NSCLC. We enrolled patients during 2022 and intend to continue enrollment in 2023.

IOV-COM-202 is a clinical trial that includes 2 active cohorts and one previously completed cohort in patients with recurrent or metastatic NSCLC as follows:

- Cohort 3A is evaluating LN-145 in combination with pembrolizumab in patients who have not received prior immunotherapy, including ICIs. Cohort 3B was previously completed and investigated LN-145 monotherapy in patients who had progressed on or after prior ICI therapy, including patients with oncogene-driven tumors who received prior tyrosine kinase inhibitor, or TKI, therapy.
- Cohort 3C is investigating LN-145 in combination with ipilimumab or nivolumab in patients who previously received only a prior line of approved systemic ICI monotherapy.

We have reported full results from Cohort 3B and initial results from Cohort 3A in the IOV-COM-202 study.

Cohort 3B results were reported in June 2021 and presented at SITC in November 2021. For the completed Cohort of 28 patients in the analysis population, the ORR was 21.4%, including one complete response and five partial responses. All patients had received prior anti-PD-1/-L1 therapy, and all six responding patients had also received prior chemotherapy. The TEAE profile was consistent with the underlying disease and known adverse event profiles of non-myeloablative lymphodepletion and IL-2. As of a data extract in November 2022 provided in a corporate slide deck, one complete response remained ongoing at 37 months following treatment with LN-145.

In a January 2023 press release, we shared initial topline results in 17 patients from Cohort 3A which comprises three distinct clinical subsets of anti-PD-1 naïve patients: 1) treatment-naïve, 2) post-chemotherapy, and 3) estimated glomerular filtration rate, or EGFR, -mutant after prior treatment with TKIs. Confirmed ORR by RECIST v1.1 was 47%, with an objective response observed in 8 patients treated with LN-145 in combination with pembrolizumab. Responses were observed regardless of PD-L1 status. Two patients achieved complete responses and remain on study, including one patient who was post-chemotherapy and anti-PD-1 naïve, and one patient who was EGFR-mutant after prior treatment with TKI. Safety was consistent with other studies of Iovance TIL therapies in combination with pembrolizumab. Study enrollment remains ongoing. Observed differences between the patient subsets are informing the design of a subsequent potential registration study. Detailed clinical results will be shared at a future medical meeting.

We plan to continue to discuss registrational strategies for LN-145 with the FDA in 2023. Based on initial results from Cohort 3A, we plan to meet with the FDA in 2023 to discuss Cohort 3A results and a potential registration clinical trial of lifileucel in frontline advanced NSCLC.

IOV-4001 for Advanced Melanoma and NSCLC

Our lead genetically modified TIL therapy, IOV-4001, utilizes the gene-editing TALEN® technology licensed from Cellectis, to inactivate the gene coding for PD-1. The worldwide exclusive license enables us to use certain TALEN® technology addressing multiple gene targets in several cancer indications, to develop genetically edited and potentially more potent TIL therapies. We are investigating the safety and efficacy of IOV-4001 in the IOV-GM1-201 multicenter, first-in-human Phase 1/2 clinical trial in previously treated patients with advanced melanoma, who have progressed following anti-PD-1/PD-L1 blocking antibody therapy and, in those patients with BRAF mutations, after BRAF/MEK inhibitor therapy in Cohort 1, or metastatic NSCLC who have received no more than three prior lines of therapy, with or without oncogene driver mutations in Cohort 2. We treated the first patient with IOV-4001 in the third quarter of 2022. We published posters that highlight the “trial in progress” for IOV-GM1-201 at SITC in November 2022 and preclinical results for antitumor activity of IOV-4001 at the AACR Annual Meeting in April 2022.

TIL Therapy for HNSCC

In metastatic head and neck cancer squamous cell carcinoma, or HNSCC, we are evaluating LN-145 as monotherapy and in combination with pembrolizumab. The Phase 2 C-145-03 trial began in June 2017 and closed in January 2021 after reaching its pre-specified enrollment target to investigate LN-145 using various manufacturing processes. Cohort 2A in IOV-COM-202 is evaluating

LN-145 in combination with pembrolizumab in patients with HNSCC who are naïve to anti-PD-1 therapy. Initial and updated Cohort 2A results were presented at the SITC Annual Meetings in November 2020 and 2021, respectively.

PBL Therapy in Blood Cancers

In blood cancers, our clinical trial IOV-CLL-01 is a Phase 1/2 clinical trial evaluating the safety and efficacy of IOV-2001, our polyclonal PBL therapy, in patients with relapsed or refractory chronic lymphocytic leukemia, or CLL, and small lymphocytic lymphoma, or SLL, to receive IOV-2001.

Next-Generation Product Candidates

We are committed to innovating individualized T-cell therapies that may recognize a multitude of diverse patient-specific cancer cells. Our current next-generation technology platforms are designed to optimize TIL therapy across four key initiatives: genetic modifications, potency, process optimization and new treatment regimens.

- *Genetic modifications:* We are pursuing several targets for genetic modification that utilize the gene-editing TALEN® platform licensed from the clinical-stage biotechnology company, Collectis. Single- and multiple- knockouts may further harness the immune system response to cancer and potentially increase the efficiency, potency and application of TIL therapy. Preclinical development is also ongoing with cytokine-tethered TIL products and additional TIL products and TIL-cell lines using transient and stable gene insertion and inactivation, which may expand and activate TIL to achieve better efficacy while avoiding systemic side effects of cytokines.
- *Potency:* We are exploring potential approaches to increase potency of the final TIL product through sorting and selection of specific TIL, such as PD-1+ selected TIL and CD39/69 double-negative TIL, and the use of certain inhibitors or other reagents in TIL expansion cultures. Our TIL candidate LN-145-S1 is manufactured from TIL selected for PD-1 expression and has been investigated in patient cohorts in our clinical trials.
- *Process optimization:* We are committed to further improving and streamlining the processes for TIL therapy manufacturing and tumor sample collection. We are investigating a 16-day Gen 3 manufacturing process in patient cohorts included in the C-145-03 clinical trial in HNSCC and the IOV-COM-202 clinical trial. We are also exploring our Gen 3 process to manufacture TIL from core biopsy as a less-invasive collection of tumor samples in a cohort of patients with NSCLC in our IOV-LUN-202 clinical trial.
- *New treatment regimens:* We are exploring potential avenues to improve aspects of the TIL treatment regimen. In 2020, we licensed an antibody cytokine-engrafted protein, or IL-2 analog, which we refer to as IOV-3001, from Novartis. IOV-3001 is in IND-enabling studies supporting its use as part of the TIL treatment regimen following TIL infusion.

Collaborations for New Tumor Types and Treatment Settings

Our ongoing academic collaborations with leading cancer research centers as well as government and corporate partners are exploring the potential for TIL therapy in other tumor types and treatment settings, such as in the following example studies:

- MDACC has sponsored two Phase 2 clinical trials that were initiated in 2018. The first clinical trial, NCT03449108, is underway to investigate LN-145 or LN-145-S1 manufactured using our proprietary processes to treat patients with soft tissue sarcoma, osteosarcoma, platinum resistant ovarian cancer, anaplastic thyroid cancer, and triple negative breast cancer. The second clinical trial, NCT03610490, was previously active to investigate TIL manufactured by MDACC in patients with platinum resistant ovarian cancer, pancreatic and colorectal cancer, which may not be representative of our data using our Iovance manufacturing process.
- Yale Comprehensive Cancer Clinical is sponsoring a trial, NCT04111510, exploring LN-145 in triple-negative breast cancer.
- Memorial Sloan Kettering Cancer Center, or MSKCC, is investigating TIL therapy LN-144 manufactured by Iovance in patients with uveal melanoma in the NCT05607095 clinical trial, and asymptomatic melanoma brain metastases in the NCT05640193 clinical trial.

- Moffitt is conducting several clinical trials with funding from Iovance. Two clinical trials, which have closed to enrollment, are evaluating TIL therapy in combination with the checkpoint inhibitor nivolumab in NSCLC in the NCT03215810 clinical trial and metastatic melanoma in the NCT02652455 clinical trial. We previously collaborated on the NCT01701674 clinical trial to evaluate TIL therapy in combination with the CTLA-4 checkpoint inhibitor ipilimumab. A Phase 1 clinical trial, NCT04052334, completed enrollment in 2022 and is investigating TIL therapy manufactured by Moffitt in adolescent and young adult patients with soft tissue sarcoma.
- The Ohio State University is investigating lifileucel manufactured by Iovance in high-risk melanoma patients in the neoadjuvant setting in the NCT05176470 clinical trial. The trial began recruiting in 2022 to assess the feasibility of TIL expansion from tumor-involved lymph nodes patients who are diagnosed with stage IIIB-D melanoma that has spread to nearby tissue or locally advanced lymph nodes.
- NCI, under our CRADA, is conducting the NCT02621021 clinical trial to evaluate TIL therapy in combination with the checkpoint inhibitor pembrolizumab in a 170-patient clinical trial in patients with advanced melanoma.

Immune System and Cancer Surveillance

The immune system recognizes danger signals and responds to threats at a cellular level. The most significant components of the cellular aspect of the adaptive immune response are T-cells, or T lymphocytes, so called because they mature in the thymus and are distinguished from B-cells which mature in the bone marrow. T-cells can be distinguished from other white blood cells by T-cell receptors present on their cell surface. These receptors contribute to tumor surveillance by helping T-cells recognize infected as well as cancerous cells. T-cells are involved in both sensing and killing infected or cancerous cells, as well as coordinating the activation of other cells in an immune response.

Challenges for Cancer Immunotherapy

Despite progress over the past several decades, effective treatment of solid tumors continues to be challenging for several reasons, including: (i) intratumoral heterogeneity, (ii) numerous mutations and tumor neoantigens, with <1% shared across patients and lack of clarity on which mutations or neoantigens are critical, and (iii) ability to adapt and evade treatments that target a single mutation. In addition, the tumor itself and the tumor microenvironment can suppress the patient's natural immune response. When T-cells with cancer-specific receptors are absent, present in low numbers, of poor quality, or rendered inactive by suppressive mechanisms employed by tumor tissue, the cancer can grow and spread to various organs. In addition, standard of care treatments for cancer can be deleterious to T-cells' ability to kill cancer.

Advancing Immuno-Oncology with Our Tumor-Infiltrating Lymphocyte Technology Platforms

Our T-cell-based immunotherapy technology platforms are potentially applicable to many solid tumor types and blood cancers. Each platform is focused on leveraging patient-specific cells to recognize and attack diverse cancer cells that are unique to each patient. Unlike cell therapies that act on a single or small number of shared antigen targets common to certain tumors, our polyclonal T-cells are personalized therapies designed to target a variety of neoantigens that are unique to the patient or tumor. We believe that adoptive cell therapy, specifically with the use of human polyclonal TIL cells to reengage the immune system, may be a significant advancement in the treatment of cancer.

Using our lead TIL immunotherapy platform, our initial strategy is to deliver polyclonal T-cell-based therapies for patients with late-stage solid tumor cancers. After infusion, TIL can potentially infiltrate the tumor to eliminate cancer cells, further proliferate in the body and potentially overcome several mechanisms of tumor escape to which endogenous T-cells may be susceptible due to the immune-suppressive tumor microenvironment.

For earlier intervention, we are investigating the potential of our TIL therapy in combination with a class of immunotherapy drugs called ICIs that seek to overcome one of the main escape mechanisms of cancer against an immune system attack. TIL therapy and ICIs may work synergistically to target and attack cancer cells while breaking down barriers for the immune system to mount a response.

There are three key steps in the TIL therapy process.

- **Step 1: Sample Collection.** A tumor sample of about 1.5 cm in diameter is removed during a surgical biopsy and shipped to our centralized manufacturing facility, where the TIL are isolated.
- **Step 2: Manufacturing.** Patient-specific TIL are amplified and reinvigorated using our proprietary Gen 2 manufacturing process, reflecting our successful efforts to centralize and streamline TIL manufacturing from several weeks to 22 days. Additional detail on Gen 2 is provided below in the Manufacturing Process section of our Annual Report on Form 10-K.
- **Step 3: Treatment.** The patient begins with a preparative regimen of non-myeloablative lymphodepletion, or NMA-LD, to suppress the immunosuppressive tumor microenvironment, which we believe will enhance the efficacy of TIL therapy. After NMA-LD, the expanded and rejuvenated, patient-specific TIL cells are delivered back into the body by infusion. The treatment regimen is completed with a short course of IL-2 of up to 6 doses to promote T-cell activity in the body after TIL infusion. If a patient is receiving TIL as a monotherapy, their treatment may be complete. If a patient is receiving TIL therapy as part of the combination approach, they will continue treatment with ICIs following TIL infusion.

Historical Clinical Results with Other TIL Therapies in Metastatic Melanoma

To date, more than 600 patients have been treated with TIL therapies manufactured using our proprietary processes. Prior to our clinical trials, hundreds of advanced melanoma patients were treated with TIL therapy produced locally using different manufacturing methods at different academic institutions and hospitals in the U.S., Europe, Canada, and Israel.

At the NCI, clinical responses have been relatively consistent in several trials of TIL therapy in anti-PD-1 naïve melanoma patients that were conducted prior to anti-PD-1 treatment becoming the available standard of care for melanoma patients. Over 50% of patients achieved an objective response, and approximately 22-24% of patients had a complete response, as defined by RECIST v1.1 criteria. Most patients who have had a complete response remained in response in 3-7 years of follow up.

In August 2021, patient outcomes based on two decades of experience with TIL therapy in a cohort of 226 patients with metastatic melanoma were published by Seitter, et al., in a collaboration led by Dr. Steven Rosenberg from the Surgery Branch of the NCI, in Clinical Cancer Research. The ORR was 51%, with a complete response rate of 22%. The 49 patients achieving a complete response had a 10-year melanoma-specific survival of 96%. In the 192 patients who had not received prior anti-PD-1 therapy, ORR was 56% with a median melanoma-specific survival of 28.5 months. Of the 43 patients who were refractory to anti-CTLA-4 therapy without exposure to anti-PD-1, the 60 % response rate showed no difference when compared to the 55% response rate in those naïve to any immune checkpoint therapy. Baseline demographic features, including BRAF status, did not influence outcome. Exposure to prior therapies, including refractoriness to anti-PD-1 and BRAF/MEK inhibitors, affected outcome. In the population most comparable to Cohorts 2 and 4 of our C-144-01 trial, 34 of the reported patients were refractory to anti-PD-1 therapy and had an ORR of 24%, with a median melanoma-specific survival of 11.6 months. Decreased melanoma-specific survival was seen in patients that are refractory to BRAF/MEK inhibitors regardless of prior anti-PD-1 exposure with a median survival of 8.7 months in patients who were refractory to anti-PD-1 and 12.1 months in patients who were naïve to anti-PD-1.

In December 2022, in the New England Journal of Medicine, a team from The Netherlands Cancer Institute and the National Center for Cancer Immune Therapy, Department of Oncology, of the Copenhagen University Hospital published the results of a multicenter, open-label phase 3 clinical trial of 168 patients with unresectable stage IIIC-IV melanoma randomized 1:1 to TIL or single agent ipilimumab. The study began in 2014. Patients in the study had received a maximum of one line of prior therapy, of which 86% were refractory to anti-PD-1 therapy. With a median follow-up of 33.0 months, median PFS was 7.2 months for TIL compared to 3.1 months for ipilimumab. ORR was 49% for TIL with 20% complete responses, compared to 21% ORR and 7% complete response rate for ipilimumab. mOS for TIL was 25.8 months compared to 18.9 months for ipilimumab. Grade 3 and higher treatment-related adverse events occurred in all TIL and 57% of ipilimumab patients.

Manufacturing Processes

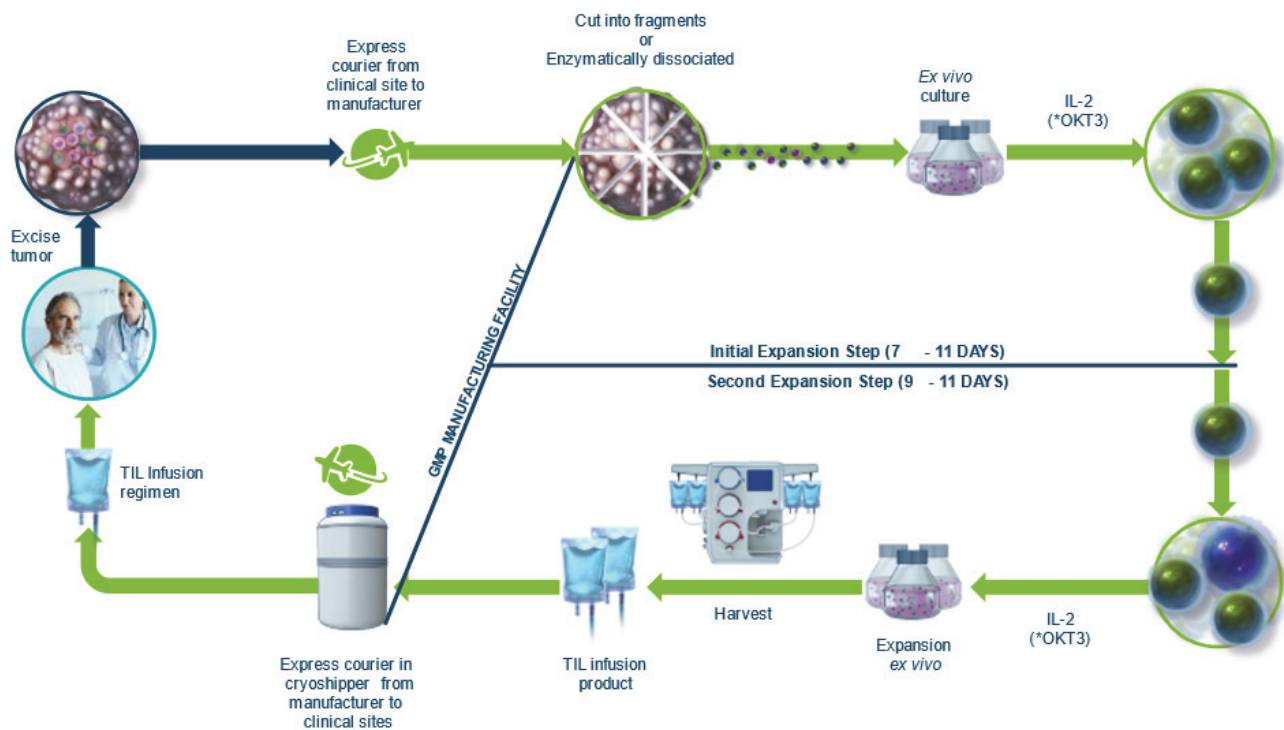
Iovance was founded to deliver broad access to TIL therapy for people with cancer by conducting multicenter clinical trials and developing centralized, scalable manufacturing processes to enable regulatory approvals and commercial launches. The NCI and other academic centers have historically manufactured TIL therapies for research purposes. To date, these site-specific processes have not been scalable or standardized to serve sizeable patient populations.

Our Gen 1 TIL manufacturing process modified the NCI’s original TIL manufacturing and processing so that it could be reproduced in a current good manufacturing practice, or cGMP, environment. TIL expansion occurred over a 5-to-6-week period and produced a non-cryopreserved product.

Our internal research and process development team developed our proprietary Gen 2 technology to include manufacturing and logistical efficiencies aimed at further optimizing treatment and streamlining distribution processes. Gen 2 manufacturing takes 22 days while allowing for a cryopreserved product. We currently use Gen 2 in almost all Iovance clinical trials for product registration and our BLA submission. We also continue to develop new processes. We have developed a shorter, 16-day, Gen 3 manufacturing process as well as next generation manufacturing processes to genetically modify TIL and to select for TIL that potentially more potent.

Gen 2 Manufacturing Process

During the Gen 2 process, TIL are expanded exponentially ex vivo to yield billions or $10^9 - 10^{11}$ of TIL. The process begins with the collection of the patient’s tumor by surgical biopsy, which is sent to a central manufacturing facility. The tumor is fragmented to facilitate a clear path for TIL to leave the tumor tissue and placed in media that optimizes the growth of TIL rather than other cell types. Initially, from days 0-11, cells grow slowly during the pre-rapid expansion, or pre-rep phase. Following the pre-rep phase, the cells are transferred to a larger bioreactor and feeder cells are introduced to further activate the TIL to proliferate during the rapid expansion, or REP phase, from days 11-22. During the REP phase, on day 16, the TIL are harvested while maintaining a closed system before they are counted and placed into multiple bioreactors which are incubated one last time until day 22. On day 22, TIL are filtered, washed, concentrated and finally formulated with cryopreservation media before being placed in up to four final product bags, depending on total cell count. The final product is shipped back to the center where it can be administered to the patient. The following diagram illustrates our Gen 2 TIL manufacturing process.



Note: Up to 10 additional days for QC required after manufacturing = Total LN-145 manufacturing time ~32 days

Our Iovance Cell Therapy Center, or iCTC, for Large-Scale Centralized Manufacturing

Our iCTC is the first centralized and scalable cGMP manufacturing facility dedicated to producing TIL as a potential therapy for patients with solid tumors. At 136,000 square feet, the iCTC is among the largest cell therapy manufacturing facilities in existence. It currently supplies investigational TIL therapy for Iovance clinical trials, with commercial manufacturing expected to begin after initial product approval. The proximity of the iCTC to multiple airports facilitates delivery of TIL therapies to treatment centers, with the iCTC expected to cover logistics and delivery of TIL therapy in both North America and Europe. This location may also offer future tax savings under Pennsylvania's Keystone Opportunity Improvement Zone, or KOIZ.

Clinical Manufacturing

In 2021, we completed the commissioning activities at the iCTC and successfully initiated manufacturing of clinical batches of lifileucel and LN-145. In addition, we have entered into MSAs with WuXi Advanced Therapies, Inc., or WuXi, and Moffitt pursuant to which they have agreed to manufacture, package, ship and handle quality assurance and quality control of certain clinical trials for our TIL products working closely with our employees. In the future, we may rely on them or other third parties, or our own manufacturing capabilities, for the manufacturing and processing of TIL-based product candidates for our clinical trials.

Commercial Manufacturing Preparations

To meet projected needs for commercial quantities, we continue our launch readiness and scale up activities to supply commercial TIL upon potential BLA approval. We expect to rely primarily on our own iCTC facility for commercial supply, with flexibility to use CMOs to meet anticipated clinical trial and, if approved, commercial demands. For example, we expect to be able to use two suites for clinical or commercial manufacturing at WuXi in Philadelphia if needed based on demand. If we are unable to meet manufacturing capabilities and demand at our own commercial manufacturing facility, we may need to rely on CMOs, including both current and alternate suppliers, to ensure sufficient capacity is available for commercial purposes. Our CMO relationship is described in more detail in the Research, Development, Manufacturing and License agreements section of this Annual Report on Form 10-K.

Cell processing activities are conducted at all facilities under cGMP, using qualified equipment and materials. We believe that all materials and components utilized in the production of the final TIL product are readily available from qualified suppliers.

Intellectual Property

We aim to lead in the field of T-cell-based immunotherapy by building and augmenting the patent rights for our proprietary TIL technology platform, which we have developed internally and licensed from third parties. Intellectual property is of importance in our field and in biotechnology generally. We seek to protect and enhance proprietary technology, inventions, and improvements that are commercially important to the development of our business by seeking, maintaining, and defending patent rights. We also plan to rely on regulatory protection afforded through Orphan Drug Designation, or ODD, available regulatory exclusivities and patent term extensions where available. To achieve this objective, our strategic focus has been to develop our own intellectual property, while also identifying and licensing patents from third parties that provide protection and serve as an optimal platform to enhance our intellectual property and technology base. We expect to further develop our patent portfolio as a strategic focus in 2023.

We currently own more than 60 U.S. patents related to TIL therapy, including patents directed to compositions and methods of treatment in a broad range of cancers, such as U.S. Patent Nos. 10,130,659; 10,166,257; 10,272,113; 10,363,273; 10,398,734; 10,420,799; 10,463,697; 10,517,894; 10,537,595; 10,639,330; 10,646,517; 10,653,723; 10,695,372; 10,894,063; 10,905,718; 10,918,666; 10,925,900; 10,933,094; 10,946,044; 10,946,045; 10,953,046; 10,953,047; 11,007,225; 11,007,226; 11,013,770; 11,026,974; 11,040,070; 11,052,115; 11,052,116; 11,058,728; 11,083,752; 11,123,371; 11,141,438; 11,168,303; 11,168,304; 11,179,419; 11,202,803; 11,202,804; 11,241,456; 11,254,913; 11,266,694; 11,273,180; 11,273,181; 11,291,687; 11,304,979; 11,304,980; 11,311,578; 11,337,998; 11,344,579; 11,344,580; 11,344,581; 11,351,197; 11,351,198; 11,351,199; 11,364,266; 11,369,637; 11,384,637; 1,433,097; 11,529,372; and 11,541,077. More than 35 of these patents are related to our Gen 2 TIL manufacturing processes and have terms that we anticipate will extend to January 2038, not including any patent term extensions or adjustments that may be available. Our owned and licensed intellectual property portfolio also includes patents and patent applications relating to TIL, MIL, and PBL therapies; frozen tumor-based TIL technologies; remnant TIL and digest TIL compositions, methods and processes; methods of manufacturing TIL, MIL, and PBL therapies; the use of costimulatory and T-cell modulating molecules in TIL therapy and manufacturing; stable and transient genetically-modified TIL therapies, including genetic knockouts of immune

checkpoints; cytokine-tethered TIL therapies; methods of using ICIs in combination with TIL therapies; TIL selection technologies; and methods of treating patient subpopulations.

Research, Development, Manufacturing and License Agreements

WuXi Advanced Therapies, Inc.

Manufacturing and Services Agreements

In November 2016, we entered into a three-year manufacturing services agreement, or the First WuXi MSA, with WuXi, pursuant to which WuXi agreed to provide manufacturing and other services, which has since been amended and assigned to our subsidiary Iovance Biotherapeutics Manufacturing LLC. Under the First WuXi MSA, we entered into two statements of work for two cGMP manufacturing suites to be operated by WuXi for us. The terms of one of these statements of work was extended to December 2022.

In October 2022, Iovance Biotherapeutics Manufacturing LLC entered into an additional three-year MSA, or the Second WuXi MSA, with WuXi and its parent company WuXi Apptec, Co, Ltd. The Second WuXi MSA and its related statement of work will supersede the statement of work under the First WuXi MSA with respect to commercial and clinical manufacturing for the two existing manufacturing suites. Both suites are expected to be capable of being used for the commercial manufacture of our products.

National Institutes of Health and the National Cancer Institute

Cooperative Research and Development Agreement

We entered into a CRADA with the NCI to develop adoptive cell immunotherapies in multiple solid tumor types, including unmodified TIL as a stand-alone therapy or in combination, improved methods for the generation and selection of TIL with anti-tumor reactivity, and strategies for more potent TILs.

In August 2011, we signed a five-year CRADA with the NCI, to work on the development of adoptive cell immunotherapies that are designed to destroy metastatic melanoma cells. The CRADA was amended in 2015 and 2016, to, among other things, extend the term of the CRADA through August 2023, include new indications such as bladder, lung, triple-negative breast, and Human Papilloma Virus, or HPV, -associated cancers and modify the focus on the development of unmodified TIL as a stand-alone therapy or in combination. The parties have continued the development of improved methods for the generation and selection of TIL with anti-tumor reactivity in metastatic melanoma, bladder, lung, breast, and HPV-associated cancers.

In August 2021, a third amendment extended the term of the CRADA by three years to August 2024, among other things. The research plan in this third amendment includes the evaluation in clinical trials of strategies for development of more potent TILs, such as selection of CD39/69 double negative cells and the use of certain inhibitors or other reagents in TIL expansion cultures.

Pursuant to the terms of the CRADA, as amended, we are required to make quarterly payments of \$0.5 million to the NCI for support of research activities. To the extent we license patent rights relating to a TIL-based product candidate, we will be responsible for all patent-related expenses and fees, past and future. In addition, we may be required to supply certain test articles, including TIL, grown and processed under Current Good Manufacturing, or cGMP, conditions, suitable for use in clinical trials. We or the NCI may unilaterally terminate the CRADA for any reason or for no reason, at any time, by providing written notice at least 60 days before the desired termination date.

Patent License Agreement Related to the Development and Manufacture of TIL Therapies

We have licensed exclusive, co-exclusive, and non-exclusive licenses from NIH to certain technologies relating to autologous tumor infiltrating lymphocyte adoptive cell therapy products.

We entered into an Exclusive Patent License Agreement, or the Patent License Agreement, with the NIH, in 2011, which was amended in 2015. Pursuant to the Patent License Agreement, as amended, the NIH granted us licenses, including exclusive, co-exclusive, and non-exclusive licenses, to certain technologies relating to autologous tumor infiltrating lymphocyte adoptive cell therapy products for the treatment of metastatic melanoma, lung, breast, bladder and HPV-positive cancers.

In May 2021, we entered into an Amended and Restated Patent License Agreement with NIH, which included the grant of additional exclusive, worldwide patent rights in the indications to interleukin-15 and interleukin-21 cytokine-tethered TIL technology, and expanded the non-exclusive, worldwide field of use to all cancers. Effective August 1, 2022, we entered into a Second Amended and Restated Patent License Agreement with NIH to include additional exclusive, worldwide patent rights to TIL products expressing interleukin-12, expanded rights to TIL selection technologies previously licensed under the Exclusive Patent License Agreement below, and additional non-exclusive, worldwide patent rights to certain technologies related to enhancing TIL potency.

The Second Amended and Restated Patent License Agreement requires us to pay royalties based on a percentage of net sales in jurisdictions where patent rights exist, which percentage can fall into a tier that may be less than one percent to mid-single digits depending upon certain events, including the exclusivity of the rights, and we expect lower overall royalty payments as a result. We also agreed to pay potential milestone payments on the achievement of certain clinical, regulatory, and commercial sales milestones for each of the indications and other direct costs incurred by the NIH pursuant to the Second Amended and Restated Patent License Agreement. We anticipate making milestone payments, including payments ranging from several hundred thousand dollars to the mid-single-digit millions of dollars, in conjunction with certain development milestones, the approval of a BLA or its foreign equivalent, or the first U.S. and foreign commercial sales of any of our product candidates covered by the Second Amended and Restated Patent License Agreement. The term of the Second Amended and Restated Patent License Agreement continues until the expiry of the last-to-expire patent rights licensed thereunder, and the agreement contains standard termination provisions.

Exclusive Patent License Agreement Related to TIL Selection

In February 2015, we entered into an exclusive patent license agreement, or the Exclusive Patent License Agreement, with the NIH under which we received an exclusive worldwide license under the selected TIL patents. This license was superseded and replaced by the Second Amended and Restated Patent License Agreement.

H. Lee Moffitt Cancer Center

Sponsored Research Agreement

In June 2016, we entered into a Sponsored Research Agreement with Moffitt, which expired in December 2019. In June 2020, we entered into a new Sponsored Research Agreement with Moffitt, with a term that ends either upon completion of the research thereunder or on July 1, 2022, whichever is sooner. In June 2022, this agreement was extended until the later of December 19, 2022 or a mutually acceptable completion of the Research Agreement, which is currently expected in mid-2023.

Clinical Grant Agreements

In December 2016, we entered into a clinical grant agreement with Moffitt to support an ongoing clinical trial at Moffitt that combines TIL therapy with nivolumab for the treatment of patients with metastatic melanoma. In June 2017, we entered into a second clinical grant agreement with Moffitt to support a new clinical trial at Moffitt that combines TIL therapy with nivolumab for the treatment of patients with non-small cell lung cancer, under which we obtained a non-exclusive, royalty-free license to any new Moffitt inventions made in the performance of the agreement. Under both clinical grant agreements with Moffitt, we have non-exclusive rights to clinical data arising from the respective clinical trials.

Exclusive License Agreements

We have exclusive license agreements to Moffitt's patent-pending technologies related to methods for improving TIL for adoptive cell therapy using toll-like receptor, or TLR, agonists, the use of 4-1BB agonists in conjunction with TIL manufacturing processes and therapies, and tumor digests in conjunction with TIL manufacturing processes and therapies.

We entered into a license agreement with Moffitt, or the First Moffitt License, effective as of June 28, 2014, under which we received a worldwide license to Moffitt's rights to patent-pending technologies related to methods for improving TIL for adoptive cell therapy using TLR agonists. Unless earlier terminated, the term of the license extends until the earlier of the expiration of the last issued patent related to the licensed technology or 20 years after the effective date of the license agreement.

Pursuant to the First Moffitt License, we paid an upfront licensing fee, and a patent issuance fee will also be payable under the First Moffitt License, upon the issuance of the first U.S. patent covering the subject technology. In addition, we agreed to pay

milestone license fees upon completion of specified milestones, customary royalties based on a specified percentage of net sales, which percentage is in the low single digits, and sublicensing payments, as applicable, and annual minimum royalties beginning with the first sale of products based on the licensed technologies, which minimum royalties will be credited against the percentage royalty payments otherwise payable in that year. We will also be responsible for all costs associated with the preparation, filing, maintenance and prosecution of the patent applications and patents covered by the First Moffitt License related to the treatment of any cancers in the U.S., Europe and Japan and in other countries designated by us in agreement with Moffitt.

In May 2018, we entered into a second license agreement with Moffitt, or the Second Moffitt License, under which we received an exclusive license to Moffitt's rights to patent-pending technologies related to the use of 4-1BB agonists in conjunction with TIL manufacturing processes and therapies. Pursuant to the Second Moffitt License, we paid an upfront licensing fee, and an annual license maintenance fee is also payable commencing on the first anniversary of the effective date. We also agreed to pay an annual commercial use payment for each indication for which a first sale has occurred.

We subsequently exercised an option to exclusively license Moffitt's rights to patent pending technologies related to the use of tumor digests in conjunction with TIL manufacturing processes and therapies and entered into an amended and restated Second Moffitt License in October 2021, or the Amended & Restated Second Moffitt License, to include these rights. Pursuant to the Amended & Restated Second Moffitt License, we paid an upfront licensing fee in 2021. We also agreed to pay an annual commercial use payment for each indication for which a first sale has occurred for products relating to the use of 4-1BB agonists and for products relating to the use of tumor digests covered by the license.

The University of Texas M.D. Anderson Cancer Center, or MDACC

Strategic Alliance Agreement

In April 2017, we entered into a Strategic Alliance Agreement, or the SAA, with MDACC, under which we and MDACC agreed to conduct clinical and preclinical research studies. We agreed in the SAA to provide total funding not to exceed approximately \$14.2 million for the performance of the multi-year studies under the SAA. In return, we acquired all rights to inventions resulting from the studies and have been granted a non-exclusive, sub-licensable, royalty-free, and perpetual license to specified background intellectual property of MDACC reasonably necessary to exploit, including the commercialization thereof. We have also been granted certain rights to clinical data generated by MDACC outside of the clinical trials to be performed under the SAA. The SAA's term shall continue in effect until the later of the fourth anniversary of the SAA or the completion or termination of the research and receipt by us of all deliverables due from MDACC thereunder.

Cellectis S.A.

Research Collaboration and Exclusive Worldwide License Agreement

In December 2019, we entered into a research collaboration and exclusive worldwide license agreement whereby we will license gene-editing technology from Cellectis, a clinical-stage biopharmaceutical company, to develop TIL therapies that have been genetically edited, including a PD-1 inactivated product that we refer to as IOV-4001. Financial terms of the license include annual license payments and development, regulatory and sales milestone payments from us to Cellectis, as well as royalty payments based on net sales of TALEN® modified TIL products.

Novartis Pharma AG

License Agreement

In January 2020, we obtained a license from Novartis, to develop and commercialize an antibody cytokine engrafted protein, which we refer to as IOV-3001. Under the agreement, we have paid an upfront payment to Novartis and may pay future milestones related to initiation of patient dosing in various phases of clinical development for IOV-3001 and approval of the product in the U.S., the European Union, or EU, and Japan. Novartis is also entitled to low-to-mid single digit percentage royalties from commercial sales of the product.

Regulatory Designations

The FDA has granted ODD for lifileucel in the U.S. to treat malignant melanoma stages IIB-IV and for the treatment of cervical cancer with a tumor size of greater than 2 cm in diameter; Fast Track and RMAT designations for lifileucel to treat advanced metastatic melanoma; Fast Track and Breakthrough Therapy Designations, or BTM, for lifileucel to treat metastatic cervical cancer; and Fast Track designation for lifileucel in combination with pembrolizumab for the treatment of ICI naïve metastatic melanoma.

Orphan Drug Designations

During 2015, we received ODD for lifileucel in the U.S. to treat malignant melanoma stages IIB-IV, and in 2018, we received an ODD for lifileucel for the treatment of cervical cancer with a tumor size of greater than 2 cm in diameter. If approved, an ODD provides seven years of market exclusivity in the U.S., subject to certain limited exceptions. However, an ODD does not convey any advantage in, or shorten the duration of, the regulatory review or approval process. The benefits and limitations of ODD are described in more under the Government Regulations section in this Annual Report on Form 10-K.

Fast Track Designations

In August 2017, we announced that the FDA had granted Fast Track designation for lifileucel for the treatment of advanced metastatic melanoma. In February 2019, we announced that the FDA had granted Fast Track designation for lifileucel in the treatment of metastatic cervical cancer. Additionally, in November 2021, we announced that the FDA granted Fast Track designation for lifileucel in combination with pembrolizumab for the treatment of ICI-naïve metastatic melanoma. The FDA's Fast Track process is designed to facilitate the development and expedite the review of drugs that treat serious conditions and fill an unmet medical need. Fast Track designation allows more frequent meetings and communications with the FDA to discuss the drug's development plans and review process. The Fast Track designation also allows for the possibility for rolling review of a BLA by FDA, where the FDA may consider beginning review portions of a marketing application before the full submission is complete, and also potential eligibility if certain criteria are met for accelerated approval.

Regenerative Medicine Advanced Therapy Designation

In October 2018, we announced that the FDA had granted RMAT designation for lifileucel for the treatment of patients with metastatic melanoma. The RMAT designation is based on data provided to the FDA from our C-144-01 trial. RMAT designation is granted for regenerative medicine drugs and allows for increased access to FDA during development. Under this designation, surrogate endpoints can be used to receive approval for a product, accelerated approval may be granted, and a rolling review of a BLA may be permitted by FDA.

Breakthrough Therapy Designation

In May 2019, we announced that the FDA had granted BTM for lifileucel for the treatment of patients with metastatic cervical cancer. The BTM was granted based on data provided to the FDA from our C-145-04 clinical trial. Under a BTM, the FDA may take actions that help expedite the development and review of the application for a product candidate, including seeking to provide timely advice and interactive communications to the sponsor with intensive guidance during development, to help the sponsor design and conduct a more efficient development program. Product candidates with BTM may be suitable for alternative clinical trial designs when scientifically appropriate, which may result in smaller clinical trials or more efficient clinical trials that require less time to complete. BTM also allows the sponsor to submit portions of the BLA on an ongoing basis for rolling review. In addition, BTM status allows for the potential to request priority review of our BLA at the time of BLA submission if supported by clinical data. The clinical evidence needed to support breakthrough designation is preliminary, and the FDA has authority to rescind a BTM if a product candidate no longer meets the qualifying criteria.

Competition

The biotechnology and pharmaceutical industries put significant resources into developing novel and proprietary therapies for the treatment of cancer. We compete with multiple entities who have developed and are developing immuno-oncology therapies, including large and specialty pharmaceutical and biotechnology companies, academic research institutions and governmental agencies and public and private research institutions, as well as companies developing novel targeted therapies for cancer. Universities and public and private research institutions in the U.S. and Europe are also potential competitors. For example, a Phase 3 M14TIL clinical

trial comparing TIL to standard ipilimumab in patients with metastatic melanoma is currently being conducted in Europe by the Netherlands Cancer Institute, the Copenhagen University Hospital at Herlev, and the University of Manchester. Results from the M14TIL clinical trial were presented at the European Society for Medical Oncology Congress in September 2022 and published in the New England Journal of Medicine in December 2022, as described in the Historical Clinical Results with Other TIL Therapies in Metastatic Melanoma section of this Annual Report on Form 10-K. While these universities and public and private research institutions primarily have educational objectives, they may develop proprietary technologies that lead to other FDA-approved therapies or that secure patent protection that we may need for the development of our technologies and products.

Due to the promising clinical therapeutic effect of competitor therapies in clinical exploratory trials, we anticipate substantial direct competition from other organizations developing advanced T-cell therapies targeting patients who have received prior anti-PD-1/L1 therapies. In particular, we expect to compete with other new therapies for our lead indications developed by companies such as Agenus, BeyondSpring, Bristol-Myers Squibb, Merck, Nektar Therapeutics, Checkmate Pharmaceuticals, Daiichi Sankyo, Eisai, Exelixis, Moderna, Mirati Therapeutics, OncoSec Medical, Replimune, Regeneron Pharmaceuticals, Seagen, and Genmab. We also may compete with other TIL therapies in development by companies such as Instil Bio, Achilles Therapeutics, KSQ Therapeutics, Obsidian Therapeutics, Immatics, TILT Biotherapeutics, WindMIL Therapeutics, GRIT Biotechnology, Lyell Immunopharma, Cellular Biomedicine Group, and others. We also may compete with therapies based on genetically engineered T-cell receptors rendered reactive against tumor-associated antigens prior to their administration to patients, as well as TIL therapies that are designed to be specific to neoantigens, including products developed by Adaptimmune Therapeutics, Alaunos Therapeutics, Intima Bioscience, Marker Therapeutics, Turnstone Biologics, Neogene and others. To date, these technologies have been primarily applicable to hematologic malignancies, but their application in solid tumor indications may create competition with us. We may also face competition from immunotherapy treatments offered by companies such as Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Regeneron Pharmaceuticals, Roche, and BioNTech. We may also face competition from novel IL-2 treatments in development by Alkermes, Werewolf, Nektar Therapeutics, Merck, Sanofi, Neoleukin Therapeutics and others. Many of these companies and our other current and potential competitors have substantially greater research and development capabilities and financial, scientific, regulatory, manufacturing, marketing, sales, human resources, and experience than we do. Many of our competitors have several therapeutic products that have already been developed, approved and successfully commercialized, or are in the process of obtaining regulatory approval for their therapeutic products in the U.S. and internationally. Our competitors may obtain regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in competitors establishing a strong market position before we are able to enter the market.

Our lead product candidate lifileucel is a TIL therapy for the treatment of advanced melanoma and advanced cervical cancer. Currently, there are numerous companies that are developing various alternate treatments for melanoma and cervical cancer, including patients that have progressed after prior treatment with checkpoint inhibitors and chemotherapy. Accordingly, lifileucel faces significant competition in the melanoma and cervical cancer treatment space from multiple companies. Even if we obtain regulatory approval for lifileucel, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our therapies.

Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These parties compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same. We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect.

We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Government Regulations

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring, and post-approval reporting of biologics such as those we are developing. We, along with our third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval and post-approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

Biologic products are regulated by the FDA under a combination of the federal Food, Drug, and Cosmetic Act, or FDCA, and Public Health Services Act, or PHSA, and the FDA's implementing regulations. Failure to comply with regulatory requirements may result in significant regulatory actions. Such actions may include refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold or termination of clinical trials, warning letters, untitled letters, modification of promotional materials or labeling, provision of corrective information, imposition of post-market requirements including the need for additional testing, imposition of distribution or other restrictions under a Risk Evaluation and Mitigation Strategy, or REMS, product recalls, product seizures or detentions, refusal to allow imports or exports, total or partial suspension of production or distribution, FDA debarment, injunctions, fines, consent decrees, corporate integrity agreements, debarment from receiving government contracts and new orders under existing contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, or civil or criminal penalties, including fines and imprisonment, and adverse publicity, among other adverse consequences.

The process required by the FDA before biologic product candidates may be marketed in the U.S. generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's current Good Laboratory Practices, or cGLP, regulation, as well as manufacturing development and formulation studies;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before clinical trials may begin and must be updated annually or when significant changes are made;
- approval by an independent Institutional Review Board, or IRB, or ethics committee at each clinical site or centrally, before the clinical trial is begun;
- performance of adequate and well-controlled human clinical trials, in accordance with the FDA's current Good Clinical Practices, or cGCP, regulation, to establish the safety, purity, and potency of the proposed biologic product candidate for its intended purpose;
- preparation of and submission to the FDA of a BLA, after completion of pivotal clinical trial(s);
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate to preserve the biological product's continued safety, purity and potency, and of selected clinical sites to assess compliance with cGCPs; and
- FDA review and approval of the BLA to permit commercial marketing of the product for particular indications for use in the U.S., which must be updated periodically when changes are made.

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Prior to beginning the first clinical trial with a new

product candidate, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical trials. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within that initial 30-day time period, raises concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor, and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during clinical trials due to safety concerns or non-compliance. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

Human immunotherapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the clinical trial period, the number of patients the FDA will require to be enrolled in the clinical trials in order to establish the safety, efficacy, purity and potency of immunotherapy products, or that the data generated in these clinical trials will be acceptable to the FDA to support marketing approval.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with cGCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated, and a statistical analysis plan. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Investigators must also provide certain information to the clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA.

Furthermore, an independent IRB for each site proposing to conduct the clinical trial or centrally must review and approve the plan for any clinical trial, its informed consent documentation and processes, and any subject communications, before the clinical trial begins at that site, and upon amendment of the clinical trial protocol, and must monitor the clinical trial until completed. An IRB considers, among other things, whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits and whether the planned human subject protections are adequate. Informed consent must be received from each clinical trial subject prior to participation in a clinical trial. Progress reports detailing the results of the clinical trials must also be submitted at least annually to the FDA and the IRB and more frequently if serious adverse events or other significant safety information is found.

Regulatory authorities, the IRB, or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk, that the clinical trial is not being conducted in accordance with regulatory or IRB requirements, or that the clinical trial is unlikely to meet its stated objectives. Sponsors may also discontinue studies or development programs for many reasons, including changing business objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board, or DSMB, which provides recommendations and assessments for whether or not a clinical trial should move forward at designated check points based on access to certain data from the clinical trial. Following a review by a DSMB, the clinical trial may be halted if there is an unacceptable safety risk for subjects or on other grounds, such as failure to demonstrate efficacy. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries. For instance, we are required to register certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes, and also to certify to FDA our compliance with these requirements when we make FDA submissions. Failure to make required ClinicalTrials.gov submissions, submitting false or misleading information to ClinicalTrials.gov, or making false certifications to FDA could result in enforcement actions, including civil money penalties and adverse publicity.

For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap. Although these are the typical phases for progression, and characteristics of the phases of a clinical development program, certain expedited programs allow for variations that could support a marketing application based on surrogate endpoints, intermediate clinical endpoints, or single-arm as opposed to comparative or placebo-controlled studies.

- Phase 1 - The investigational product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the

investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

- Phase 2 - The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- Phase 3 - The investigational product is administered to an expanded patient population in adequate and well-controlled studies to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit relationship of the investigational product and to provide an adequate basis for product approval. Typically, two Phase 3 studies are required by the FDA for product approval.
- Phase 4 - In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product, known as post-approval requirements or commitments, respectively. These so-called Phase 4 studies may be made a condition to approval of the BLA.

Additional types of data may also help to support a BLA, such as real-world evidence and patient experience data. Phase 1, Phase 2 and Phase 3, and Phase 4 testing, if applicable, may not be completed successfully within a specified period, if at all, and there can be no assurance that the data collected will support FDA approval or licensure of the product. Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life and manufacturing processes must be validated.

The manufacture of investigational biologics for the conduct of human clinical trials is subject to cGMP requirements. Investigational biologics and active ingredients imported into the U.S. are also subject to regulation by the FDA relating to their labeling and distribution. Further, the export of investigational products outside of the U.S. is subject to regulatory requirements of the importing country as well as U.S. export requirements under the FDCA. Additional U.S. and foreign laws and regulations may also be applicable to the handling, import, export, and transportation of biological materials, including tissue samples.

During the development of a new therapeutic, a sponsor may be able to request a Special Protocol Assessment, or SPA, the purpose of which is to reach an agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of product approval and an efficacy claim, as well as preclinical carcinogenicity trials and stability studies. An SPA may only be modified with the agreement of the FDA and the clinical trial sponsor, or if the director of the FDA reviewing division determines that a substantial scientific issue essential to determining the safety or efficacy of the product was identified after the testing began. An SPA is intended to provide assurance that, in the case of clinical trials, if the agreed upon clinical trial protocol is followed, the clinical trial endpoints are achieved, and there is a favorable risk-benefit profile, the data may serve as the primary basis for an efficacy claim in support of a BLA. However, SPA agreements are not a guarantee of approval of a product candidate or any permissible claims about the product candidate. In particular, SPAs are not binding on the FDA if, among other reasons, previously unrecognized public health concerns arise during the performance of the clinical trial, other new scientific concerns regarding the product candidate's safety or efficacy arise, or if the sponsoring company fails to comply with the agreed upon clinical trial protocol.

In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA for a new active ingredient, indication, dosage form, dosage regimen, or route of administration, must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Also, under the FDA Reauthorization Act of 2017, beginning in 2020, sponsors submitting applications for product candidates intended for the treatment of adult cancer which are directed at molecular targets that the FDA determines to be substantially relevant to the growth or progression of pediatric cancer must submit, with the application, reports from molecularly targeted pediatric cancer investigations designed to yield clinically meaningful pediatric clinical trial data, using appropriate formulations, to inform potential pediatric labeling. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Orphan products are also exempt from PREA requirements.

The FDA also may require submission of REMS, to ensure that the benefits of the biologic outweigh the risks. The REMS plan could include medication guides, physician communication plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. An assessment of the REMS must also be conducted at set intervals. Following product approval, a REMS may also be required by the FDA if new safety information is discovered, and the FDA determines that a REMS is necessary to ensure that the benefits of the biologic outweigh the risks.

BLA Submission and Review by the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The BLA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of the product, or from a number of alternative sources, including studies initiated by investigators. The submission of a BLA requires payment of a substantial user fee to the FDA, under the Prescription Drug User Fee Act, and the sponsor of an approved BLA is also subject to annual program fees. These fees are typically increased annually. A waiver of user fees may be obtained under certain limited circumstances.

Once a BLA has been submitted, the FDA has sixty days to determine whether it will accept the application for filing. The FDA accepts applications for filing if it determines that the application is substantially complete to permit a substantive review. The FDA may request additional information rather than accept a BLA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review.

The FDA's goal is to review the application within ten months after it accepts the application for filing, or, if the application relates to a serious or life-threatening indication and, if approved, the product would provide a significant improvement in safety and efficacy, six months after the FDA accepts the application for filing, which is referred to as Priority Review. The review process is often significantly extended if the FDA requests additional information or clarification. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency. There are numerous FDA personnel assigned to review different aspects of a BLA, and uncertainties can be presented by their ability to exercise judgment and discretion during the review process. The development and provision of additional data and information requested by FDA during review of a BLA may be time consuming and expensive.

The FDA may convene an advisory committee to provide clinical insight on application review questions. Before approving a novel biologic, the FDA must either refer that biologic to an external advisory committee or provide in an action letter, a summary of the reasons why the FDA did not refer the product candidate to an advisory committee. An advisory committee is typically a panel that includes clinicians and other experts, which review, evaluate, and make a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent commercial production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to ensure compliance with cGCP.

If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing, clinical trials, application modifications, or information in a complete response letter, or CRL. A CRL indicates that the review cycle for the application is complete, and that the application is not ready for approval. If a CRL is issued, the applicant may either: resubmit the BLA, addressing all the deficiencies identified in the letter; withdraw the application; or request an opportunity for a hearing. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than an applicant interprets the same data.

If the FDA finds that a BLA is approvable, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. However, even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings, or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a product's safety and efficacy after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may also not approve label statements that are necessary for successful commercialization and marketing.

If compliance with the pre-and post-marketing regulatory standards are not maintained or if problems occur after the product reaches the marketplace, the FDA may also withdraw the product approval. Further, should new safety information arise, additional testing, product labeling, or FDA notification may be required.

A sponsor may seek approval of its product candidate under programs designed to accelerate the FDA's review and approval of new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. For a Fast Track designation, the FDA may consider sections of the BLA for review on a rolling basis before the complete application is submitted if relevant criteria are met. Fast Track-designated products are also eligible for more frequent FDA interactions. A Fast Track-designated product candidate may also qualify for Priority Review, under which the FDA sets the target date for FDA action on the BLA at six months after the FDA accepts the application for filing. Priority Review is granted when there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for Priority Review, the application is subject to the standard FDA review period of 10 months after the FDA accepts the application for filing. Priority Review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the Accelerated Approval Program, the FDA may approve a BLA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. To qualify for Accelerated Approval, the product must be intended to treat a serious condition and must generally provide a meaningful advantage over available therapies. Post-marketing studies or completion of ongoing studies after marketing approval are required to verify the biologic's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. If this clinical trial is not conducted, if it fails to verify the benefit, if other evidence demonstrates that the product is not safe, pure or potent, or if the applicant disseminates false or misleading promotional material, the FDA may withdraw approval of the application on an expedited basis. Sponsors of products under the Accelerated Approval Pathway must further submit promotional materials to the FDA before dissemination.

In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new BTB. A sponsor may seek FDA designation of its product candidate as a Breakthrough Therapy if the product candidate is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Sponsors may request the FDA to designate a Breakthrough Therapy at the time of or any time after the submission of an IND, but ideally before an end-of-Phase 2 meeting with the FDA. If the FDA designates a Breakthrough Therapy, it may take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the therapy; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and considering alternative clinical trial designs when scientifically appropriate, which may result in smaller clinical trials or more efficient clinical trials that require less time to complete and may minimize the number of patients exposed to a potentially less efficacious treatment. BTB also allows the sponsor to file sections of the BLA for review on a rolling basis.

Through the 21st Century Cures Act, or Cures Act, Congress also established another expedited program, called a RMAT designation. The Cures Act directs the FDA to facilitate an efficient development program for and expedite review of RMATs. To qualify for this program, the product must be a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or a combination of such products, and not a product solely regulated as a human cell and tissue product. The product must be intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and preliminary clinical evidence must indicate that the product has the potential to address an unmet need for such disease or condition. Advantages of the RMAT designation include all the benefits of the Fast Track and breakthrough therapy designation programs, including early interactions with the FDA. These early interactions may be used to discuss potential surrogate or intermediate endpoints to support accelerated approval.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant ODD to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 individuals in the U.S., or a patient population greater than 200,000 individuals in the U.S. and when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the U.S. will be recovered from sales in the U.S. for that drug or biologic. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain ODD if there is a product already approved by the FDA that is intended for the same indication and that is considered by the FDA to be the same product as the already approved product. This hypothesis for clinical superiority must be demonstrated to obtain orphan exclusivity. ODD must be requested before submitting a BLA. After the FDA grants ODD, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

If a product that has ODD subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, a seven-year period of marketing exclusivity, which means that the FDA may not approve any other applications, including a full BLA, to market the same biologic, as sameness is defined in the FDA's regulations, for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of ODD are tax credits for certain research, opportunities for certain research grant funding, and a waiver of the BLA application fees. The tax credit, however, was recently limited through Congress's tax reform efforts. Despite these benefits, the ODD does not convey any advantage in, or shorten the duration of, the regulatory review or approval process.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the U.S. may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. The FDA may also approve a product deemed to be the same as an approved orphan product for the same orphan indication, despite periods of exclusivity, if the new product is demonstrated to be clinically superior to the former product.

We plan to seek ODD for some or all of our other product candidates in specific orphan indications in which there is a medically plausible basis for the use of such products.

Market and Data Exclusivity and Biosimilars

While under the Biologics Price Competition and Innovation Act of 2009, or BPCIA, the FDA may eventually license products, as further described below, that are biosimilar to any of our product candidates that are approved, our products may receive periods of regulatory exclusivity, separately from orphan drug exclusivity for those products with ODDs, providing additional protection from certain forms of competition. For instance, our products may receive 12 years of reference product exclusivity that begins running at the time of first licensure. During this 12-year time period, the period of marketing exclusivity, the FDA may not make an approval of a biosimilar product effective. In addition, the FDA may not accept a biosimilar application until after four years from the date of first licensure, the period of data exclusivity. However, certain changes and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the exclusivity period. The PHSA also includes provisions governing patent litigation over patents that are directed to the reference products. The biosimilar product sponsor and reference product sponsor may, but are not required to, exchange certain patent and product information for the purpose of negotiating and determining the scope of patent litigation, including the patents to be asserted and

challenged. Based on the outcome of negotiations surrounding the exchanged information, the reference product sponsor may bring a patent infringement suit and injunction proceedings against the biosimilar product sponsor. The biosimilar applicant may also be able to bring an action for declaratory judgment concerning the patent under certain circumstances.

The BPCIA created an abbreviated approval pathway for biological products shown to be highly similar to or interchangeable with an FDA-licensed reference biological product. Accordingly, if we receive FDA licensure, we may face competition from biosimilar products. Biosimilarity sufficient to reference a prior FDA-approved product requires a high similarity to the reference product notwithstanding minor differences in clinically inactive components, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical studies, animal studies, and at least one clinical trial, absent a waiver by the FDA. There must be no difference between the reference product and a biosimilar in conditions of use, route of administration, dosage form, and strength. Further, a biosimilar product may be deemed interchangeable with a prior approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Pediatric Exclusivity and Patent Term Extension

Pediatric exclusivity is another type of non-patent marketing exclusivity in the U.S. and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity. Under the Best Pharmaceuticals for Children Act, a six-month exclusivity may be granted if a sponsor submits pediatric data that fairly responds to a written request from the FDA for such data. The FDA may issue such a written request on its own initiative or at the request of the sponsor. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA, whatever regulatory periods of exclusivity that already cover the product are extended by six months. Pediatric exclusivity is thus an "add-on" exclusivity and is unique in this regard among the various regulatory exclusivities provided by FDA. The FDA can also require pediatric studies of a drug submitted in a new drug application if the FDA determines that the product is likely to be used in a substantial number of pediatric patients, or if the product would provide a meaningful benefit in the pediatric population over existing treatments. This requirement may be waived in certain circumstances, for example, where the indication does not occur or is not highly prevalent in the pediatric population.

If approved, biologics may also be eligible for periods of U.S. patent term restoration. If granted, patent term restoration extends the patent life of a single unexpired patent that has not previously been extended, for a maximum of five years. The total patent life of the product with the extension also cannot exceed fourteen years from the product's approval date. Subject to the prior limitations, the period of the extension is calculated by adding half of the time from the effective date of an IND to the initial submission of a marketing application, and all the time between the submission of the marketing application and its approval. This period may also be reduced by any time that the applicant did not act with due diligence. Whether any of our product candidates will be eligible for patent term restoration is currently unknown. Even if any of our product candidates are found to be eligible for patent term protection, the applicable authorities may subsequently determine that we are not eligible for such restoration periods.

Post-Approval Requirements

Any products for which we receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product and deviations, annual reporting and monitoring and providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, certain electronic records and signature requirements, fulfilling post-marketing clinical trial and REMS commitments, and complying with FDA promotion and advertising requirements, which include, among other things, standards for direct-to-consumer advertising, restrictions on promoting products for uses or in patient populations that are not described in the product's approved uses or otherwise consistent with the FDA-approved product labeling (known as "off-label use"), limitations on industry-sponsored scientific and educational activities, rules regarding communication of health care economic information regarding biopharmaceutical products to payors and formularies, and requirements for promotional activities involving the internet. Although physicians may prescribe legally available products for off-label use, if they deem such use to be appropriate in their professional medical judgment, manufacturers may not market or promote such off-label uses. In the past several years, certain court decisions have impacted FDA's enforcement activity regarding off-label promotion in light of First Amendment considerations; however, there are still significant risks in this area, in part due to the potential for False Claims Act exposure.

In addition, quality control and manufacturing procedures must continue to conform to applicable manufacturing requirements after approval to ensure the long-term stability of the product. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments and list their products with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other applicable laws. Accordingly, manufacturers must continue to expend time, money, and effort in the areas of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including, among other things, withdrawal of approval, recall or withdrawal of the product from the market. In addition, changes to the manufacturing process are strictly regulated, and depending on the significance of the change, may require prior FDA approval or notification before being implemented. Other types of changes to the approved product, such as adding new indications and claims to the product labeling, are also subject to further FDA review and approval.

Commercial products must meet the requirements of the Drug Supply Chain Security Act, or DSCSA, which imposes obligations on manufacturers of prescription biopharmaceutical products for commercial distribution, regulating the distribution of the products at the federal level, and sets certain standards for federal or state registration and compliance of entities in the supply chain, including manufacturers and repackagers, wholesale distributors, third-party logistics providers, and dispensers. The DSCSA preempts previously enacted state laws and the pedigree requirements of the Prescription Drug Marketing Act, or PDMA. Trading partners within the drug supply chain must now ensure certain product tracing requirements are met that they are doing business with other authorized trading partners; and they are required to exchange transaction information, transaction history, and transaction statements. Product identifier information, an aspect of the product tracing scheme, is required. The DSCSA requirements, development of standards, and the system for product tracing have been and will continue to be phased in over a period of years, with the FDA indicating that it would permit certain exemptions and exclusions, and exercise enforcement discretion on certain aspects of the law due to the COVID-19 pandemic, although this situation may continue to evolve. The distribution of product samples continues to be regulated under the PDMA, and some states also impose regulations on drug sample distribution.

As previously mentioned, the FDA may also require Phase 4 testing and surveillance to monitor the effects of an approved product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Additional Biologic Requirements

To help reduce the increased risk of the introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases in the U.S. and between states.

After a BLA is approved, the product may also be subject to official lot release as a condition of approval. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA, together with a release protocol showing the results of all the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products before releasing the lots for distribution by the manufacturer.

In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products. After approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

Other Healthcare Laws and Compliance Requirements

Our sales, promotion, medical education and other activities following product approval will be subject to regulation by numerous regulatory and law enforcement authorities in the U.S., and in addition to the FDA, these entities may include the Federal Trade Commission, the Department of Justice, the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services and state and local governments. Our promotional and scientific/educational programs must comply with the federal Anti-Kickback Statute, or AKS, the Foreign Corrupt Practices Act, or FCPA, the False Claims Act, or FCA, the Veterans Health Care Act, physician payment transparency laws, privacy laws, security laws, and additional state laws similar to the foregoing.

The federal AKS prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs, in whole or in part. The term remuneration has been interpreted broadly to include anything of value. The federal AKS has been interpreted broadly to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. The term "remuneration" includes kickbacks, bribes or rebates and also has been broadly interpreted to include anything of value, including, for example, gifts, discounts, waivers of payment, ownership interest and providing anything at less than its fair market value. Additionally, the intent standard under the federal AKS provides that a person or entity need not have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, a claim including items or services resulting from a violation of the federal AKS constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution or other regulatory sanctions. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the AKS. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Our practices may not in all cases meet all the criteria for protection under a statutory exception or regulatory safe harbor. The safe harbors are subject to change through legislative and regulatory action, and we may decide to adjust our business practices or be subject to heightened scrutiny as a result.

The civil monetary penalties statute imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim for payment, or approval to a federal healthcare program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The FCA imposes liability on persons who, among other things, knowingly present or cause to be presented false or fraudulent claims for payment to, or approval by the federal government knowingly making or using, or causing to be made or used a false statement or record material to a claim to the federal government, or avoiding, decreasing or concealing an obligation to pay money to the federal government. A claim includes "any request or demand" for money or property presented directly or indirectly to the federal government. The civil FCA has been or can be used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price and Average Manufacturer Price, improper promotion of uses not expressly approved by the FDA in a drug's label, false statements associated with government grants, and allegations of misrepresentations with respect to services rendered, as well as claims for payment that are inaccurate or fraudulent, that are for services not provided as claimed, or for services that are not medically necessary. FCA claims may be based on noncompliance with regulatory requirements under an implied certification theory if material to the government's decision to buy or pay for a drug. Intent to deceive is not required to establish liability under the civil FCA. Civil FCA liability may also be imposed for Medicare or Medicaid overpayments caused by understated rebate amounts that are not refunded within 60 days of discovering the overpayment, even if the overpayment was not caused by a false or fraudulent act. Actions under the FCA may be brought by the government or as a qui tam action by a private individual in the name of the government. If the government intervenes in a qui tam action, and prevails, the qui tam plaintiff will share in the proceeds from damages and fines or settlement funds. If the government declines to intervene, the qui tam plaintiff may pursue the case alone. Violations of the FCA can result in significant monetary penalties and treble damages. The government may further prosecute conduct under the criminal FCA, which prohibits the making or presenting of a claim to the government knowing the claim to be false, fictitious or fraudulent. Unlike the civil FCA, conviction requires proof of intent to submit a false claim. In addition, federal AKS violations (which may be alleged based on certain marketing practices, including allegations of off-label promotion) implicate the FCA.

The compliance and enforcement landscape, and related risk, is informed by government litigation and settlement precedent, Advisory Opinions, and Special Fraud Alerts. Our approach to compliance may evolve over time in light of these types of developments.

Additionally, the FCPA, and similar worldwide anti-bribery laws, generally prohibit companies and their intermediaries from making, offering or authorizing improper payments or other items of value, directly or indirectly, to foreign officials, political parties, or candidates for the purpose of obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the U.S. to comply with accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities that violate the FCPA, even if they occur wholly outside the U.S., can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from securing government contracts. We cannot assure you that our internal control policies and procedures will protect us from reckless or negligent acts committed by our employees, future distributors, partners, collaborators or agents. Violations of these laws, or allegations of such violations, could result in fines, penalties or prosecution and have a negative impact on our business, results of operations and reputation.

Payment or reimbursement of prescription drugs by Medicaid or Medicare requires manufacturers of the drugs to submit pricing information to the Centers for Medicare & Medicaid Services, or CMS. The Medicaid Drug Rebate statute requires manufacturers to calculate and report price points, which are used to determine Medicaid rebate payments shared between the states and the federal government and Medicaid payment rates for the drug. For drugs paid under Medicare Part B, manufacturers must also calculate and report their Average Sales Price or ASP, which is used to determine the Medicare Part B payment rate for the drug. Drugs that are approved under a BLA or a New Drug Application, or NDA, including 505(b)(2) drugs, are subject to an additional inflation penalty which can substantially increase rebate payments. In addition, for BLA and NDA drugs, the Veterans Health Care Act, or VHCA, requires manufacturers to calculate and report to the Veterans Administration, or VA, a different price called the Non-Federal Average Manufacturing Price, which is used to determine the maximum price that can be charged to certain federal agencies, referred to as the Federal Ceiling Price, or FCP. Like the Medicaid rebate amount, the FCP includes an inflation penalty. A Department of Defense regulation requires manufacturers to provide this discount on drugs dispensed by retail pharmacies when paid by the TRICARE Program. All these price reporting requirements create risk of submitting false information to the government, and potential FCA liability.

The VHCA also requires manufacturers of covered drugs participating in the Medicaid program to enter into Federal Supply Schedule contracts with the VA through which their covered drugs must be sold to certain federal agencies at FCP and to report pricing information. This necessitates compliance with applicable federal procurement laws and regulations and subjects us to contractual remedies as well as administrative, civil, and criminal sanctions. In addition, the VHCA requires manufacturers participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil penalties prohibits, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of whether the payor is public or private third-party, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense, and knowingly and willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items, or services relating to healthcare matters. A person or entity does not need to have actual knowledge of the statute, or the specific intent to violate it, to have committed a violation.

We may also be subject to data privacy and security laws and regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specific requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. While we would not be a "covered entity" under HIPAA, it is possible that we may enter into a service or business arrangement that would cause us to serve as a "business associates," defined as a person or entity that performs certain functions or activities that involve the use or disclosure of protected health information in connection with providing a service for or on behalf of, or provide services to, a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil

actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect. The Department of Health and Human Services Office of Civil Rights, or the OCR, has increased its focus on compliance and continues to train state attorneys general for enforcement purposes.

Even for entities that are not deemed "covered entities" or "business associates" under HIPAA, according to the U.S. Federal Trade Commission, or the FTC, failing to take appropriate steps to keep consumers' personal information secure constitutes unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act, or the FTCA, 15 USC § 45(a). The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. Medical data is considered sensitive data that merits stronger safeguards. The FTC's guidance for appropriately securing consumers' personal information is similar to what is required by the HIPAA Security Rule.

In addition to the laws discussed above, we may see more stringent state and federal privacy legislation in 2021 and beyond, as the increased cyber-attacks during the pandemic have heightened attention data privacy and security in the U.S. and other jurisdictions. We cannot predict where new legislation might arise, the scope of such legislation, or the potential impact to our business and operations.

Payments made to physicians and other healthcare providers, and other financial interests, have been the subject of a range of federal and state laws. The federal physician payment transparency requirements, sometimes referred to as the Physician Payments Sunshine Act, or the Sunshine Act, was created under the ACA. The Sunshine Act, among other things, imposes reporting requirements on drug manufacturers for payments or other transfers of value made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians, other healthcare providers, and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of \$150,000 per year and up to an additional aggregate of \$1 million per year for "knowing failures," for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. The Sunshine Act was amended requiring applicable manufacturers, in 2021, to begin tracking payments and transfers of value to physician assistants, nurse practitioners, and other mid-level HCPs as well as physicians, with reporting relative to these mid-level practitioners first due in 2022. Additionally, certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians and other HCPs.

Analogous state laws and regulations, such as state anti-kickback and false claims laws, and other state laws addressing the pharmaceutical and healthcare industries, which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and in some cases may apply regardless of payor, i.e., even if reimbursement is not available. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines, known as the PhRMA Code, and the relevant compliance program guidance promulgated by the federal government in addition to requiring drug manufacturers to report pricing and marketing information, including, among other things, information related to gifts, payments, or other remuneration to physicians and other healthcare providers or marketing expenditures, state and local laws that require the registration of pharmaceutical sales representatives, and state laws governing the privacy and security of health information and the use of prescriber-identifiable data in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. For example, California enacted the California Consumer Privacy Act, or CCPA, which went into effect on January 1, 2020, and was recently amended and expanded by the California Privacy Rights Act, or CPRA, passed on November 3, 2020. While the majority of the CPRA's substantive provisions will not take effect until January 1, 2023, the CPRA's expansion of the "Right to Know" impacts personal information collected on or after January 1, 2022. Companies must still comply with the CCPA during the ramp up period before CPRA goes into effect. The CCPA and CPRA, among other things, create new data privacy obligations for covered companies and provide new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also created a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. It remains unclear what, if any, additional modifications will be made to the CPRA by the California legislature or how it will be interpreted. Therefore, the effects of the CCPA and CPRA are significant and will likely require us to modify our data processing practices and may cause us to incur substantial costs and expenses to comply.

To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to HCPs.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under such laws, it is possible that certain business activities could be subject to challenge under one or more of such laws. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring that business arrangements with third parties comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert management's attention from the business.

If our operations are found to be in violation of any of such health regulatory laws described above or any other governmental laws and regulations that apply to us, we may be subject to penalties, including, without limitation, civil, administrative, and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and individual imprisonment, injunctions, private qui tam actions brought by individual whistleblowers in the name of the government, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

Coverage and Reimbursement

Sales of pharmaceutical products depend significantly on the availability of third-party coverage and reimbursement. Third-party payors include Medicare, Medicaid, and other government programs at the federal and state level, managed care providers, private health insurers and other organizations. Third party payors decide which drugs they will pay for on behalf of their beneficiaries and establish reimbursement levels for health care. Although we currently believe that third-party payors will provide coverage and reimbursement for our product candidates, if approved, these third-party payors are increasingly challenging the price and examining the cost-effectiveness of medical products and services, with a recent focus on prioritization of “equivalent,” less expensive alternatives when available. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive clinical trials to demonstrate the comparative cost-effectiveness of our products. The product candidates that we develop may not be considered cost-effective. It is time-consuming and expensive for us to seek coverage and reimbursement from third-party payors. Moreover, a payor’s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved, especially for product candidates such as ours, which are used in the inpatient setting, usually resulting in no separate reimbursement for pharmaceuticals. There are additional pressures on pricing as a result of other, peripheral policies impacting reimbursement across both government and private payors. Non-health specific policies may impart downstream impacts on private insurance reimbursement decision-making. In consideration of these numerous factors, reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis.

Medicare is a federally funded program managed by CMS through local contractors that administer coverage and reimbursement for certain healthcare items and services furnished to the elderly and disabled. Medicare Part A covers inpatient hospitalization and Medicare Part B covers outpatient medical services. Medicare coverage of drugs and biological products and payment rates to providers are established by federal law and regulations. Medicaid is an insurance program for certain categories of low-income patients who are otherwise uninsured and is both federally and state funded and managed by each state. The federal government sets general guidelines for Medicaid and requires rebates on outpatient drugs and biological products, including those administered by physicians if the cost is billed separately. Each state creates specific regulations that govern its individual program, including supplemental rebate programs that prioritize coverage for drugs on the state Preferred Drug List. Government laws and regulations also establish price controls on prescription drugs purchased by government agencies that provide health care and certain federally funded hospital outpatient departments and clinics. In the U.S., private health insurers and other third-party payors often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services. These restrictions and limitations influence the purchase of healthcare services and products. In addition, government programs like Medicaid include substantial penalties for increasing commercial prices over the rate of inflation which can affect realization and return on investment. Further, some stakeholders have recently questioned whether the market price of prescription drugs may be inflated by virtue of the built-in cost imparted by the government rebate model, often negotiated indirectly in exchange for a coverage determination or formulary placement where relevant.

In the U.S., the European Union, and other potentially significant markets for our product candidates, government authorities and private third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Manufacturers frequently must rebate a portion of the prescription price to the third-party payors as a condition of coverage, which can greatly reduce realization on the sale. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy, and are developing increasingly sophisticated methods of controlling healthcare costs. They may limit coverage to specific drug products on an approved list, or formulary, which might not include all the FDA-approved drug products for a particular indication, or they may control costs, particularly for new expensive therapies, by requiring prior authorization or imposing other restrictions before covering certain products, or they may condition payment based on achieving performance metrics. Legislative proposals to reform healthcare or reduce costs under government programs may result in lower reimbursement for our product candidates or exclusion of our product candidates from coverage.

Achieving favorable CMS coverage and reimbursement is usually a significant gating issue for successful introduction of a new product, because Medicare and Medicaid can represent a sizeable share of the market and because private payors often rely on the lead of the governmental payors in rendering coverage and reimbursement determinations. Further, the increased emphasis on managed healthcare in the U.S. and on country and regional pricing and reimbursement controls in the European Union will likely put additional pressure on product pricing, reimbursement, and utilization, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, competition within therapeutic classes, availability of generic equivalents, judicial decisions and governmental laws and regulations related to Medicare, Medicaid, and healthcare reform, pharmaceutical coverage and reimbursement policies, and pricing in general. Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Sales of our product candidates will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, such as Medicare and Medicaid, private health insurers, and other third-party payors.

As a result of the above, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to ensure acceptance and use of our products and product candidates or enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative and regulatory proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third-party coverage or adequate reimbursement for our product candidates in whole or in part.

Healthcare Reform

The U.S. and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major federal and state legislative initiatives.

In addition, other legislative and regulatory changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013, which will remain in effect through 2025 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In 2017, CMS promulgated a rule reducing Medicare Part B reimbursement to hospitals for drugs purchased under the 340B program by 30%. Although hospital trade associations filed a lawsuit challenging the regulation, the final rule is now in effect.

In recent years, there have been and continue to be proposals by the federal government, state governments, regulators, and third-party payors to control these costs and, more generally, to reform the U.S. health care system. Certain of these proposals could limit the prices we are able to charge for our products or the amounts of reimbursement available for our products. These laws and future laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our product candidates, if approved, and, accordingly, our financial operations.

Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

The cost of pharmaceuticals continues to generate substantial governmental and third-party payor interest and states have begun to take action to increase transparency in drug pricing through mandatory reporting requirements. We expect that the pharmaceutical industry will experience pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations, and additional legislative proposals. Our results of operations could be adversely affected by current and future healthcare reforms. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, the announcement or adoption of these proposals could have a material adverse effect on our ability to obtain adequate prices for our product candidates and operate profitably.

Foreign Regulation

In addition to regulations in the U.S., we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products to the extent we choose to develop or sell any products outside of the U.S. The approval process varies from country to country and the time may be longer or shorter than that required to obtain FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

In the EU and the United Kingdom, member states require both regulatory clearances by the national competent authority and a favorable ethics committee opinion prior to the commencement of a clinical trial. Under the EU regulatory systems, marketing authorization applications may be submitted under either a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization that is valid for all EU member states. It is compulsory for medicines produced by certain biotechnological processes. Because our products are produced in that way, we would be subject to the centralized process. Under the centralized procedure, pharmaceutical companies submit a single marketing authorization application to the European Medicines Agency. Once granted by the European Commission, a centralized marketing authorization is valid in all EU member states, as well as the European Economic Area countries. By law, a company can only start to market a medicine once it has received a marketing authorization.

Employees and Human Capital Management

As of December 31, 2022, we had 503 employees, 379 of whom were engaged in research and development activities and 124 of whom were engaged in general and administrative support activities. None of our employees are subject to a collective bargaining agreement. Our employees are highly skilled, and many hold advanced degrees. Most of our employees have experience with the development of cell therapies. We consider our relationship with our employees to be good. Our future performance depends significantly upon the continued service of our key scientific, technical and senior management personnel and our continued ability to attract and retain highly skilled employees. We provide our employees with competitive salaries and bonuses, opportunities for equity ownership, development programs that enable continued learning and growth and a robust employment package that promotes well-being across all aspects of their lives. In addition to salaries, these programs include potential annual discretionary bonuses, stock awards, Employee Stock Purchase Plan, a 401(k) plan, healthcare and insurance benefits, health savings and flexible spending accounts, paid time off, family leave, and flexible work schedules, among other benefits. We have taken proactive, aggressive action throughout the COVID-19 pandemic to protect the health and safety of our employees. We expect to continue to implement these measures until we determine that the COVID-19 pandemic is adequately contained for purposes of our business. We may take further actions, in compliance with all appropriate government regulations, that we determine to be in the best interest of our employees.

Available Information

We maintain a website at www.iovance.com and make available there, free of charge, our periodic reports filed with the Securities and Exchange Commission, or SEC, as soon as is reasonably practicable after filing. The SEC maintains a website at <http://www.sec.gov> that contains reports, proxy and information statements, and other information regarding issuers such as us that file electronically with the SEC.

Item 1A. Risk Factors

The risks described below may not be the only ones relating to our company. Additional risks that we currently believe are immaterial may also impair our business operations. Our business, financial conditions and future prospects and the trading price of our common stock could be harmed as a result of any of these risks. Investors should also refer to the other information contained or incorporated by reference in this Annual Report on Form 10-K, including our financial statements and related notes, and our other filings from time to time with the Securities and Exchange Commission, or SEC.

Risk Factors Summary

Our business is subject to a number of risks and uncertainties, including those risks discussed at length below. These risks include, among others, the brief bulleted list of our principal risk factors set forth below that make an investment in our company speculative or risky. You are encouraged to carefully review our full discussion of the material risk factors relevant to an investment in our business, which follows the brief bulleted list of our principal risk factors set forth below:

Risks Related to Our Business:

- We are substantially dependent on the success of our product candidates and cannot guarantee that these product candidates will successfully complete development, receive regulatory approval, or be successfully commercialized;
- We may encounter substantial delays in our clinical trials or may not be able to conduct our clinical trials on the timelines we expect and we may be required to conduct additional clinical trials or modify current or future clinical trials based on feedback we receive from the FDA;
- It may take longer and cost more to complete our clinical trials than we project, or we may not be able to complete them at all;
- Our clinical trials may fail to demonstrate adequately the safety and efficacy of our product candidates, which would prevent or delay regulatory approval and commercialization;
- The manufacture of our product candidates is complex, and we may encounter difficulties in production, particularly with respect to process development, quality control, or scaling-up of our manufacturing capabilities. If we, or any of our third-party manufacturers encounter such difficulties, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure;
- Cell-based therapies and biologics rely on the availability of reagents, specialized equipment, and other specialty materials, which may not be available to us on acceptable terms or at all. For some of these reagents, equipment, and materials, we rely or may rely on sole source vendors or a limited number of vendors, which could impair our ability to manufacture and supply our products;
- We collaborate with governmental, academic and corporate partners to improve and develop TIL therapies for new indications for use in combination with other therapies and to evaluate new TIL manufacturing methods, the results of which, because the manufacturing processes are not within our control, may be incorrect or unreliable;
- We may need additional financing to fund our operations and complete the development and commercialization of our various product candidates, and if we are unable to obtain such financing, we may be unable to complete the development and commercialization of our product candidates. Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates;
- We are subject to extensive regulation, which can be costly, time consuming and can subject us to unanticipated delays; even if we obtain regulatory approval for some of our products, those products may still face regulatory difficulties;
- We are required to pay substantial royalties and lump sum benchmark payments under our license agreements with the NIH, Moffitt, Novartis, and Cellectis, and we must meet certain milestones to maintain our license rights;

- Because our current products represent, and our other potential product candidates will represent novel approaches to the treatment of disease, there are many uncertainties regarding the development, the market acceptance, third-party reimbursement coverage and the commercial potential of our product candidates;
- No assurance can be given that the Gen 2 manufacturing process we have selected will be FDA-compliant, more efficient and lower the cost to manufacture TIL products;
- We face significant competition from other biotechnology and pharmaceutical companies and from non-profit institutions;
- Development of a product candidate intended for use in combination with an already approved product may present more or different challenges than development of a product candidate for use as a single agent;
- A Fast Track product designation, Breakthrough Therapy designation or other designation to facilitate product candidate development may not lead to faster development or a faster regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval;
- While lifileucel has received Orphan Drug Designation, or ODD, for melanoma stages IIB-IV and for cervical cancer patients with tumors greater than 2 cm, there is no guarantee that we will be able to maintain this designation, receive these designations for any of our other product candidates, or receive or maintain any corresponding benefits, including periods of exclusivity;
- As a condition of approval, the FDA may require that we implement various post-marketing requirements and conduct post-marketing studies, any of which would require a substantial investment of time, effort, and money, and which may limit our commercial prospects;
- We may be unable to establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, if they are approved, and as a result, we may be unable to generate product revenues;
- If our product candidates do not achieve broad market acceptance, the revenues that we generate from their sales will be limited;
- Our business could be adversely affected by the effects of health epidemics, including the recent spread of the COVID-19 pandemic, in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or other business operations. The COVID-19 pandemic could materially affect our operations, including at our headquarters in San Carlos, California and at our manufacturing facility in Philadelphia, Pennsylvania, which are currently subject to state executive orders and shelter-in-place orders, and at our clinical trial sites, as well as the business or operations of our other manufacturers, CROs or other third parties with whom we conduct business;
- We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth;
- We are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by geopolitical instability, an ongoing military conflict between Russia and Ukraine and record inflation. Our business, financial condition and results of operations could be materially adversely affected by any negative impact on the global economy and capital markets resulting from the conflict in Ukraine, geopolitical tensions or record inflation;
- Climate change or legal, regulatory or market measures to address climate change may negatively affect our business, results of operations, cash flows and prospects;
- Environmental, social and governance matters may impact our business and reputation; and
- We may rely on third parties to perform many essential services for any products that we commercialize, including services related to distribution, government price reporting, customer service, accounts receivable management, cash collection, and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize our current or future product candidates will be significantly impacted and we may be subject to regulatory sanctions.

Risks Related to Government Regulation:

- The FDA regulatory approval process is lengthy and time-consuming, and we may experience significant delays in the clinical development and regulatory approval of our product candidates;
- Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions;
- Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably; and

- Governments outside the U.S. tend to impose strict price controls, which may adversely affect our revenues, if any.

The summary risk factors described above should be read together with the text of the full risk factors below in this section entitled “*Risk Factors*” and the other information set forth in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes, as well as in other documents that we file with the SEC. The risks summarized above or described in full below are not the only risks that we face. Additional risks and uncertainties not precisely known to us or that we currently deem to be immaterial may also materially adversely affect our business, financial condition, results of operations and future growth prospects.

Risks Related to Our Business

We have a history of operating losses; we expect to continue to incur losses and we may never be profitable.

We are a clinical-stage biotechnology company focused on the development and commercialization of novel cancer immunotherapy products designed to harness the power of a patient's own immune system to eradicate cancer. We do not have products approved for commercial sale and have not generated revenue from operations. As of December 31, 2022, we had an accumulated deficit of \$1.6 billion. In addition, during the year ended December 31, 2022, we incurred a net loss of \$395.9 million. Since our inception we have not generated any revenues from operations. We are preparing for the commercial launch of our products, if approved, in 2023. We do not expect to generate any meaningful product sales or royalty revenues until we have a product approved. We expect to incur significant additional operating losses in the future as we expand our development and clinical trial activities in support of demonstrating the effectiveness of our products.

Our ability to achieve long-term profitability is dependent upon obtaining regulatory approvals for our products and successfully commercializing our products alone or with third parties. However, our operations may not be profitable even if any of our products under development are successfully developed and produced and thereafter commercialized.

Our current line of business, and the biotechnology industry in which we operate, makes it difficult to evaluate our business plan and our prospects.

We have only a limited operating history in our current line of business on which a decision to invest in our company can be based. The future of our company currently is dependent upon our ability to implement our business plan, as that business plan may be modified from time to time by our management and Board of Directors. While we believe that we have a reasonable business plan and research and development strategy, we have only a limited operating history against which we can test our plans and assumptions, and investors therefore cannot evaluate the likelihood of our success.

We face the problems, expenses, difficulties, complications and delays normally associated with a pre-commercial biotechnology company, many of which are beyond our control. Accordingly, our prospects should be considered in light of the risks, expenses and difficulties frequently encountered in the establishment of a new business developing technologies in an industry that is characterized by a number of market entrants and intense competition. Because of our size and limited resources, we may not possess the ability to successfully overcome many of the risks and uncertainties frequently encountered by pre-commercial companies involved in the rapidly evolving field of immunotherapy. If our research and development efforts are successful, we may also face the risks associated with the shift from development to commercialization of new products based on innovative technologies. There can be no assurance that we will be successful in developing our business.

We are substantially dependent on the success of our product candidates and cannot guarantee that these product candidates will successfully complete development, receive regulatory approval, or be successfully commercialized.

We currently have no products approved for commercial sale. We have invested a significant portion of our efforts and financial resources in the development of our current product candidates, including lifileucel, LN-145, IOV-4001, IOV-2001, and IOV-3001, and expect that we will continue to invest heavily in our current product candidates, as well as in any future product candidates we may develop. Our business depends entirely on the successful development and commercialization of our product candidates, which may never occur. Our ability to generate revenues in the future is substantially dependent on our ability to develop, obtain regulatory approval for, and then successfully commercialize our product candidates. We currently generate no revenue from the sale of any products, and we may never be able to develop or commercialize a marketable product.

Our product candidates will require additional clinical and non-clinical development, regulatory approval, commercial manufacturing arrangements, establishment of a commercial organization, significant marketing efforts, and further investment before

we generate any revenue from product sales. We cannot assure you that we will meet our timelines for our current or future clinical trials, which may be delayed or not completed for a number of reasons, including the negative impact of the COVID-19 pandemic.

We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates or regulatory approval that will allow us to successfully commercialize our product candidates. If we do not receive FDA approval with the necessary conditions to allow successful commercialization, and then successfully commercialize our product candidates, we will not be able to generate revenue from those product candidates in the U.S. in the foreseeable future, or at all. Any significant delays in obtaining approval for and commercializing our product candidates will have a material adverse impact on our business and financial condition.

Prior to our initiation of a rolling BLA for lifileucel, we have not previously submitted a BLA to the FDA, or similar marketing application to comparable foreign authorities, for any product candidate, and we cannot be certain that our current or any future product candidates will be successful in clinical trials or receive regulatory approval. Furthermore, although we have not submitted our BLA with comparisons to existing or more established therapies and likewise do not expect the FDA to base its determination with respect to product approval on such comparisons, the FDA may factor these comparisons into its decision whether to approve our TIL therapies, including lifileucel for metastatic melanoma. The FDA may also consider its approvals of competing products, which may alter the treatment landscape concurrently with their review of our BLA filings, and which may lead to changes in the FDA's review requirements that have been previously communicated to us and our interpretation thereof, including changes to requirements for clinical data or clinical trial design. Such changes could delay approval or necessitate withdrawal of our BLA filings.

Our product candidates are susceptible to the risks of failure inherent at any stage of product development, including the appearance of unexpected adverse events or failure to achieve primary endpoints in clinical trials. Further, our product candidates may not receive regulatory approval even if they are successful in clinical trials.

If approved for marketing by applicable regulatory authorities, our ability to generate revenues from our product candidates will depend on our ability to:

- price our product candidates competitively such that third-party and government reimbursement leads to broad product adoption;
- prepare a broad network of clinical sites for administration of our product;
- create market demand for our product candidates through our own marketing and sales activities, and any other arrangements to promote these product candidates that we may otherwise establish;
- receive regulatory approval for the targeted patient population(s) and claims that are necessary or desirable for successful marketing;
- effectively commercialize our products;
- manufacture product candidates through CMOs or in our own manufacturing facility in sufficient quantities and at acceptable quality and manufacturing cost to meet commercial demand at launch and thereafter;
- establish and maintain agreements with wholesalers, distributors, pharmacies, and group purchasing organizations on commercially reasonable terms;
- maintain patent and trade secret protection and regulatory exclusivity for our product candidates;
- launch commercial sales of our product candidates;
- maintain compliance with applicable laws, regulations, and guidance specific to commercialization including interactions with health care professionals, patient advocacy groups, and communication of health care economic information to payors and formularies;
- achieve market acceptance of our product candidates by patients, the medical community, and third-party payors;
- achieve appropriate reimbursement for our product candidates;
- maintain a distribution and logistics network capable of product storage within our specifications and regulatory guidelines, and further capable of timely product delivery to commercial clinical sites;
- effectively compete with other therapies or competitors; and
- following launch, assure that our product will be used as directed and that additional unexpected safety risks will not arise.

We may face risks due to the need to rely on third parties, including clinical trial sites.

We are heavily reliant on third parties to conduct our clinical trials. We have a limited history of conducting clinical trials and have no experience as a company in filing and supporting the applications necessary to gain marketing approvals. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety, purity, and potency for that indication. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities and clinical trial sites by, applicable regulatory authorities. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. As a result of the COVID-19 pandemic, institutions and research sites that currently conduct clinical trials may not be able to return to normal clinical trial operations for some time or may no longer choose to participate in studies in the future. Furthermore, clinical trials may be delayed or otherwise may be more difficult to execute in the future.

We have recruited a team that has experience with clinical trials and in the development of preclinical assets for translation into clinical trials; however, we as a company have limited experience completing pivotal clinical trials for cell therapy products or developing preclinical immunotherapy products. In part because of this lack of experience, we cannot be certain that our ongoing pivotal clinical trials will be completed on time, if at all, will progress according to our plans or expectations, or that our planned clinical trials will be initiated or initiated in a timely manner, progress according to our plans or expectations, or be completed on time, if they are completed at all.

Large-scale clinical trials require significant financial and management resources, and reliance on third-party clinical investigators, Contract Research Organizations, or CROs, Contract Manufacturing Organizations, or CMOs, or consultants. Relying on third-party clinical investigators, CROs or CMOs may force us to encounter delays and challenges that are outside of our control. In addition to manufacturing TIL at the iCTC, we rely on CMOs in the U.S. and Europe to manufacture TIL for use in our clinical trials and commercial use upon approval. We may not be able to demonstrate sufficient comparability between products manufactured at different facilities to allow for inclusion of the clinical results from patients treated with products from these different facilities, or with our own manufacturing facility, in our product registrations. Further, our CMOs may not be able to manufacture TIL or otherwise fulfill their obligations to us because of interruptions to their business, including the loss of their key staff or interruptions to their raw material supply.

We rely on third party CROs and clinical trial sites to conduct, supervise, and monitor our clinical trials for our product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions, independent review organizations and clinical investigators, to conduct our clinical trials. While we have agreements governing their activities, we have limited influence over their actual performance and control only certain aspects of their activities. The failure of these third parties to successfully carry out their contractual duties or meet expected deadlines could substantially harm our business because we may be delayed in completing or unable to complete the clinical trials required to support future approval of our product candidates, or we may not obtain marketing approval for or commercialize our product candidates in a timely manner or at all. Moreover, these agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that could delay our product development activities and adversely affect our business.

Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on the CROs, clinical trial sites, and other third parties do not relieve us of these oversight responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the clinical trial and for ensuring that our preclinical studies are conducted in accordance with Good Laboratory Practices, or GLPs, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with GCPs for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of clinical trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections (including pre-approval inspections once a BLA is filed with the FDA) of clinical trial sponsors, clinical investigators, clinical trial sites and certain third parties including CMOs. If we, our CROs, clinical trial sites, or other third parties fail to comply with Good Clinical Practices, or applicable GCPs, or other regulatory requirements, we or they may be subject to enforcement or other legal actions, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations.

In addition, we will be required to report certain financial interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA or comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators that are determined to have conflicts of interest.

In addition, our clinical trials must be conducted with product candidates that were produced under cGMP regulations. Our failure to comply or our CMOs' failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so could result in enforcement actions and adverse publicity.

Our CROs, clinical trial sites, and other third parties may also have relationships with other entities, some of which may be our competitors, for whom they may also be conducting clinical trials or other therapeutic development activities that could harm our competitive position. In addition, these third parties are not our employees, and except for remedies available to us under our agreements with them, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements or for other reasons, our clinical trials may be repeated, extended, delayed, or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be materially and adversely affected.

If any of our relationships with these third parties terminate, we may not be able to enter into alternative arrangements or do so on commercially reasonable terms. Switching or adding additional contractors involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our third-party service providers, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects or results of operations.

We also rely on other third parties to manufacture and ship our products for the clinical trials that we conduct. Any performance failure on the part of these third parties could delay clinical development or marketing approval of our product candidates or any additional product candidates or commercialization of our product candidates, if approved, producing additional losses and depriving us of potential product revenue.

We may encounter substantial delays in our clinical trials or may not be able to conduct our clinical trials on the timelines we expect and we may be required to conduct additional clinical trials or modify current or future clinical trials based on feedback we receive from the FDA.

Clinical testing is expensive, time consuming, and subject to uncertainty. We cannot guarantee that any current or future clinical trials will be conducted as planned or completed on schedule, if at all, or that any of our product candidates will receive regulatory approval. We initiated clinical trials in patients with metastatic melanoma, cervical, head and neck and non-small cell lung cancers, and in other indications in collaboration with third parties. We have completed enrollment in the pivotal clinical trial for melanoma, C-144-01. In June 2022, we announced that initial Cohort 4 data read by the independent review committee, or IRC, met the primary endpoint in this clinical trial. We plan to initiate clinical trials in new indications, and new cohorts in existing clinical trials. Even as these clinical trials progress, issues may arise that could require us to suspend or terminate such clinical trials or could cause the results of one cohort to differ from a prior cohort. For example, we may experience slower than anticipated enrollment in our pivotal clinical trials, which may consequently delay our BLA filing timelines or permit competitors to obtain approvals that may alter our BLA filing strategy. A failure of one or more clinical trials can occur at any stage of testing, and our future clinical studies may not be successful. Events that may prevent successful or timely initiation or completion of clinical development, or product approval include:

- regulators or IRBs may not authorize us or our investigators to commence a clinical trial, conduct a clinical trial at a prospective clinical trial site, or amend clinical trial protocols, or regulators or IRBs may require that we modify or amend our clinical trial protocols;
- delays in reaching a consensus or inability to obtain agreement with regulatory agencies on clinical trial design;
- the FDA or comparable foreign regulatory authorities may disagree with our intended indications, clinical trial design or our interpretation of data from preclinical studies and clinical trials or find that a product candidate's benefits do not outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may not accept data from studies with clinical trial sites in foreign countries;
- the FDA may not allow us to use the clinical trial data from a research institution to support an IND if we cannot demonstrate the comparability of our product candidates with the product candidate used by the relevant research institution in its clinical trials;
- delays in or failure to reach an agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- delays in obtaining required IRB approval at each clinical trial site;
- imposition of a temporary or permanent clinical hold, suspensions or terminations by regulatory agencies, IRBs, or us for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks, undesirable side effects, or other unexpected characteristics of the product candidate, or due to findings of undesirable effects caused by a biologically or mechanistically similar therapeutic or therapeutic candidate;
- delays in recruiting suitable patients to participate in our clinical trials;
- delay in adding new investigators or clinical trial sites, or withdrawal of clinical trial sites from a clinical trial;
- delay or change in strategic direction for an indication resulting from differences in results between cohorts in a clinical trial, such as Cohort 2 and Cohort 4 of the C-144-01 clinical trial or the previously disclosed preliminary results for the C-145-04 clinical trial and the final patient population and results, including differences in patient population, such as differences that might arise due to the impact of the existing immunotherapy treatment landscape, or from different interpretations of investigator results by IRC;
- failure by our CROs, clinical trial sites, patients, or other third parties, or us to adhere to clinical trial requirements, including regulatory, contractual or protocol requirements;
- failure to perform in accordance with the FDA's cGCP requirements, or applicable regulatory guidelines in other countries;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate or enrollment in these clinical trials may be slower than we anticipate, potentially affecting our timelines for approval of our product candidates;
- patients that enroll in our studies may misrepresent their eligibility or may otherwise not comply with the clinical trial protocol, resulting in the need to drop such patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;
- patients dropping out of a clinical trial;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols to regulatory authorities and IRBs, and which may cause delays in our development programs, or changes to regulatory review times;
- there may be regulatory questions or disagreements regarding interpretations of data and results, or new information may emerge regarding our product candidates;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional clinical trials;
- the cost of clinical trials of our product candidates being greater than we anticipate, or we may have insufficient funds for a clinical trial or to pay the substantial user fees required by the FDA upon the filing of a BLA;
- clinical trials of our product candidates producing negative or inconclusive results may fail to provide sufficient data and information to support product approval, or our studies may fail to reach the necessary level of statistical or clinical significance, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials studies, or preclinical studies, or abandon product development programs;
- early results from our clinical trials of our product candidates may be negatively affected by changes in efficacy measures such as overall response rate and duration of response as more patients are enrolled in our clinical trials or as new cohorts of our clinical trials are tested, and overall response rate and duration of response may be negatively affected by the inclusion of unconfirmed responses in preliminary results that we report if such responses are not later confirmed;

- we may not be able to demonstrate that a product candidate provides an advantage over current standards of care or current or future competitive therapies in development;
- there may be changes to the therapeutics or their regulatory status which we are administering in combination with our product candidates;
- delays in patient enrollment due to the ongoing COVID-19 pandemic;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or our manufacturing facilities for clinical and future commercial supplies;
- the FDA or comparable regulatory authorities may take longer than we anticipate making a decision on our product candidates;
- transfer of our manufacturing processes to our CMOs or other larger-scale facilities operated by a CMO or by us and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process;
- our use of different manufacturing processes within our clinical trials, including our Gen 1 and Gen 2 manufacturing processes, and any effects that may result from the use of different processes on the clinical data that we have reported and will report in the future; and
- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical trials or the inability to do any of the foregoing, including as a result of any quality issues associated with the contract manufacturer.

We also may conduct clinical and preclinical research in collaboration with other academic, pharmaceutical, biotechnology and biologics entities in which we combine our technologies with those of our collaborators. Such collaborations may be subject to additional delays because of the management of the clinical trials, contract negotiations, the need to obtain agreement from multiple parties, and the necessity of obtaining additional approvals for therapeutics used in the combination clinical trials. These combination therapies will require additional testing and clinical trials will require additional FDA regulatory approval and will increase our future cost of expenses.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenue. In addition, if we make manufacturing changes to our product candidates, we may be required to, or we may elect to, conduct additional studies to bridge our modified product candidates to earlier versions. These changes may require FDA approval or notification, may not have their desired effect, or the FDA may not accept data from prior versions of the product to support an application, delaying our clinical trials or programs or necessitating additional clinical trials or preclinical studies. For example, while our first BLA submission includes our Gen 2 manufacturing process, in the future we may seek to commercialize other manufacturing processes, such as our Gen 3 manufacturing process or our PD-1 selected TIL manufacturing process. We may find that commercialization of these manufacturing processes has unintended consequences that necessitate additional development and manufacturing work or additional clinical trials and preclinical studies, or results in a refusal to file or non-approval of a BLA.

Clinical trial delays could shorten any periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. The number and types of preclinical studies and clinical trials that will be required for regulatory approval also varies depending on the product candidate, the disease or condition that the product candidate is designed to address, and the regulations applicable to any particular product candidate. Approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. It is possible that any product candidates we may seek to develop in the future will never obtain the appropriate regulatory approvals necessary for us or any future collaborators to commence product sales. Any delay in completing development, obtaining or failure to obtain required approvals could also materially adversely affect our ability or that of any of our collaborators to generate revenue from any such product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

It may take longer and cost more to complete our clinical trials than we project, or we may not be able to complete them at all.

For budgeting and planning purposes, we have projected the date for the commencement of future clinical trials, and continuation and completion of our ongoing clinical trials. However, a number of factors, including scheduling conflicts with participating clinicians and clinical institutions, difficulties in identifying and enrolling patients who meet clinical trial eligibility

criteria, and the ongoing COVID-19 pandemic, may cause significant delays. We may not commence or complete clinical trials involving any of our products as projected or may not conduct them successfully.

We are currently enrolling six company-sponsored clinical trials to assess the overall safety and efficacy of Iovance TIL monotherapy and TIL combinations in patients with melanoma, cervical, head and neck and lung cancers across late-line and early treatment settings, as well as our genetically modified TIL therapy IOV-4001 and our peripheral blood lymphocyte, or PBL, technology for hematological malignancies. However, we may experience difficulties in patient enrollment in our clinical trials for a variety of reasons. Our ability to enroll or treat patients in our other studies, or the duration or costs of those studies, could be affected by multiple factors, including, preliminary clinical results, which may include efficacy and safety results from our ongoing Phase 2 studies, but may not be reflected in the final analyses of these clinical trials.

For example, our current clinical trials utilize an “open-label” trial design. An open-label trial is one where both the patient and investigator know whether the patient is receiving the test article or either an existing approved drug or placebo, which has the potential to create selection bias in the investigators. In our Phase 2 open-label studies, the investigators have significant discretion over the selection of patient participants. Although preliminary data from certain clinical trials were generally positive, that data may not necessarily be representative of interim or final results, as new patients are cycled through the applicable treatment regimes. As the clinical trials continue, the investigators may prioritize patients with more progressed forms of cancer than the initial patient population, based on the success or perceived success of that initial population. Patients with more progressed forms of cancer may be less responsive to treatment, and accordingly, interim efficacy data may show a decline in patient response rate or other assessment metrics. As the trials continue, investigators may shift their approach to the patient population, which may ultimately result in a decline in both interim and final efficacy data from the preliminary data, or conversely, an increase in final efficacy data following a decline in the interim efficacy data, as patients with more progressed forms of cancer are cycled out of the clinical trials and replaced by patients with less advanced forms of cancer. This opportunity for investigator selection bias in our clinical trials as a result of open-label design may not be adequately handled and may cause a decline in or distortion of clinical trial data from our preliminary results. Depending on the outcome of our open-label studies, we may need to conduct one or more follow-up or supporting studies in order to successfully develop our products for FDA approval. Many companies in the biotechnology, pharmaceutical and medical device industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face such setbacks.

Furthermore, the timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the clinical trial until its conclusion, including the ability of us or our collaborators to conduct clinical trials under the constraints of the COVID-19 pandemic. In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our clinical trials may instead opt to enroll in a clinical trial being conducted by one of our competitors. Accordingly, we cannot guarantee that the clinical trial will progress as planned or as scheduled. Delays in patient enrollment may result in increased costs or may affect the timing or outcome of our ongoing clinical trial and planned clinical trials, which could prevent completion of these clinical trials and adversely affect our ability to advance the development of our product candidates.

We expect to rely on medical institutions, academic institutions or CROs to conduct, supervise or monitor some or all aspects of clinical trials involving our products. We will have less control over the timing and other aspects of these clinical trials than if we conducted them entirely on our own. If we fail to commence or complete, or experience delays in, any of our planned clinical trials, our stock price and our ability to conduct our business as currently planned could be harmed.

We currently anticipate that we will have to rely on our CMOs to supplement the manufacturing capacity at the *i*CTC in manufacturing our adoptive cell therapy and biologic products for clinical trials. If they fail to commence or complete, or experiences delays in, manufacturing our adoptive cell therapy and other biologic products, our planned clinical trials will be delayed, which will adversely affect our stock price and our ability to conduct our business as currently planned.

Clinical trials are expensive, time-consuming and difficult to design and implement, and our clinical trial costs may be higher than for more conventional therapeutic technologies or drug products.

Clinical trials are expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. Because our product candidates include candidates based on new cell therapy technologies and manufactured on a patient-by-patient basis, we expect that they will require extensive research and development and have substantial manufacturing costs. In addition, costs to treat patients with relapsed/refractory cancer and to treat potential side effects that may result from our product candidates can be significant. Some clinical trial sites may not bill, or obtain coverage from Medicare, Medicaid, or other

third-party payors for some or all of these costs for patients enrolled in our clinical trials, and we may be required by those clinical trial sites to pay such costs. Accordingly, our clinical trial costs are likely to be significantly higher per patient than those of more conventional therapeutic technologies or drug products. In addition, our proposed personalized product candidates involve several complex and costly manufacturing and processing steps, the costs of which will be borne by us. We are also responsible for the manufacturing costs of products for patients that may have a tumor resection but ultimately do not receive an infusion. Depending on the number of patients that we ultimately screen and enroll in our clinical trials, and the number of clinical trials that we may need to conduct, our overall clinical trial costs may be higher than for more conventional treatments.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of our product candidates, which would prevent or delay regulatory approval and commercialization.

The clinical trials of our product candidates are, and the manufacturing and marketing of our products will be, subject to extensive and rigorous review and regulation by numerous government authorities in the U.S. and in other countries where we intend to test and market our product candidates. Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. Because our product candidates are subject to regulation as biological drug products, we will need to demonstrate that they are safe, pure, and potent for use in their target indications. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use. The risk/benefit profile required for product licensure will vary depending on these factors and may include not only the ability to show tumor shrinkage, but also adequate duration of response, a delay in the progression of the disease, and/or an improvement in survival. For example, response rates from the use of our product candidates may not be sufficient to obtain regulatory approval unless we can also show an adequate duration of response. Regulatory authorities may ultimately disagree with our chosen endpoints or may find that our studies or clinical trial results do not support product approval. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates with small patient populations may not be predictive of the results of later-stage clinical trials or the results once the applicable clinical trials are completed. Preliminary, single cohort, or top-line results from clinical trials may not be representative of the final clinical trial results. The results of studies in one set of patients or line of treatment may not be predictive of those obtained in another and the results in various human clinical trials reported in scientific and medical literature may not be indicative of results we obtain in our clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. Preclinical studies may also reveal unfavorable product candidate characteristics, including safety concerns.

We expect there may be greater variability in results for products processed and administered on a patient-by-patient basis, as anticipated for our product candidates, than for “off-the-shelf” products, like many other drugs. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. Many companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or unacceptable safety issues, notwithstanding promising results in earlier clinical trials. Most product candidates that begin clinical trials are never approved by regulatory authorities for commercialization.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in clinical trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the clinical trial protocols and the rate of dropout among clinical trial participants. Our current and future clinical trial results may not be successful. Moreover, should there be a flaw in a clinical trial, it may not become apparent until the clinical trial is well advanced. Further, because we currently plan to test our product candidates for use with other oncology products, the design, implementation, and interpretation of the clinical trials necessary for marketing approval may be more complex than if we were developing our product candidates alone.

In addition, even if such clinical trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more clinical trials could be required before we submit our product candidates for approval. To the extent that the results of the clinical trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional clinical trials in support of potential approval of our product candidates.

We have reported preliminary results for clinical trials of our product candidates, including TIL for the treatment of metastatic melanoma, cervical cancer, and head and neck cancers. These preliminary results, which include assessments of efficacy such as

ORR, are subject to substantial risk of change due to small sample sizes and may change as patients are evaluated or as additional patients are enrolled in these clinical trials. These outcomes may be unfavorable, deviate from our earlier reports, and/or delay or prevent regulatory approval or commercialization of our product candidates, including candidates for which we have reported preliminary efficacy results. In clinical trials where a staged expansion is expected, such as studies using a Simon's two stage design, these outcomes may result in the failure to meet an initial efficacy threshold for the first stage. Furthermore, other measures of efficacy for these clinical trials and product candidates may not be as favorable.

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients, or similar patients from a Phase 2 clinical trial to a pivotal program, who remain in the clinical trial until its conclusion. We may experience difficulties or delays in patient enrollment in our clinical trials for a variety of reasons, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the patient eligibility criteria defined in the protocol;
- the size of the clinical trial population required for analysis of the clinical trial's primary endpoints;
- the proximity of patients to clinical trial sites;
- the design of the clinical trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the efforts to facilitate timely enrollment in clinical trials and the effectiveness of recruiting publicity;
- the patient referral practices of physicians;
- competing clinical trials for similar therapies or other new therapeutics not involving cell-based immunotherapy;
- clinicians' and patients' perceptions as to the potential advantages and side effects of the product candidate being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating;
- clinical investigators enrolling patients who do not meet the enrollment criteria, requiring the inclusion of additional patients in the clinical trial;
- the ongoing COVID-19 pandemic limiting our access to patients who would otherwise be eligible for enrollment, including treatment-naïve patients who may be more likely to seek standard of care therapies available at local treatment centers rather than enroll in a clinical trial at a larger hospital;
- approval of new indications for existing therapies or approval of new therapies in general;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will not complete a clinical trial, return for post-treatment follow-up, or follow the required clinical trial procedures. For instance, patients, including patients in any control groups, may withdraw from the clinical trial if they are not experiencing improvement in their underlying disease or condition. Withdrawal of patients from our clinical trials may compromise the quality of our data.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our clinical trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitor's use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. Moreover, because our product candidates represent a departure from more commonly used methods for cancer treatment, potential patients and their doctors may be inclined to use conventional therapies, such as chemotherapy and approved immunotherapies, rather than enroll patients in any future clinical trial. In addition, potential enrollees may opt to participate in other clinical trials because of the length of time between the time that their tumor is excised and the TIL is infused back into the patient.

Amendments to our clinical protocols may affect enrollment in, or results of, our trials, including amendments we have made to further define the patient population to be studied.

Even if we are able to enroll a sufficient number of patients in our clinical trials, delays in patient enrollment or small population size may result in increased costs or may affect the timing or outcome of the planned clinical trials, which could prevent completion of these clinical trials and adversely affect our ability to advance the development of our product candidates.

Our product candidates may cause undesirable side effects or have other properties that could halt their clinical development, prevent their regulatory approval, limit their commercial potential or result in significant negative consequences.

Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could cause us, IRBs, DSMBs, or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authorities. Even if we were to receive product approval, such approval could be contingent on inclusion of unfavorable information in our product labeling, such as limitations on the indications for use for which the products may be marketed or distributed, a label with significant safety warnings, including boxed warnings, contraindications, and precautions, a label without statements necessary or desirable for successful commercialization, or requirements for costly post marketing testing and surveillance, or other requirements, including a Risk Evaluation and Mitigations Strategy or REMS, to monitor the safety or efficacy of the products, and in turn prevent us from commercializing and generating revenues from the sale of our current or future product candidates.

If unacceptable toxicities or side effects arise in the development of our product candidates, we, an IRB, DSMB or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials, order our clinical trials to be placed on clinical hold, or deny approval of our product candidates for any or all targeted indications. The FDA or comparable foreign regulatory authorities may also require additional data, clinical, or preclinical studies should unacceptable toxicities arise. We may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk/benefit perspective. Toxicities associated with our clinical trials and products may also negatively impact our ability to conduct clinical trials using TIL therapy in larger patient populations, such as in patients that have not yet been treated with other therapies or have not yet progressed on other therapies.

Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete our clinical trials or result in potential product liability claims. Such toxicities, which may arise from TIL therapy in general, including co-therapies, may include, for example, thrombocytopenia, chills, anemia, pyrexia, febrile neutropenia, diarrhea, neutropenia, vomiting, hypotension, and dyspnea. For example, the update in October 2018 from the C-144-01 clinical trial included two grade 5 treatment emergent adverse events. In addition, these side effects and deaths may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from personalized cell therapy are not normally encountered in the general patient population and by medical personnel. Any of these occurrences may harm our business, financial condition and prospects significantly.

The manufacture of our product candidates is complex, and we may encounter difficulties in production, particularly with respect to process development, quality control, or scaling-up of our manufacturing capabilities. If we, or any of our third-party manufacturers encounter such difficulties, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

Our product candidates are biologics and the process of manufacturing our products is complex, highly regulated and subject to multiple risks. The manufacture of our product candidates involves complex processes, including harvesting tumor fragments from patients, isolating the T-cells from the tumor fragments, multiplying the T-cells to obtain the desired dose, and ultimately infusing the T-cells back into a patient. As a result of the complexities, the cost to manufacture biologics is generally higher than traditional small molecule chemical compounds, and the manufacturing process is less reliable and is more difficult to reproduce. Our manufacturing process will be susceptible to product loss or failure due to logistical issues associated with the collection of tumor fragments, or starting material, from the patient, shipping such material to the manufacturing site, shipping the final product back to the patient, and infusing the patient with the product, manufacturing issues associated with the differences in patient starting material, interruptions in the manufacturing process, contamination, equipment failure, assay failures, improper installation or operation of equipment, vendor or operator error, inconsistency in cell growth, meeting pre-specified release criteria, and variability in product characteristics. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects, and other supply disruptions. If for any reason we lose a patient's starting material, or later-developed product at any point in the process, or if any product does not meet the applicable specifications, the manufacturing process for that patient will need to be restarted, including

resection of the proper amount of tumor fragment and the resulting delay may adversely affect that patient's outcome. If microbial, viral, environmental or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination.

Because our product candidates are manufactured specifically for each individual patient, we will be required to maintain a chain of identity with respect to the patient's tumor as it moves from the patient to the manufacturing facility, through the manufacturing process, and back to the patient. Maintaining such a chain of identity is difficult and complex, and failure to do so could result in adverse patient outcomes, loss of product, or regulatory action including withdrawal of our products from the market. Further, as product candidates are developed through preclinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials or otherwise necessitate the conduct of additional studies.

Currently, our product candidates are manufactured using processes developed or modified by us or by our third-party research institution collaborators that we may not intend to use for more advanced clinical trials or commercialization. We have selected Gen 2 as the manufacturing process for product registration, and all ongoing and future company-sponsored clinical trials. Although we believe Gen 2 is a commercially viable process, there are risks associated with scaling to the level required for advanced clinical trials or commercialization, including, among others, cost overruns, potential problems with process scale-up, process reproducibility, stability issues, lot consistency, and timely availability of raw materials. This includes potential risks associated with the FDA not agreeing with all of the details of our validation data or other aspects of our potency assay or assays for Cohort 4 of our C-144-01 clinical trial. For example, on October 5, 2020, we announced that we and the FDA were not able to agree on the required potency assays to fully define our TIL therapy, which is required as part of a BLA submission, and that as a result of these developments, our BLA submission was not expected by the end of 2020 and was anticipated instead to occur in 2021. Previously, we reported the submission of assay data to the FDA, and on May 18, 2021, we announced that we had received regulatory feedback from the FDA regarding our potency assays for lifileucel. Following FDA feedback regarding the potency assays for lifileucel, we continued work developing and validating our potency assays and engaged in discussions with the FDA during the second half of 2021 and first quarter of 2022. Based on feedback received from these discussions, we held a pre-BLA meeting in July 2022. We initiated a rolling BLA for lifileucel in metastatic melanoma in August 2022, which we plan to complete in the first quarter of 2023. In addition, as previously disclosed, we have begun a confirmatory Phase 3 clinical trial of lifileucel in combination with pembrolizumab in frontline metastatic melanoma in late 2022 which we expect to utilize significant manufacturing capacity.

As a result of these challenges, we may experience delays in our clinical development and/or commercialization plans. Furthermore, we may ultimately be unable to reduce the cost of goods for our product candidates to levels that will allow for an attractive return on investment if and when those product candidates are commercialized.

In May 2019 we entered into a lease agreement to build a commercial-scale manufacturing facility, the *i*CTC, in Philadelphia, Pennsylvania for commercial and clinical production of autologous TIL products, including our product candidate lifileucel. The *i*CTC is currently manufacturing TIL for our ongoing clinical trials and preparing to provide commercial supply upon potential BLA approval; as of the end of 2021, we had completed the commissioning activities at the *i*CTC and successfully initiated manufacturing of clinical batches of lifileucel and LN-145, representing our first internally manufactured TIL product, as we continue our launch readiness activities to supply commercial TIL upon potential BLA approval. We expect our manufacturing facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins. We are building capacity to treat thousands of cancer patients annually. However, we may not be successful in finalizing the development of our own manufacturing facility or capability. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

The manufacture of cell therapy products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of cell therapy products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields, quality control, including stability of the product candidate and quality assurance testing, shortages of qualified personnel, and compliance with strictly enforced federal, state, local and foreign regulations.

Our current manufacturing strategy involves the use of CMOs to supplement the manufacturing capacity at the *i*CTC. Currently our product candidates are also manufactured by WuXi and Moffitt. Any problems or delays we or our CMOs experience in preparing for commercial scale manufacturing of a product candidate or component may result in a delay in the FDA approval of the product candidate or may impair our ability to manufacture commercial quantities or such quantities at an acceptable cost, which could result in the delay, prevention, or impairment of clinical development and commercialization of our product candidates and could adversely affect our business. Furthermore, if we or our commercial manufacturers fail to deliver the required commercial quantities of our product candidates on a timely basis and at reasonable costs, we would likely be unable to meet demand for our products and we would lose potential revenues.

Moreover, should we continue to use CMOs, we may not succeed in maintaining our relationships with our current CMOs or establishing relationships with additional or alternative CMOs. Our product candidates may compete with other products and product candidates for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that are both capable of manufacturing for us and willing to do so. If our CMOs should cease manufacturing for us, we would experience delays in obtaining sufficient quantities of our product candidates for clinical trials and, if approved, commercial supply. Further, our CMOs may breach, terminate, or not renew these agreements. If we were to need to find alternative manufacturing facilities it would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. The commercial terms of any new arrangement could be less favorable than our existing arrangements and the expenses relating to the transfer of necessary technology and processes could be significant.

Reliance on third-party manufacturers entails exposure to risks to which we would not be subject if we manufactured the product candidate ourselves, including:

- inability to negotiate manufacturing and quality agreements with third parties under commercially reasonable terms;
- reduced day-to-day control over the manufacturing process for our product candidates as a result of using third-party manufacturers for all aspects of manufacturing activities;
- reduced control over the protection of our trade secrets and know-how from misappropriation or inadvertent disclosure;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that may be costly or damaging to us or result in delays in the development or commercialization of our product candidates; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

In addition, the manufacturing process and facilities for any products that we may develop at the *i*CTC and or our CMOs is subject to FDA and foreign regulatory authority approval processes, and we or our CMOs will need to meet all applicable FDA and foreign regulatory authority requirements, including cGMPs, on an ongoing basis. The cGMP requirements include quality control, quality assurance, and the maintenance of records and documentation. The FDA and other regulatory authorities enforce these requirements through facility inspections. Manufacturing facilities must submit to pre-approval inspections by the FDA that will be conducted after we submit our marketing applications, including our BLAs, to the FDA. Manufacturers are also subject to continuing regulatory oversight by FDA and other regulatory authorities, including inspections following marketing approval. Further, we, in cooperation with our CMOs, must supply all necessary chemistry, manufacturing, and control documentation for a pre-approval inspection in support of a BLA on a timely basis. There is no guarantee that we or our CMOs will be able to successfully pass all aspects of a pre-approval inspection by the FDA or other foreign regulatory authorities.

Our, or our CMOs', manufacturing facilities may be unable to comply with our specifications, cGMPs, and with other FDA, state, and foreign regulatory requirements. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of product candidate that may not be detectable in final product testing. If we or our CMOs are unable to reliably produce products to specifications acceptable to the FDA or other regulatory authorities, or in accordance with the strict regulatory requirements, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CMOs will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Deviations from manufacturing requirements may further require remedial measures that may be costly and/or time-consuming for us or a third party to implement and may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

Even to the extent we use and continue to use CMOs, we are ultimately responsible for the manufacture of our products and product candidates. A failure to comply with these requirements may result in regulatory enforcement actions against our manufacturers or us, including fines and civil and criminal penalties, which could result in imprisonment, suspension or restrictions of production, injunctions, delay or denial of product approval or supplements to approved products, clinical holds or termination of clinical trials, warning or untitled letters, regulatory authority communications warning the public about safety issues with the biologic, refusal to permit the import or export of the products, product seizure, detention, or recall, operating restrictions, suits under the civil False Claims Act, corporate integrity agreements, consent decrees, or withdrawal of product approval.

Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects.

Cell-based therapies and biologics rely on the availability of reagents, specialized equipment, and other specialty materials, which may not be available to us on acceptable terms or at all. For some of these reagents, equipment, and materials, we rely or may rely on sole source vendors or a limited number of vendors, which could impair our ability to manufacture and supply our products.

Manufacturing our product candidates requires many reagents, which are substances used in our manufacturing processes to bring about chemical or biological reactions, and other specialty materials and equipment, some of which are manufactured or supplied by small companies with limited resources and experience to support commercial biologics production. We currently depend on a limited number of vendors for certain materials and equipment used in the manufacture of our product candidates. Some of these suppliers may not have the capacity to support clinical trials and commercial products manufactured under cGMP by biopharmaceutical firms or may otherwise be ill-equipped to support our needs. We also do not have supply contracts with many of these suppliers and may not be able to obtain supply contracts with them on acceptable terms or at all. Accordingly, we may experience delays in receiving key materials and equipment to support clinical or commercial manufacturing.

For some of these reagents, equipment, and materials, we rely and may in the future rely on sole source vendors or a limited number of vendors. An inability to continue to source product from any of these suppliers, which could be due to a number of issues, including regulatory actions or requirements affecting the supplier, adverse financial or other strategic developments experienced by a supplier, labor disputes or shortages, unexpected demands, or quality issues, could adversely affect our ability to satisfy demand for our product candidates, which could adversely and materially affect our product sales and operating results or our ability to conduct clinical trials, either of which could significantly harm our business.

As we continue to develop and scale our manufacturing process, we expect that we will need to obtain rights to and supplies of certain materials and equipment to be used as part of that process. We may not be able to obtain rights to such materials on commercially reasonable terms, or at all, and if we are unable to alter our process in a commercially viable manner to avoid the use of such materials or find a suitable substitute, it would have a material adverse effect on our business. Even if we are able to alter our process so as to use other materials or equipment, such a change may lead to a delay in our clinical development and/or commercialization plans. If such a change occurs for product candidate that is already in clinical testing, the change may require us to perform both *ex vivo* comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials.

We will be unable to commercialize our products if our trials are not successful.

With the exception of lifileucel currently undergoing human clinical trials for advanced melanoma, cervical cancer and metastatic non-small cell lung cancer, or NSCLC, our research and development programs are at various stages of clinical development, including several at an early stage. We must demonstrate our products' safety and efficacy in humans through extensive clinical testing. We may experience numerous unforeseen events during, or as a result of, the testing process that could delay or prevent commercialization of our products, including but not limited to the following:

- safety and efficacy results in various human clinical trials reported in scientific and medical literature may not be indicative of results we obtain in our clinical trials;
- after reviewing test results, we or our collaborators may abandon projects that we might previously have believed to be promising;
- we, our collaborators or regulators, may suspend or terminate clinical trials if the participating subjects or patients are being exposed to unacceptable health risks;

- the effects our potential products have may not be the desired effects or may include undesirable side effects or other characteristics that preclude regulatory approval or limit their commercial use if approved;
- manufacturers may not meet the necessary standards for the production of the product candidates or may not be able to supply the product candidates in a sufficient quantity; and
- regulatory authorities may find that our clinical trial design or conduct does not meet the applicable approval requirements.

Clinical testing is very expensive, can take many years, and the outcome is uncertain. It could take as much as 12 months or more before we learn the results from any clinical trial using our adoptive cell therapy with TIL. The data collected from our clinical trials may not be sufficient to support approval by the FDA of our TIL-based product candidates for the treatment of solid tumors. The clinical trials for our products under development may not be completed on schedule and the FDA may not ultimately approve any of our product candidates for commercial sale. If we fail to adequately demonstrate the safety and efficacy of any product candidate under development, we may not receive regulatory approval for those products, which would prevent us from generating revenues or achieving profitability.

Even if our lead product lifileucel is approved and commercialized, we may not become profitable.

Our lead product, lifileucel, is initially targeting a small population of refractory patients that suffer from metastatic melanoma and metastatic cervical cancer. Even if the FDA approves these new therapies, and even if we obtain significant market share for each product candidate, because the potential target population for lifileucel in refractory patients may be small, we may never achieve profitability without obtaining regulatory approval for additional indications. The FDA often approves new therapies initially only for use in patients with relapsed or refractory metastatic disease. We expect to initially seek approval of our product candidates in this setting and are currently conducting clinical trials on these patient populations.

We collaborate with governmental, academic and corporate partners to improve and develop TIL therapies for new indications for use in combination with other therapies and to evaluate new TIL manufacturing methods, the results of which, because the manufacturing processes are not within our control, may be incorrect or unreliable.

In addition to our own research and process development efforts, we seek to collaborate with government, academic research institutions and corporate partners to improve TIL manufacturing and to develop TIL therapies for new indications. In 2017-2020, we announced our continued collaborations with Moffitt, MDACC, and The Ohio State University to evaluate several new solid tumor and hematologic indications for TIL therapy in clinical trials and preclinical studies as well as, in some cases, new TIL manufacturing approaches. The results of these collaborations may be used to support our filing with the FDA of INDs to conduct more advanced clinical trials of our product candidates, or to otherwise analyze or make predictions or decisions with respect to our current or future product candidates. However, because the majority of our collaborations are conducted at outside laboratories and we do not have complete control over how the studies are conducted or reported or over the manufacturing methods used to manufacture TIL product, the results of such studies, which we may use as the basis for our conclusions, projections or decisions with respect to our current or future product candidates, may be incorrect or unreliable, or may have a negative impact on us if the results of such studies are imputed to our products or proposed indications, even if such imputation is improper. For example, we have entered into collaborations with Moffitt, and MDACC to perform clinical trials using TIL products that differ from our products, but the results of these clinical trials, if negative, may adversely impact our stock price and our development plans for our products. Additionally, we may use third party data to analyze, reach conclusions or make predictions or decisions with respect to our product candidates that may be incomplete, inaccurate or otherwise unreliable.

We may need additional financing to fund our operations and complete the development and commercialization of our various product candidates, and if we are unable to obtain such financing, we may be unable to complete the development and commercialization of our product candidates. Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Our operations have consumed substantial amounts of cash since inception. From our inception to December 31, 2022, we have an accumulated deficit of \$1.6 billion. In addition, our research and development and our operating costs have also been substantial and are expected to increase. For example, in October 2018, we closed an underwritten public offering of our common stock. The net proceeds from the offering, after deducting the underwriting discounts and commissions and other offering expenses payable by us, were \$236.7 million. In June 2020, we closed another underwritten offering of our common stock. The net proceeds from the offering, after deducting the underwriting discounts and commissions and other offering expenses payable by us, were \$567.0 million. In February 2021 we entered into an open market sale agreement, or the First Sales Agreement, with Jefferies LLC, which provided for the sale of up to \$350.0 million of our common stock from time to time, which was subsequently increased to \$500.0 million in

November 2022 upon the execution of an updated open market sale agreement, or the Second Sales Agreement, with Jefferies LLC. As of December 31, 2022, we had \$478.3 million in cash, cash equivalents and investments (\$231.7 million of cash and cash equivalents, \$240.1 million in short-term investments, and restricted cash of \$6.4 million).

Accordingly, we believe that our existing cash, cash equivalents and investments will be sufficient to fund our operations for at least the next twelve months from the date this Annual Report on Form 10-K is issued. However, in order to complete the development of our current product candidates, and in order to affect our business plan, including establishing our own manufacturing facility, we anticipate that we will have to spend more than the funds currently available to us. Furthermore, changing circumstances may cause us to increase our spending significantly faster than we currently anticipate, and we may require additional capital for the further development and commercialization of our product candidates and may need to raise additional funds sooner if we choose to expand more rapidly than we presently anticipate. Moreover, our fixed expenses such as rent, minimum payments to our contract manufacturers, and other contractual commitments, including those for our research collaborations, are substantial and are expected to increase in the future.

We will need to obtain additional financing to fund our future operations, including completing the development and commercialization of our product candidates. Our future funding requirements will depend on many factors, including, but not limited to:

- progress, timing, scope and costs of our clinical trials, including the ability to timely initiate clinical sites, enroll subjects and manufacture TIL for treatment for patients in our ongoing, planned and potential future clinical trials;
- time and cost necessary to obtain regulatory approvals that may be required by regulatory authorities to execute clinical trials or commercialize our product;
- our ability to successfully commercialize our product candidates, if approved;
- our ability to have clinical and commercial product successfully manufactured consistent with FDA and European Medicines Agency, or EMA, regulations;
- amount of sales and other revenues from product candidates that we may commercialize, if any, including the selling prices for such potential products and the availability of adequate third-party coverage and reimbursement for patients;
- sales and marketing costs associated with commercializing our products, if approved, including the cost and timing of building our marketing and sales capabilities;
- cost of building, staffing and validating our own manufacturing facility in the U.S.;
- terms and timing of our current and any potential future collaborations, licensing or other arrangements that we have established or may establish;
- cash requirements of any future acquisitions or the development of other product candidates;
- costs of operating as a public company;
- time and cost necessary to respond to technological, regulatory, political and market developments;
- costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights; and
- costs associated with any potential business or product acquisitions (such as the anticipated acquisition of Proleukin®), strategic collaborations, licensing agreements or other arrangements that we may establish.

Unless and until we can generate a sufficient amount of revenue, we may finance future cash needs through public or private equity offerings, license agreements, debt financings, collaborations, strategic alliances and marketing or distribution arrangements. Additional funds may not be available when we need them on terms that are acceptable to us, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may be required to delay or reduce the scope of or eliminate one or more of our research or development programs or our commercialization efforts. Our current license and collaboration agreements may also be terminated if we are unable to meet the payment obligations under those agreements. As a result, we may seek to access the public or private capital markets whenever conditions are favorable, even if we do not have an immediate need for additional capital at that time.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. The incurrence of indebtedness would result in increased fixed payment obligations and could involve certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms unfavorable to us.

Subject to various spending levels approved by our Board of Directors, our management will have broad discretion in the use of the net proceeds from our capital raises, including our June 2020, October 2018 and January 2018 public offerings and the proceeds from sales pursuant to our “at-the-market” sales agreement with Jefferies LLC, and may not use them effectively.

Our management will have discretion in the application of the net proceeds from our capital raises, including our June 2020, October 2018, and January 2018 public offerings, and the proceeds from sales pursuant to the First Sales Agreement with Jefferies LLC, which provided for the sale of up to \$350.0 million of our common stock from time to time, which was subsequently increased to \$500.0 million in November 2022 upon the execution of the Second Sales Agreement with Jefferies LLC, and our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds from our capital raises are being used appropriately. You may not agree with our decisions, and our use of the proceeds from our capital raises may not yield any return to stockholders. Because of the number and variability of factors that will determine our use of the net proceeds from our capital raises, their ultimate use may vary substantially from their currently intended use. Our failure to apply the net proceeds of our capital raises effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of those net proceeds. Stockholders will not have the opportunity to influence our decisions on how to use our net proceeds from our capital raises. Pending their use, we may invest the net proceeds from our capital raises in interest and non-interest-bearing cash accounts, short-term, investment-grade, interest-bearing instruments and U.S. government securities. These temporary investments are not likely to yield a significant return.

The use of our net operating loss carryforwards and research tax credits may be limited.

Our net operating loss carryforwards and any future research and development tax credits may expire and not be used. As of December 31, 2022, we had U.S. federal net operating loss carryforwards of approximately \$1.0 billion. Our net operating loss carryforwards arising in taxable years ending on or prior to December 31, 2017, will begin expiring in 2027 if we have not used them prior to that time. Net operating loss carryforwards arising in taxable years ending after December 31, 2017, are no longer subject to expiration under the Internal Revenue Code of 1986, as amended, or the Code. Additionally, our ability to use any net operating loss and credit carryforwards to offset taxable income or tax, respectively, in the future will be limited under Sections 382 and 383 of the Code, respectively, if we have a cumulative change in ownership of more than 50% within a three-year period.

Prior to December 31, 2022, we have experienced multiple ownership changes. As a result, the federal and state carryforwards associated with the net operating loss and credit deferred tax assets were reduced by the amount of tax attributes estimated to expire during their respective carryforward periods. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further ownership changes in the future. Any such annual limitation may significantly reduce the utilization of the net operating loss carryforwards and research tax credits before they expire. Depending on our future tax position, limitation of our ability to use net operating loss carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition.

Recently enacted tax reform legislation in the U.S., changes to existing tax laws, or challenges to our tax positions could adversely affect our business and financial condition.

In recent years, various tax legislations were signed into law. On December 22, 2017, the Tax Cuts and Jobs Act of 2017, or the Tax Act, was signed into law, making significant changes to the Internal Revenue Code.

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, was enacted in response to the COVID-19 pandemic. Certain provisions of the CARES Act amend or suspend certain provisions of the Tax Act. For example, the tax relief measures under the CARES Act for businesses include a five-year net operating loss carryback, suspension of annual deduction limitation of 80% of taxable income from net operating losses generated in a tax year beginning after December 31, 2017, changes in the deductibility of interest, acceleration of alternative minimum tax credit refunds, payroll tax relief, and a technical correction to allow accelerated deductions for qualified improvement property. On June 15, 2020, Assembly Bill 85 was passed in California which suspended the use of net operating losses and limited the use of credits for certain corporations. Changes to existing federal and state tax laws could adversely impact our business, results of operations and financial position as the impact of recent tax legislation is uncertain.

In addition, U.S. federal, state and local tax laws are extremely complex and subject to various interpretations. Although we believe that our tax estimates and positions are reasonable, including our decision to build our *i*CTC facility at the Navy Yard in Philadelphia in order to take advantage of the site's designation as a Keystone Opportunity Zone, Keystone Opportunity Expansion Zone, or Keystone Opportunity Improvement Zone, or collectively KOZ, which allows incentives for business development, as well as certain other financial incentives provided by the Commonwealth of Pennsylvania, the City of Philadelphia and the Philadelphia Industrial Development Corporation, there can be no assurance that our tax positions will not be challenged by relevant tax authorities or that we would be successful in any such challenge. Further, challenges to the site's designation as a KOZ or broader challenges to Pennsylvania's KOZ program could result in the revocation of the site's designation as a KOZ and the attendant tax advantages associated with such designation. If we are unsuccessful in such a challenge, or if the site's status as a KOZ is revoked, the relevant tax authorities may assess additional taxes, which could result in adjustments to, or impact the timing or amount of, taxable income, deductions or other tax allocations, which may adversely affect our results of operations and financial position.

We are subject to extensive regulation, which can be costly, time consuming and can subject us to unanticipated delays; even if we obtain regulatory approval for some of our products, those products may still face regulatory difficulties.

Our potential products, cell processing and manufacturing activities, are subject to comprehensive regulation by the FDA in the U.S. and by comparable authorities in other countries. The process of obtaining FDA and other required regulatory approvals, including foreign approvals, is expensive and often takes many years and can vary substantially based upon the type, complexity and novelty of the products involved. In addition, regulatory agencies may lack experience with our technologies and products, which may lengthen the regulatory review process, increase our development costs and delay or prevent their commercialization.

No adoptive cell therapy using TIL has been approved for marketing by the FDA. Consequently, there is no precedent for the successful commercialization of products based on our technologies. In addition, we have had only limited experience in filing and pursuing applications necessary to gain regulatory approvals, which may impede our ability to obtain timely FDA approvals, if at all. We have initiated the process for FDA approval for one adoptive cell therapy product. We will not be able to commercialize any of our potential products until we obtain FDA approval, and so any delay in obtaining, or inability to obtain, FDA approval would harm our business.

If we fail to comply with regulatory requirements at any stage, whether before or after marketing approval is obtained, we may face a number of regulatory consequences, including refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold or termination of clinical trials, warning letters, untitled letters, modification of promotional materials or labeling, provision of corrective information, imposition of post-market requirements including the need for additional testing, imposition of distribution or other restrictions under a REMS, product recalls, product seizures or detentions, refusal to allow imports or exports, total or partial suspension of production or distribution, FDA debarment, injunctions, fines, consent decrees, corporate integrity agreements, debarment from receiving government contracts, and new orders under existing contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, or civil or criminal penalties, including fines and imprisonment, and adverse publicity, among other adverse consequences. Additionally, we may not be able to obtain the labeling claims necessary or desirable for the promotion of our products. We may also be required to undertake post-marketing trials. In addition, if we or others identify side effects after any of our adoptive cell therapies are on the market, or if manufacturing problems occur, regulatory approval may be withdrawn, and reformulation of our products may be required.

We may not be able to license new technology from third parties.

An element of our intellectual property portfolio is to license additional rights and technologies from third parties, including the NIH and others. Our inability to license the rights and technologies that we have identified, or that we may in the future identify, could have a material adverse impact on our ability to complete the development of our products or to develop additional products. No assurance can be given that we will be successful in licensing any additional rights or technologies from third parties, including the NIH and others. Failure to obtain additional rights and licenses may detrimentally affect our planned development of additional product candidates and could increase the cost, and extend the timelines associated with our development of such other products.

Our projections regarding the market opportunities for our product candidates may not be accurate, and the actual market for our products may be smaller than we estimate.

Our projections of both the number of people who have the cancers we are targeting, as well as the subset of people with these cancers who are in a position to receive second- or third- line therapy, and who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research by third parties, and may prove to be incorrect. Further, new studies or approvals of new therapeutics may change the estimated incidence or prevalence of these cancers. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates and may also be limited by the cost of our treatments and the reimbursement of those treatment costs by third-party payors. For instance, we expect lifileucel to initially target a small patient population that suffers from metastatic melanoma. Even if we obtain significant market share for our product candidates, because the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

We are required to pay substantial royalties and lump sum benchmark payments under our license agreements with the NIH, Moffitt, Novartis, and Cellectis, and we must meet certain milestones to maintain our license rights.

Under our license agreements with the NIH, Moffitt, Novartis, and Cellectis for our adoptive cell therapy and immunotherapy technologies, we are currently required to pay both substantial benchmark payments and royalties to that institution based on our revenues from sales of our products utilizing the licensed technologies. These payments could adversely affect the overall profitability for us of any products that we may seek to commercialize under these license agreements. In order to maintain our license rights under the NIH, Moffitt, Novartis, and Cellectis license agreements, we will need to meet certain specified milestones, subject to certain cure provisions, in the development of our product candidates. There is no assurance that we will be successful in meeting these milestones on a timely basis, or at all.

Because our current products represent, and our other potential product candidates will represent novel approaches to the treatment of disease, there are many uncertainties regarding the development, the market acceptance, third-party reimbursement coverage and the commercial potential of our product candidates.

Human immunotherapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there are many uncertainties related to development, marketing, reimbursement, and the commercial potential for our product candidates. There can be no assurance as to the length of the clinical trial period, the number of patients the FDA will require to be enrolled in the clinical trials in order to establish the safety, efficacy, purity and potency of immunotherapy products, or that the data generated in these clinical trials will be acceptable to the FDA to support marketing approval. The FDA may take longer than usual to come to a decision on any BLA that we submit and may ultimately determine that there is not enough data, information, or experience with our product candidates to support an approval decision. The FDA may also require that we conduct additional post-marketing studies or implement risk management programs, such as REMS until more experience with our product candidates is obtained. Finally, after increased usage, we may find that our product candidates do not have the intended effect or have unanticipated side effects, potentially jeopardizing initial or continuing regulatory approval and commercial prospects.

We may also find that the manufacture of our product candidates is more difficult than anticipated, resulting in an inability to produce a sufficient amount of our product candidates for our clinical trials or, if approved, commercial supply. Moreover, because of the complexity and novelty of our manufacturing process, there are only a limited number of manufacturers who have the capability of producing our product candidates. Should any of our contract manufacturers no longer produce our product candidates, it may take us significant time to find a replacement, if we are able to find a replacement at all.

There is no assurance that the approaches offered by our products will gain broad acceptance among doctors or patients or that governmental agencies or third-party medical insurers will be willing to provide reimbursement coverage for proposed product candidates. Moreover, we do not have verifiable internal marketing data regarding the potential size of the commercial market for our product candidates, nor have we obtained current independent marketing surveys to verify the potential size of the commercial markets for our current product candidates or any future product candidates. Since our current product candidates and any future product candidates will represent novel approaches to treating various conditions, it may be difficult, in any event, to accurately estimate the potential revenues from these product candidates. Accordingly, we may spend significant capital trying to obtain approval for product candidates that have an uncertain commercial market. The market for any products that we successfully develop will also depend on the cost of the product.

We do not yet have sufficient information to reliably estimate what it will cost to commercially manufacture our current product candidates, and the actual cost to manufacture these products could materially and adversely affect the commercial viability of these products. Our goal is to reduce the cost of manufacturing and providing our therapies. However, unless we can reduce those costs to an acceptable amount, we may never be able to develop a commercially viable product. If we do not successfully develop and commercialize products based upon our approach or find suitable and economical sources for materials used in the production of our products, we will not become profitable, which would materially and adversely affect the value of our common stock.

Our TIL therapies and our other therapies may be provided to patients in combination with other agents provided by third parties. The cost of such combination therapy may increase the overall cost of therapy and may result in issues regarding the allocation of reimbursements between our therapy and the other agents, all of which may affect our ability to obtain reimbursement coverage for the combination therapy from governmental or private third-party medical insurers.

No assurance can be given that the Gen 2 manufacturing process we have selected will be FDA-compliant, more efficient and lower the cost to manufacture TIL products.

Pursuant to the CRADA, and in cooperation with our contract manufacturers and potentially other manufacturers, we have developed and are developing improved methods for the generating and selecting autologous TILs, and methods for large-scale production of autologous TILs that are in accord with current cGMP procedures. We have developed a new and more efficient TIL manufacturing process that we believe can be more efficient and cost effective, and in a more automated manner than previous processes. The production and control of the physical and/or chemical attributes of our products in a cGMP facility is subject to many uncertainties and difficulties. We have never manufactured our adoptive cell therapy product candidate on a commercial scale, nor have our partners. As a result, we cannot give any assurance that the Gen 2 process or any future process that we select will be a manufacturing process that can produce our products in compliance with the applicable regulatory requirements, at a cost or in quantities necessary to make them commercially viable. Moreover, we and our third-party manufacturers will have to continually adhere to current cGMP regulations enforced by the FDA through its facilities inspection program. If our facilities or any of the facilities of these manufacturers cannot demonstrate adequate assurance of compliance with FDA standards during a pre-approval inspection, the FDA approval of our products will not be granted. In complying with cGMP and foreign regulatory requirements, we and any of our third-party manufacturers will be obligated to expend time, money and effort in production, record-keeping and quality control to assure that our products meet applicable specifications and other requirements. If we or any of our third-party manufacturers fail to comply with these requirements, we may be subject to regulatory action. No assurance can be given that we will be able to develop such a manufacturing process, or that our partners will thereafter be able to establish and operate such a production facility.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. Large judgements have also been awarded in class action lawsuits based on therapeutics that had unanticipated side effects. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation;
- withdrawal of clinical trial participants or sites and potential termination of clinical trial sites or entire clinical programs;
- initiation of investigations by regulators, refusal to approve marketing applications or supplements, and withdrawal or limitation of product approvals;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to clinical trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- significant negative media attention;

- decrease in the price of our stock and overall value of our company;
- exhaustion of our available insurance coverage and our capital resources; or
- the inability to commercialize our product candidates.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with corporate collaborators. Our insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. While we have obtained clinical trial insurance for our Phase 2 clinical trials, we may have to pay amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

We face significant competition from other biotechnology and pharmaceutical companies and from non-profit institutions.

Competition in the field of cancer therapy is intense and is accentuated by the rapid pace of technological development. Research and discoveries by others may result in breakthroughs which may render our products obsolete even before they generate any revenue. There are products that are approved and currently under development by others that could compete with the products that we are developing. Many of our potential competitors have substantially greater research and development capabilities and approval, manufacturing, marketing, financial and managerial resources and experience than we do. Our competitors may:

- develop safer, more convenient or more effective immunotherapies and other therapeutic products;
- develop therapies that are less expensive or have better reimbursement from private or public payors;
- reach the market more rapidly, reducing the potential sales of our products; or
- establish superior proprietary positions.

Due to the promising clinical therapeutic effect of competitor therapies in clinical exploratory trials, we anticipate substantial direct competition from other organizations developing advanced T-cell therapies targeting patients who have received prior anti-PD-1/PD-L1 therapies. In particular, we expect to compete with other new therapies for our lead indications developed by companies such as Agenus, BeyondSpring, Bristol-Myers Squibb, Merck, Nektar Therapeutics, Checkmate Pharmaceuticals, Daiichi Sankyo, Eisai, Exelixis, Moderna, Mirati Therapeutics, OncoSec Medical, Replimune, Regeneron Pharmaceuticals, Seagen, and Genmab. We also may compete with other TIL therapies in development by companies such as Instil Bio, Achilles Therapeutics, KSQ Therapeutics, Obsidian Therapeutics, Immatics, TILT Biotherapeutics, WindMIL Therapeutics, GRIT Biotechnology, Lyell Immunopharma, Cellular Biomedicine Group, and others. We also may compete with therapies based on genetically engineered T-cell receptors rendered reactive against tumor-associated antigens prior to their administration to patients, as well as TIL therapies that are designed to be specific to neoantigens, including products developed by Adaptimmune Therapeutics, Alaunos Therapeutics, Intima Bioscience, Marker Therapeutics, Turnstone Biologics, Neogene, and others. To date, these technologies have been primarily applicable to hematologic malignancies, but their application in solid tumor indications may create competition with us. We may also face competition from immunotherapy treatments offered by companies such as Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Regeneron Pharmaceuticals, Roche, and BioNTech. We may also face competition from novel IL-2 treatments in development by Alkermes, Werewolf, Nektar Therapeutics, Merck, Sanofi, Neoleukin Therapeutics and others. Many of these companies and our other current and potential competitors have substantially greater research and development capabilities and financial, scientific, regulatory, manufacturing, marketing, sales, human resources, and experience than we do. Many of our competitors have several therapeutic products that have already been developed, approved and successfully commercialized, or are in the process of obtaining regulatory approval for their therapeutic products in the U.S. and internationally. Our competitors may obtain regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in competitors establishing a strong market position before we are able to enter the market.

Universities and public and private research institutions in the U.S. and Europe are also potential competitors. For example, a Phase 3 M14TIL clinical trial comparing TIL to standard ipilimumab in patients with metastatic melanoma is currently being conducted in Europe by the Netherlands Cancer Institute, the Copenhagen County Herlev University Hospital, and the University of Manchester. Results from the M14TIL clinical trial were presented at the European Society for Medical Oncology Congress in September 2022. While these universities and public and private research institutions primarily have educational objectives, they may develop proprietary technologies that lead to other FDA approved therapies or that secure patent protection that we may need for the development of our technologies and products.

Our lead product candidate lifileucel is a therapy for the treatment of metastatic melanoma and metastatic cervical cancer. Currently, there are numerous companies that are developing various alternate treatments for melanoma and cervical cancer, including patients that have progressed after prior treatment with checkpoint inhibitors and chemotherapy. Accordingly, lifileucel faces significant competition in the melanoma and cervical cancer treatment space from multiple companies. Even if we obtain regulatory approval for lifileucel, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our therapies. We may not be able to implement our business plan if the acceptance of our products is inhibited by price competition or the reluctance of physicians to switch from other methods of treatment to our product, or if physicians switch to other new therapies, drugs or biologic products or choose to reserve our product for use in limited circumstances.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We are dependent on third parties to support our research, development and manufacturing activities and, therefore, are subject to the efforts of these parties and our ability to successfully collaborate with these third parties.

As a result of our current strategy to outsource most of our manufacturing, we rely very heavily on third parties to perform for us the manufacturing of our products for our clinical trials. We also license a portion of our technology from others. We intend to rely upon our contract manufacturers to produce large quantities of materials needed for clinical trials and potentially product commercialization. Third party manufacturers may not be able to meet our needs with respect to timing, quantity or quality. If we are unable to contract for a sufficient supply of needed materials on acceptable terms, or if we should encounter delays or difficulties in our relationships with manufacturers, our clinical testing may be delayed, thereby delaying the submission of products for regulatory approval or the market introduction and subsequent sales of our products. Any such delay may lower our revenues and potential profitability.

In addition, in order to supplement our own efforts to improve TIL manufacturing and develop TIL therapies in new indications in clinical trials, we currently work and collaborate with government and academic research institutions, medical institutions and corporate partners such as the NCI, Moffitt, Cellectis, Yale University, the Ohio State University, and Novartis. We also intend to continue to enter into additional third-party collaborative agreements in the future. However, we may not be able to successfully negotiate any additional collaborative arrangements. If established, these relationships may not be scientifically or commercially successful, or may be unable to enroll patients, which has occurred in one of our prior collaborations. The success of these and future collaborations and joint development arrangements may be subject to numerous risks and uncertainties, including the inability or unwillingness of our partners to perform in the manner, or to the extent anticipated, and may also be subject to disagreements regarding the rights, interests, and performance of the counterparties under our licenses and development agreements. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercialization of the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority under the collaboration agreement.

With regard to future collaboration efforts, we face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and, an evaluation by the proposed collaborator of a number of similar or unique factors.

Collaborations with biopharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation. Any collaboration may pose a number of risks, including the following:

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product candidate or product;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- collaborators may be involved in a business combination, resulting in the decreased emphasis or termination of development or commercialization of any product candidate subject to the collaboration agreement; and
- termination of a collaboration agreement may make it more difficult to attract new collaborators and our and our products' or product candidates' reputation in the medical, business, and financial communities could be adversely affected.

If any third-party collaborator breaches or terminates its agreement with us or fails to conduct its activities in a timely manner, the commercialization of our products under development could be delayed or blocked completely. It is possible that our collaborators will change their strategic focus, pursue alternative technologies or develop alternative products, either on their own or in collaboration with others, as a means for developing treatments for the diseases targeted by our collaborative programs. The effectiveness of our collaborators in marketing our products will also affect our revenues and earnings.

Our collaborators will also be required to comply with the applicable regulatory requirements, and, as such, are subject to the same risks as we are. If they do not or are not able to comply with these requirements, we may not be able to use the data generated through their studies to support our future investigational or marketing applications. Collaborator noncompliance may also expose them and us to regulatory enforcement actions.

No assurance can be given that we will be able to successfully collaborate with our partners as anticipated and that our current or future collaborations and clinical trials will be completed as contemplated, support the regulatory approval of our current product candidates, or result in any viable additional product candidates. For instance, to the extent that these collaborators conduct their studies with manufacturing processes that are different than ours or product that is different than ours, the results generated from their studies may not be seen in our current or future studies that employ our manufacturing processes and the results generated from their studies may not support approval of our product candidates.

If we are unable to obtain or maintain suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

Development of a product candidate intended for use in combination with an already approved product may present more or different challenges than development of a product candidate for use as a single agent.

We are currently developing lifileucel as part of a regimen which uses IL-2. We and our collaborators are also clinical trialing TIL therapy along with other products, such as pembrolizumab, ipilimumab and nivolumab. The development of product candidates for use in combination with another product may present challenges. For example, the FDA may require us to use more complex clinical trial designs, in order to evaluate the contribution of each product and product candidate to any observed effects. It is possible that the results of these clinical trials could show that any positive results are attributable to the already approved product. Moreover, following product approval, the FDA may require that products used in conjunction with each other be cross labeled for combined use. Additionally, the FDA review process can be more complicated for combination products, and may result in delays, particularly if complex therapeutics are involved. To the extent that we do not have rights to already approved products, this may require us to work with another company to satisfy such a requirement. Moreover, developments related to the already approved products may impact our clinical trials for the combination as well as our commercial prospects should we receive marketing approval. Such developments may include changes to the approved product's safety or efficacy profile, changes to the availability of the approved product, and changes to the standard of care.

A Fast Track product designation, Breakthrough Therapy designation or other designation to facilitate product candidate development may not lead to faster development or a faster regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We were granted Fast Track designation by the FDA for lifileucel in metastatic melanoma and metastatic cervical cancer, as well as for lifileucel in combination with pembrolizumab in advanced melanoma. We were granted BTM, for lifileucel for metastatic cervical cancer and Regenerative Medicine Advanced Therapy, or RMAT, designation for lifileucel in advanced melanoma. We may seek Fast Track or Breakthrough designation for other of our current or future product candidates. Receipt of a designation to facilitate product candidate development is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for a designation, the FDA may disagree. In any event, the receipt of such a designation for a product candidate may not result in a faster development process, review, or approval compared to product candidates considered for approval under conventional the FDA procedures and does not assure ultimate marketing approval by the FDA. In addition, the FDA may later decide that the products no longer meet the designation conditions.

While lifileucel has received Orphan Drug Designation, or ODD, for melanoma stages IIB-IV and for cervical cancer patients with tumors greater than 2 cm, there is no guarantee that we will be able to maintain this designation, receive these designations for any of our other product candidates, or receive or maintain any corresponding benefits, including periods of exclusivity.

We received ODD in the U.S. for lifileucel to treat malignant melanoma stages IIB-IV and cervical cancer patients with tumors greater than 2 cm. We may also seek ODD for our other product candidates, as appropriate. ODD, however, may be lost if the indication for which we develop our designated product candidates does not meet the orphan criteria. Moreover, following product approval, orphan exclusivity may be lost if the FDA determines, among other reasons, that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. Even if we obtain orphan exclusivity, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition and the same product can be approved for different conditions. Even after an orphan product is approved, the FDA can subsequently approve a product containing the same principal molecular features for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer or more effective or makes a major contribution to patient care.

Moreover, the FDA may grant ODDs to multiple of the same products for the same indication. If another sponsor receives FDA approval for an ODD-designated product that is the same as our product candidates and intended for the same indication before we do, we would be prevented from launching our product in the U.S. for this indication for a period of at least 7 years.

In response to a court decision regarding the plain meaning of the exclusivity provision of the Orphan Drug Act, the FDA may undertake a reevaluation of aspects of its orphan drug regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business, financial condition, results of operations, and prospects could be harmed.

As a condition of approval, the FDA may require that we implement various post-marketing requirements and conduct post-marketing studies, any of which would require a substantial investment of time, effort, and money, and which may limit our commercial prospects.

As a condition of biologic licensing, the FDA is authorized to require that sponsors of approved BLAs implement various post-market requirements, including REMS and Phase 4 studies. For example, we reached an agreement with the FDA regarding a confirmatory trial to support full approval of lifileucel in post-anti-PD-1 advanced melanoma, which we refer to as TILVANCE-301. We began startup activities for the randomized Phase 3 TILVANCE-301 trial in the fourth quarter of 2022. If we receive approval of our product candidates, the FDA may determine that similar or additional post-approval requirements are necessary to ensure that our product candidates are safe, pure, and potent. To the extent that we are required to establish and implement any post-approval requirements, we will likely need to invest a significant amount of time, effort, and money. Such post-approval requirements may also limit the commercial prospects of our product candidates.

We may be unable to establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, if they are approved, and as a result, we may be unable to generate product revenues.

We currently have a small commercial team focused on our commercial strategy, but we do not have a commercial infrastructure for the marketing, sale, and distribution of biopharmaceutical products. If approved, in order to commercialize our products, we must build our marketing, sales, and distribution capabilities or make arrangements with third parties to perform these services, which will take time and require significant financial expenditures and we may not be successful in doing so. Even if we are able to effectively establish a sales force and develop a marketing and sales infrastructure, our sales force and marketing teams may not be successful in commercializing our current or future product candidates. To the extent we rely on third parties to commercialize any products for which we obtain regulatory approval, we would have less control over their sales efforts, and could be held liable if they failed to comply with applicable legal or regulatory requirements.

We have no prior experience in the marketing, sale, and distribution of biopharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure. The establishment and development of commercial capabilities, including a comprehensive healthcare compliance program, to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. We, or our collaborators, will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage, and retain marketing, sales and commercial support personnel. In the event we are unable to develop a commercial infrastructure, we may not be able to commercialize our current or future product candidates, which would limit our ability to generate product revenues. Factors that may inhibit our efforts to commercialize our current or future product candidates and generate product revenues include:

- if the COVID-19 pandemic continues or reoccurs it may negatively impact our ability to establish commercial operations, educate and interact with healthcare professionals, and successfully launch our product on a timely basis;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe our current or future product candidates;
- our inability to effectively oversee a geographically dispersed sales and marketing team;
- the costs and time associated with the initial and ongoing training of sales and marketing personnel on legal and regulatory compliance matters and monitoring their actions;
- an inability to secure adequate coverage and reimbursement by government and private health plans;
- the clinical indications for which the products are approved and the claims that we may make for the products;
- limitations or warnings, including distribution or use restrictions, contained in the products' approved labeling;
- any distribution and use restrictions imposed by the FDA or to which we agree as part of a mandatory REMS or voluntary risk management plan;
- liability for sales or marketing personnel who fail to comply with the applicable legal and regulatory requirements;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization or engaging a contract sales organization.

If our product candidates do not achieve broad market acceptance, the revenues that we generate from their sales will be limited.

We have never commercialized a product candidate for any indication. Even if our product candidates are approved by the appropriate regulatory authorities for marketing and sale, they may not gain acceptance among physicians, patients, third-party payors, and others in the medical community. If any product candidate for which we obtain regulatory approval does not gain an adequate level of market acceptance, we may not generate significant product revenues or become profitable. Market acceptance of our product candidates by the medical community, patients, and third-party payors will depend on a number of factors, some of which are beyond our control. For example, physicians are often reluctant to switch their patients and patients may be reluctant to switch from existing therapies even when new and potentially more effective or safer treatments enter the market.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of any of our product candidates will depend on a number of factors, including:

- the efficacy of our product candidates;
- the prevalence and severity of adverse events associated with such product candidates;
- the clinical indications for which the products are approved and the approved claims that we may make for the products;
- limitations or warnings contained in the approved product's FDA-required labeling, including potential limitations or warnings for such products that may be more restrictive than other competitive products;
- changes in the standard of care for the targeted indications for such product candidates;
- the relative difficulty of administration of such product candidates;
- cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies;
- the availability of adequate coverage or reimbursement by third parties, such as insurance companies and other healthcare payors, and by government healthcare programs, including Medicare and Medicaid;
- the extent and strength of our marketing and distribution of such product candidates;
- the safety, efficacy, and other potential advantages over, and availability of, alternative treatments already used or that may later be approved for any of our intended indications;
- distribution and use restrictions imposed by the FDA with respect to such product candidates or to which we agree as part of a mandatory risk evaluation and mitigation strategy or voluntary risk management plan;
- the timing of market introduction of such product candidates, as well as competitive products;
- our ability to offer such product candidates for sale at competitive prices;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the extent and strength of our third-party manufacturer and supplier support;
- the approval of other new products for the same indications;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Even if the medical community accepts that our product candidates are safe and effective for their approved indications, physicians and patients may not immediately be receptive to such product candidates and may be slow to adopt them as an accepted treatment of the approved indications. If our current or future product candidates are approved but do not achieve an adequate level of acceptance among physicians, patients, and third-party payors, we may not generate meaningful revenues from our product candidates, and we may not become profitable.

Our product candidates may face competition sooner than anticipated.

The enactment of the BPCIA created an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as "interchangeable" based on its similarity to an existing brand product. Under the BPCIA, the FDA cannot make an approval of an application for a biosimilar product effective until 12 years after the original branded product was approved under a BLA. Certain changes, however, and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the 12-year exclusivity period.

Our product candidates may qualify for the BPCIA's 12-year period of exclusivity. However, there is a risk that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not block companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Changes may also be made to this exclusivity period as a result of future legislation as there has been ongoing efforts to reduce the period of exclusivity. Even if we receive a period of BPCIA exclusivity for our first licensed product, if subsequent products do not include a modification to the structure of the product that impacts safety, purity, or potency, we may not receive additional periods of exclusivity for those products. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. Medicare Part B encourages use of biosimilars by paying the provider the same percentage of the reference product, average sale price, or ASP as a mark-up, regardless of which product is reimbursed. It is also possible that payors will give reimbursement preference to biosimilars even over reference biologics absent a determination of interchangeability.

We will need to obtain FDA approval of any proposed proprietary branded product names, and any failure or delay associated with such approval may adversely affect our business.

Any name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the U.S. Patent and Trademark Office, or USPTO. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies medical claims or contributes to an overstatement of efficacy. If the FDA objects to any of our proposed proprietary product names, we may be required to adopt alternative names for our product candidates. If we adopt alternative names, we would lose the benefit of any existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties, and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

Our internal computer systems, or those used by our contract research organizations or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our contract research organizations and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized and authorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event was to occur and cause interruptions in our operations, it could result in a disruption of our drug development programs. For example, the loss of clinical trial data from completed or ongoing clinical trials for a product candidate could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of any product candidates could be delayed.

We are dependent on information technology, systems, infrastructure and data.

We are dependent upon information technology systems, infrastructure and data. The multitude and complexity of our computer systems make them inherently vulnerable to service interruption or destruction, malicious intrusion and random attack. Likewise, data privacy or cybersecurity breaches by third parties, employees, contractors or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, or other business partners may be exposed to unauthorized persons or to the public. Cyberattacks are increasing in their frequency, sophistication and intensity. The Russia-Ukraine conflict may also increase cybersecurity risks on a global basis. Cyberattacks could include the deployment of harmful malware, denial-of-service, ransomware, social engineering and other means to affect service reliability and threaten data confidentiality, privacy, integrity and availability. Our business and technology partners face similar risks, and any security breach of their systems could adversely affect our security posture. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts, or the efforts of our partners and vendors, will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyberattacks and other cybersecurity related breaches.

Our business could be adversely affected by the effects of health epidemics, including the continued spread of the COVID-19 pandemic, in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or other business operations. The COVID-19 pandemic could materially affect our operations, including at our headquarters in San Carlos, California, at our manufacturing facility in Philadelphia, Pennsylvania, and at our clinical trial sites, as well as the business or operations of our other manufacturers, CROs or other third parties with whom we conduct business.

Our business could be adversely affected by health epidemics in regions where we have offices, manufacturing facilities, concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of clinical trial sites, third party manufacturers and CROs upon whom we rely. For example, starting in December 2019, a novel strain of coronavirus (“COVID-19”) was reported to have surfaced in Wuhan, China and has spread to multiple countries, including the U.S. and several European countries. In March 2020, the World Health Organization declared COVID-19 a global pandemic and the U.S. declared the COVID-19 pandemic a national emergency. Similarly, during that time, the State of California declared a state of emergency related to the spread of the COVID-19 pandemic and the health officers of six San Francisco Bay Area counties, including San Mateo County where our headquarters in San Carlos is located, issued shelter-in-place orders. In addition, on March 19, 2020, the Governor of California and the State Public Health Officer and Director of the California Department of Public Health ordered all individuals living in the State of California to stay at their place of residence for an indefinite period of time (subject to certain exceptions to facilitate authorized necessary activities) to mitigate the impact of the COVID-19 pandemic. Throughout 2020 and 2021, similar executive orders were issued by state and local governments, and states of emergency had been declared at the state and local level in most jurisdictions throughout the U.S. As recently as April 2022, ports and airports in Shanghai, China have been closed due to another outbreak of COVID-19, resulting in a lockdown of the city and disruption to export and import activities. In the U.S., many of these executive orders have been rescinded, however, the Company remains vigilant and continues to monitor the ongoing COVID-19 pandemic closely to determine if additional actions are required.

Quarantines, shelter-in-place and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, related to the COVID-19 pandemic or other infectious diseases could impact personnel at third-party manufacturing facilities in the U.S. and other countries, or the availability or cost of materials, which would disrupt our supply chain. In addition, our clinical trials may be affected by the COVID-19 pandemic. Clinical site initiation, patient enrollment and patient monitoring may be delayed due to prioritization of hospital resources toward the COVID-19 pandemic. Some sites may no longer be available to see patients for clinical trials. Some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Patients may also miss follow-up visits after receiving our therapies during our clinical trials, which may or may not be rectified by future patient visits and which may result in the exclusion of data from such patients from the clinical trial data. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to the virus that causes the COVID-19 pandemic and adversely impact our clinical trial operations. The COVID-19 pandemic may also affect our ability to recruit treatment-naïve patients into our clinical trials, because those patients may be more likely to seek standard of care therapies available at local treatment centers rather than enroll in a clinical trial at a larger hospital.

We continue to monitor the impact, if any, of the COVID-19 pandemic on our current and future operations, including our regulatory filing timelines and strategy as well as our preparation for commercial launch. Despite the wide-spread availability of COVID-19 vaccines, it is unclear the extent to which the COVID-19 pandemic (including future variants) will impact our business, results of operations, financial condition and our future strategic plans as future developments of the outbreak are highly uncertain and cannot be predicted. New information is constantly emerging concerning the severity of COVID-19 and the actions to contain COVID-19 or treat its impact, among others. As the COVID-19 pandemic continues for an extended period of time, and with travel, face to face interactions, and resources are not allowed or are severely limited, either by us or our contractors, including our CMOs, our regulatory strategy, BLA filing timelines, or commercial launch preparations may be negatively impacted. The COVID-19 pandemic may also impact the FDA and their ability to timely review our regulatory filings and conduct the pre-approval inspections necessary for ultimate approval of BLA. We cannot predict at this time whether and how FDA operations may be impacted at relevant times for our planned regulatory submissions.

Our failure to comply with international data protection laws and regulations could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

European Union, or EU, member states and other foreign jurisdictions, including Switzerland, the United Kingdom and Canada, have adopted data protection laws and regulations which impose significant compliance obligations on us. Moreover, the collection and use of personal health data in the EU, which was formerly governed by the provisions of the EU Data Protection Directive, was replaced with the EU General Data Protection Regulation, or the GDPR, in May 2018. The GDPR, which is wide-ranging in scope, imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and the use of third-party processors in connection with the processing of personal data.

The GDPR also imposes strict rules on the transfer of personal data out of the EU to the U.S., provides an enforcement authority and imposes large penalties for noncompliance, including the potential for fines of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. The GDPR requirements apply not only to third-party transactions, but also to transfers of information between us and our subsidiaries. The implementation of the GDPR has increased our responsibility and liability in relation to personal data that we process, including in clinical trials, and we may in the future be required to put in place additional mechanisms to ensure compliance with the GDPR, which could divert management's attention and increase our cost of doing business. In addition, new regulation or legislative actions regarding data privacy and security (together with applicable industry standards) may increase our costs of doing business. If we fail to comply with the data protection laws in any EU member country or other jurisdiction, the data protection authority of such country or other jurisdiction may, in addition to fines, impose sanctions on us, which may include a prohibition that prevents us from transferring and/or processing personal data of data subjects from such country or other jurisdiction for a duration determined by the sanctioning authority. Our inability to transfer and/or process personal data of data subjects could preclude us from conducting clinical trials of our products in the EU member country or other jurisdiction for the duration of the sanction. Our inability to conduct clinical trials in the EU member country or other jurisdiction for the duration of the sanction may delay and increase the cost of development of our products, with a material adverse effect on our business. In this regard, we expect that there will continue to be new proposed laws, regulations and industry standards relating to privacy and data protection in the U.S., the EU and other jurisdictions, and we cannot determine the impact such future laws, regulations and standards may have on our business.

Our failure to comply with state and/or national data protection laws and regulations could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results.

There are numerous other laws and legislative and regulatory initiatives at the federal and state levels addressing privacy and security concerns, and some state privacy laws apply more broadly than the Health Insurance Portability and Accountability Act, or HIPAA, and associated regulations. For example, California recently enacted legislation, the California Consumer Privacy Act, or CCPA, which went into effect January 1, 2020, and was recently amended and expanded by the California Privacy Rights Act, or CPRA, which will take effect on January 1, 2023. The CCPA and CPRA, among other things, create new data privacy obligations for covered companies and provides new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also created a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach.

Although the law includes limited exceptions, including for certain information collected as part of clinical trials as specified in the law, it may regulate or impact our processing of personal information depending on the context. It remains unclear what, if any, additional modifications will be made to the CPRA by the California legislature or how it will be interpreted. Therefore, the effects of the CCPA and CPRA are significant and will likely require us to modify our data processing practices and may cause us to incur substantial costs and expenses to comply.

We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

Our operations are dependent upon the services of our executives and our employees who are engaged in research and development. The loss of the services of our executive officers or senior research personnel could delay our product development programs and our research and development efforts. In order to develop our business in accordance with our business plan, we will have to hire additional qualified personnel, including in the areas of research, manufacturing, clinical trials management, regulatory affairs, and sales and marketing. We are continuing our efforts to recruit and hire the necessary employees to support our planned operations in the near term.

For example, we continue to recruit for a new Chief Executive Officer. However, competition for qualified employees among companies in the biotechnology and biopharmaceutical industry is intense, and no assurance can be given that we will be able to attract, hire, retain and motivate the highly skilled employees that we need. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining, and motivating additional employees;
- managing our internal development efforts effectively, including the clinical and FDA review process for our product candidates, while complying with our contractual obligations to contractors and other third parties; and
- improving our operational, financial and management controls, reporting systems, and procedures.

Our future financial performance and our ability to commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services. There can be no assurance that the services of these independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality, compliance or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, if at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development, and commercialization goals on a timely basis, or at all.

If we engage in future acquisitions or strategic partnerships, this may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

We may evaluate various acquisitions and strategic partnerships, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- the issuance of our equity securities;
- assimilation of operations, intellectual property and products of an acquired company or product, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing product programs and initiatives in pursuing such a strategic merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

Depending on the size and nature of future strategic acquisitions, we may acquire assets or businesses that require us to raise additional capital or to operate or manage businesses in which we have limited experience. Making larger acquisitions that require us to raise additional capital to fund the acquisition will expose us to the risks associated with capital raising activities. Acquiring and thereafter operating larger new businesses will also increase our management, operating and reporting costs and burdens. In addition, if we undertake acquisitions, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. Moreover, we may not be able to locate suitable acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business. In addition, even if we are able to pursue certain strategic acquisition opportunities,

such as the anticipated acquisition of Proleukin®, we cannot guarantee that such acquisitions may be completed in a timely manner, if at all, or that all conditions necessary to consummate such transactions will be satisfied, including the receipt of all required regulatory approvals.

We are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by geopolitical instability, an ongoing military conflict between Russia and Ukraine, and record inflation. Our business, financial condition and results of operations could be materially adversely affected by any negative impact on the global economy and capital markets resulting from the conflict in Ukraine, geopolitical tensions or record inflation.

U.S. and global markets are experiencing volatility and disruption following the escalation of geopolitical tensions and the start of the military conflict between Russia and Ukraine. On February 24, 2022, a full-scale military invasion of Ukraine by Russian troops was reported. Although the length and impact of the ongoing military conflict is highly unpredictable, the conflict in Ukraine could lead to market disruptions, including significant volatility in commodity prices, credit and capital markets, as well as supply chain interruptions, which has led to record inflation globally. We are continuing to monitor inflation, the situation in Ukraine and global capital markets and assessing the potential impacts on our business.

The global economy has been, and may continue to be, negatively impacted by Russia's invasion of Ukraine. As a result of Russia's invasion of Ukraine, the U.S., the European Union, the United Kingdom, and other G7 countries, among other countries, have imposed substantial financial and economic sanctions on certain industry sectors and parties in Russia. Broad restrictions on exports to Russia have also been imposed. These measures include: (i) comprehensive financial sanctions against major Russian banks; (ii) additional designations of Russian individuals with significant business interests and government connections; (iii) designations of individuals and entities involved in Russian military activities; and (iv) enhanced export controls and trade sanctions limiting Russia's ability to import various goods. Russian military actions and the resulting sanctions could continue to adversely affect the global economy and financial markets and lead to instability and lack of liquidity in capital markets, potentially making it more difficult for us to obtain additional funds. Further, there are current geopolitical tensions with China. Recently, the Biden administration has signed multiple executive orders regarding China. One particular executive order titled Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy signed on September 12, 2022 will likely impact the pharmaceutical industry to encourage U.S. domestic manufacturing of pharmaceutical products. Any additional executive orders or potential sanctions with China could materially impact our current manufacturing partners.

Although our business has not been materially impacted by the ongoing military conflict between Russia and Ukraine, geopolitical tensions, or record inflation to date, it is impossible to predict the extent to which our operations, or those of our suppliers and manufacturers, will be impacted in the short and long term, or the ways in which the conflict may impact our business. The extent and duration of the conflict in Ukraine, geopolitical tensions, record inflation, sanctions and resulting market disruptions are impossible to predict, but could be substantial. Any such disruptions may also magnify the impact of other risks described herein.

We may rely on third parties to perform many essential services for any products that we commercialize, including services related to distribution, government price reporting, customer service, accounts receivable management, cash collection, and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize our current or future product candidates will be significantly impacted and we may be subject to regulatory sanctions.

We may retain third-party service providers to perform a variety of functions related to the sale and distribution of our current or future product candidates, key aspects of which will be out of our direct control. These service providers may provide key services related to distribution, customer service, accounts receivable management, and cash collection. If we retain a service provider, we would substantially rely on it as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired and we may be subject to regulatory enforcement action.

In addition, we may engage third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions.

Additionally, we may contract with a third-party to calculate and report pricing information mandated by various government programs. If a third party fails to timely report or adjust prices as required or errs in calculating government pricing information from transactional data in our financial records, it could impact our discount and rebate liability, and potentially subject us to regulatory sanctions or False Claims Act lawsuits.

Climate change or legal, regulatory or market measures to address climate change may negatively affect our business, results of operations, cash flows and prospects.

We believe that climate change has the potential to negatively affect our business and results of operations, cash flows and prospects. We are exposed to physical risks (such as extreme weather conditions or rising sea levels), risks in transitioning to a low-carbon economy (such as additional legal or regulatory requirements, changes in technology, market risk and reputational risk) and social and human effects (such as population dislocations and harm to health and well-being) associated with climate change. These risks can be either acute (short-term) or chronic (long-term).

The adverse impacts of climate change include increased frequency and severity of natural disasters and extreme weather events such as hurricanes, tornados, wildfires (exacerbated by drought), flooding, and extreme heat. Extreme weather and sea-level rise pose physical risks to our facilities as well as those of our suppliers. Such risks include losses incurred as a result of physical damage to facilities, loss or spoilage of inventory, and business interruption caused by such natural disasters and extreme weather events. Other potential physical impacts due to climate change include reduced access to high-quality water in certain regions and the loss of biodiversity, which could impact future product development. These risks could disrupt our operations and its supply chain, which may result in increased costs.

New legal or regulatory requirements may be enacted to prevent, mitigate, or adapt to the implications of a changing climate and its effects on the environment. These regulations, which may differ across jurisdictions, could result in us being subject to new or expanded carbon pricing or taxes, increased compliance costs, restrictions on greenhouse gas emissions, investment in new technologies, increased carbon disclosure and transparency, upgrade of facilities to meet new building codes, and the redesign of utility systems, which could increase our operating costs, including the cost of electricity and energy used by us. Our supply chain would likely be subject to these same transitional risks and would likely pass along any increased costs to us.

Environmental, social and governance matters may impact our business and reputation.

Governmental authorities, non-governmental organizations, customers, investors, external stakeholders and employees are increasingly sensitive to environmental, social and governance, or ESG, concerns, such as diversity and inclusion, climate change, water use, recyclability or recoverability of packaging, and plastic waste. This focus on ESG concerns may lead to new requirements that could result in increased costs associated with developing, manufacturing and distributing our products. Our ability to compete could also be affected by changing customer preferences and requirements, such as growing demand for more environmentally friendly products, packaging or supplier practices, or by failure to meet such customer expectations or demand. While we strive to improve our ESG performance, we risk negative stockholder reaction, including from proxy advisory services, as well as damage to our brand and reputation, if we do not act responsibly, or if we are perceived to not be acting responsibly in key ESG areas, including equitable access to medicines and vaccines, product quality and safety, diversity and inclusion, environmental stewardship, support for local communities, corporate governance and transparency, and addressing human capital factors in our operations. If we do not meet the ESG expectations of our investors, customers and other stakeholders, we could experience reduced demand for our products, loss of customers, and other negative impacts on our business and results of operations.

Risks Related to Government Regulation

The FDA regulatory approval process is lengthy and time-consuming, and we may experience significant delays in the clinical development and regulatory approval of our product candidates.

We have recently commenced our first submission of a rolling BLA to the FDA for lifileucel in August 2022 and expect to complete the BLA submission in the first quarter of 2023. A BLA must include extensive preclinical and clinical data and supporting information to establish the product candidate's safety and effectiveness for each desired indication. Our BLA submission and current expected timelines for our lifileucel product candidate for the treatment of metastatic melanoma are based on our interpretation of communications received from the FDA to date regarding this product candidate and are subject to revision if additional communications are received from the FDA.

Following our End of Phase 2 meeting with the FDA in June 2019, we increased enrollment in Cohort 1 of our ongoing C-145-04 clinical trial of TIL therapy lifileucel to at least 75 patients of the appropriate population to address the expected sample size in anticipation of a BLA submission in 2021. Additionally, the patient population was defined per the discussion with FDA as patients who have progressed following initial systemic therapy for recurrent or metastatic disease which include many of the more advanced patients enrolled to date. In January 2021, we announced that Cohort 2 of the C-145-04 clinical trial had completed enrollment and that the landscape of care for cervical cancer patients had changed because of a recent FDA approval for pembrolizumab in the frontline cervical cancer setting. In August 2022 we announced that following FDA discussions and feedback on a registration strategy to address the shift in frontline standard of care, we reopened Cohort 2 of the ongoing C-145-04 clinical trial to enroll additional patients. The expanded Cohort 2 is intended to support a BLA submission in cervical cancer following progression on or after chemotherapy and PD-1 therapy. Our current beliefs regarding the registration pathway for the lifileucel product candidate in metastatic cervical cancer are based on our interpretation of communications with the FDA to date and our efforts to address such communications, which may be incorrect. Our statements that the clinical trial may support a BLA submission also assume that our as-adjusted clinical trial has addressed the additional requests and feedback by the FDA. Further, enrollment in this clinical trial may need to be further adjusted based on future feedback from the FDA, changes in the competitive environment, or other regulatory agency input. Protocol revisions may have an adverse effect on the results reported to date. Changes to implement an independent review committee and assay validation and implementation, and the data within this clinical trial may not ultimately be supportive of product approval, all of which could result in significant delays to our currently anticipated timeline for development and approval of lifileucel product candidate or prevent its approval for the treatment of cervical cancer.

A BLA must also include significant information regarding the chemistry, manufacturing and controls for the product. We expect the novel nature of our product candidates to create further challenges in obtaining regulatory approval. For example, the FDA has limited experience with commercial development of cell therapies for cancer. We may also not be able to successfully utilize the BTD or RMAT designations we have received for metastatic cervical cancer and advanced melanoma, respectively, to successfully complete the development and commercialization of lifileucel. We may not be able to reach agreement with FDA on an interpretation of outcomes from our meetings, including meetings we have held with FDA in relation to our C-145-04 and C-144-01 clinical trials and future meetings. For example, on October 5, 2020, we reported the submission of additional potency assay data to the FDA, and at the same time, we also announced that we had reached agreement with the FDA on the minimum duration of follow up for Cohort 4 to support our BLA submission for lifileucel in the treatment of metastatic melanoma. In May 2021, we announced that we had received regulatory feedback from the FDA regarding our potency assays for lifileucel. Following FDA feedback, we continued our work developing and validating our potency assays and engaged in discussions with the FDA during the second half of 2021 and the first quarter of 2022. Based on the FDA feedback we received from these discussions, we held a pre-BLA meeting in July 2022, and initiated a rolling BLA for lifileucel in metastatic melanoma in August 2022, which we plan to complete in the first quarter of 2023. In addition, as previously disclosed, Iovance plans to open a confirmatory Phase 3 clinical trial of lifileucel in combination with pembrolizumab in frontline metastatic melanoma in late 2022. The FDA previously granted Fast Track Designation for lifileucel in combination with pembrolizumab for the treatment of immune checkpoint inhibitor naïve metastatic melanoma. However, the regulatory approval pathway for our product candidates may be uncertain, complex, expensive and lengthy, and approval may not be obtained.

We may also experience delays, including delays arising from the need to increase enrollment, in completing planned clinical trials for a variety of reasons, including delays related to:

- the availability of financial resources to commence and complete the planned clinical trials;
- reaching agreement on acceptable contract terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- obtaining approval at each clinical trial site by an independent IRB, or central IRB;
- recruiting suitable patients to participate in a clinical trial;
- having patients complete a clinical trial or return for post-treatment follow-up;
- clinical trial sites deviating from clinical trial protocol or dropping out of a clinical trial;
- adding new clinical trial sites;
- manufacturing sufficient quantities of qualified materials under cGMPs and applying them on a subject-by-subject basis for use in clinical trials; or
- timely implementing or validating changes to our manufacturing or quality control processes and methods needed to address FDA feedback.

We could also encounter delays if there are unresolved ethical issues associated with physicians enrolling patients in clinical trials of our product candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, the IRBs for the institutions in which such clinical trials are being conducted by the FDA or other regulatory authorities, or recommended for suspension or termination by DSMBs due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or clinical trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, including as a result of genetic editing methods, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience termination of, or delays in the completion of, any clinical trial of our product candidates, the commercial prospects for our product candidates will be harmed, and our ability to generate product revenue will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenue.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

In order to market and sell our products outside the U.S., we or our third-party collaborators may be required to obtain separate marketing approvals and comply with numerous and varying regulatory requirements. Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, while a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. Approval policies and requirements may vary among jurisdictions. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the U.S., including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the U.S., a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval. We or our collaborators may not be able to file for regulatory approval of our product candidates in international jurisdictions or obtain approvals from regulatory authorities outside the U.S. on a timely basis, if at all.

We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the U.S. have requirements for approval of product candidates with which we must comply prior to marketing in those jurisdictions. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

We are, and if we receive regulatory approval of our product candidates, will continue to be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

Any regulatory approvals that we receive for our product candidates will require ongoing surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS to approve our product candidates, which could entail requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA may also require post-approval Phase 4 studies. Moreover, the FDA and comparable foreign regulatory authorities will continue to closely monitor the safety profile of any product even after approval. If the FDA or comparable foreign regulatory authorities become aware of new safety information after approval of any of our product candidates, they may withdraw approval, require labeling changes or establishment of a REMS or similar strategy, impose significant restrictions on a product's indicated uses or marketing, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. Any such restrictions could limit sales of the product.

In addition, we, our contractors, and our collaborators are and will remain responsible for FDA compliance, including requirements related to product design, testing, clinical trials and preclinical studies approval, manufacturing processes and quality, labeling, packaging, distribution, adverse event and deviation reporting, storage, advertising, marketing, promotion, sale, import, export, submissions of safety and other post-marketing information and reports such as deviation reports, establishment registration, product listing, annual user fees, and recordkeeping for our product candidates.

We and any of our collaborators, including our contract manufacturers, could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with regulatory requirements. Application holders must further notify the FDA, and depending on the nature of the change, obtain FDA pre-approval for product and manufacturing changes. The cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Later discovery of previously unknown problems with our product candidates, including adverse events of unanticipated severity or frequency, that the product is less effective than previously thought, problems with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing, distribution, or manufacturing of our product candidates, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- restrictions on the labeling of our product candidates, including required additional warnings, such as black box warnings, contraindications, precautions, and restrictions on the approved indication or use;
- modifications to promotional pieces;
- changes to product labeling or the way the product is administered;
- liability for harm caused to patients or subjects;
- fines, restitution, disgorgement, warning letters, untitled letters, or holds on or termination of clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- product seizure or detention, or refusal to permit the import or export of our product candidates;
- injunctions or the imposition of civil or criminal penalties, including imprisonment;
- FDA debarment, debarment from government contracts, and refusal of future orders under existing contracts, exclusion from federal healthcare programs, consent decrees, or corporate integrity agreements;
- regulatory authority issuance of safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about the biologic;
- reputational harm; or
- the product becoming less competitive.

Any of these events could further have other material and adverse effects on our operations and business and could adversely impact our stock price and could significantly harm our business, financial condition, results of operations, and prospects.

The FDA's and other regulatory authorities' policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the U.S. or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, be subject to other regulatory enforcement action, and we may not achieve or sustain profitability.

If we fail to comply with federal and state healthcare and promotional laws, including fraud and abuse and information privacy and security laws, we could face substantial penalties and our business, financial condition, results of operations, and prospects could be adversely affected.

As a biopharmaceutical company, we are subject to many federal and state healthcare laws, including the federal AKS, the federal civil and criminal FCA, the civil monetary penalties statute, the Medicaid Drug Rebate statute and other price reporting requirements, the Veterans Health Care Act of 1992, the federal Health Insurance Portability and Accountability Act of 1996 (as amended by the Health Information Technology for Economics and Clinical Health Act), the Foreign Corrupt Practices Act of 1977, the Patient Protection and Affordable Care Act of 2010, and similar state laws. Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid, or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. If we do not comply with all applicable fraud and abuse laws, we may be subject to enforcement by both the federal government and the states in which we conduct our business.

Laws and regulations require calculation and reporting of complex pricing information for prescription drugs, and compliance will require us to invest in significant resources and develop a price reporting infrastructure or depend on third parties to compute and report our drug pricing. Pricing reported to CMS must be certified. Non-compliant activities expose us to FCA risk if they result in overcharging agencies, underpaying rebates to agencies, or causing agencies to overpay providers.

If we or our operations are found to be in violation of any federal or state healthcare law, or any other governmental regulations that apply to us, we may be subject to penalties, including civil, criminal, and administrative penalties, damages, fines, disgorgement, debarment from government contracts, refusal of orders under existing contracts, exclusion from participation in U.S. federal or state health care programs, corporate integrity agreements, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, they may be subject to criminal, civil, or administrative sanctions, including but not limited to, exclusions from participation in government healthcare programs, which could also materially affect our business.

In particular, if we are found to have impermissibly promoted any of our product candidates, we may become subject to significant liability and government fines. We, and any of our collaborators, must comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain marketing approval. Promotional communications with respect to therapeutics are subject to a variety of legal and regulatory restrictions and continuing review by the FDA, Department of Justice, Department of Health and Human Services' Office of Inspector General, state attorneys general, members of Congress, and the public. When the FDA or comparable foreign regulatory authorities issue regulatory approval for a product candidate, the regulatory approval is limited to those specific uses and indications for which a product is approved. If we are not able to obtain FDA approval for desired uses or indications for our products and product candidates, we may not market or promote our products for those indications and uses, referred to as off-label uses, and our business may be adversely affected. We further must be able to sufficiently substantiate any claims that we make for our products including claims comparing our products to other companies' products and must abide by the FDA's strict requirements regarding the content of promotion and advertising.

While physicians may choose to prescribe products for uses that are not described in the product's labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications and uses that are not specifically approved by the FDA. These off-label uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the U.S. generally do not restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by biopharmaceutical companies concerning off-label use.

The FDA and other agencies actively enforce the laws and regulations regarding product promotion, particularly those prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted a product may be subject to significant sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees of permanent injunctions under which specified promotional conduct is changed or curtailed. Thus, we and any of our collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In the U.S., engaging in the impermissible promotion of our products, following approval, for off-label uses can also subject us to false claims and other litigation under federal and state statutes, including fraud and abuse and consumer protection laws, which can lead to civil and criminal penalties and fines, agreements with governmental authorities that materially restrict the manner in which we promote or distribute therapeutic products and do business through, for example, corporate integrity agreements, suspension or exclusion from participation in federal and state healthcare programs, and debarment from government contracts and refusal of future orders under existing contracts. These false claims statutes include the federal civil False Claims Act, which allows any individual to bring a lawsuit against a biopharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing others to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government decides to intervene and prevails in the lawsuit, the individual will share in the proceeds from any fines or settlement funds. If the government declines to intervene, the individual may pursue the case alone. These False Claims Act lawsuits against manufacturers of drugs and biologics have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements, up to \$3.0 billion, pertaining to certain sales practices and promoting off-label uses. In addition, False Claims Act lawsuits may expose manufacturers to follow-on claims by private payors based on fraudulent marketing practices. This growth in litigation has increased the risk that a biopharmaceutical company will have to defend a false claim action, pay settlement fines or restitution, as well as criminal and civil penalties, agree to comply with burdensome reporting and compliance obligations, and be excluded from Medicare, Medicaid, or other federal and state healthcare programs. If we or our future collaborators do not lawfully promote our approved products, if any, we may become subject to such litigation and, if we do not successfully defend against such actions, those actions may have a material adverse effect on our business, financial condition, results of operations and prospects.

Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Moreover, achieving and sustaining compliance with applicable federal and state fraud laws may prove costly. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.

In both domestic and foreign markets, sales of our product candidates, if approved, depend on the availability of coverage and adequate reimbursement from third-party payors. Such third-party payors include government health programs such as Medicare and Medicaid, managed care providers, private health insurers, and other organizations. In addition, because our product candidates represent new approaches to the treatment of cancer, we cannot accurately estimate the potential revenue from our product candidates.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Obtaining coverage and adequate reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance.

Government authorities and third-party payors decide which drugs and treatments they will cover and the amount of reimbursement. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. If reimbursement is not available, or is available only to limited levels, our product candidates may be competitively disadvantaged, and we, or our collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or our collaborators, to establish or maintain a market share sufficient to realize a sufficient return on our or their investments. Alternatively, securing favorable reimbursement terms may require us to compromise pricing and prevent us from realizing an adequate margin over cost. Reimbursement by a third-party payor may depend upon a number of factors, including, but not limited to, the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical and cost-effectiveness data for the use of our products. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Moreover, the factors noted above have continued to be the focus of policy and regulatory debate that has, thus far, shown the potential for movement towards permanent policy changes; this trend is apt to continue, and may result in more or less favorable impacts on pricing. Patients are unlikely to use our product candidates unless coverage is provided, and reimbursement is adequate to cover a significant portion of the cost of our product candidates.

In the U.S., no uniform policy of coverage and reimbursement for products exists among third-party payors. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained.

Prices paid for a drug also vary depending on the class of trade. Prices charged to government customers are subject to price controls, including ceilings, and private institutions obtain discounts through group purchasing organizations. Net prices for drugs may be further reduced by mandatory discounts or rebates required by government healthcare programs and demanded by private payors. It is also not uncommon for market conditions to warrant multiple discounts to different customers on the same unit, such as purchase discounts to institutional care providers and rebates to the health plans that pay them, which reduces the net realization on the original sale.

In addition, federal programs impose penalties on manufacturers of drugs marketed under an NDA or BLA, in the form of mandatory additional rebates and/or discounts if commercial prices increase at a rate greater than the Consumer Price Index-Urban, and these rebates and/or discounts, which can be substantial, may impact our ability to raise commercial prices. Regulatory authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of our collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of our collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost control initiatives could cause us, or our collaborators, to decrease, discount, or rebate a portion of the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the realized prices for our products, if any, decrease or if governmental and other third-party payors do not provide adequate coverage or reimbursement, our prospects for revenue and profitability will suffer. Moreover, the recent and ongoing series of congressional hearings relating to drug pricing has presented heightened attention to the biopharmaceutical industry, creating the potential for political and public pressure, while the potential for resulting legislative or policy changes presents uncertainty.

Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. If payors subject our product candidates to maximum payment amounts or impose limitations that make it difficult to obtain reimbursement, providers may choose to use therapies which are less expensive when compared to our product candidates. Additionally, if payors require high copayments, beneficiaries may decline prescriptions and seek alternative therapies. We may need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to the satisfaction of hospitals and other target customers and their third-party payors. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We, and our collaborators, cannot be sure that coverage will be available for any product candidate that we, or they, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any our product candidates for which we obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

There have been, and likely will continue to be, legislative and regulatory proposals at the federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability. A particular challenge for our product candidates arises from the fact that they will primarily be used in an inpatient setting. Inpatient reimbursement generally relies on stringent packaging rules that may mean that there is no separate payment for our product candidates. Additionally, data used to set the payment rates for inpatient admissions is usually several years old and would not take into account all of the additional therapy costs associated with the administration of our product candidates. If special rules are not created for reimbursement for immunotherapy treatments such as our product candidates, hospitals might not receive enough reimbursement to cover their costs of treatment, which will have a negative effect on their adoption of our product candidates.

We are subject to new legislation, regulatory proposals, and healthcare payor initiatives that may increase our costs of compliance, and adversely affect our ability to market our products, obtain collaborators, and raise capital.

In the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, and affect our ability, or the ability of our collaborators, to profitably sell any products for which we obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or our collaborators, may receive for any approved products.

Since enactment of the Patient Protection and Affordable Care Act, as amended (the “ACA”) in 2010, in both the U.S. and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect on April 1, 2013, and were to remain in effect until 2024. The Bipartisan Budget Act of 2015 extended the 2% sequestration to 2025. In January 2013, the American Taxpayer Relief Act of 2012, or ATRA, was approved which, among other things, reduced Medicare payments to several providers, with primary focus on the hospital outpatient setting and ancillary services, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On January 20, 2017, the new administration signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices, and, for that reason, some final regulations have yet to take effect. In December 2017, Congress repealed the individual mandate for health insurance required by the ACA and could consider further legislation to repeal other elements of the ACA. At the end of 2017, CMS promulgated regulations that reduce the amount paid to hospitals for outpatient drugs purchased under the 340B program, and some states have enacted transparency laws requiring manufacturers to report information on drug prices and price increases. In June 2021, the Supreme Court issued its opinion in *California v. Texas*, upholding the constitutionality of the ACA.

Additional federal and state healthcare reform measures may be adopted in the future that may result in more rigorous coverage criteria, increased regulatory burdens and operating costs, decreased net revenue from our pharmaceutical products, decreased potential returns from our development efforts, and additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products.

Legislative and regulatory proposals may also be made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance, or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by Congress of the FDA’s approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

In addition, there have been a number of other policy, legislative and regulatory proposals aimed at changing the pharmaceutical industry. The U.S. government, state legislatures and foreign governmental entities have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and coverage and requirements for substitution of generic products for branded prescription drugs. Adoption of government controls and measures and tightening of restrictive policies in jurisdictions with existing controls and measures, could exclude or limit our product candidates from coverage and limit payments for pharmaceuticals. Under the Biden Administration’s Build Back Better Agenda, for example, Medicare negotiation of prescription drug costs with biopharmaceutical companies is proposed to lower prescription drug costs. We continue to monitor the potential impact of these and other proposals to lower prescription drug costs at the federal and state level.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We are unable to predict the future course of federal or state healthcare legislation in the U.S. directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. The ACA and any further changes in the law or regulatory framework that reduce our revenue or increase our costs could also have a material and adverse effect on our business, financial condition and results of operations.

Governments outside the U.S. tend to impose strict price controls, which may adversely affect our revenues, if any.

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the EU and the United Kingdom, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be available, or that the third-party payors' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of employee fraud or other illegal activity by our employees, independent contractors, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to: comply with the laws of the FDA and other similar foreign regulatory bodies, provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies, comply with manufacturing standards we have established, comply with healthcare fraud and abuse laws in the U.S. and similar foreign fraudulent misconduct laws, or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the U.S., our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials.

We have adopted a Code of Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent inappropriate conduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with such laws or regulations. Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our, or our employees', consultants', collaborators', contractors', or vendors' business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, compliance agreements, withdrawal of product approvals, and curtailment of our operations, among other things, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the U.S. will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Risks Related to Our Intellectual Property

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, or lawsuits accusing our products of patent infringement, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one or more of our patents is not valid or is unenforceable or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable, or interpreted narrowly and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may be enjoined from manufacturing, use, and marketing our products, or may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. Patent and Trademark Office, or USPTO, and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may incur substantial costs as a result of litigation or other proceedings relating to patent and other intellectual property rights.

The cost to us of any litigation or other proceeding relating to intellectual property rights, even if resolved in our favor, could be substantial. Some of our competitors may be better able to sustain the costs of complex patent litigation because they have substantially greater resources. If there is litigation against us, we may not be able to continue our operations.

Should third parties file patent applications or be issued patents claiming technology also used or claimed by us, we may be required to participate in interference proceedings in the USPTO to determine priority of invention. We may be required to participate in interference proceedings involving our issued patents and pending applications. We may be required to cease using the technology or to license rights from prevailing third parties as a result of an unfavorable outcome in an interference proceeding. A prevailing party in that case may not offer us a license on commercially acceptable terms.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court or the USPTO.

If we or one of our licensing partners initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate, as applicable, is invalid and/or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity and/or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). For example, on November 24, 2021, an opposition proceeding was initiated in the European Patent Office against our European Patent No. 3601533 B1. This opposition proceeding, or any similar proceedings that may arise in the U.S. or foreign jurisdictions, could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we, our patent counsel and the patent examiner were unaware during prosecution. If a defendant or third party were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection could have a material adverse impact on our business.

If we are unable to protect our proprietary rights, we may not be able to compete effectively or operate profitably.

Our success is dependent in part on maintaining and enforcing the patents and other proprietary rights that we have licensed and may develop, and on our ability to avoid infringing the proprietary rights of others. Certain of our intellectual property rights are licensed from another entity, and as such the preparation and prosecution of these patents and patent applications was not performed by us or under our control. Furthermore, patent law relating to the scope of claims in the biotechnology field in which we operate is still evolving and, consequently, patent positions in our industry may not be as strong as in other more well-established fields. The patent positions of biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date.

The issuance of a patent is not conclusive as to its validity or enforceability and it is uncertain how much protection, if any, will be given to the patents we have licensed from the NIH, Moffitt, or MDACC if any of these parties, or we, attempt to enforce the patents and/or if they are challenged in court or in other proceedings, such as oppositions, which may be brought in foreign jurisdictions to challenge the validity of a patent. A third party may challenge the validity or enforceability of a patent after its issuance by the Patent Office. It is possible that a competitor may successfully challenge our patents or that a challenge will result in limiting their coverage. Moreover, the cost of litigation to uphold the validity of patents and to prevent infringement can be substantial. If the outcome of litigation is adverse to us, third parties may be able to use our patented invention without payment to us. Moreover, it is possible that competitors may infringe our patents or successfully avoid the patented technology through design innovation. To stop these activities, we may need to file a lawsuit. These lawsuits are expensive and would consume time and other resources, even if we were successful in stopping the violation of our patent rights. In addition, there is a risk that a court would decide that our patents are not valid and that we do not have the right to stop the other party from using the inventions. There is also the risk that, even if the validity of our patents were upheld, a court would refuse to stop the other party on the grounds that its activities are not covered by, that is, do not infringe, our patents.

Should third parties file patent applications, or be issued patents claiming technology also used or claimed by our licensor(s) or by us in any future patent application, we may be required to participate in interference proceedings in the USPTO to determine priority of invention for those patents or patent applications that are subject to the first-to-invent law in the U.S., or may be required to participate in derivation proceedings in the USPTO for those patents or patent applications that are subject to the first-inventor-to-file law in the U.S. We may be required to participate in such interference or derivation proceedings involving our issued patents and pending applications. We may be required to cease using the technology or to license rights from prevailing third parties as a result of an unfavorable outcome in an interference proceeding or derivation proceeding. A prevailing party in that case may not offer us a license on commercially acceptable terms.

We cannot prevent other companies from licensing most of the same intellectual properties that we have licensed or from otherwise duplicating our business model and operations.

Certain intellectual properties that we are using to develop TIL-based cancer therapy products were licensed to us by the NIH. The issued or pending patents that the NIH licensed to us are exclusive, and specific with respect to melanoma, breast, HPV-associated, bladder and lung cancers. No assurance can be given that the NIH has not previously licensed, or that the NIH hereafter will not license to other biotechnology companies some or all of the non-exclusive technologies available to us under the NIH License Agreement. In addition, one pending U.S. patent application in the NIH License Agreement is not owned solely by the NIH. No assurance can be given that NIH's co-owner of the certain pending U.S. patent application in the NIH License Agreement has not previously licensed, or that the co-owner thereafter will not license, to other biotechnology companies some or all of the technologies available to us. Co-ownership of these intellectual properties will create issues with respect to our ability to enforce the intellectual property rights in courts and will create issues with respect to the accountability of one entity with respect to the other.

Since the NCI, Moffitt, MDACC, and others already use TIL therapy for the treatment of metastatic melanoma and other indications, their methods and data are also available to third parties, who may want to enter into our line of business and compete against us. Other than the Gen 2 manufacturing process, we currently do not own any exclusive rights on our entire product portfolio that could be used to prevent third parties from duplicating our business plan or from otherwise directly competing against us. While additional technologies that may be developed under our CRADA may be licensed to us on an exclusive basis, no assurance can be given that our existing exclusive rights and will be sufficient to prevent others from competing with us and developing substantially similar products.

The use of our technologies could potentially conflict with the rights of others.

Our potential competitors or others may have or acquire patent rights that they could enforce against us. If they do so, then we may be required to alter our products, pay licensing fees or cease activities. If our products conflict with patent rights of others, third parties could bring legal actions against us or our collaborators, licensees, suppliers or customers, claiming damages and seeking to enjoin manufacturing, use and marketing of the affected products. If these legal actions are successful, in addition to any potential liability for damages (including treble damages and attorneys' fees for willful infringement), we could be required to obtain a license to continue manufacturing, promoting the use or marketing the affected products. We may not prevail in any legal action and a required license under the patent may not be available on acceptable terms or at all.

We have conducted an extensive freedom-to-operate, or FTO, analyses of the patent landscape with respect to our lead product candidates. Although we continue to undertake FTO analyses of our manufacturing processes, our lead TIL products, and contemplated future processes and products, because patent applications do not publish for 18 months, and because the claims of patent applications can change over time, no FTO analysis can be considered exhaustive. Furthermore, patent and other intellectual property rights in biotechnology remains an evolving area with many risks and uncertainties. As such, we may not be able to ensure that we can market our product candidates without conflict with the rights of others.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other cell therapy and biopharmaceutical companies, our success is dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the U.S. has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. While we do not believe that any of the patents owned or licensed by us will be found invalid based on this decision, we cannot predict how future decisions by the courts, the U.S. Congress or the USPTO may impact the value of our patents.

We have limited foreign intellectual property rights and may not be able to protect our intellectual property rights throughout the world.

We have limited intellectual property rights outside the U.S. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the U.S. can be less extensive than those in the U.S. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the U.S. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biopharmaceutical products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties and our employees and contractors. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former employers. Litigation may be necessary to defend against or pursue these claims. For example, we are currently engaged in litigation involving counterclaims that we have brought relating to theft of certain of our trade secrets, breach of confidentiality, and related counterclaims. Even if we are successful in resolving these claims, litigation could result in substantial cost and be a distraction to our management and employees.

Risks Related to Our Securities

Our officers, directors and principal stockholders own a substantial percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our officers, directors, and principal stockholders currently beneficially own a substantial portion of our outstanding voting stock. Therefore, these stockholders have the ability and may continue to have the ability to influence our corporate decision making. Given current ownership levels, these stockholders may be able to determine some or all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control or influence elections of directors, amendments to our certificate of incorporation or bylaws, or approval of any merger, sale of assets, or other major corporate transaction. This level of control may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

Our stock price may be volatile, and our stockholders' investment in our stock could decline in value.

The market price of our common stock is likely to be volatile and could fluctuate widely in response to many factors, including but not limited to:

- volatility and instability in the capital markets due to the COVID-19 pandemic;
- announcements of the results of clinical trials by us, our collaborators, or our competitors, or negative developments with respect to similar products, including those being developed by our collaborators;
- developments with respect to patents or proprietary rights;
- announcements of technological innovations by us or our competitors;
- announcements of new products or new contracts by us or our competitors;
- actual or anticipated variations in our operating results due to the level of development expenses and other factors;
- changes in financial estimates by equities research analysts and whether our earnings meet or exceed such estimates;
- conditions and trends in the pharmaceutical, biotechnology and other industries;
- receipt, or lack of receipt, of funding in support of conducting our business;
- regulatory developments within, and outside of, the U.S.;
- litigation or arbitration;
- general volatility in the financial markets;
- general economic, political and market conditions and other factors; and
- the occurrence of any of the risks described in this Annual Report on Form 10-K.

You may experience future dilution as a result of future equity offerings or other equity issuances.

We may have to raise additional capital in the future. To raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may be lower than the current price per share of our common stock. In addition, investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors in prior offerings. Any such issuance could result in substantial dilution to our existing stockholders.

Future sales of our common stock in the public market could cause our stock price to fall.

Our stock price could decline as a result of sales of a large number of shares of our common stock or the perception that these sales could occur. These sales, or the possibility that these sales may occur, also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

As of December 31, 2022, we had 187,812,072 shares of common stock outstanding. In addition, we had 20,876,978 shares of common stock equivalents that would increase the number of common stock outstanding if these instruments were exercised or converted to purchase common stock based on vesting requirements of stock options and common stock issuable through purchases of employee stock purchase plan, or upon the conversion of preferred stock. The issuance and subsequent sale of the shares underlying these common stock equivalents could depress the trading price of our common stock. On June 10, 2019, our certificate of incorporation was amended to increase the number of authorized shares of our common stock, par value \$0.000041666, from 150,000,000 shares to 300,000,000 shares, which was approved by our stockholders on that date.

In addition, in the future, we may issue additional shares of common stock or other equity or debt securities convertible into common stock in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise. For example, in June 2020, we issued 19,475,806 shares of common stock in connection with an underwritten public offering, and we may offer additional shares under our automatic shelf registration statement in the future. Future issuances may result in substantial dilution to our existing stockholders and could cause our stock price to decline.

If equities or industry analysts do not publish research or reports about our company, or if they issue adverse or misleading opinions regarding us or our stock, our stock price and trading volume could decline.

Although we have research coverage by equities analysts, if coverage is not maintained, the market price for our stock may be adversely affected. Our stock price also may decline if any analyst who covers us issues an adverse or erroneous opinion regarding us, our business model, our intellectual property or our stock performance, or if our clinical trials and operating results fail to meet analysts' expectations. If one or more analysts cease coverage of us or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our stock price or trading volume to decline and possibly adversely affect our ability to engage in future financings.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results. As a result, we could become subject to sanctions or investigations by regulatory authorities and/or stockholder litigation, which could harm our business and have an adverse effect on our stock price.

As a public reporting company, we are subject to various regulatory requirements, including the Sarbanes-Oxley Act of 2002, which requires our management to assess and report on our internal controls over financial reporting. Nevertheless, in future years, our testing, or the subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls that we would be required to remediate in a timely manner to be able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act each year. If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act each year, we could be subject to sanctions or investigations by the SEC, Nasdaq or other regulatory authorities which would require additional financial and management resources and could adversely affect the market price of our common stock. In addition, material weaknesses in our internal controls could result in a loss of investor confidence in our financial reports.

We are, and in the future may be, subject to federal or state securities or related legal actions that could adversely affect our results of operations and our business.

Federal and state securities and related legal actions may result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business or affect our reputation. We may not be successful in defending future claims and cannot provide assurance that insurance proceeds will be sufficient to cover any costs or liability under such claims.

For example, on December 11, 2020, a purported stockholder derivative complaint was filed by plaintiff Leo Shumacher against us, as nominal defendant, and then current directors, as defendants, in the Court of Chancery in the State of Delaware (the "Court"). The complaint alleges breach of fiduciary duty and a claim for unjust enrichment in connection with alleged excessive compensation of certain of our non-executive directors and seeks unspecified damages on behalf of our company. The parties have agreed to a proposed settlement, which was submitted to the Court on June 15, 2022. The parties continue to work toward settlement

after a hearing on November 17, 2022, where the Court required additional steps to be taken by the parties before it will determine whether final approval will be given to the settlement. The outcome of this and other future litigation is uncertain.

Our Board of Directors could issue one or more additional series of preferred stock without stockholder approval with the effect of diluting existing stockholders and impairing their voting and other rights.

Our certificate of incorporation, as amended, authorizes the issuance of up to 50,000,000 shares of “blank check” preferred stock (of which only 17,000 shares were issued as Series A Convertible Preferred Stock and 11,500,000 shares were issued as Series B Convertible Preferred Stock) with designations, rights and preferences as may be determined from time to time by our Board of Directors. Our Board of Directors is empowered, without stockholder approval, to issue one or more series of preferred stock with dividend, liquidation, conversion, voting or other rights which could dilute the interest of, or impair the voting power of, our common stockholders. The issuance of a series of preferred stock could be used as a method of discouraging, delaying or preventing a change in control. For example, it would be possible for our Board of Directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to effect a change in control of our company.

We do not anticipate paying cash dividends for the foreseeable future, and therefore investors should not buy our stock if they wish to receive cash dividends.

We have never declared or paid any cash dividends or distributions on our common stock. We currently intend to retain our future earnings to support operations and to finance expansion and, therefore, we do not anticipate paying any cash dividends on our common stock in the foreseeable future.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our certificate of incorporation, as amended, and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our Board of Directors has the authority to issue up to 38,483,000 additional shares of preferred stock and to fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our certificate of incorporation, as amended, designates the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation, as amended, provides that, subject to limited exceptions, the Court of Chancery of the State of Delaware shall, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or agents to us or our stockholders, creditors or other constituents, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our certificate of incorporation, as amended, or our amended bylaws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage such lawsuits against us and our directors, officers, and employees. Further, this choice of forum provision does not preclude or contract the scope of exclusive federal or concurrent jurisdiction for any actions brought under the Securities Act or the Exchange Act. Section 27

of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction.

In addition, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Securities Act or any other claim for which the federal and state courts have concurrent jurisdiction. Accordingly, our exclusive forum provision will not relieve us of our duties to comply with the federal securities laws and the rules and regulations thereunder, and our stockholders will not be deemed to have waived our compliance with these laws, rules and regulations.

If a court were to find these provisions of our certificate of incorporation, as amended inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business, results of operations and financial condition. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management and other employees.

Provisions in our amended and restated bylaws could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated bylaws provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the U.S. shall be the exclusive forum for the resolution of any complaint asserting a cause of action under the Securities Act. This provision limits the ability of our shareholders to bring claims under the Securities Act in any court other than the U.S. federal courts, which ultimately may disadvantage our shareholders or be cost prohibitive. Notwithstanding the foregoing, there is uncertainty as to whether a court (other than state courts in the State of Delaware, which have recently upheld the validity of such a provision) would enforce such a provision and whether investors can waive compliance with the federal securities laws and the rules and regulations thereunder. Furthermore, the exclusive forum provision only applies to claims brought under the Securities Act and does not apply to actions arising under the Exchange Act, which is already subject to federal courts as the exclusive forum.

If a court were to find these provisions of our amended and restated bylaws inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business, results of operations and financial condition. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management and other employees.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

San Carlos New Headquarters Lease

On February 8, 2021, we entered into a lease agreement with ARE-San Francisco No. 63, LLC, or the New Headquarters Lease, for laboratories and offices to be constructed in Suite 400 of an existing building located at 825 Industrial Road, San Carlos, California, or the Building. Under the New Headquarters Lease, we lease approximately 49,918 rentable square feet of space in the Building that serves as our headquarters premises. The New Headquarters Lease, which commenced in January 2022, has an initial term of 120 months. The New Headquarters Lease includes an option to extend the term of the lease for 60 months, exercisable under certain conditions and at a market rate as described in the New Headquarters Lease.

Commencing 210 days after the Rent Commencement Date as the result of a rent abatement, our monthly base rent under the New Headquarters Lease is approximately \$0.3 million, subject to an annual increase of 3%. Beginning in 2022, we are also responsible for paying operating expenses, such as common area maintenance.

Minimum rental payments under the New Headquarters Lease total \$36.7 million for the entire term of the lease, which does not include rental payments related to our one-time option to extend for an additional five years. In addition, the lessor has provided a

tenant improvement allowance of up to \$8.2 million. We have received reimbursements associated with this tenant improvement allowance totaling \$8.1 million. We do not expect to receive any additional reimbursements associated with this tenant improvement allowance.

San Carlos Former Headquarters Lease

Since August 2016, we had leased 8,733 square feet of space for our former corporate headquarters, or the Suite 150 Lease, in San Carlos, California. The term of the Suite 150 Lease was 54 months beginning on the commencement date. Monthly lease payments were approximately \$38,000.

On October 19, 2018, we entered into an agreement, or the Lease, to lease 12,322 square feet of office space located adjacent to our former corporate headquarters in San Carlos, California. Monthly lease payments were approximately \$59,000, subject to an annual increase of 3%.

On June 19, 2019, we entered into a first amendment, or the Amended Lease, to the Lease, for additional space at our corporate headquarters in San Carlos, California. Under the Amended Lease, we leased an additional 8,110 square feet, or the Expansion Space, for a total of approximately 20,432 square feet of space. Monthly lease payments were approximately \$39,000 for the first year, and \$40,000 for the second year.

On February 8, 2021, we entered into two amendments, the Suite 100 and 125 Second Amendment and the Suite 150 First Amendment, to the Amended Lease and the Suite 150 Lease, respectively. Under the Suite 100 and Suite 125 Second Amendment, we extended the Amended Lease to December 31, 2021. Our monthly base rent under the Suite 100 and Suite 125 Second Amendment were approximately \$103,000. We were also responsible for paying our portion of operating expenses, including common area maintenance, and real estate taxes. We had an option to extend the expiration of the Suite 100 and Suite 125 Second Amendment for one month or nine months, at its discretion, by providing notice as specified in the Suite 100 and Suite 125 Second Amendment. On September 1, 2021, we entered into an agreement to extend the lease term to January 31, 2022, for approximately \$0.1 million a month.

Under the Suite 150 First Amendment, we extended the Suite 150 Lease, which also expired on April 30, 2021, to December 31, 2021. Our monthly base rent under the Suite 150 First Amendment is approximately \$44,000. We were also responsible for paying our portion of operating expenses and real estate taxes. We had an option to extend the expiration of the Suite 150 First Amendment for one month or nine months, at our discretion, by providing notice as specified in the Suite 150 First Amendment. On September 1, 2021, we entered into an agreement to extend the lease term to January 31, 2022, for approximately \$46,000 a month. As of January 31, 2022, these leases have expired, and we had taken possession of Headquarters Premises under the New Headquarters Lease referred to above.

Commercial Manufacturing Facility Agreement

On May 28, 2019, we entered into a lease agreement with 300 Rouse Boulevard, LLC, or the Commercial Manufacturing Facility Lease, for a build-to-suit commercial manufacturing facility, laboratories, and offices located in Philadelphia, Pennsylvania. Under the Commercial Manufacturing Facility Lease, we lease approximately 136,000 rentable square feet of space in a building located at 300 Rouse Boulevard, Philadelphia, Pennsylvania known as the Iovance Cell Therapy Center, or the *i*CTC. The construction of the *i*CTC began in July 2019 and in the third quarter of 2021 we completed the commissioning activities as well as certain tenant improvements. The Commercial Manufacturing Facility Lease includes an option to extend the term of the lease by giving the landlord prior written notice thereof at least 18 months in advance of expiration date, exercisable under certain conditions as described in the Commercial Manufacturing Facility Lease, such that the overall term, when added to the initial term, shall be 359 months.

Our monthly base rent under the Commercial Manufacturing Facility Lease is approximately \$0.3 million, subject to an annual increase of 2% for the first ten years. Commencing on the first day of each lease year thereafter, for the remainder of the lease term, monthly rent is subject to an annual increase of the greater of 2% or 75% of the average ten-year consumer price index. We are also responsible for paying operating expenses, such as common area maintenance.

Tampa Lease

Our research and development facilities consist of 8,673 square feet in a facility located at the University of South Florida Research Park in Tampa, Florida. These facilities are leased under an agreement with a lease term through December 2024 for approximately \$20,500 a month. In June 2020, we amended the lease agreement to further increase the rentable space to 13,139 square feet and extend the lease term to June 5, 2025, for approximately \$34,500 a month. On December 22, 2021, we entered into a second amendment to lease an additional 2,731 square feet of space through June 5, 2025, co-terminus with the existing leased space. Upon completion of tenant improvements of the premise, lease payments will be approximately \$42,500 per month.

Philadelphia Office Lease

On May 2, 2019, we entered into an agreement to lease approximately 1,500 square feet of office space in Philadelphia, Pennsylvania until July 1, 2019, for a rate of \$2,000 a month, and then approximately 4,500 square feet of office space for the remainder of a three-year term at an initial rate of \$11,063 per month, subject to annual increases of 2.5%. On September 1, 2021, we entered into an agreement to extend the lease term for an additional three years to July 31, 2025, for approximately \$11,900 a month, effective as of June 1, 2022, subject to annual increases of 2.5%.

On August 1, 2020, we entered into an agreement to lease approximately 2,965 square feet of a training facility space in Plymouth Meeting, Pennsylvania for a twelve-month term at a rate of approximately \$6,500 per month.

We believe that our existing facilities are adequate to meet our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms.

Item 3. Legal Proceedings

The information in Note 11 to the Consolidated Financial Statements contained in Part III, Item 15 of this Annual Report on Form 10-K is incorporated herein by reference. There are no matters which constitute material pending legal proceedings to which we are a party other than those incorporated into this item by reference from Note 11 to our Consolidated Financial Statements for the year ended December 31, 2022, contained in this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

Not Applicable.

PART II

Item 5. Market for Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock is traded on the Nasdaq Global Market under the symbol "IOVA".

Stockholders

As of December 31, 2022, there were approximately 17 holders of record of our common stock.

Dividends

We have never declared or paid any cash dividends on our common stock or any other securities. We anticipate that we will retain all available funds and any future earnings, if any, for use in the operation of our business and do not anticipate paying cash dividends in the foreseeable future. Payment of future cash dividends, if any, will be at the discretion of the board of directors after considering various factors, including our financial condition, operating results, current and anticipated cash needs.

Under the terms of our Series A Convertible Preferred Stock, we may not declare, pay or set aside any dividends on shares of any class or series of capital stock (other than dividends on shares of common stock payable in shares of common stock) unless the

holders of our Series A Convertible Preferred Stock first receive, or simultaneously receive, an equal dividend on each outstanding share of Series A Convertible Preferred Stock.

Under the terms of our Series B Convertible Preferred Stock, holders shall be entitled to receive dividends on shares equal (on an as-if-converted-to-Common-Stock basis) to and in the same form as dividends (other than dividends in the form of common stock) actually paid on shares of our Series A Convertible Preferred Stock, common stock or other junior securities when, as and if such dividends (other than dividends in the form of common stock) are paid on shares of our Series A Convertible Preferred Stock, common stock or other junior securities. No other dividends shall be paid on shares of Series B Convertible Preferred Stock, and we may not pay dividends (other than dividends in the form of common stock) on shares of our Series A Convertible Preferred Stock, common stock or other junior securities unless it simultaneously complies with the previous sentence.

Unregistered Sales of Equity Securities

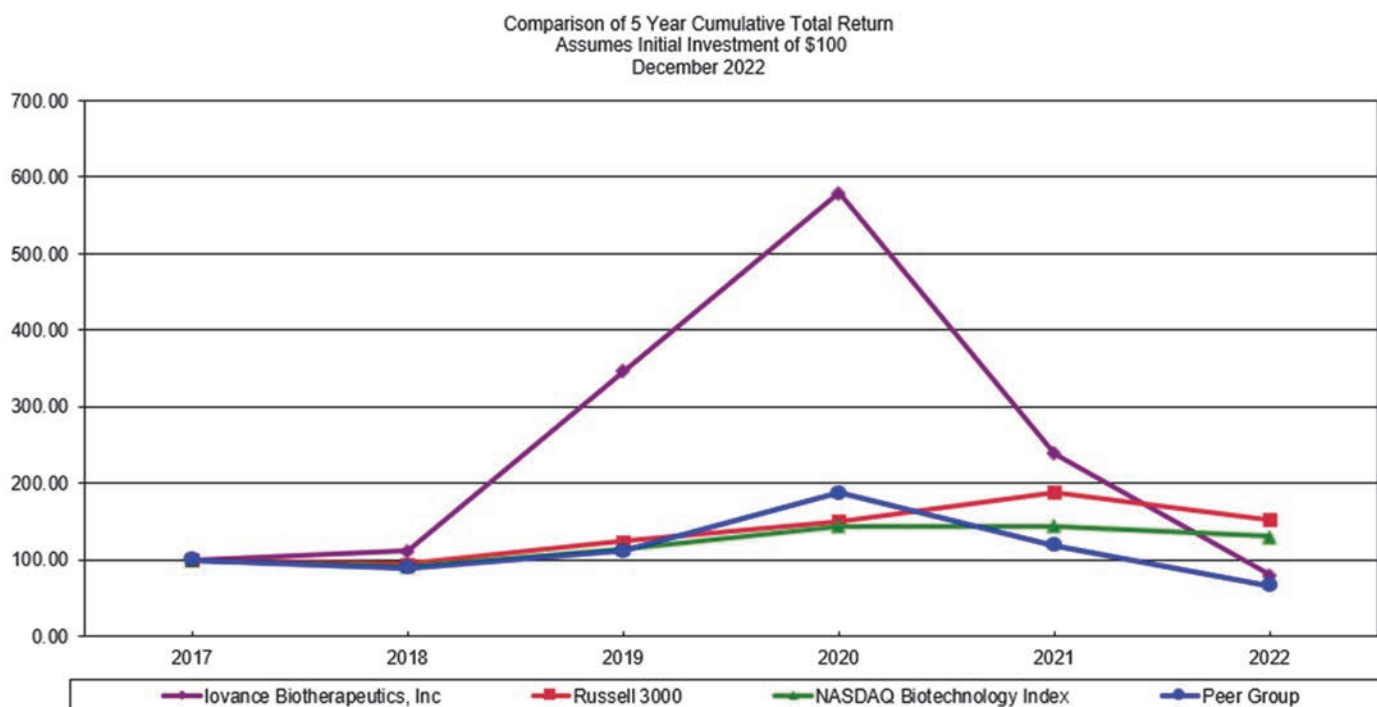
None.

Repurchases of Common Stock

There were no share repurchases during the year ended December 31, 2022.

Stock Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return on our common stock since December 31, 2017, to two indices: the Russell 3000 and the NASDAQ Biotechnology Index. The stockholder return shown in the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



Equity Compensation Plan Information

Information regarding our equity compensation plans is incorporated by reference from the information in our Proxy Statement for our 2023 Annual Meeting of Stockholders, which we will file with the SEC within 120 days after the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 6. [Reserved]

Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our results of operations and financial condition should be read in conjunction with our financial statements and the notes to those financial statements that are included elsewhere in this report. Our discussion includes forward-looking statements based upon current expectations that involve risks and uncertainties, such as our plans, objectives, expectations and intentions. Actual results and the timing of events could differ materially from those anticipated in these forward-looking statements as a result of a number of factors, including those set forth under the “Business” section and elsewhere in this report. We use words such as “may,” “will,” “might,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “anticipate,” “believe,” “estimate,” “predict,” “project,” “aim,” “potential,” “continue,” “ongoing,” “goal,” “forecast,” “guidance,” “outlook,” or the negative of these terms or other similar expressions to identify forward-looking statements, although not all forward-looking statements contain these words. All forward-looking statements included in this report are based on information available to us on the date hereof and, except as required by law, we assume no obligation to update any such forward-looking statements.

Overview

We are a clinical-stage biopharmaceutical company pioneering a transformational approach to treating cancer by harnessing the human immune system's ability to recognize and destroy diverse cancer cells using therapies personalized for each patient. We are preparing for potential U.S. regulatory approval and commercialization of the first autologous T-cell therapy to address a solid tumor cancer. Our mission is to be the global leader in innovating, developing and delivering tumor infiltrating lymphocyte, or TIL, therapies for patients with solid tumor cancers. Our autologous TIL therapy platform uses a centralized, scalable and proprietary 22-day manufacturing process to grow polyclonal T-cells unique to each patient and yields a cryopreserved, individualized therapy. We have applied multiple TIL therapy modalities in clinical trials in solid tumors, including TIL monotherapies for patients with later stage disease who have progressed on or after standard of care, as well as TIL combinations with standard of care therapies in patients who are earlier in their disease, to potentially improve outcomes compared to current standard(s) of care.

Our lead product candidate, lifileucel, is being developed in advanced, or metastatic or unresectable, melanoma as well as in other indications. Lifileucel was investigated in two consecutive cohorts in a clinical trial of advanced melanoma patients post-anti-PD-1 therapy, including in a prospectively defined pivotal cohort. These patients had progressed on or after standard of care therapy, which is immune checkpoint inhibitors, or ICIs, and targeted BRAF/MEK inhibitor therapy where appropriate. Based on the positive results of these cohorts, we initiated a rolling Biologics License Application, or BLA, submission to the U.S. Food and Drug Administration, or FDA, for lifileucel in August 2022. We expect to complete this rolling BLA submission in the first quarter of 2023. Our Phase 3 clinical trial of lifileucel in combination with pembrolizumab, TILVANCE-301, is intended to be registrational in frontline advanced melanoma and serve as a confirmatory clinical trial to support full approval of lifileucel monotherapy in post-anti-PD-1 melanoma.

We are also pursuing registrational strategies for lifileucel in advanced cervical cancer and for our TIL therapy, LN-145, in metastatic non-small cell lung cancer, or NSCLC. To continuously innovate and maintain our global leadership within the field, we are investigating next generation approaches to optimize TIL products, manufacturing processes and treatment regimens, including a first-in-human clinical trial of our lead genetically modified TIL therapy, IOV-4001. We are also exploring a 16-day manufacturing process, tumor tissue procurement via core biopsy, additional genetically modified TIL therapies including multiple immune checkpoint gene edits and cytokine-tethered TIL therapies, and a novel interleukin-2, or IL-2, analog, designated IOV-3001, as potential avenues to improve manufacturing timelines, sample collection and supportive treatments involved in the overall TIL therapy process and treatment regimen.

Highlights of our current development pipeline are presented in the figure below:

Iovance Solid Tumor Pipeline Highlights

	PRODUCT CANDIDATE	INDICATION(S)	PHASE 1	PHASE 2	PIVOTAL
Advanced Melanoma (Metastatic or Unresectable)	Lifileucel + pembro	Frontline	TILVANCE-301 Phase 3		Confirmatory, FTD
	TIL (Lifileuce/LN-144)	Post-anti-PD-1	C-144-01, Cohorts 2 & 4		Rolling BLA In Progress, RMAT
	Lifileucel + pembro	Anti-PD-1 naive	IOV-COM-202, Cohort 1A		
<i>Next Generation</i>	PD-1 Inactivated TIL (IOV-4001)	Post-anti-PD-1	IOV-GM1-201, Cohort 1		
Metastatic NSCLC	LN-145	2L post-chemo & post-anti-PD-1	IOV-LUN-202, Cohorts 1 & 2		
	LN-145 + pembro	Anti-PD-1 naive	IOV-COM-202, Cohort 3A		
	LN-145	2-4L incl. post-anti-PD-1	IOV-COM-202, Cohort 3B*		
	LN-145 + ipi/nivo	Post-anti-PD-1	IOV-COM-202, Cohort 3C		
	<i>Next Generation</i>	LN-145 Gen 3 + core biopsy	2L post-chemo & post-anti-PD-1	IOV-LUN-202 Cohort 3	
	PD-1 Inactivated TIL (IOV-4001)	2-4L incl. post-anti-PD-1	IOV-GM1-201, Cohort 2		
Cervical	Lifileucel	Post-chemo & post-anti-PD-1	C-145-04, Cohort 2		BTD, ODD
	LN-145 + pembro	1L - chemo and anti-PD-1 naive	C-145-04, Cohort 3*		

Platform Technologies and Manufacturing

Our T-cell-based immunotherapy technology platforms are potentially applicable to many solid tumor types and blood cancers. Each platform is focused on leveraging patient-specific cells to recognize and attack diverse cancer cells that are unique to each patient. Unlike cell therapies that act on a single or small number of shared antigen targets common to certain tumors, our polyclonal T-cells are personalized therapies designed to target a variety of neoantigens that are unique to the patient or tumor. The majority of solid tumor immune targets are patient-specific, with fewer than 1% shared among patients. TIL therapy is our lead T-cell-based immunotherapy platform in multiple advanced solid tumor cancers. For blood cancers, our peripheral blood lymphocyte, or PBL, therapy platform is based on polyclonal T-cells that are collected from a patient's blood sample, and then amplified and reinvigorated.

TIL Clinical Development in Advanced, Metastatic or Unresectable Solid Tumor Cancers

Building on the prior TIL therapy clinical trials conducted at single academic centers, including the National Cancer Institute, or NCI, we have investigated TIL therapy in global, multi-center Phase 2 clinical trials in advanced melanoma, cervical cancer, NSCLC and head and neck squamous cell carcinoma, or HNSCC. Additional information about our clinical trials is summarized below.

In post-anti-PD-1 advanced melanoma, we are investigating lifileucel in our C-144-01 clinical trial that supports our BLA submission and potential approval of lifileucel in advanced post-anti-PD-1 melanoma.

In frontline advanced melanoma patients who are naïve to anti-PD-1 therapy, we are investigating lifileucel in combination with pembrolizumab in the IOV-COM-202 clinical trial and the Phase 3 TILVANCE-301 clinical trial. TILVANCE-301 is a randomized Phase 3 clinical trial intended to support registration in advanced frontline melanoma as well as to serve as a confirmatory trial for full approval in advanced post-anti-PD-1 melanoma.

We are also executing a registrational strategy for lifileucel in advanced cervical cancer. C-145-04 is a multicenter Phase 2 clinical trial that is currently enrolling a pivotal cohort to support a BLA in cervical cancer following progression on or after chemotherapy and pembrolizumab.

In NSCLC, we are investigating our TIL therapy, LN-145, in two clinical trials in several NSCLC patient populations with significant unmet need. IOV-LUN-202 is a clinical trial of LN-145 in advanced NSCLC patients who have progressed following chemotherapy and anti-PD-1 therapy. IOV-COM-202 also includes cohorts of NSCLC patients treated with LN-145 monotherapy and combination therapy.

Our first genetically modified, PD-1 inactivated TIL therapy, IOV-4001, entered a first-in-human Phase 1/2 clinical trial, IOV-GM1-201, in 2022 in patients with previously treated advanced melanoma and NSCLC. IOV-4001 utilizes the gene-editing TALEN® technology, licensed from Collectis S.A., or Collectis, to inactivate the gene coding for the programmed cell death protein-1, or PD-1.

In metastatic head and neck cancer squamous cell carcinoma, or HNSCC, we are evaluating LN-145 as monotherapy and in combination with pembrolizumab. The Phase 2 C-145-03 trial began in June 2017 and closed in January 2021 after reaching its pre-specified enrollment target to investigate LN-145 using various manufacturing processes. Cohort 2A in IOV-COM-202 is evaluating LN-145 in combination with pembrolizumab in patients with HNSCC who are naïve to anti-PD-1 therapy.

PBL Therapy in Blood Cancers

In blood cancers, our clinical trial IOV-CLL-01 is a Phase 1/2 clinical trial evaluating the safety and efficacy of IOV-2001, our polyclonal PBL therapy, in patients with relapsed or refractory chronic lymphocytic leukemia, or CLL, and small lymphocytic lymphoma, or SLL, to receive IOV-2001.

Beyond our Iovance-sponsored clinical trials, we have academic collaborations with leading cancer research centers to investigate TIL therapy, including next-generation processes and technologies, in other cancers and treatment settings.

Next-Generation Therapeutic and Manufacturing Approaches

Our current next-generation technology platforms are designed to optimize TIL therapy, as well as TIL treatment regimen and manufacturing processes, across four key initiatives: genetic modifications, potency, process optimization and new treatment regimens.

- *Genetic modifications:* We are pursuing several targets for genetic modification that utilize the gene-editing TALEN® platform licensed from the clinical-stage biotechnology company, Collectis. Programs include single- and double-knockout candidates to further harness the immune system response to cancer and potentially increase the efficiency, potency and application of TIL therapy. Preclinical development is also ongoing with cytokine-tethered TIL products and additional TIL products and TIL-cell lines using transient and stable gene insertion and inactivation. Additional transient and permanent genetic modifications of TIL, such as cytokine-tethered TIL, may expand and activate TIL to achieve better efficacy while avoiding systemic side effects of cytokines.
- *Potency:* Potential approaches to increase potency of the final TIL product include the sorting and selection of specific TIL, such as PD-1+ selected TIL and CD39/69 double-negative TIL, and the use of certain inhibitors or other reagents in TIL expansion cultures. Our TIL candidate LN-145-S1 is manufactured from TIL selected for PD-1 expression and has been investigated in post-anti-PD-1 melanoma and post-anti-PD-1 HNSCC patient cohorts in our clinical trials.
- *Process optimization:* We are committed to further optimizing and streamlining the processes for manufacturing TIL therapy and collecting tumor samples. We are investigating a 16-day manufacturing process, or Gen 3, in patient cohorts included in the C-145-03 clinical trial in HNSCC and the IOV-COM-202 clinical trial. We are also exploring our Gen 3 process to manufacture TIL from core biopsy as a less-invasive collection of tumor samples in a cohort of patients with NSCLC in our IOV-LUN-202 clinical trial.
- *New treatment regimens:* We are exploring potential avenues to improve aspects of the TIL treatment regimen. In 2020, we licensed an antibody cytokine-engrafted protein, or IL-2 analog, which we refer to as IOV-3001, from Novartis. IOV-4001 is in IND-enabling studies supporting its use as part of the TIL treatment regimen following TIL infusion.

Intellectual Property

We have established a leading intellectual property portfolio developed internally and licensed from third parties. We currently own more than 60 U.S. patents related to TIL therapy, including patents directed to compositions and methods of treatment in a broad range of cancers, such as U.S. Patent Nos. 10,130,659; 10,166,257; 10,272,113; 10,363,273; 10,398,734; 10,420,799; 10,463,697; 10,517,894; 10,537,595; 10,639,330; 10,646,517; 10,653,723; 10,695,372; 10,894,063; 10,905,718; 10,918,666; 10,925,900; 10,933,094; 10,946,044; 10,946,045; 10,953,046; 10,953,047; 11,007,225; 11,007,226; 11,013,770; 11,026,974; 11,040,070; 11,052,115; 11,052,116; 11,058,728; 11,083,752; 11,123,371; 11,141,438; 11,168,303; 11,168,304; 11,179,419; 11,202,803; 11,202,804; 11,241,456; 11,254,913; 11,266,694; 11,273,180; 11,273,181; 11,291,687; 11,304,979; 11,304,980; 11,311,578; 11,337,998; 11,344,579; 11,344,580; 11,344,581; 11,351,197; 11,351,198; 11,351,199; 11,364,266; 11,369,637; 11,384,637; 1,433,097; 11,529,372; and 11,541,077. More than 35 of these patents are related to our Gen 2 TIL manufacturing processes and have terms that we anticipate will extend to January 2038, not including any patent term extensions or adjustments that may be available. Our owned and licensed intellectual property portfolio also includes patents and patent applications relating to TIL, MIL, and PBL therapies; frozen tumor-based TIL technologies; remnant TIL and digest TIL compositions, methods and processes; methods of manufacturing TIL, MIL, and PBL therapies; the use of costimulatory and T-cell modulating molecules in TIL therapy and manufacturing; stable and transient genetically-modified TIL therapies, including genetic knockouts of immune checkpoints; cytokine-tethered TIL therapies; methods of using ICIs in combination with TIL therapies; TIL selection technologies; and methods of treating patient subpopulations.

Impact of COVID-19 on our Business

Operations and Liquidity

The full impact of the novel strain of coronavirus, or COVID-19, pandemic is unknown and continuously evolving. While the potential economic impact brought by and over the duration of the COVID-19 pandemic may be difficult to assess or predict, the COVID-19 pandemic has resulted in significant disruption of global financial markets, which could in the future negatively affect our liquidity. In addition, a recession or market volatility resulting from the COVID-19 pandemic could affect our business. We have taken proactive, aggressive action throughout the COVID-19 pandemic to protect the health and safety of our employees and expect to continue to implement these measures until we determine that the COVID-19 pandemic is adequately contained for purposes of our business. We may take further actions as government authorities require or recommend or as we determine to be in the best interests of our employees. We do not believe that the COVID-19 pandemic had a material impact on our liquidity or results of operations for the year ended December 31, 2022. Further, to date, the COVID-19 pandemic has not had significant effects on our clinical trial enrollment. Given the nature and type of our short-term investments in U.S. government securities, we do not believe that the COVID-19 pandemic will have a material impact on our current investment liquidity.

Outlook

Although there is uncertainty related to the anticipated impact of the recent COVID-19 pandemic on our future results, we believe our current cash reserves leave us well positioned to manage our business in light of the COVID-19 pandemic. However, the impacts of the COVID-19 pandemic are broad-reaching and continuing and the financial impacts associated with the COVID-19 pandemic are still uncertain.

The COVID-19 pandemic is ongoing, and its dynamic nature, including uncertainties relating to the ultimate geographic spread of the virus, the severity of the disease, the duration of the pandemic, and actions that would be taken by governmental authorities to contain the pandemic or to treat its impact, makes it difficult to forecast any effects on our results for future periods. Despite the economic uncertainty resulting from the COVID-19 pandemic, we intend to continue to focus on the development of our product candidates. We continue to monitor the rapidly evolving situation and guidance from international and domestic authorities, including federal, state and local public health authorities and may take additional actions based on their recommendations. In these circumstances, there may be developments outside our control requiring us to adjust our operating plan. As such, given the dynamic nature of this situation, we cannot reasonably estimate the impacts of COVID-19 on our financial condition, results of operations or cash flows in the future.

Components of Operating Results

Revenues

We have not yet generated any revenues since our formation, With the submission of the rolling BLA for lifileucel for metastatic melanoma and our expected completion of the submission in the first quarter of 2023, we anticipate generating revenues from the sale of products during the 12 months from the date these financial statements are issued, however, such revenue may not be material. Our ability to generate revenues in the future will depend on our ability to complete the development of our product candidates and to obtain regulatory approval for them.

Operating Expenses

Research and Development

Research and development expenses include personnel and facility-related expenses, outside contracted services including clinical trial costs, manufacturing and process development costs, research costs and other consulting services. Research and development costs are expensed as incurred. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and amortized over the period that the goods are delivered, or the related services are performed, subject to an assessment of recoverability.

Clinical development costs are a significant component of research and development expenses. We have a history of contracting with third parties that perform various clinical trial activities on our behalf in connection with the ongoing development of our product candidates. The financial terms of these contracts are subject to negotiations and may vary from contract to contract and may result in uneven payment flow. We accrue and expense costs for clinical trial activities performed by third parties based upon estimates of work completed to date of the individual trial in accordance with agreements established with contract research organizations and clinical trial sites. The duration, costs and timing of our clinical trials and development of our product candidates will depend on a number of factors that include, but are not limited to, the number of patients that enroll in the trial, per patient trial costs, number of sites included in the trial, discontinuation rates of patients, duration of patient follow-up, efficacy and safety profile of the product candidate, and the length of time required to enroll eligible patients.

We expect our research and development expenses to continue to increase as we prepare for commercial manufacturing of our products and continue to conduct our clinical trials for other indications. However, it is difficult to determine with certainty the duration and completion costs of our current or future preclinical programs and clinical trials of our product candidates.

General and Administrative

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, procurement, legal, investor relations, facilities, business development, marketing, commercial, information technology and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to corporate matters and intellectual property, insurance, public company expenses relating to maintaining compliance with Nasdaq listing rules and SEC requirements, investor relations costs, and fees for accounting and consulting services. General and administrative costs are expensed as incurred, and we accrue for services provided by third parties related to the above expenses by monitoring the status of services provided and receiving estimates from its service providers and adjusting its accruals as actual costs become known.

We anticipate general and administrative expenses will increase as we continue to prepare for commercialization and support an expected growth of the internal general and administrative team.

Interest income, net

Interest income, net results from our interest-bearing cash and investment balances.

Results of Operations for the Years Ended December 31, 2022 and 2021

Research and development activities are central to our business model. Product candidates in later stage of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. As a clinical stage company that is currently engaged in the development of novel cancer immunotherapy products, we have not yet generated any revenues from our biotechnology business or otherwise since our formation. Our ability to generate revenues in the future will depend on our ability to complete the development of our product candidates and to

obtain regulatory approval for them. Our major sources of funding to date have been proceeds from various public and private offerings of our equity securities (both common stock and preferred stock), option and warrant exercises, and interest income. Since 2017 our primary source of funds has been from the public sale of our common stock.

Costs and expenses

Research and Development Expense (in thousands)

	Years Ended December 31,		Increase (Decrease)	
	2022	2021	\$	%
Research and development expense	\$ 294,781	\$ 259,039	\$ 35,742	14 %
Stock-based compensation expense included in research and development expense	50,242	40,833	9,409	23 %

Research and development expense for the year ended December 31, 2022 increased by \$35.7 million, or 14%, compared to the year ended December 31, 2021. The increase was primarily attributable to (i) a \$23.9 million increase in payroll and related expenses and a \$9.4 million increase in stock-based compensation expenses, both driven by increased hiring of research and development employees to support our on-going and planned clinical development activities, (ii) a \$16.2 million increase in facility related expenses, including depreciation expenses associated with the iCTC and the build-out of our new corporate headquarters office, (iii) a \$3.5 million increase in research and research alliance activities due to increased spend in lab supplies and consumables to support preclinical activities, (iv) a \$2.7 million increase in patient advocacy and physician outreach and travel to support our planned commercial launch, and (v) a \$2.4 million increase in license costs associated with the expansion of our information technology infrastructure to support our clinical and manufacturing activities at the iCTC. These increases were partially offset by a \$17.4 million decrease in clinical trial costs, including clinical trial drug costs, and a \$5.0 million decrease in manufacturing costs driven by completion of enrollment in pivotal cohorts of our clinical trials.

General and Administrative Expense (in thousands)

	Years Ended December 31,		Increase (Decrease)	
	2022	2021	\$	%
General and administrative expense	\$ 104,097	\$ 83,664	\$ 20,433	24 %
Stock-based compensation expense included in general and administrative expense	33,780	28,932	4,848	17 %

General and administrative expense for the year ended December 31, 2022, increased by \$20.4 million, or 24%, compared to the year ended December 31, 2021. The increase was primarily attributable to (i) a \$10.0 million increase in payroll and related expenses and a \$4.8 million increase in stock-based compensation expenses, both resulting from increases in headcount to support the growth in the overall business and related corporate infrastructure, (ii) a \$3.4 million increase in marketing, advertising and travel related costs related to branding awareness to support our planned commercial launch, (iii) a \$1.7 million increase in other costs, including professional fees and costs associated with the build-out of our new headquarter office and our information technology infrastructure to support the continued growth in the overall company, and (iv) a \$0.5 million increase in depreciation expenses and facility related costs associated with the build-out of our new corporate headquarters.

Interest income, net (in thousands)

	Years Ended December 31,		Increase (Decrease)	
	2022	2021	\$	%
Interest income, net	\$ 2,985	\$ 451	\$ 2,534	562 %

Interest income results from our interest-bearing cash and investment balances. Net interest income increased by \$2.5 million, or 562%, due primarily to an increase in cash and cash equivalents as well as returns resulting from increased interest rates in 2022 as compared to the same period in 2021.

Net Loss (in thousands)

	Years Ended December 31,		(Increase) Decrease	
	2022	2021	\$	%
Net loss	\$ (395,893)	\$ (342,252)	\$ (53,641)	16 %

Net loss for the year ended December 31, 2022, increased by \$53.6 million or 16%, compared to the year ended December 31, 2021. The increase in our net loss was due to the continued expansion of our research and development activities, and the overall growth of our corporate infrastructure. We anticipate that we will continue to incur net losses in the future as we further invest in our research and development activities, including our commercial readiness and clinical development.

Results of Operations for the Years Ended December 31, 2021 and 2020

Costs and expenses

Research and Development Expense (in thousands)

	Years Ended December 31,		Increase (Decrease)	
	2021	2020	\$	%
Research and development expense	\$ 259,039	\$ 201,727	\$ 57,312	28 %
Stock-based compensation expense included in research and development expense	40,833	19,727	21,106	107 %

Research and development expense for the year ended December 31, 2021, increased by \$57.3 million, or 28%, compared to the year ended December 31, 2020. The increase was primarily attributable to (i) a \$29.2 million increase in payroll and related expenses and a \$21.1 million increase in stock-based compensation expenses, both driven by increased hiring of research and development employees to support our on-going and planned clinical development activities, (ii) a \$14.9 million increase in facility and related costs associated with the iCTC and the build-out of our new corporate headquarters office, (iii) a \$5.1 million increase in clinical trial costs driven by continued enrollment in our IOV-COM-202 and IOV-LUN-202 clinical trials and purchases of clinical trial drug used in these clinical trials, and (iv) a \$2.2 million increase in travel and others, including allocated costs associated with the expansion of our infrastructure, including information systems, to further support the growth in the organization and operations associated with our clinical trials and pre-commercial efforts. These increases were partially offset by a \$10.0 million decrease in research alliance costs due to a one-time license fee from Novartis to further develop IOV-3001 which was recognized in full in 2020, and a \$5.2 million decrease in manufacturing costs driven by completion of our pivotal clinical trials.

General and Administrative Expense (in thousands)

	Years Ended December 31,		Increase (Decrease)	
	2021	2020	\$	%
General and administrative expense	\$ 83,664	\$ 60,210	\$ 23,454	39 %
Stock-based compensation expense included in general and administrative expense	28,932	21,160	7,772	37 %

General and administrative expense for the year ended December 31, 2021, increased by \$23.5 million, or 39%, compared to the year ended December 31, 2020. The increase was primarily attributable to (i) a \$9.8 million increase in payroll and related expenses and a \$7.8 million increase in stock-based compensation expenses, both resulting from increases in headcount to support the growth in the overall business and related corporate infrastructure (ii) a \$4.3 million increase in insurance and intellectual property filing related costs, and (iii) a \$2.8 million increase in other costs, including professional fees and costs associated with the build-out of our new headquarter office and IT infrastructure to support the continued growth in the overall company. These costs were partially offset by a \$1.2 million decrease in pre-commercial and marketing costs due to reprioritization of corporate initiatives during the year ended December 31, 2021.

Interest income, net (in thousands)

	Years Ended December 31,		Increase (Decrease)	
	2021	2020	\$	%
Interest income, net	\$ 451	\$ 2,356	\$ (1,905)	(81)%

Interest income results from our interest-bearing cash and investment balances. Net interest income decreased by \$1.9 million, or 81%, due primarily to a decrease in interest rates in 2021 as compared to the same period in 2020.

Net Loss (in thousands)

	Years Ended December 31,		(Increase) Decrease	
	2021	2020	\$	%
Net loss	\$ (342,252)	\$ (259,581)	\$ (82,671)	32 %

Net loss for the year ended December 31, 2021, increased by \$82.7 million or 32%, compared to the year ended December 31, 2020. The increase in our net loss was due to the continued expansion of our research and development activities, increased clinical trials, and the overall growth of our corporate infrastructure. We anticipate that we will continue to incur net losses in the future as we further invest in our research and development activities, including our commercial readiness and clinical development.

Liquidity and Capital Resources

We have incurred losses and generated negative cash flows from operations since inception. Historically, we have funded our operations from various public and private offerings of our equity securities, both common stock and preferred stock, from option and warrant exercises, and from interest income. Since 2017, our primary source of funds has been from the public sale of our common stock. With the submission of the rolling BLA for lifileucel for metastatic melanoma and the expected completion of the submission in the first quarter of 2023, we anticipate generating revenue from the sale of products during the 12 months from the date these consolidated financial statements are issued, however such revenues may not be material. We expect to continue to incur significant expenses to support our research and development activities, on-going pre-commercial activities and completion of the construction of tenant improvements for the *i*CTC facility during the remainder of 2023 and beyond. Specifically, we expect increased spending on clinical trials, research and development activities, and higher payroll expenses as we increase our professional and scientific staff and continue our expansion of manufacturing activities, including the ramp-up of the *i*CTC. Based on the funds we have available as of the date of our consolidated financial statements, we believe that we have sufficient capital to fund our anticipated operating expenses and capital expenditures as planned for at least the next twelve months from the date these consolidated financial statements are issued.

We currently anticipate making aggregate capital expenditures of approximately \$20.0 million during the next 12 months, which is expected to primarily include equipment to be used for clinical trials, research and manufacturing at the *i*CTC, as well as spending associated with the expansion of our manufacturing facilities of offices.

As of December 31, 2022, we had \$478.3 million in cash, cash equivalents, investments, and restricted cash (\$231.7 million of cash and cash equivalents, \$240.1 million in short-term investments, and \$6.4 million in restricted cash). Based on the funds we have available as of the date of the filing of this Annual Report on Form 10-K, we believe that we have sufficient capital to fund our anticipated operating expenses and capital expenditure for at least 12 months from the date of filing this report.

Corporate Capitalization

As of December 31, 2022, we had outstanding 187,812,072 shares of our \$0.000041666 par value common stock, 194 shares of our \$0.001 par value Series A Convertible Preferred Stock, and 2,842,158 shares of our \$0.001 par value Series B Convertible Preferred Stock. The outstanding shares of Series A Convertible Preferred Stock are currently convertible into 97,000 shares of our common stock, and the outstanding shares of Series B Convertible Preferred Stock are currently convertible into 2,842,158 shares of our common stock. The shares of Series A Convertible Preferred Stock and Series B Convertible Preferred Stock do not have voting rights or accrue dividends.

On September 17, 2019, we filed a shelf registration statement, or the 2019 Shelf Registration Statement, with the SEC for the issuance up to an aggregate amount of \$400 million, which was declared effective on September 24, 2019. The 2019 Shelf

Registration Statement was terminated upon effectiveness of the 2020 Automatic Shelf Registration Statement as discussed below. No shares were sold under the 2019 Shelf Registration Statement prior to its termination.

On May 27, 2020, we filed an automatic shelf registration statement, or the 2020 Automatic Shelf Registration Statement, with the SEC for the issuance of an indeterminate amount of securities (the “Shelf Securities”), which was immediately effective upon filing with the SEC. Upon filing of the 2020 Automatic Shelf Registration Statement, the 2019 Shelf Registration Statement was terminated.

On June 2, 2020, we sold 19,475,806 shares of our common stock at a public offering price of \$31.00 per share pursuant to the 2020 Automatic Shelf Registration Statement, or the June 2020 Public Offering. We received gross proceeds of \$603.7 million and net proceeds of \$567.0 million from the June 2020 Public Offering, after deducting underwriting discounts and offering expenses. Following the June 2020 Public Offering, the 2020 Automatic Shelf Registration Statement remains available for the future issuance of an indeterminate amount of Shelf Securities.

On February 8, 2021, we entered into an Open Market Sales Agreement, or the First Sales Agreement, with Jefferies LLC, or Jefferies, with respect to an “at the market” offering program, under which we may, from time to time, in our sole discretion, issue and sell through Jefferies, acting as sales agent, up to \$350.0 million of shares of our common stock.

On November 18, 2022, we entered into a new Open Market Sales Agreement, or the Second Sales Agreement, with Jefferies, which superseded and replaced the First Sales Agreement dated February 8, 2021. Pursuant to the terms of the Second Sales Agreement, we may, from time to time, in our sole discretion, issue and sell through Jefferies, acting as sales agent, up to \$500.0 million of shares of our common stock. The issuance and sale, if any, of shares of our common stock under the First Sales Agreement and the Second Sales Agreement will be made pursuant to a prospectus supplement, dated February 8, 2021, and November 18, 2022, respectively, to the 2020 Automatic Shelf Registration Statement. During the year ended December 31, 2022, we received gross proceeds of \$194.2 million and net proceeds of \$189.5 million, after deducting underwriting discounts and offering expenses, through the sale of 29,788,993 of our common stock, under both the First Sales Agreement and Second Sales Agreement. During the year ended December 31, 2021, we received gross proceeds of \$207.9 million and net proceeds of \$203.2 million, after deducting underwriting discounts and offering expenses, through the sale of 6,474,099 shares of our common stock, under the First Sales Agreement.

In the future, we may periodically offer one or more of these securities in amounts, prices and terms to be announced when and if the securities are offered. If any of the securities covered by the 2020 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of such offering at that time.

Cash Flows

Cash flows from operating, investing and financing activities (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Net cash (used in) provided by:			
Operating activities	\$ (292,757)	\$ (227,941)	\$ (205,134)
Investing activities	256,455	132	(317,853)
Financing activities	190,150	239,268	576,422
Net increase in cash, cash equivalents and restricted cash	<u>\$ 153,848</u>	<u>\$ 11,459</u>	<u>\$ 53,435</u>

Operating Activities

Net cash used in operating activities represents cash disbursements related to all of our activities other than investing and financing activities. Operating cash flow is derived by adjusting our net loss for non-cash items and changes in operating assets and liabilities. Net cash used in operating activities for the year ended December 31, 2022, was \$292.8 million compared to \$227.9 million for the same period in 2021. The increase of \$64.8 million in cash used in operating activities was primarily due to an increase in net loss driven by increased costs in research and development and pre-commercial activities, which was partially offset by an increase in non-cash charges of \$16.3 million primarily driven by higher stock-based compensation expenses, operating right-of-use assets associated with our office and manufacturing facility as well as embedded leases, and depreciation expenses, partially offset by accretion of discount on investments. In addition, it reflects a \$31.4 million increase in cash used by assets and liabilities driven

primarily by changes in accruals and accounts payable as well as prepaid assets, resulting from the increased workforce, overall growth in the business and operations, and the timing of vendor invoicing and related payments. These increases were offset by a net increase in our operating lease liabilities primarily driven by receipts of tenant improvement allowances for our new corporate headquarters office.

Net cash used in operating activities for the year ended December 31, 2021 was \$227.9 million compared to \$205.1 million for the same period in 2020. The increase of \$22.8 million in cash used in operating activities was primarily due to an increase in net loss driven by increased costs in research and development and pre-commercial activities, which was partially offset by an increase in non-cash charges of \$38.3 million primarily driven by higher stock-based compensation expenses, amortization of premiums on investments and operating right-of-use assets associated with our office and manufacturing facility as well as embedded leases, and depreciation expenses. In addition, it reflects a \$5.6 million reduction in our operating lease liabilities associated with payments on lease arrangements, offset by a \$16.0 million increase in accruals and accounts payable primarily related to our increased workforce, overall growth in the business and operations, and the timing of vendor invoicing and related payments.

Net cash used in operating activities for the year ended December 31, 2020 was \$205.1 million compared to \$158.9 million for the same period in 2019. The increase of \$46.2 million in cash used in operating activities was primarily attributable to an increase in net loss and increase in accruals primarily related to our research and development activities, which were partially offset by an increase in non-cash charges of \$22.8 million, primarily driven by higher-stock-based compensation expenses and amortization of premiums on investments.

Investing Activities

Net cash (used in) / provided by investing activities primarily consists of purchases, maturities of our investments and capital expenditures. Net cash provided by investing activities for the year ended December 31, 2022 was \$256.5 million compared to net cash provided by investing activities of \$0.1 million for the same period in 2021. The increase in cash provided by investing activities of \$256.4 million was primarily due to the timing of maturities and purchases of investments and lower capital expenditures in 2022.

Net cash provided by investing activities for the year ended December 31, 2021 was \$0.1 million compared to net cash used in investing activities of \$317.9 million for the same period in 2020. The increase in cash provided by investing activities of \$318.0 million was primarily due to the timing of maturities and purchases of investments and lower capital expenditures in 2021.

Net cash used in investing activities for the year ended December 31, 2020 was \$317.9 million compared to net cash provided by \$90.0 million for the same period in 2019. The increase in net cash used in investing activities of \$407.9 million was due primarily to purchases of investments with the proceeds received from the June 2020 Public Offering and an increase in capital expenditures to support the iCTC build-out.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2022 was \$190.2 million compared to net cash provided of \$239.3 million for the same period in 2021. The net cash provided by financing activities during the year ended December 30, 2022, related to \$189.5 million net cash proceeds from our “at the market” offering, \$1.7 million of cash receipts from the issuance of common stock under the 2020 ESPP, and \$1.6 million of cash receipts from the issuance of common stock upon the exercise of stock options. This was offset by cash used of \$2.6 million for tax payments related to vested RSUs.

Net cash provided by financing activities for the year ended December 31, 2021 was \$239.3 million compared to net cash provided of \$576.4 million for the same period in 2020. The net cash provided by financing activities during the year ended December 30, 2021, related to \$203.2 million net cash proceeds from our “at the market” offering and \$33.5 million of cash receipts from the issuance of common stock upon the exercise of stock options. The net cash provided by financing activities during the year ended December 31, 2020, primarily related to \$567.0 million net cash proceeds received in the June 2020 public offering and \$9.7 million cash proceeds from issuance of common stock upon exercise of stock options in 2021.

Net cash provided by financing activities for the year ended December 31, 2020, was \$576.4 million compared to net cash provided of \$6.1 million for the same period in 2019. The net cash provided in financing activities during the year ended December 31, 2020, primarily related to net cash proceeds of \$567.0 million received from the June 2020 Public Offering and \$9.7 million cash

proceeds received in issuing common stock upon exercise of stock options. Net cash provided by financing activities for the year ended December 31, 2019, related to cash proceeds received in issuing common stock upon exercise of stock options.

Contractual Obligations

The following table summarizes our non-cancellable contractual obligations as of December 31, 2022, and the effects that such obligations are expected to have on our liquidity and cash flows in future periods (in thousands):

	Payments due by period						
	Total	2023	2024	2025	2026	2027	Thereafter
Operating lease obligations - facilities							
(1)	\$ 124,970	\$ 8,304	\$ 8,424	\$ 8,240	\$ 7,989	\$ 8,186	\$ 83,827
Total (2), (3)	\$ 124,970	\$ 8,304	\$ 8,424	\$ 8,240	\$ 7,989	\$ 8,186	\$ 83,827

- (1) Our operating lease obligations consist of obligations under non-cancellable operating leases for our facilities in San Carlos, CA, Philadelphia, PA, and Tampa, FL. Excluded from the above are contractual obligations with certain Contract Manufacturing Organizations, or CMO, for the manufacturing facilities and minimum fixed commitment fees included in our manufacturing contracts, such as personnel, general support fee, and minimum production or material fees. These obligations met the conditions of embedded leases under Topic ASC 842 and were included in the Operating lease liabilities in the Consolidated Balance Sheets. However, these contracts are cancellable upon prior notice and as a result, are not included in the above table.
- (2) We acquire assets still in development and enter into research and development arrangements with third parties that often require milestone and royalty payments to the third-party contingent upon the occurrence of certain future events linked to the success of the asset in development. Milestone payments may be required, contingent upon the successful achievement of an important point in the development life-cycle of the pharmaceutical product (e.g., approval of the product for marketing by a regulatory agency). If required by the arrangement, we may have to make royalty payments based upon a percentage of the sales of the pharmaceutical product in the event that regulatory approval for marketing is obtained. Because of the contingent nature of these milestone payments, they are not included in the table of contractual obligations. These arrangements may be material individually, and in the event that milestones for multiple products covered by these arrangements were reached in the same period, the aggregate charge to expense could be material to the results of operations in any one period. In addition, these arrangements often give us the discretion to unilaterally terminate development of the product, which would allow us to avoid making contingent payments.
- (3) The contractual obligations table above excludes estimated equipment and construction costs of approximately \$20.0 million over the next year for the iCTC facility in Philadelphia, PA.

Off-Balance Sheet Arrangements

As of December 31, 2022 we did not have, and currently do not have, any off-balance sheet arrangements.

Critical Accounting Estimates

Our accounting policies are more fully described in Note 2 of the consolidated financial statements included in this Annual Report on Form 10-K. As described in Note 2, the preparation of our consolidated financial statements requires us to make estimates and judgments that affect the reported amounts in the financial statements and related disclosures. On an ongoing basis, we evaluate our significant accounting policies and estimates. We base our estimates on historical experience and on various market-specific and other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Estimates are assessed each period and updated to reflect current information. Actual results may differ from these estimates. We believe that the following discussion addresses our most critical accounting policies, which are those that are most important to the portrayal of our financial condition and results of operations and require management's most difficult, subjective and complex judgments.

Accrued Research and Development Costs

Research and development costs are expensed as incurred. Clinical development costs compose a significant component of research and development costs. We have a history of contracting with third parties, including contract research organizations (“CROs”), independent clinical investigators, and contract manufacturing organizations (“CMOs”) that perform various clinical trial activities on our behalf in connection with the ongoing development of our product candidates. The financial terms of these contracts are subject to negotiations and may vary from contract to contract and may result in uneven payment flow. We accrue and expense costs for clinical trial activities performed by third parties based upon the work completed to date for each clinical trial in accordance with agreements established with CROs, hospitals, and clinical investigators. Accruals for CROs and CMOs are recorded based on services received and efforts expended pursuant to agreements established with CROs, CMOs and other outside service providers. We determine our costs through discussions with internal clinical stakeholders and outside service providers as to the progress or stage of completion of clinical trials or services and the contracted fee to be paid for such services.

Included in our clinical development costs are investigator costs, which are costs associated with treatments administered at clinical sites as required under each clinical trial protocol. Our estimates for clinical investigator costs and timing of expense recognition will depend on a number of factors that include, but are not limited to, (i) the overall number of patients that enroll in the trial at each individual site, (ii) the length of clinical trial enrollment period, (iii) discontinuation and completion rates of patients, (iv) duration of patient safety follow-ups, (v) the number of sites included in the clinical trial, and (vi) the contracted fee of each participating site for patient treatment while on clinical trial, which can vary greatly for several reasons including, but not limited to, geographic region, medical center or physician costs, and overhead costs. In addition, our estimates for per patient trial costs will vary based on a number of factors that include, but are not limited to, the extent of additional treatments that may be administered by investigators as a result of patient health status, recoverability of patient costs through insurance carriers of patients, and unanticipated cost of injuries incurred as a result of the clinical trial treatment. We accrue estimated expenses resulting from obligations under investigator site agreements as the timing of payments does not always timely align with the periods over which the treatments are administered by the clinical investigators. These estimates are typically based on contracted amounts, patient visit data, discussions with internal clinical stakeholders and outside service providers, and historical look-back analysis of actual payments made to date.

We make judgements and estimates in determining the accrual balance in each reporting period. In the event advance payments are made to a CRO, CMO or other outside service provider, the payments are recorded within prepaid expenses and other current assets and subsequently recognized as research and development expense when the associated services have been performed. As actual costs become known, we adjust our estimates, liabilities and assets. Inputs used in our determination of estimates discussed above may vary from actual, which will result in adjustments to research and development expense in future periods.

Inflation

Inflation has not had a material effect on our business, financial condition, or results of operations over our two most recent fiscal years.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Interest Rate Risk

Our exposure to market risk is limited primarily to interest income sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because a significant portion of our investments are in interest bearing cash accounts consisting of short-term debt securities issued by the U.S. government. The primary objective of our investment activities is to preserve principal. We adhere to an investment policy that requires us to limit amounts invested in securities based on credit rating, maturity, industry group and investment type and issuer, except for securities issued by the U.S. government. We do not have any derivative financial instruments or foreign currency instruments. As of December 31, 2022, we had \$372.5 million invested in marketable securities with a maturity date of less than one year. As such we believe that we are not exposed to any material market risk. If interest rates had varied by 1% in the year ended December 31, 2022, the fair value of our investment portfolio would increase or decrease by approximately \$0.6 million.

Inflation Risk

Inflation has not had a material effect on our business, financial condition or results of operations during the years ended December 31, 2022, 2021, or 2020.

Item 8. Financial Statements and Supplementary Data

Financial Statements are referred to in Item 15, listed in the Index to Financial Statements as a part of this Annual Report on Form 10-K, and are incorporated herein by this reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

(a) Evaluation of Disclosure Controls and Procedures:

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow for timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and in reaching a reasonable level of assurance, management is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

As of the end of the period covered by this Annual Report on Form 10-K, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures. Based on the foregoing, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level.

(b) Management's Annual Report on Internal Control Over Financial Reporting:

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rules 13a-15(f) and 15d-15(f). Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2022, based on the framework in *Internal Control—Integrated Framework 2013* issued by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO. Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

The independent registered public accounting firm, Ernst and Young LLP, has issued an audit report on our internal control over financial reporting. The report on the audit of internal control over financial reporting is included in this Annual Report on Form 10-K.

(c) Changes in Internal Control Over Financial Reporting:

There has been no change in our internal control over financial reporting during our most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Subsequent Event – Acquisition of Proleukin®

Pursuant to that certain Option Agreement entered into on January 23, 2023 or the Option Agreement, between Iovance and Clinigen Holdings Limited, Clinigen Healthcare Limited and Clinigen, Inc., collectively, Clinigen, we will acquire worldwide rights to Proleukin®, aldesleukin, an IL-2 product used to promote T-cell activity following TIL infusion.

Material terms of the Option Agreement include an upfront payment of £167.7 million, or approximately \$200 million, a £41.7 million, or approximately \$50 million, milestone payment upon first approval of lifileucel in advanced melanoma, and deferred consideration based on double-digit rates on Proleukin® global net sales payable from Iovance to Clinigen following the completion of the transaction for the applicable deferred consideration term.

Subject to the terms and conditions of the Option Agreement, Clinigen granted us a call option to purchase (i) all issued and outstanding shares of Clinigen SP Limited, the Target, (ii) the business of the Target and Clinigen comprising the manufacturing, supply, commercialization and the generation of income from Proleukin® rights and the undertaking of an active role in the development, maintenance and exploitation of those rights, and (iii) certain specified assets identified in the Option Agreement and we granted Clinigen a put option to sell them.

The Option Agreement is subject to customary termination provisions, and we would be required to pay to Clinigen a reverse termination fee, less certain transaction fees and expenses incurred by us, upon certain events as described in the Option Agreement.

We have provided Clinigen with a parent guarantee in favor of Clinigen, which guarantees that we will promptly fulfill all its obligations under the Option Agreement, subject to the conditions set forth in the Option Agreement.

The closing of the transaction is subject to required regulatory approvals and clearances and other customary closing conditions.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K because we will file a definitive Proxy Statement for the Annual Meeting of Stockholders pursuant to Regulation 14A of the Securities Exchange Act of 1934 (the Proxy Statement), not later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K, and the applicable information included in the Proxy Statement is incorporated herein by reference.

Item 10. Directors, Executive Officers, and Corporate Governance

Information required by this Item 10 will be presented in the Proxy Statement “Election of Directors,” “Management Executive Officers,” “Section 16(a) Beneficial Ownership Reporting Compliance” and “Board of Directors and Corporate Governance,” and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this Item is incorporated herein by reference to the sections entitled “Executive Compensation,” “Executive Compensation—Compensation Discussion and Analysis” and “Directors’ Compensation” in the Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item is incorporated herein by reference to the sections entitled “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information” in the Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated herein by reference to the section entitled “Certain Relationships and Related Transactions” in the Proxy Statement.

Item 14. Principal Accountant's Fees and Services

Information required by this Item is incorporated herein by reference to the section of the Proxy Statement entitled "Principal Accountant Fees and Services."

PART IV

Item 15. Exhibits, Financial Statements Schedules

The Company's consolidated financial statements and related notes thereto are listed and included in this Annual Report on Form 10-K beginning on page F-1. The following exhibits are filed with, or are incorporated by reference into, this Annual Report on Form 10-K.

EXHIBIT INDEX

Exhibit	Description
2.1	Plan of Conversion (incorporated herein by reference to Exhibit 2.1 to the Registrant's Current Report on Form 8-K filed with the Commission on June 2, 2017).
3.1	Articles of Conversion (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the Commission on June 2, 2017).
3.2	Certificate of Conversion (incorporated herein by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K filed with the Commission on June 2, 2017).
3.3	Certificate of Incorporation (incorporated herein by reference to Exhibit 3.3 to the Registrant's Current Report on Form 8-K filed with the Commission on June 2, 2017).
3.4	Certificate of Designations of Rights, Preferences and Privileges of Series A Convertible Preferred Stock (incorporated herein by reference to Exhibit 3.4 to the Registrant's Post-Effective Amendment No. 1 to the Registration Statement on Form S-3 (file no. 333-214073) filed with the Commission on July 31, 2017).
3.5	Certificate of Designations of Rights, Preferences and Privileges of Series B Preferred Stock (incorporated herein by reference to Exhibit 3.5 to the Registrant's Post-Effective Amendment No. 1 to the Registration Statement on Form S-3 (file no. 333-214073 incorporated by reference into file no. 333-212373) filed with the Commission on July 31, 2017).
3.6	Certificate of Amendment of Certificate of Incorporation (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the Commission on June 27, 2017).
3.7	Certificate of Amendment of Certificate of Incorporation (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8 K filed with the Commission on June 11, 2019).
3.8	Third Amended and Restated Bylaws (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the Commission on April 29, 2022).
4.1	Specimen of Stock Certificate (incorporated herein by reference to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K filed with the Commission on March 12, 2018).
4.2	Description of Securities (incorporated herein by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K filed with the Commission on March 6, 2019).
10.1	Genesis Biopharma, Inc. 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8 K filed with the Commission on October 20, 2011).#
10.2	Form of Incentive Stock Option Agreement under the Genesis Biopharma Inc. 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.4 to the Registrant's Annual Report on Form 10-K filed with the Commission on February 25, 2020).#
10.3	Form of Non-Qualified Stock Option Agreement under the Genesis Biopharma Inc. 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.5 to the Registrant's Annual Report on Form 10-K filed with the Commission on February 25, 2020).#
10.4	Lion Biotechnologies, Inc. 2014 Equity Incentive Plan, as amended (incorporated herein by reference to Appendix A to the Registrant's Definitive Proxy Statement on Schedule 14A filed with the Commission on July 7, 2016).#
10.5	Form of Incentive Stock Option Agreement under the Lion Biotechnologies, Inc. 2014 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.7 to the Registrant's Annual Report on Form 10-K filed with the Commission on February 25, 2020).#

- 10.6 Form of Non-Qualified Stock Option Agreement under the Lion Biotechnologies, Inc. 2014 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.8 to the Registrant's Annual Report on Form 10-K filed with the Commission on February 25, 2020).#
- 10.7 Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan, as amended (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Quarterly Report on Form 10-Q filed with the Commission on August 4, 2022).#
- 10.8 Form of Incentive Stock Option Agreement under the Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.10 of Registrant's Annual Report on Form 10-K filed with the Commission on February 25, 2020).#
- 10.9 Form of Non-Qualified Stock Option Agreement under the Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.11 of Registrant's Annual report on Form 10-K filed with the Commission on February 25, 2020).#
- 10.10 Form of Stock Unit Notice and Stock Unit Agreement under the Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan, as amended (June 2021 Retention Equity Awards) (incorporated herein by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed with the Commission on August 5, 2021).#
- 10.11 Form of Nonqualified Stock Option Award Agreement under the Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan, as amended (June 2021 Retention Equity Awards) (incorporated herein by reference to Exhibit 10.3 to the Registrant's Current Report on Form 10-Q filed with the Commission on August 5, 2021).#
- 10.12 Iovance Biotherapeutics, Inc. 2020 Employee Stock Purchase Plan (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed with the Commission on June 9, 2020).#
- 10.13 Iovance Biotherapeutics, Inc. Amended and Restated 2021 Inducement Plan (incorporated herein by reference to Exhibit 10.13 to the Registrant's Annual Report on Form 10-K filed with the Commission on February 24, 2022).#**
- 10.14 Form of Stock Option Grant Notice and Stock Option Agreement under the 2021 Inducement Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed with the Commission on September 23, 2021).#
- 10.15 Form of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement under the 2021 Inducement Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K filed with the Commission on September 23, 2021).#
- 10.16 Form of Deferred Stock Unit Notice and Deferred Stock Unit Agreement under the Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed with the Commission on August 4, 2022).#
- 10.17 Patent License Agreement by and between Genesis Biopharma, Inc. and the National Institutes of Health effective October 5, 2011 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K/A filed with the Commission on December 13, 2011).*
- 10.18 Cooperative Research and Development Agreement for Intramural-PHS Clinical Research, dated August 5, 2011, by and between the U.S. Department of Health and Human Services, as represented by the National Cancer Institute, and Genesis Biopharma, Inc. (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K/A (Amendment No. 2) filed with the Commission on November 29, 2011).
- 10.19 Form of Director Stock Award Agreement (incorporated herein by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed with the Commission on July 25, 2013).#
- 10.20 Form of Registration Rights Agreement by and among Lion Biotechnologies, Inc. and the Investors thereunder (incorporated herein by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed with the Commission on October 31, 2013).
- 10.21 Cooperative Research and Development Agreement for the Development and Evaluation of the NCI Proprietary Adoptive Cell Transfer Immunotherapy Using Tumor Infiltrating Lymphocytes in Patients with Metastatic Melanoma, Bladder, Lung, Triple-negative Breast, and HPV-associated Cancers, Utilizing Lion Biotechnologies, Inc.'s Business Development Expertise in Adoptive Cell Transfer Immunotherapy, executed by Lion Biotechnologies, Inc. on January 22, 2015 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed with the Commission on January 27, 2015).*
- 10.22 Patent License Agreement, dated February 9, 2015, by and between Lion Biotechnologies, Inc. and the National Institutes of Health (incorporated herein by reference to Exhibit 10.47 to the Registrant's Annual Report on Form 10 K filed with the Commission on March 16, 2015).*
- 10.23 Patent License Agreement, dated February 10, 2015, by and between Lion Biotechnologies, Inc. and the National Institutes of Health (incorporated herein by reference to Exhibit 10.46 to the Registrant's Annual Report on Form 10-K filed with the Commission on March 16, 2015).*

- 10.24 First Amendment to Patent License Agreement, effective October 2, 2015, by and between Lion Biotechnologies, Inc. and the National Institutes of Health (incorporated herein by reference to Exhibit 10.47 to the Registrant's Quarterly Report on Form 10-Q filed with the Commission on November 6, 2015).*
- 10.25 Amended and Restated Patent License Agreement, by and between Iovance Biotherapeutics, Inc. and the National Institutes of Health (incorporated herein by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10 Q filed with the Commission on August 5, 2021).*
- 10.26 Form of Securities Purchase Agreement, dated June 2, 2016, by and among Lion Biotechnologies, Inc. and the Investors thereunder (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed with the Commission on June 3, 2016).
- 10.27 Form of Registration Rights Agreement, dated June 2, 2016, by and among Lion Biotechnologies, Inc. and the Investors thereunder (incorporated herein by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed with the Commission on June 3, 2016).
- 10.28 Amendment #2 to the Cooperative Research and Development Agreement #02734, dated August 18, 2016, by and between the National Cancer Institute and Lion Biotechnologies, Inc. (incorporated herein by reference to Exhibit 10.3 to Amendment No. 2 to Registrant's Registration Statement on Form S 1 filed with the Commission on August 31, 2016).
- 10.29 Manufacturing Services Agreement, dated November 23, 2015, by and between WuXi Advanced Therapies, Inc. and Lion Biotechnologies, Inc. (incorporated herein by reference to Exhibit 10.36 to the Registrant's Annual Report on Form 10-K filed with the Commission on March 9, 2017).*
- 10.30 Strategic Alliance Agreement, effective as of April 17, 2017, between Lion Biotechnologies, Inc. and The University of Texas M.D. Anderson Cancer Center (incorporated herein by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10 Q filed with the Commission on August 3, 2017).*
- 10.31 First Amendment to the Strategic Alliance Agreement by and between Iovance Biotherapeutics, Inc. and The University of Texas M.D. Anderson Cancer Center, effective as of August 2, 2017 (incorporated herein by reference to Exhibit 10.34 to the Registrant's Annual Report on Form 10-K filed with the Commission on March 12, 2018).
- 10.32 Second Amendment to the Strategic Alliance Agreement by and between Iovance Biotherapeutics, Inc. and The University of Texas M.D. Anderson Cancer Center, effective February 16, 2018 (incorporated herein by reference to Exhibit 10.35 to the Registrant's Annual Report on Form 10-K filed with the Commission on March 12, 2018).
- 10.33 Executive Employment Agreement, effective as of June 1, 2016, by and between Maria Fardis and Lion Biotechnologies, Inc. (incorporated herein by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10 Q filed with the Commission on August 9, 2016).*#
- 10.34 Severance Agreement and General Release, effective as of July 8, 2020, between Iovance Biotherapeutics, Inc. and Timothy Morris (incorporated herein by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed with the Commission on August 6, 2020).*#
- 10.35 Executive Employment Agreement, effective as of September 30, 2016, by and between Frederick G. Vogt and Lion Biotechnologies, Inc. (incorporated herein by reference to Exhibit 10.32 to the Registrant's Annual Report on Form 10 K filed with the Commission on March 12, 2018).#
- 10.36 Executive Employment Agreement effective as of July 18, 2019, by and between Friedrich-Reinhard Graf Finck von Finckenstein, M.D. and Iovance Biotherapeutics, Inc. (incorporated herein by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed with the Commission on August 1, 2019).
- 10.37 Executive Employment Agreement, effective as of December 14, 2020, by and between Jean-Marc Bellemin and Iovance Biotherapeutics, Inc. (incorporated herein by reference to Exhibit 10.30 of the Registrant's Annual Report on Form 10-K filed with the Commission on February 25, 2021).#+
- 10.38 Executive Employment Agreement, effective as of March 15, 2021, by and between Igor Bilinsky, Ph.D. and Iovance Biotherapeutics, Inc. (incorporated herein by reference to Exhibit 10.4 of the Registrant's Current Report on Form 10-K filed with the Commission on May 6, 2021).#+
- 10.39 Office Lease, effective as of August 4, 2016, by and between Lion Biotechnologies, Inc. and Hudson Skyway Landing, LLC (incorporated herein by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8 K filed with the Commission on August 8, 2016).
- 10.40 Office Lease, effective as of October 19, 2018, by and between Iovance Biotechnologies, Inc. and Hudson Skyway Landing, LLC (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8 K filed with the Commission on October 25, 2018).
- 10.41 First Amendment to the Office Lease, effective as of June 19, 2019, between Iovance Biotherapeutics, Inc. and Hudson Skyway Landing, LLC (incorporated herein by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed with the Commission on November 4, 2019).

- 10.42 Second Amendment to the Office Lease, effective as of February 8, 2021, by and between Iovance Biotherapeutics, Inc. and Hudson Skyway Landing, LLC (incorporated herein by reference to Exhibit 10.2 of the Registrant’s Current Report on Form 8-K filed with the Commission on February 9, 2021).
- 10.43 First Amendment to the Office Lease, effective as of February 8, 2021, by and between Iovance Biotherapeutics, Inc. and Hudson Skyway Landing, LLC (incorporated herein by reference to Exhibit 10.3 of the Registrant’s Current Report on Form 8-K filed with the Commission on February 9, 2021).
- 10.44 Lease Agreement, effective as of May 28, 2019, by and between Iovance Biotherapeutics, Inc. and 300 Rouse Boulevard, LLC (incorporated herein by reference to Exhibit 10.1 of the Registrant’s Current Report on Form 8-K filed with the Commission on June 3, 2019).
- 10.45 First Amendment to the Lease Agreement, effective as of August 20, 2019, between Iovance Biotherapeutics, Inc. and 300 Rouse Boulevard, LLC (incorporated herein by reference to Exhibit 10.2 of the Registrant’s Quarterly Report on Form 10-Q filed with the Commission on November 4, 2019).
- 10.46 Second Amendment to the Lease Agreement, effective as of June 30, 2020, between Iovance Biotherapeutics, Inc. and 300 Rouse Boulevard, LLC (incorporated herein by reference to Exhibit 10.3 of the Registrant’s Quarterly Report on Form 10-Q filed with the Commission on August 6, 2020).
- 10.47 Third Amendment to the Lease Agreement, effective as of November 1, 2021, between Iovance Biotherapeutics, Inc. and 300 Rouse Boulevard, LLC (incorporated herein by reference to Exhibit 10.46 to the Registrant’s Annual Report on Form 10-K filed with the Commission on February 24, 2022).
- 10.48 Lease Agreement, effective as of February 8, 2021, by and between Iovance Biotherapeutics, Inc. and ARE-San Francisco No. 63, LLC (incorporated herein by reference to Exhibit 10.1 of the Registrant’s Current Report on Form 8-K filed with the Commission on February 9, 2021).
- 10.49 Option Agreement, dated January 23, 2023, by and among Iovance Biotherapeutics, Inc., Iovance Biotherapeutics UK Ltd, Clinigen Holdings Limited, Clinigen Healthcare Limited, and Clinigen, Inc. (incorporated herein by reference to Exhibit 10.1 of the Registrant’s Current Report on Form 8-K/A filed with the Commission on January 27, 2023).
- 21.1 Subsidiaries of the Company.**
- 23.1 Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.**
- 23.2 Consent of Marcum, LLP, Independent Registered Public Accounting Firm.**
- 24.1 Power of Attorney (included on the signature page of this Annual Report).
- 31.1 Rule 13a-14(a)/15d-14(a) Certification of Chief Executive Officer.**
- 31.2 Rule 13a-14(a)/15d-14(a) Certification of Chief Financial Officer.**
- 32.1 Section 1350 Certification of Chief Executive Officer (furnished herewith).**
- 32.2 Section 1350 Certification of Chief Financial Officer (furnished herewith).**
- 101 The following financial information from the Annual Report on Form 10-K of Iovance Biotherapeutics, Inc. for the year ended December 31, 2022, formatted inline XBRL (eXtensible Business Reporting Language): (1) Balance Sheets as of December 31, 2022 and 2021 (2) Statements of Income for the years ended December 31, 2022 and 2021; (3) Statements of Shareholders’ Equity for the years ended December 31, 2022 and 2021; (4) Statements of Cash Flows for the years ended December 31, 2022 and 2021; and (5) Notes to Financial Statements.
- 104 Cover Page Interactive Data File – the cover page interactive date file does not appear in the Interactive Date File because its XBRL tags are embedded within the Inline XBRL document.

* Certain portions of the Exhibit have been omitted based upon a request for confidential treatment filed by us with the Commission. The omitted portions of the Exhibit have been separately filed by us with the Commission.

** Filed herewith.

Indicates a management contract or compensatory plan or arrangement.

+ Certain portions of the Exhibit have been redacted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

Item 16. Form 10-K Summary

We may voluntarily include a summary of information required by Form 10-K under this Item 16. We have elected not to include such summary information.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

IOVANCE BIOTHERAPEUTICS, INC.

Date: February 28, 2023

By: /s/ Frederick G. Vogt

Name: Frederick G. Vogt, Ph.D., J.D.

Title: Interim Chief Executive Officer and President, and General Counsel

POWER OF ATTORNEY

Know all persons by these presents, that each person whose signature appears below constitutes and appoints Frederick G. Vogt, and Jean-Marc Bellemin, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place, and stead, in any and all capacities, to sign any and all amendments to this Annual Report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming that all said attorneys-in-fact and agents, or any of them or their or his or her substitute or substituted, may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Frederick G. Vogt</u> Frederick G. Vogt, Ph.D., J.D.	Interim Chief Executive Officer and President, and General Counsel (Principal Executive Officer)	February 28, 2023
<u>/s/ Jean-Marc Bellemin</u> Jean-Marc Bellemin	Chief Financial Officer and Treasurer (Principal Financial Officer and Accounting Officer)	February 28, 2023
<u>/s/ Merrill A. McPeak</u> Merrill A. McPeak	Director	February 28, 2023
<u>/s/ Michael Weiser</u> Michael Weiser, M.D., Ph.D.	Director	February 28, 2023
<u>/s/ Ryan D. Maynard</u> Ryan D. Maynard	Director	February 28, 2023
<u>/s/ Iain Dukes</u> Iain Dukes, D.Phil.	Director	February 28, 2023
<u>/s/ Wayne Rothbaum</u> Wayne Rothbaum	Director	February 28, 2023
<u>/s/ Athena Countouriotis</u> Athena Countouriotis, M.D.	Director	February 28, 2023
<u>/s/ Wendy L. Dixon</u> Wendy L. Dixon, Ph.D.	Director	February 28, 2023

IOVANCE BIOTHERAPEUTICS, INC.
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REPORT OF ERNST & YOUNG LLP, INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Iovance Biotherapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Iovance Biotherapeutics, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 28, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued clinical development costs

Description of the Matter During 2022, the Company incurred \$294.8 million of research and development expenses and accrued \$14.8 million of clinical development costs as of December 31, 2022. As described in Note 2 to the Financial Statements, the Company determines accruals for clinical development costs based on the various clinical trial activities performed pursuant to contracts with third-party contract research organizations (“CROs”), which comprise a significant component of the Company’s research and development expenses. Clinical development costs are accrued and expensed based on the percentage of work completed in accordance with agreements established with CROs. The timing and amount of payments required under each individual arrangement are often different from the pattern of costs actually incurred. The Company accrues clinical development costs under its contracts with third-party service providers based on the progress or stage of completion of trials or services completed by vendors over the life of the individual trial, number of subjects enrolled, and number of sites activated.

Auditing management’s accounting for accrued clinical development costs is especially challenging because the evaluation is dependent on a high volume of data exchanged between third-party service providers, internal clinical personnel, and the Company’s finance team. Determining accrued amounts is based on an evaluation of the unique terms and conditions set in each respective CRO agreement. Additionally, due to the duration of clinical trial activities and the timing of invoices received from third parties, the determination of the accrual for services incurred requires management to ensure they have complete and accurate information from vendors.

How We Addressed the Matter in Our Audit To test accrued clinical development costs, our audit procedures included, among others, testing the accuracy and completeness of the inputs used in management’s analysis to determine costs incurred. We also inspected terms and conditions for selected CRO contracts and change orders and compared these to the cost models management used in tracking the progress of service agreements. We met with internal clinical personnel to understand the status of significant clinical activities. We evaluated services provided by third parties by understanding the terms and timeline of significant projects, evaluated management’s determination of work performed, subjects enrolled, sites activated and costs incurred, and obtained external confirmation of the direct cost, and contracts and change orders executed by the Company for selected CROs as well as key terms and conditions of those contracts. Further, we inspected selected invoices received from third parties after the balance sheet date and evaluated whether services performed prior to the balance sheet date had been properly included in costs accrued.

/s/ Ernst & Young LLP

We have served as the Company’s auditor since 2021.
San Mateo, California
February 28, 2023

REPORT OF ERNST & YOUNG LLP, INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Iovance Biotherapeutics, Inc.

Opinion on Internal Control over Financial Reporting

We have audited Iovance Biotherapeutics, Inc.'s internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Iovance Biotherapeutics, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the balance sheets of the Company as of December 31, 2022 and 2021, the related statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2022, and the related notes, and our report dated February 28, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

San Mateo, California
February 28, 2023

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and Board of Directors of
Iovance Biotherapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Iovance Biotherapeutics, Inc. (the “Company”) as of December 31, 2020, the related consolidated statements of operations, comprehensive loss, stockholders’ equity and cash flows for the year ended December 31, 2020, and the related notes (collectively referred to as the “financial statements”). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020, and the results of its operations and its cash flows for the year ended December 31, 2020, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audit included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audit provides a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Incremental Borrowing Rate (Leases)

Description of the Matter

As discussed in Note 10 to the 2020 consolidated financial statements, the Company’s reported right-of-use assets, current lease liabilities and long-term lease liabilities, utilize discount rates to calculate the estimated present value of future lease payments. Since the Company’s leases do not provide an implicit rate, management utilized a third-party valuation specialist to assist in estimating the incremental borrowing rates used in its present value calculation, which required subjectivity. The incremental borrowing rate is the rate of interest that a lessee would have to pay to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment. As of December 31, 2020, the weighted average incremental borrowing rate used to determine the operating lease liability is 8.3%.

Auditing management's assessment of its incremental borrowing rate is highly subjective and judgmental as the Company has no outstanding debt nor committed credit facilities, secured or otherwise, that would have comparable collateral or similar terms as their underlying leases. Further, changes in the incremental borrowing rate may have a material impact on the measurement of the Company's right-of-use assets, current lease liabilities and long-term lease liabilities. Based on the level of management judgment, we have determined the incremental borrowing rate to be a critical audit matter. This required a high degree of auditor judgment and an increased extent of effort, including the need to involve our valuation specialists, when performing audit procedures to evaluate the reasonableness of management's estimation of the incremental borrowing rate.

How We Addressed the Matter in Our Audit

Our audit procedures included, amongst others:

- We obtained an understanding, evaluated the design, and tested the operating effectiveness of management's controls with regards to the methodology, inputs, and assumptions used to determine the incremental borrowing rate, including those over management's review of its third-party specialist valuation report.
- We obtained an understanding of the factors considered and assumptions made by management and the valuation specialists in developing the estimate of the incremental borrowing rate, the sources of data relevant to these factors and assumptions and the procedures used to obtain the data, and the methods used to calculate the estimate.
- We reviewed the contractual terms of the lease agreements to ensure the commencement dates, any lease term extensions and/or early termination clauses were properly considered in determining the appropriate lease term for calculating the incremental borrowing rates.
- With the assistance of our valuation specialists, we performed an independent estimate of the incremental borrowing rate and compared the results to the Company's estimate.
- We evaluated the reasonableness of the valuation methods and assumptions used by management and the Company's valuation specialist to estimate the incremental borrowing rates for borrowing amounts and terms comparable to their outstanding leases by:
 - Developing an independent estimate of the incremental borrowing rates with the assistance of our valuation specialists by utilizing third party data related to comparable company borrowings with comparable payment terms.
 - Performing a sensitivity analysis on incremental borrowing rates used to determine the impact rate changes could have on the present value calculation of the Company's operating lease right-of-use assets and operating lease liabilities.

/s/ Marcum LLP

Marcum LLP

We served as the Company's auditor from 2016 to 2021.

New York, NY
February 25, 2021

IOVANCE BIOTHERAPEUTICS, INC.
Consolidated Balance Sheets
(In thousands, except share and per share information)

	December 31, 2022	December 31, 2021
ASSETS		
Current Assets		
Cash and cash equivalents	\$ 231,731	\$ 78,229
Short-term investments	240,114	426,181
Prepaid expenses and other assets	7,271	3,546
Total Current Assets	<u>479,116</u>	<u>507,956</u>
Property and equipment, net	105,232	100,938
Operating lease right-of-use assets	73,015	68,983
Long-term investments	—	91,588
Restricted cash	6,430	6,084
Long-term assets	189	1,784
Total Assets	<u>\$ 663,982</u>	<u>\$ 777,333</u>
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current Liabilities		
Accounts payable	\$ 26,603	\$ 27,377
Accrued expenses	52,295	56,766
Operating lease liabilities	12,587	5,057
Total Current Liabilities	<u>91,485</u>	<u>89,200</u>
Non-Current Liabilities		
Operating lease liabilities – non-current	71,859	65,474
Long-term note payable	1,000	1,000
Total Non-Current Liabilities	<u>72,859</u>	<u>66,474</u>
Total Liabilities	<u>164,344</u>	<u>155,674</u>
Commitments and contingencies		
Stockholders' Equity		
Series A Convertible Preferred stock, \$0.001 par value; 17,000 shares designated, 194 shares issued and outstanding as of December 31, 2022 and December 31, 2021	—	—
Series B Convertible Preferred stock, \$0.001 par value; 11,500,000 shares designated, 2,842,158 shares issued and outstanding as of December 31, 2022 and December 31, 2021	3	3
Common stock, \$0.000041666 par value; 300,000,000 shares authorized, 187,812,072 and 157,004,742 shares issued and outstanding as of December 31, 2022 and December 31, 2021, respectively	8	7
Accumulated other comprehensive loss	(902)	(601)
Additional paid-in capital	2,068,867	1,794,695
Accumulated deficit	(1,568,338)	(1,172,445)
Total Stockholders' Equity	<u>499,638</u>	<u>621,659</u>
Total Liabilities and Stockholders' Equity	<u>\$ 663,982</u>	<u>\$ 777,333</u>

The accompanying notes are an integral part of these consolidated financial statements.

IOVANCE BIOTHERAPEUTICS, INC.
Consolidated Statements of Operations
(In thousands, except per share information)

	Years Ended December 31,		
	2022	2021	2020
Costs and expenses			
Research and development	\$ 294,781	\$ 259,039	\$ 201,727
General and administrative	104,097	83,664	60,210
Total costs and expenses	<u>398,878</u>	<u>342,703</u>	<u>261,937</u>
Loss from operations	(398,878)	(342,703)	(261,937)
Other income			
Interest income, net	2,985	451	2,356
Net Loss	<u>(395,893)</u>	<u>(342,252)</u>	<u>(259,581)</u>
Net Loss Per Share of Common Stock, Basic and Diluted	\$ (2.49)	\$ (2.23)	\$ (1.88)
Weighted Average Shares of Common Stock Outstanding, Basic and Diluted	<u>159,259</u>	<u>153,406</u>	<u>138,301</u>

The accompanying notes are an integral part of these consolidated financial statements.

IOVANCE BIOTHERAPEUTICS, INC.
Consolidated Statements of Comprehensive Loss
(in thousands)

	Years Ended December 31,		
	2022	2021	2020
Net Loss	\$ (395,893)	\$ (342,252)	\$ (259,581)
Other comprehensive loss:			
Unrealized loss on investments	(301)	(620)	(201)
Comprehensive Loss	\$ (396,194)	\$ (342,872)	\$ (259,782)

The accompanying notes are an integral part of these consolidated financial statements.

IOVANCE BIOTHERAPEUTICS, INC.
Consolidated Statements of Stockholders' Equity
(In thousands, except share information)

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated other Comprehensive Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount	Shares	Amount				
Balance - January 1, 2020	194	\$ —	3,581,119	\$ 4	126,411,808	\$ 5	\$ 869,354	\$ 220	\$ (570,612)	\$ 298,971
Stock-based compensation expense	—	—	—	—	—	—	40,775	—	—	40,775
Vesting of restricted stock shares issued for services	—	—	—	—	13,449	—	112	—	—	112
Tax payments related to shares withheld for vested restricted stock units	—	—	—	—	—	—	(284)	—	—	(284)
Common stock issued upon exercise of stock options	—	—	—	—	973,854	—	9,663	—	—	9,663
Common stock sold in public offering, net of offering costs	—	—	—	—	19,475,806	1	567,042	—	—	567,043
Unrealized loss on investments	—	—	—	—	—	—	—	(201)	—	(201)
Net loss	—	—	—	—	—	—	—	—	(259,581)	(259,581)
Balance - December 31, 2020	194	\$ —	3,581,119	\$ 4	146,874,917	\$ 6	\$ 1,486,662	\$ 19	\$ (830,193)	\$ 656,498
Stock-based compensation expense	—	—	—	—	—	—	69,765	—	—	69,765
Common stock issued upon purchase through employee stock purchase plan	—	—	—	—	94,148	—	1,586	—	—	1,586
Common stock issued upon exercise of stock options	—	—	—	—	2,822,617	—	33,526	—	—	33,526
Common stock sold in public offering, net of offering costs	—	—	—	—	6,474,099	1	203,155	—	—	203,156
Common stock issued from preferred stock conversion	—	—	(738,961)	(1)	738,961	—	1	—	—	—
Unrealized loss on investments	—	—	—	—	—	—	—	(620)	—	(620)
Net loss	—	—	—	—	—	—	—	—	(342,252)	(342,252)
Balance - December 31, 2021	194	\$ —	2,842,158	\$ 3	157,004,742	\$ 7	\$ 1,794,695	\$ (601)	\$ (1,172,445)	\$ 621,659
Stock-based compensation expense	—	—	—	—	—	—	84,022	—	—	84,022
Common stock issued upon purchase through employee stock purchase plan	—	—	—	—	262,701	—	1,655	—	—	1,655
Vesting of restricted shares issued for services	—	—	—	—	894,760	—	—	—	—	—
Tax payments related to shares retired for vested restricted stock units	—	—	—	—	(342,703)	—	(2,649)	—	—	(2,649)
Common stock issued upon exercise of stock options	—	—	—	—	203,579	—	1,642	—	—	1,642
Unrealized loss on investments	—	—	—	—	—	—	—	(301)	—	(301)
Common stock sold in public offering, net of offering costs	—	—	—	—	29,788,993	1	189,501	—	—	189,502
Net loss	—	—	—	—	—	—	—	—	(395,893)	(395,893)
Balance - December 31, 2022	194	\$ —	2,842,158	\$ 3	187,812,072	\$ 8	\$ 2,068,867	\$ (902)	\$ (1,568,338)	\$ 499,638

The accompanying notes are an integral part of these consolidated financial statements.

IOVANCE BIOTHERAPEUTICS, INC.
Consolidated Statements of Cash Flows
(In thousands)

	Years Ended December 31,		
	2022	2021	2020
Cash Flows from Operating Activities			
Net loss	\$ (395,893)	\$ (342,252)	\$ (259,581)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	84,022	69,765	40,887
Amortization of right of use asset	11,825	10,869	7,572
Depreciation and amortization	9,310	3,111	1,140
Accretion of discounts and premiums on investments	474	6,013	1,865
Loss on write-off of fixed assets	397	—	—
Changes in assets and liabilities:			
Prepaid expenses, other assets and long-term assets	(2,130)	2,775	(6,688)
Operating lease liabilities, net of tenant improvement allowance received	(1,942)	(5,882)	(11,474)
Accounts payable	5,883	6,976	(2,964)
Accrued expenses and other liabilities	(4,703)	20,684	24,109
Net cash used in operating activities	<u>(292,757)</u>	<u>(227,941)</u>	<u>(205,134)</u>
Cash Flows from Investing Activities			
Maturities of investments	522,696	762,914	676,601
Purchase of investments	(245,816)	(725,208)	(947,663)
Purchase of property and equipment	(20,425)	(37,574)	(46,791)
Net cash provided by / (used in) investing activities	<u>256,455</u>	<u>132</u>	<u>(317,853)</u>
Cash Flows from Financing Activities			
Tax payments related to shares withheld for vested restricted stock units	(2,649)	—	(284)
Proceeds from the issuance of common stock under employee stock purchase plan	1,655	1,586	—
Proceeds from the issuance of common stock upon exercise of options	1,642	33,526	9,663
Proceeds from the issuance of common stock, net	189,502	203,156	567,043
Proceeds from the issuance of debt	—	1,000	—
Net cash provided by financing activities	<u>190,150</u>	<u>239,268</u>	<u>576,422</u>
Net increase in cash, cash equivalents and restricted cash	153,848	11,459	53,435
Cash, Cash Equivalents and Restricted Cash Beginning of Period	84,313	72,854	19,419
Cash, Cash Equivalents and Restricted Cash End of Period	<u>\$ 238,161</u>	<u>\$ 84,313</u>	<u>\$ 72,854</u>
Supplemental disclosure of non-cash investing and financing activities:			
Net unrealized loss on investments	\$ (301)	\$ (620)	(201)
Acquisition of property and equipment included in accounts payable and accrued expenses	5,985	12,410	5,094
Conversion of convertible preferred stock to common stock	—	1	—
Lease liabilities arising from obtaining right-of-use asset from new leases	553	17,275	45,968
Lease liabilities arising from obtaining right-of-use asset from lease modifications	15,304	7,800	826

The accompanying notes are an integral part of these consolidated financial statements.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 1. GENERAL ORGANIZATION, BUSINESS AND LIQUIDITY

General Organization and Business

Iovance Biotherapeutics, Inc. (the “Company”) is a clinical-stage biopharmaceutical company pioneering a transformational approach to treating cancer by harnessing the human immune system’s ability to recognize and destroy diverse cancer cells using therapies personalized for each patient. The Company’s mission is to be the global leader in innovating, developing and delivering tumor infiltrating lymphocyte (“TIL”) therapies for patients with solid tumor cancers. The Company’s autologous TIL therapy platform uses a centralized, scalable, and proprietary 22-day manufacturing process to grow polyclonal T-cells unique to each patient and yields a cryopreserved, individualized therapy. The Company is currently conducting clinical trials to investigate multiple TIL therapies for multiple indications, including its lead product candidate, lifileucel, for advanced, or metastatic or unresectable melanoma. The Company initiated a rolling Biologics License Application (“BLA”) submission to the U.S. Food and Drug Administration (“FDA”) for lifileucel in August 2022 and expects to complete the rolling BLA submission in the first quarter of 2023. The Company is also pursuing registrational strategies for lifileucel in advanced cervical cancer and for its TIL therapy LN-145 in metastatic non-small cell lung cancer (“NSCLC”). In addition, the Company is investigating next generation approaches to optimize TIL products, manufacturing processes and treatment regimens, including a first-in-human clinical trial of its lead genetically modified TIL therapy, IOV-4001. The Company is also exploring a 16-day manufacturing process, tumor tissue procurement via core biopsy, additional genetically modified TIL therapies including multiple immune checkpoint gene edits and cytokine-tethered TIL therapies, as well as, a novel interleukin-2 (“IL-2”) analog, designated IOV-3001, as potential avenues to improve manufacturing timelines, sample collection and supportive treatments involved in the overall TIL therapy process and treatment regimen.

Liquidity

The Company is currently engaged in the development of therapeutics to fight cancer, specifically solid tumors. The Company currently does not have any commercial products and has not yet generated any revenues from its business, nor does the Company currently anticipate that it will generate any significant revenues from the sale or licensing of any of its product candidates during the twelve months from the date these consolidated financial statements are issued. The Company has incurred a net loss of \$395.9 million for the year ended December 31, 2022 and used \$292.8 million of cash in its operating activities during the year ended December 31, 2022. As of December 31, 2022, the Company had \$478.3 million in cash, cash equivalents, investments, and restricted cash (\$231.7 million of cash and cash equivalents, \$240.1 million in short-term investments and \$6.4 million in restricted cash).

The Company expects to continue to incur significant expenses to support its research and development activities, on-going pre-commercial activities and completion of the construction of tenant improvements for the Iovance Cell Therapy Center (the “iCTC”) facility during 2023 and beyond. Specifically, the Company expects continued spending on its current and planned clinical trials, continued expansion of manufacturing activities, higher payroll expenses as the Company increases its professional and scientific staff and continuation of pre-commercial activities. Based on the funds the Company has available as of the date these consolidated financial statements are issued, the Company believes that it has sufficient capital to fund its anticipated operating expenses and capital expenditures as planned for at least the next twelve months from the date these consolidated financial statements are issued.

Concentrations of Risk

The Company is subject to credit risk from its portfolio of cash, cash equivalents and investments. Under its investment policy, the Company limits amounts invested in securities by credit rating, maturity, industry group, investment type and issuer, except for securities issued by the U.S. government. The Company does not believe it is exposed to any significant concentrations of credit risk from these financial instruments. The goals of its investment policy are safety and preservation of principal, diversification of risk, and liquidity of investments sufficient to meet cash flow requirements.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 2. SUMMARY OF SIGNIFICANT ACCOUNTING PRACTICES

Cash, Cash Equivalents, and Investments

The Company's cash and cash equivalents include short-term investments with original maturities of three months or less when purchased. The Company's investments are classified as "available-for-sale." The Company includes these investments in current assets or non-current assets in the Consolidated Balance Sheets based on the length of maturity from the reporting date and carries them at fair value. Unrealized gains and losses on available-for-sale securities are recorded in accumulated other comprehensive loss. Impairment losses related to credit losses (if any) are recorded as an allowance for credit losses with an offsetting entry to Interest income, net. No impairment losses related to credit losses were recognized for the years ended December 31, 2022, and 2021. The cost of debt securities is adjusted for the amortization of premiums and accretion of discounts to maturity. Such amortization and accretion are included in Interest income, net in the Consolidated Statements of Operations. Gains and losses on securities sold are recorded based on the specific identification method and are included in Interest income, net in the Consolidated Statements of Operations. The Company has not incurred any realized gains or losses from sales of securities to date. The Company's investment policy limits investments to certain types of instruments such as certificates of deposit, money market instruments, obligations issued by the U.S. government and U.S. government agencies as well as corporate debt securities and commercial paper, and places restrictions on maturities and concentration by type and issuer, except for securities issued by the U.S. government.

Restricted Cash

The Company maintains a required minimum balance in a segregated bank account in connection with its letters of credit for which amounts are restricted as to their use by the Company. Currently, the Company's letters of credit are primarily comprised of one for the benefit of the landlord for the iCTC used as a security deposit for the lease in the amount \$5.45 million (See Note 10 - Leases) and one for \$0.6 million for the benefit of the landlord for the Company's current headquarters' lease. The total amount of the Company's letters of credit is classified as Restricted Cash on the Consolidated Balance Sheets. The letter of credit for \$5.45 million originally expired on May 28, 2020, however, it automatically extends for additional one-year periods, without written agreement, to May 28 in each succeeding calendar year, through at least 60 days after the lease expiration date. Further, on the expiration of the seventh year of the lease, and each anniversary date thereafter, the letter of credit may be decreased by \$1.0 million with a minimum security deposit of \$1.5 million maintained through the end of the lease term. The letter of credit with the landlord for the Company's current headquarters' lease expires on February 1, 2032, however, it will be automatically extended, without written agreement, for one-year periods to February in each succeeding calendar year. As of December 31, 2022 and December 31, 2021, restricted cash consisted of \$6.4 million and \$6.1 million, respectively. This amount has been classified as a non-current asset in the Company's Consolidated Balance Sheets.

The following table provides a reconciliation of cash and cash equivalents and restricted cash reported within the Consolidated Balance Sheets that sum to the total of the same such amounts shown in the Consolidated Statements of Cash Flows (in thousands):

	December 31,		
	2022	2021	2020
Cash and cash equivalents	\$ 231,731	\$ 78,229	\$ 67,329
Restricted cash	6,430	6,084	5,525
Total cash, cash equivalents and restricted cash	<u>\$ 238,161</u>	<u>\$ 84,313</u>	<u>\$ 72,854</u>

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Property and Equipment, net

Property and equipment are stated at cost, net of accumulated depreciation and amortization. The cost of property and equipment is depreciated or amortized on the straight-line method over the following estimated useful lives. The depreciation or amortization of capitalized construction in progress costs, a component of property and equipment, net, begins once the underlying asset is placed into service and is recognized over the estimated useful lives:

Computer equipment	2 years
Computer software	5 years
Office furniture and equipment	5 years
Lab, process, and validation equipment	5 years
Machinery and equipment	5 – 7 years
Utility equipment	Lesser of the remaining economic life of the asset or the lease-term
Leasehold improvements	Lesser of the remaining economic life of the asset or the lease-term

Expenditures for maintenance and repairs are charged to operations as incurred while renewals and betterments are capitalized. Gains and losses on disposals are included within operating expenses in the Consolidated Statements of Operations.

Management assesses the carrying value of property and equipment whenever events or changes in circumstances indicate that the carrying value may not be recoverable. If there is an indication of impairment, management prepares an estimate of future undiscounted cash flows expected to result from the use of the asset and its eventual disposition. If these cash flows are less than the carrying amount of the asset, an impairment loss is recognized to write down the asset to its estimated fair value. For the years ended December 31, 2022, 2021, and 2020, the Company did not recognize any impairments for its property and equipment.

Net Loss per Share

Basic net loss per share is computed by dividing the net loss by the weighted average number of common shares outstanding during the period.

Diluted net loss per share is computed by dividing the net loss by the sum of the weighted average number of shares of common stock outstanding and the dilutive common stock equivalent outstanding during the period. The Company's potentially dilutive common stock equivalent shares, which include incremental common shares issuable upon (i) the exercise of outstanding stock options, (ii) purchases through the 2020 Employee Stock Purchase Plan (the "2020 ESPP"), (iii) vesting of restricted stock units, and (vi) conversion of preferred stock, are only included in the calculation of diluted net loss per share when their effect is dilutive.

As of December 31, 2022, 2021, and 2020, the following outstanding common stock equivalents have been excluded from the calculation of net loss per share because their impact would be anti-dilutive.

	As of December 31,		
	2022	2021	2020
Stock options	15,240,197	12,520,865	12,615,638
Employee Stock Purchase Plan	260,859	85,227	37,259
Restricted stock units	2,436,764	1,110,010	—
Series A Convertible Preferred Stock*	97,000	97,000	97,000
Series B Convertible Preferred Stock*	2,842,158	2,842,158	3,581,119
	<u>20,876,978</u>	<u>16,655,260</u>	<u>16,331,016</u>

* on an as-converted basis

The dilutive effect of potentially dilutive securities would be reflected in diluted earnings per common share by application of the treasury stock method. Under the treasury stock method, an increase in the fair market value of the Company's common stock could result in a greater dilutive effect from potentially dilutive securities.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Fair Value Measurements

Under Accounting Standards Codification (“ASC”) 820, *Fair Value Measurements and Disclosures*, fair value is defined as the price at which an asset could be exchanged, or a liability transferred in a transaction between knowledgeable, willing parties in the principal or most advantageous market for the asset or liability. Where available, fair value is based on observable market prices or parameters or derived from such prices or parameters. Where observable prices or parameters are not available, valuation models are applied.

Assets and liabilities recorded at fair value in the Company’s financial statements are categorized based upon the level of judgment associated with the inputs used to measure their fair value. Hierarchical levels directly related to the amount of subjectivity associated with the inputs to fair valuation of these assets and liabilities, are as follows:

- Level 1—These are investments where values are based on unadjusted quoted prices for identical assets in an active market that the Company has the ability to access.
- Level 2—These are investments where values are based on quoted market prices in markets that are not active or model derived valuations in which all significant inputs are observable in active markets.
- Level 3—These are financial instruments where values are derived from techniques in which one or more significant inputs are unobservable.

The Company’s financial instruments consist of cash, cash equivalents, short and long-term investments, and long-term notes payable, all of which are reported at their respective fair value or approximate fair value on its Consolidated Balance Sheets.

A financial instrument’s categorization within the valuation hierarchy is based upon the lowest level of input that is significant to the fair value measurement. Where quoted prices are available in an active market, securities are classified as Level 1.

When quoted market prices are not available for a specific security, the Company estimates the fair value by using quoted prices for identical or similar instruments in markets that are not active and model-based valuation techniques for which all significant inputs are observable in the market or can be corroborated by observable market data for substantially the full term of the assets. Where applicable, these models project future cash flows and discount the future amounts to a present value using market-based observable inputs obtained from various third-party data providers, including but not limited to, benchmark yields, interest rate curves, reported trades, broker/dealer quotes, and market reference data. Level 2 assets consist of commercial paper, corporate securities and government agency securities. Level 2 inputs for the valuations are limited to quoted prices for similar assets or liabilities in active markets and inputs other than quoted prices that are observable for the asset.

The Company’s financial instruments consist of Level 1 and Level 2 assets.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates. Significant items subject to such estimates and assumptions include assumptions made in the fair value of equity awards and related stock-based compensation, assumptions used in measuring operating right-of-use assets and operating lease liabilities, accounting for potential liabilities, including estimates inherent in accruals related to clinical trials, and the realizability of the Company’s deferred tax assets.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of Iovance Biotherapeutics, Inc. and its wholly-owned subsidiaries, Iovance Biotherapeutics Manufacturing LLC, Iovance Biotherapeutics GmbH, and Iovance Biotherapeutics B.V. All intercompany accounts and transactions have been eliminated. The U.S. dollar is the functional currency for all the Company's consolidated operations.

Leases

The Company determines if an arrangement includes a lease at inception and thereafter, if modified. Operating leases are included in its Consolidated Balance Sheets as Operating lease right-of-use assets and Operating lease liabilities as of December 31, 2022 and 2021. Operating lease right-of-use assets represent the Company's right to use an underlying asset for the lease term and operating lease liabilities represent the Company's obligation to make lease payments arising from the lease. Operating lease right-of-use assets and liabilities are recognized at the lease commencement date or modification date based on the present value of lease payments over the lease term. In determining the net present value of lease payments, the Company uses an estimated incremental borrowing rate that is applicable to the Company based on the information available at the later of the lease commencement or modification date.

The operating lease right-of-use assets also include any lease payments made less lease incentives. The Company's leases may include options to extend or terminate the lease, which is considered in the lease term when it is reasonably certain that the Company will exercise any such options. Lease expense is recognized on a straight-line basis over the expected lease term and recorded in costs and expenses in the Consolidated Statements of Operations. The Company has elected not to apply the recognition requirements of Accounting Standards Update ("ASU") No. 2016-02 and No. 2018-10 (together "Topic 842") for short-term leases.

For lease agreements entered into by the Company that include lease and non-lease components, such components are generally accounted for separately.

Stock-Based Compensation

The Company periodically grants stock options to employees and non-employees as compensation for services rendered. The Company accounts for all stock-based payment awards made to employees, including the employee stock purchase plans, and non-employees in accordance with the authoritative guidance provided by the Financial Accounting Standards Board ("FASB") where the value of the award is measured on the date of grant and recognized over the vesting period. Forfeitures are recognized in the period in which they occur. The Company accounts for stock option grants to non-employees in a similar manner as stock option grants to employees except for the term used in the grant date fair value, therefore no longer requiring a re-measurement at the then-current fair values at each reporting date until the shares underlying the options have vested. The non-employee awards that contain a performance condition that affects the quantity or other terms of the award are measured based on the outcome that is probable.

The fair value of the Company's common stock option grants is estimated using a Black-Scholes option pricing model, which uses certain assumptions related to risk-free interest rates, expected volatility, expected term of the common stock options, and future dividends. The stock-based compensation expense is recorded based upon the value derived from the Black-Scholes option pricing model. The assumptions used in the Black-Scholes option pricing model could affect compensation expense recorded in future periods.

The Company issues restricted stock units ("RSUs") from time to time as part of its equity incentive plans. The Company measures the compensation cost with respect to RSUs issued to employees based upon the estimated fair value of the equity instruments at the date of the grant, which is recognized as an expense over the period during which an employee is required to provide services in exchange for the awards. The fair value of RSUs is based on the closing price of the Company's common stock on the grant date. In addition to RSUs that have time-based vesting requirements, from time to time the Company may issue RSUs that include certain performance vesting criteria based upon the satisfaction of stated objectives ("PRSU"). The Company measures the compensation cost with respect to PRSUs issued to employees based upon the estimated fair value of the equity instruments at the date of grant, which is recognized as an expense over the period that achievement is determined to be probable through the stated service period associated with the award.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Accrued Research and Development Costs

Research and development costs are expensed as incurred. Clinical development costs compose a significant component of research and development costs. The Company has a history of contracting with third parties, including contract research organizations (“CROs”), independent clinical investigators, and contract manufacturing organizations (“CMOs”) that perform various clinical trial activities on the Company’s behalf in connection with the ongoing development of the Company’s product candidates. The financial terms of these contracts are subject to negotiations and may vary from contract to contract and may result in uneven payment flow. The Company accrues and expenses costs for clinical trial activities performed by third parties based upon the work completed to date for each clinical trial in accordance with agreements established with CROs, hospitals, and clinical investigators. Accruals for CROs and CMOs are recorded based on services received and efforts expended pursuant to agreements established with CROs, CMOs and other outside service providers. The Company determines its costs through discussions with internal clinical stakeholders and outside service providers as to the progress or stage of completion of clinical trials or services and the contracted fee to be paid for such services.

Included in the Company’s clinical development costs are investigator costs, which are costs associated with treatments administered at clinical sites as required under each clinical trial protocol. The Company’s estimates for clinical investigator costs and timing of expense recognition will depend on a number of factors that include, but are not limited to, (i) the overall number of patients that enroll in the trial at each individual site, (ii) the length of clinical trial enrollment period, (iii) discontinuation and completion rates of patients, (iv) duration of patient safety follow-ups, (v) the number of sites included in the clinical trial, and (vi) the contracted fee of each participating site for patient treatment while on clinical trial, which can vary greatly for several reasons including, but not limited to, geographic region, medical center or physician costs, and overhead costs. In addition, the Company’s estimates for per patient trial costs will vary based on a number of factors that include, but are not limited to, the extent of additional treatments that may be administered by investigators as a result of patient health status, recoverability of patient costs through insurance carriers of patients, and unanticipated cost of injuries incurred as a result of the clinical trial treatment. The Company accrues estimated expenses resulting from obligations under investigator site agreements as the timing of payments does not always timely align with the periods over which the treatments are administered by the clinical investigators. These estimates are typically based on contracted amounts, patient visit data, discussions with internal clinical stakeholders and outside service providers, and historical look-back analysis of actual payments made to date.

The Company makes judgements and estimates in determining the accrual balance in each reporting period.

In the event advance payments are made to a CRO, CMO or other outside service provider, the payments are recorded within prepaid expenses and other current assets in the Consolidated Balance Sheets and subsequently recognized as research and development expense in the Consolidated Statements of Operations when the associated services have been performed. As actual costs become known, the Company adjusts its estimates, liabilities and assets. Inputs used in the determination of estimates discussed above may vary from actual, which will result in adjustments to research and development expense in future periods.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, procurement, legal, investor relations, facilities, business development, marketing, commercial and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, sublicense royalty expenses, legal fees relating to corporate matters, insurance, public company expenses relating to maintaining compliance with Nasdaq listing rules and Securities and Exchange Commission (“SEC”) requirements, investor relations costs, and fees for accounting and consulting services. General and administrative costs are expensed as incurred.

Income Taxes

The Company accounts for income taxes using the asset and liability method whereby deferred tax assets are recognized for deductible temporary differences, and deferred tax liabilities are recognized for taxable temporary differences. Temporary differences are the differences between the reported amounts of assets and liabilities and their tax bases. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some or all of the deferred tax assets will not be realized. Deferred tax assets and liabilities are adjusted for the effects of changes in tax laws and rates on the date of enactment.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

ASC Topic 740, *Income Taxes*, clarifies the accounting for uncertainty in income taxes recognized in an enterprise's financial statements and prescribes a recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. ASC Topic 740 provides guidance on de-recognition, classification, interest and penalties, accounting in interim periods, disclosure, and transition. The Company will classify as income tax expense any interest and penalties. The Company has no material uncertain tax positions for any of the reporting periods presented.

Concentrations

The Company is subject to credit risk from its portfolio of cash, cash equivalents and investments. Under its investment policy, the Company limits amounts invested in such securities by credit rating, maturity, industry group, investment type and issuer, except for securities issued by the U.S. government. The Company does not believe it is exposed to any significant concentrations of credit risk from these financial instruments. The Company maintains cash, cash equivalents and investment balances at four financial institutions. Management believes that the financial institutions which hold its cash are financially sound and, accordingly, minimal credit risk exists. As of December 31, 2022 and 2021, respectively, the Company's cash balances were in excess of insured limits maintained at the financial institutions.

Segment Reporting

The Company operates in one segment, focused on developing and commercializing therapies using autologous TIL for the treatment of metastatic melanoma and other solid tumor cancers.

NOTE 3. CASH EQUIVALENTS AND INVESTMENTS

The amortized cost and fair value of cash equivalents and investments as of December 31, 2022 and December 31, 2021 were as follows (in thousands):

<u>As of December 31, 2022</u>	<u>Amortized Cost</u>	<u>Gross Unrealized Gains</u>	<u>Gross Unrealized Losses</u>	<u>Fair Value</u>
U.S. treasury securities	\$ 118,570	\$ —	\$ (850)	\$ 117,720
U.S. government agency securities	11,272	—	(7)	11,265
Corporate securities	7,230	—	—	7,230
Commercial paper	148,299	8	(53)	148,254
Money market funds	88,001	—	—	88,001
Total investments	<u>\$ 373,372</u>	<u>\$ 8</u>	<u>\$ (910)</u>	<u>\$ 372,470</u>

<u>As of December 31, 2021</u>	<u>Amortized Cost</u>	<u>Gross Unrealized Gains</u>	<u>Gross Unrealized Losses</u>	<u>Fair Value</u>
U.S. treasury securities	\$ 247,287	\$ —	\$ (520)	\$ 246,767
U.S. government agency securities	5,104	—	(7)	5,097
Corporate securities	35,627	—	(39)	35,588
Commercial paper	235,352	10	(46)	235,316
Money market funds	56,250	—	—	56,250
Total investments	<u>\$ 579,620</u>	<u>\$ 10</u>	<u>\$ (612)</u>	<u>\$ 579,018</u>

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

The fair value of cash equivalents and investments as of December 31, 2022 and December 31, 2021 are classified as follows in the Company's Consolidated Balance Sheets (in thousands):

Classified as:	December 31, 2022	December 31, 2021
Cash equivalents	\$ 132,356	\$ 61,249
Short-term investments	240,114	426,181
Long-term investments	—	91,588
Total investments	<u>\$ 372,470</u>	<u>\$ 579,018</u>

Cash equivalents in the tables above exclude cash demand deposits of \$99.4 million and \$17.0 million as of December 31, 2022 and 2021, respectively. Unrealized gains and losses are included in accumulated other comprehensive (loss) income, and as of December 31, 2022 and 2021 no unrealized losses on available-for-sale securities have resulted from credit risk. All available-for-sale securities held as of December 31, 2022 and December 31, 2021 had contractual maturities of less than one year. No significant available-for-sale securities held as of the periods presented have been in a continuous unrealized loss position for more than 12 months. The Company determined that it has the ability and intent to hold all marketable securities that have been in a continuous loss position until maturity or recovery. To date, the Company has not recorded any impairment charges on its marketable securities.

Recurring Fair Value Measurements

The following table summarizes the Company's available-for-sale investments by contractual maturity (in thousands):

	December 31, 2022	
	Amortized Cost	Fair Value
Within one year	\$ 373,372	\$ 372,470
Total investments	<u>\$ 373,372</u>	<u>\$ 372,470</u>

As of December 31, 2022 and 2021, the fair value of the Company's financial assets that are measured at fair value on a recurring basis, which consist of cash equivalents and short-term and long-term investments classified as available-for-sale securities, are categorized in the table below based upon the lowest level of significant input to the valuations (in thousands):

	Assets at Fair Value as of December 31, 2022			
	Level 1	Level 2	Level 3	Total
U.S. treasury securities	\$ 117,720	\$ —	\$ —	\$ 117,720
U.S. government agency securities	—	11,265	—	11,265
Corporate securities	—	7,230	—	7,230
Commercial paper	—	148,254	—	148,254
Money market funds	88,001	—	—	88,001
Total	<u>\$ 205,721</u>	<u>\$ 166,749</u>	<u>\$ —</u>	<u>\$ 372,470</u>

	Assets at Fair Value as of December 31, 2021			
	Level 1	Level 2	Level 3	Total
U.S. treasury securities	\$ 246,767	\$ —	\$ —	\$ 246,767
U.S. government agency securities	—	5,097	—	5,097
Corporate securities	—	35,588	—	35,588
Commercial paper	—	235,316	—	235,316
Money market funds	56,250	—	—	56,250
Total	<u>\$ 303,017</u>	<u>\$ 276,001</u>	<u>\$ —</u>	<u>\$ 579,018</u>

Level 2 assets consist of commercial paper and government agency securities. Level 2 inputs for the valuations are limited to quoted prices for similar assets or liabilities in active markets and inputs other than quoted prices that are observable for the asset.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 4. PROPERTY AND EQUIPMENT, NET

Property and equipment, net consists of the following (in thousands):

	December 31, 2022	December 31, 2021
Leasehold improvements	\$ 74,305	\$ 57,817
Lab, process, and validation equipment	22,136	8,686
Utility equipment	5,951	4,179
Office furniture and equipment	2,927	1,244
Computer software	6,736	1,163
Computer equipment	695	674
Machinery and equipment	82	82
Construction in progress	9,118	35,782
Total property and equipment, cost	121,950	109,627
Less: Accumulated depreciation and amortization	(16,718)	(8,689)
Property and equipment, net	<u>\$ 105,232</u>	<u>\$ 100,938</u>

Depreciation expense for the years ended December 31, 2022, 2021, and 2020 was approximately \$9.3 million, \$3.1 million and \$1.1 million, respectively. During the years ended December 31, 2022 and 2021, the Company placed \$27.2 million and \$62.4 million of assets related to the *iCTC* in service and initiated depreciation of these assets. The depreciation expense related to these assets for the years ended December 31, 2022 and 2021 was \$2.7 million and \$1.6 million, respectively.

NOTE 5. ACCRUED EXPENSES

Accrued expenses consist of the following (in thousands):

	December 31, 2022	December 31, 2021
Accrued payroll and employee related expenses	\$ 19,407	\$ 21,513
Clinical related	14,812	18,167
Manufacturing related	4,652	6,566
Facilities related	6,510	4,857
Legal and related services	3,015	1,907
Other accrued expenses	3,899	3,756
Total accrued expenses	<u>\$ 52,295</u>	<u>\$ 56,766</u>

NOTE 6. STOCKHOLDERS' EQUITY

Common Stock

The Company's certificate of incorporation, as amended, authorizes the issuance of up to 300,000,000 shares of the Company's common stock, par value \$0.000041666. As of December 31, 2022, 187,812,072 shares of the Company's common stock were issued and outstanding.

Public Offerings

In June 2020, the Company closed an underwritten public offering of 16,935,484 shares of the Company's common stock at a public offering price of \$31.00 per share, before underwriting discounts, which included 2,540,322 shares issued upon the exercise in full by the underwriter of its option to purchase additional shares at the public offering price less the underwriting discount (the "June 2020 Public Offering"). The gross proceeds from the offering, before deducting the underwriting discounts and commissions and other offering expenses payable by the Company, were \$603.7 million, with net proceeds to the Company of \$567.0 million.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

At the Market Offering Program

On February 8, 2021, the Company entered into an Open Market Sale Agreement (the “First Sales Agreement”) with Jefferies LLC (“Jefferies”) with respect to an “at the market” offering program, under which the Company may, from time to time, in its sole discretion, issue and sell through Jefferies, acting as sales agent, up to \$350.0 million of shares of the Company’s common stock (the “Common Shares”). On November 18, 2022, the Company entered into a new Open Market Sales Agreement (the “Second Sales Agreement”), which superseded and replaced the First Sales Agreement dated February 8, 2021. Under the terms of the Second Sales Agreement, the Company may, from time to time, in its sole discretion, issue and sell up to \$500.0 million of shares of the Company’s Common Shares. The issuance and sale, if any, of the Common Shares by the Company under the First Sales Agreement and Second Sales Agreement (together, the “Sales Agreements”) will be made pursuant to a prospectus supplement, dated February 8, 2021 and November 18, 2022, to the Company’s Registration Statement on Form S-3ASR, which became effective immediately upon filing with the Securities and Exchange Commission on May 27, 2020.

Pursuant to the Sales Agreements, Jefferies may sell the Common Shares by any method permitted by law deemed to be an “at the market” offering as defined in Rule 415 of the Securities Act of 1933, as amended. Jefferies will use commercially reasonable efforts consistent with its normal trading and sales practices to sell the Common Shares from time to time, based upon instructions from the Company (including any price or size limits or other customary parameters or conditions the Company may impose). The Company will pay Jefferies a commission of up to 3.0% of the gross sales proceeds of any Common Shares sold through Jefferies under the Sales Agreements.

The Company is not obligated to make any sales of Common Shares under the Sales Agreements. The offering of Common Shares pursuant to the Sales Agreement will terminate upon the earlier to occur of (i) the issuance and sale, through Jefferies, of all Common Shares subject to the Sales Agreement and (ii) termination of the Sales Agreements in accordance with its terms.

For the years ended December 31, 2022 and 2021, the Company received \$189.5 million and \$203.2 million in net proceeds, net of offering costs, through the sale of 29,788,993 shares and 6,474,099 shares of its common stock through the Sales Agreements at a weighted average price per share of \$6.52 and \$32.12, respectively.

Preferred Stock

The Company’s certificate of incorporation authorizes the issuance of up to 50,000,000 shares of “blank check” preferred stock. As of December 31, 2022, 17,000 shares were designated as Series A Convertible Preferred Stock and 11,500,000 shares were designated as Series B Convertible Preferred Stock.

Series A Convertible Preferred Stock

A total of 17,000 shares of Series A Convertible Preferred Stock have been authorized for issuance under the Company’s Certificate of Designation of Preferences and Rights of Series A Convertible Preferred Stock. The shares of Series A Convertible Preferred Stock have a stated value of \$1,000 per share and are initially convertible into shares of common stock at a price of \$2.00 per share, subject to adjustment. Each share of Series A Preferred Stock is initially convertible into 500 shares of common stock.

The Series A Convertible Preferred Stock may, at the option of each investor, be converted into fully paid and non-assessable shares of common stock. The holders of shares of Series A Convertible Preferred Stock do not have the right to vote on matters that come before the Company’s stockholders. In the event of any dissolution or winding up of the Company, proceeds shall be paid *pari passu* among the holders of common stock and preferred stock, *pro rata* based on the number of shares held by each holder. The Company may not declare, pay or set aside any dividends on shares of capital stock of the Company (other than dividends on shares of common stock payable in shares of common stock) unless the holders of the Series A Convertible Preferred Stock shall first receive an equal dividend on each outstanding share of Series A Convertible Preferred Stock.

No shares of Series A Convertible Preferred Stock were converted to common stock during the year ended December 31, 2022 and 2021. As of December 31, 2022, and 2021, 194 shares of Series A Convertible Preferred Stock (that are convertible into 97,000 shares of common stock) remained outstanding.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Series B Convertible Preferred Stock

A total of 11,500,000 shares of Series B Convertible Preferred Stock are authorized for issuance under the Company's Series B Certificate of Designation of Rights, Preferences and Privileges of Series B Convertible Preferred Stock. The shares of Series B Convertible Preferred Stock have a stated value of \$4.75 per share and are convertible into shares of the Company's common stock at an initial conversion price of \$4.75 per share. Each share of Series B Preferred Stock is initially convertible into 1 share of common stock.

The Series B Convertible Preferred Stock may, at the option of each investor, be converted into fully paid and non-assessable shares of common stock. The holders of Series B Convertible Preferred Stock do not have the right to vote on matters that come before the Company's stockholders. In the event of any dissolution or winding up of the Company, proceeds shall be paid *pari passu* among the holders of common stock and preferred stock, *pro rata* based on the number of shares held by each holder. Holders of Series B Convertible Preferred Stock are entitled to dividends on an *as-if-converted* basis in the same form as any dividends actually paid on shares of the Series A Convertible Preferred Stock or the Company's common stock. So long as any Series B Convertible Preferred Stock remains outstanding, the Company may not redeem, purchase or otherwise acquire any material amount of the Series A Convertible Preferred Stock or any securities junior to the Series B Convertible Preferred Stock.

No shares of Series B Convertible Preferred Stock were converted to common stock during the year ended December 31, 2022. During the year ended December 31, 2021, 738,961 shares of Series B Convertible Preferred Stock were converted to common stock. At December 31, 2022 and 2021, 2,842,158 shares of Series B Preferred Stock (that are convertible into 2,842,158 shares of common stock) remained outstanding.

Equity Incentive Plans

The Company has multiple equity incentive plans under which it grants awards. As of December 31, 2022, there are 38,298 shares available to grant under the 2014 Equity Incentive Plan (the "2014 Plan").

On April 22, 2018, the Company's board of directors (the "Board") adopted the Iovance Biotherapeutics, Inc. 2018 Equity Incentive Plan (the "2018 Plan"), which was approved by the Company's stockholders in June 2018. The 2018 Plan as approved initially authorized the issuance up to an aggregate of 6,000,000 shares of common stock in the form of incentive (qualified) stock options, non-qualified options, common stock, stock appreciation rights, restricted stock awards, restricted stock units, other stock-based awards, other cash-based awards or any combination of the foregoing. On June 8, 2020, the Company's stockholders approved an amendment to the 2018 Plan to increase the number of shares available for issuance upon the exercise of stock options under the 2018 Plan from 6,000,000 to 14,000,000 shares, which became effective immediately. Additionally, on June 10, 2022, the Company's stockholders approved an amendment to the 2018 Plan to increase the number of shares available for issuance upon the exercise of stock options under the 2018 Plan from 14,000,000 to 20,700,000 shares, which became effective immediately. As of December 31, 2022, 6,881,610 shares of common stock were available for grant under the Company's 2018 Plan.

On September 22, 2021, the Board adopted the Iovance Biotherapeutics, Inc. 2021 Inducement Plan (the "2021 Inducement Plan"). The 2021 Inducement Plan provides for the grant of non-qualified options, common stock, stock appreciation rights, restricted stock awards, restricted stock units, other stock-based awards, other cash-based awards, or any combination of the foregoing. The 2021 Inducement Plan was recommended for approval by the Compensation Committee of the Board (the "Compensation Committee"), and subsequently approved and adopted by the Board without stockholder approval pursuant to Rule 5635(c)(4) of the rules and regulations of The Nasdaq Stock Market, LLC (the "Nasdaq Listing Rules").

The Board initially reserved 1,000,000 shares of the Company's common stock for issuance pursuant to equity awards granted under the 2021 Inducement Plan, and the 2021 Inducement Plan is administered by the Compensation Committee. On January 12, 2022, the Compensation Committee approved an amendment to the 2021 Inducement Plan solely to increase the number of shares reserved for issuance under the 2021 Inducement Plan from 1,000,000 shares of the Company's common stock to 1,750,000 shares of the Company's common stock without stockholder approval pursuant to Rule 5635(c)(4) of the Nasdaq Listing Rules.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

In accordance with Rule 5635(c)(4) of the Nasdaq Listing Rules, equity awards under the 2021 Inducement Plan may only be made to an employee if such employee is granted such equity awards in connection with his or her commencement of employment with the Company or a subsidiary and such grant is an inducement material to his or her entering into employment with the Company or such subsidiary. In addition, awards under the 2021 Inducement Plan may only be made to employees who have not previously been an employee or member of the Board (or any parent or subsidiary of the Company) or following a bona fide period of non-employment of the employee by the Company (or a parent or subsidiary of the Company). As of December 31, 2022, 55,925 shares of common stock were available for grant under the Inducement Plan.

Stock Options

A summary of the status of stock options as of December 31, 2022, and the changes during the three years then ended, is presented in the following table:

	Number of Options	Weighted Average Exercise Price	Weighted Average Remaining Contract Life	Aggregate Intrinsic Value (in thousands)
Outstanding at January 1, 2020	9,494,712	\$ 12.00		
Issued	4,981,001	28.17		
Exercised	(973,854)	9.92		
Expired/Cancelled	(886,221)	18.67		
Outstanding at December 31, 2020	12,615,638	\$ 18.08		
Issued	5,528,724	38.05		
Exercised	(2,822,617)	11.88		
Expired/Cancelled	(2,800,880)	32.58		
Outstanding at December 31, 2021	12,520,865	\$ 25.05		
Issued	3,455,027	13.31		
Exercised	(203,579)	8.06		
Expired/Cancelled	(532,116)	29.65		
Outstanding at December 31, 2022	15,240,197	\$ 22.45	7.27	\$ 245
Ending vested and expected to vest at December 31, 2022	15,240,197	\$ 22.45	7.27	\$ 245
Options exercisable at December 31, 2022	9,639,339	\$ 22.82	6.34	\$ 243

As of December 31, 2022, there was \$58.9 million of total unrecognized compensation expense related to unvested employee stock options, which the Company expects to recognize over a remaining weighted average period of 1.81 years.

The weighted average grant date fair value for employee options granted under the Company's stock option plans during the years ended December 31, 2022, 2021, and 2020 was \$8.29, \$22.28, and \$17.32 per option, respectively.

The aggregate intrinsic value in the table above reflects the total pre-tax intrinsic value (the difference between the Company's closing stock price on the last trading day of the year ended December 31, 2022 and the exercise price of the options, multiplied by the number of in-the-money stock options) that would have been received by the option holders had all option holders exercised their options on December 31, 2022. The intrinsic value of the Company's stock options changes based on the closing price of the Company's common stock.

The aggregate intrinsic value of stock options exercised during the year ended December 31, 2022, 2021, and 2020 were \$0.04 million, \$21.3 million, and \$21.4 million, respectively.

Employee Stock Purchase Plan

In June 2020, the Company adopted the 2020 ESPP upon its approval by the Company's shareholders at its Annual Stockholders Meeting on June 8, 2020. The Company reserved 500,000 shares of its common stock for issuance under the 2020 ESPP.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Under the 2020 ESPP, employees of the Company can purchase shares of our common stock based on a percentage of their compensation subject to certain limits. The purchase price per share is equal to the lower of 85% of the fair market value of its common stock on the offering date or the purchase date with a six-month look-back feature. The 2020 ESPP purchases are settled with common stock from the 2020 ESPP's previously authorized and available pool of shares.

The compensation expense related to the 2020 ESPP for the years ended December 31, 2022, 2021 and 2020 was \$1.3 million, \$1.2 million and \$0.1 million, respectively. Under the 2020 ESPP, for the years ended December 31, 2022, and 2021, the Company received proceeds of \$1.7 million for the issuance of 262,701 shares, and \$1.6 million for the issuance of 94,148 shares, respectively. As of December 31, 2020, no shares were issued un the 2020 ESPP. As of December 31, 2022, there was \$0.5 million of unrecognized compensation cost associated with the 2020 ESPP, which is expected to be recognized over 5.33 months.

Restricted Stock Units and Performance Restricted Stock Units

In addition to RSUs that have time-based vesting requirements, from time to time the Company may issue RSUs that include certain performance vesting criteria based upon the satisfaction of stated objectives ("PRSUs"). Compensation expense related to PRSUs is based on the grant date fair value of the award and recorded from the period that achievement is determined to be probable through the stated service period associated with the award.

A summary of the RSU and PRSU activity during the years ended December 31, 2022, and 2021 is presented in the following table:

	Number of RSUs and PRSUs	Weighted Average Grant Date Fair Value
Outstanding, non-vested as of December 31, 2020	—	\$ —
Granted	1,253,540	23.87
Vested	—	—
Canceled/Forfeited	(143,530)	23.87
Outstanding, non-vested as of December 31, 2021	1,110,010	\$ 23.87
Granted	2,391,203	14.13
Vested/Released	(894,760)	23.87
Canceled/Forfeited	(169,689)	17.77
Outstanding as of December 31, 2022	2,436,764	\$ 14.74
Ending vested and expected to vest at December 31, 2022	2,267,659	\$ 14.06

During the year ended December 31, 2022, 2.4 million restricted units were granted, of which only 100,000 were PRSUs. No PRSUs were granted during the year ended December 31, 2021.

As of December 31, 2022, there was \$20.6 million of unrecognized stock-based compensation expense associated with unvested RSUs and PRSUs, which the Company expects to recognize over a remaining weighted-average period of 1.72 years. The aggregate intrinsic value of the unvested RSUs and PRSUs outstanding as of December 31, 2022 and 2021, was \$14.5 million and \$21.2 million, respectively.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Stock-Based Compensation

Total stock-based compensation expense related to the Company's stock-based awards was recorded on the Consolidated Statements of Operations as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Research and development	\$ 50,242	\$ 40,833	\$ 19,727
General and administrative	33,780	28,932	21,160
Total stock-based compensation expense	\$ 84,022	\$ 69,765	\$ 40,887

Total stock-based compensation expense by type of award was as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Stock option expense	\$ 58,308	\$ 56,305	\$ 40,714
Restricted stock expense	24,436	12,247	112
ESPP expense	1,278	1,213	61
Total stock-based compensation expense	\$ 84,022	\$ 69,765	\$ 40,887

The following table summarizes the assumptions relating to options granted pursuant to the Company's equity incentive plans for the years ended December 31, 2022, 2021, and 2020:

Assumptions:	Stock Option			ESPP		
	Years Ended December 31,			Years Ended December 31,		
	2022	2021	2020	2022	2021	2020
Expected term (years)	4.94 - 5.12	4.94 - 5.28	5.18 - 6.19	0.50	0.50	0.50
Expected volatility	73.73% - 83.90%	70.35% - 73.88%	69.99% - 70.99%	73.02% - 137.42%	52.04% - 94.56%	54.90%
Risk-free interest rate	1.25% - 4.05%	0.36% - 0.97%	0.28% - 1.83%	1.98% - 4.78%	0.06% - 0.13%	0.09%
Expected dividend yield	0%	0%	0%	0%	0%	0%

- *Expected Term (Years)*—The expected term of the stock option grants was calculated based on historical exercises, cancellations, and forfeitures of stock options and outstanding option shares
- *Expected Volatility* —The expected volatility is based on the historical volatility for the Company's stock over a period equal to the expected terms of the options.
- *Risk-Free Interest Rate* —The risk-free interest rate was based on the market yield currently available on United States Treasury securities with maturities approximately equal to the option's expected term.
- *Expected Dividend Yield* —The Company has never paid dividends and does not expect to pay dividends in the foreseeable future.
- *Forfeiture Rate* —The Company recognizes forfeitures as they occur.

Each of the inputs discussed above is subjective and generally requires significant management judgment.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 7. EMPLOYEE BENEFIT PLAN

The Company maintains a defined contribution plan covering substantially all U.S. employees under Section 401(k) of the Internal Revenue Code of 1986, as amended (the “IRC”). The Company's matching contribution to the defined contribution plan was \$3.0 million, \$2.2 million, and \$1.2 million for the years ended December 31, 2022, 2021 and 2020, respectively.

NOTE 8. INCOME TAXES

The Company did not record a provision or benefit for income taxes for the years ended December 31, 2022, 2021 or 2020.

The significant components of the Company’s net deferred tax assets and liabilities are summarized as follows (in thousands):

	As of December 31,	
	2022	2021
Deferred income tax assets:		
Net operating loss carryforwards	\$ 225,904	\$ 203,298
Stock-based compensation	24,920	18,319
Tax credit carryforwards	46,957	40,851
Lease liabilities	18,017	14,970
Capitalized R&D	47,755	—
Depreciation and amortization	—	228
Reserves and accruals	3,997	4,445
Deferred tax assets before valuation allowance	367,550	282,111
Less: valuation allowance	(350,418)	(267,469)
Net deferred income tax assets	17,132	14,642
Deferred tax liabilities:		
Depreciation and amortization	(17,132)	(14,642)
Net deferred tax assets (liabilities)	\$ —	\$ —

The reconciliation of the effective income tax rate to the U.S. statutory rate is as follows:

	Years ended December 31,		
	2022	2021	2020
Federal statutory tax rate	21 %	21 %	21 %
Orphan drug and research credits	1	2	3
Permanent and other differences	(1)	—	(1)
Stock Based Compensation	(1)	—	—
State tax, net of federal benefit	1	—	—
	21 %	23 %	23 %
Valuation allowance	(21)%	(23)%	(23)%
Effective tax rate	— %	— %	— %

The Company had net operating loss carryforwards (“NOLs”) for federal and state income tax purposes of approximately \$1.0 billion and \$158.1 million, respectively, as of December 31, 2022. \$142.4 million of federal NOLs will expire beginning in 2027, while \$898.9 million generated after the recently enacted tax reform will have an indefinite life under the Tax Cuts and Jobs Act of 2017 (the “Tax Act”). The state NOLs will expire if unused in years 2030 through 2042.

The Company’s utilization of NOLs is subject to an annual limitation due to ownership changes that have occurred previously or that could occur in the future as provided in Section 382 of the Internal Revenue Code (“Section 382”), as well as similar state provisions. Section 382 limits the utilization of NOLs when there is a greater than 50% change of ownership as determined under the regulations. Since its formation, the Company has raised capital through the issuance of capital stock and various convertible instruments which, combined with the purchasing shareholders’ subsequent disposition of these shares, has resulted in multiple ownership changes as defined by Section 382, and could result in ownership change in the future upon subsequent disposition. The Company’s utilization of NOLs may also be adversely affected by future changes in federal and state tax laws and regulations.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

In assessing the realization of deferred tax assets, management considers whether it is more likely than not that some portion or all the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon future generation for taxable income during the periods in which temporary differences representing net future deductible amounts become deductible. Management considers the scheduled reversal of deferred tax liabilities, projected future taxable income and tax planning strategies in making this assessment. After consideration of all the information available, management believes that significant uncertainty exists with respect to future realization of the deferred tax assets and has therefore established a full valuation allowance. For the years ended December 31, 2022, 2021 and 2020, the change in the valuation allowance was approximately \$82.9 million, \$78.1 million, and \$60.7 million, respectively.

The Company evaluated the provisions of ASC 740 related to the accounting for uncertainty in income taxes recognized in an enterprise's financial statements. ASC 740 prescribes a comprehensive model for how a company should recognize, present, and disclose uncertain positions that the Company has taken or expects to take in its tax return. For those benefits to be recognized, a tax position must be more-likely-than-not to be sustained upon examination by taxing authorities. Differences between tax positions taken or expected to be taken in a tax return and the net benefit recognized and measured pursuant to the interpretation are referred to as "unrecognized benefits." A liability is recognized (or amount of net operating loss carry forward or amount of tax refundable is reduced) for unrecognized tax benefit because it represents an enterprise's potential future obligation to the taxing authority for a tax position that was not recognized as a result of applying the provisions of ASC 740.

If applicable, interest costs related to the unrecognized tax benefits are required to be calculated and would be classified as income tax expenses in the Consolidated Statements of Operations. Penalties would be recognized as a component of "General and Administrative Expenses" in the Consolidated Statements of Operations.

A reconciliation of the beginning and ending balances of the unrecognized tax benefits during the years ended December 31, 2022, 2021 and 2020 is as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Unrecognized benefit - beginning of period	\$ 18,171	\$ 14,432	\$ 10,038
Gross decreases - prior period tax positions	—	(159)	—
Gross increase current period tax positions	3,474	3,898	4,394
Unrecognized benefit - end of period	<u>\$ 21,645</u>	<u>\$ 18,171</u>	<u>\$ 14,432</u>

No interest or penalties on unpaid tax were recorded during the years ended December 31, 2022, 2021, or 2020. The Company does not anticipate any significant changes within 12 months of this reporting date of its uncertain tax positions.

The Company files tax returns in the U.S. federal and state jurisdictions. The U.S. federal and U.S. state taxing authorities may choose to audit tax returns for tax years beyond the statute of limitation period due to significant tax attribute carryforwards from prior years, making adjustments only to carryforward attributes. The Company is not currently under examination by income tax authorities in federal, state or other foreign jurisdictions.

The Inflation Reduction Act of 2022 (the "Act"), which includes certain new tax measures, was signed into law in August 2022. The Act contains two main tax provisions, a new corporate alternative minimum tax imposed on certain corporations meeting average annual financial statement income of more than \$1 billion during a three-year tax period, and an excise tax imposed upon share repurchases by certain publicly traded corporations. The Act is effective for tax years beginning after December 31, 2022; the Company is evaluating the provisions of the Act but currently does not believe these provisions will have a material impact on its consolidated financial statements.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 9. LICENSES AND AGREEMENTS

National Institutes of Health (the “NIH”) and the National Cancer Institute (the “NCI”)

Cooperative Research and Development Agreement (the “CRADA”)

In August 2011, the Company signed a five-year CRADA with the NCI to work on the development of adoptive cell immunotherapies that are designed to destroy metastatic melanoma cells. The CRADA was amended in 2015 and 2016 to, among other things, extend the term of the CRADA through August 2021, include new indications such as the development of TIL therapy for the treatment of patients with bladder, lung, triple-negative breast, and Human Papilloma Virus (“HPV”)-associated cancers, and modify the focus on the development of unmodified TIL as a stand-alone therapy or in combination. The parties have continued the development of improved methods for the generation and selection of TIL with anti-tumor reactivity in metastatic melanoma, bladder, lung, breast, and HPV-associated cancers.

In August 2021, the NCI and the Company entered into a third amendment to the CRADA. The third amendment, among other things, extended the term of the CRADA by three years to August 2024. The research plan in this amendment includes the evaluation in clinical trials of strategies for development of more potent TILs, such as selection of CD39/69 double negative cells and the use of certain inhibitors or other reagents in TIL expansion cultures.

Pursuant to the terms of the CRADA, as amended, the Company is required to make quarterly payments of \$0.5 million to the NCI for support of research activities. To the extent the Company licenses patent rights relating to a TIL-based product candidate, the Company will be responsible for all patent-related expenses and fees, past and future, relating to the TIL-based product candidate. In addition, the Company may be required to supply certain test articles, including TIL, grown and processed under Current Good Manufacturing Practice (“cGMP”) conditions, suitable for use in clinical trials. The extended CRADA has a three-year term expiring in August 2024. The Company or the NCI may unilaterally terminate the CRADA for any reason or for no reason at any time by providing written notice at least 60 days before the desired termination date. The Company recorded costs associated with the CRADA of \$2.0 million for each of the years ended December 31, 2022, 2021 and 2020, respectively, as research and development expenses.

Patent License Agreement Related to the Development and Manufacture of TIL Therapies

The Company entered into an Exclusive Patent License Agreement (the “Patent License Agreement”) with the NIH, an agency of the U.S. Public Health Service within the Department of Health and Human Services, in 2011, as amended in 2015. Pursuant to the Patent License Agreement, as amended, the NIH granted the Company licenses, including exclusive, co-exclusive, and non-exclusive licenses, to certain technologies relating to autologous tumor infiltrating lymphocyte adoptive cell therapy products for the treatment of metastatic melanoma, lung, breast, bladder and HPV-positive cancers.

Effective May 6, 2021, the Company entered into an Amended and Restated Patent License Agreement with NIH, which included the grant of additional exclusive, worldwide patent rights in the indications to interleukin-15 and interleukin-21 cytokine-tethered TIL technology, and expanded the non-exclusive, worldwide field of use to all cancers. Effective August 1, 2022, the Company entered into a Second Amended and Restated Patent License Agreement with NIH to include additional exclusive, worldwide patent rights to TIL products expressing interleukin-12, expanded rights to TIL selection technologies previously licensed under the Exclusive Patent License Agreement below, and additional non-exclusive, worldwide patent rights to certain technologies related to enhancing TIL potency.

The Second Amended and Restated Patent License Agreement requires the Company to pay royalties based on a percentage of net sales in jurisdictions where patent rights exist, which percentage can fall into a tier that may be less than one percent to mid-single digits depending upon certain events, including the exclusivity of the rights, and the Company expects lower overall royalty payments as a result. The Company also agreed to potential milestone payments on the achievement of certain clinical, regulatory, and commercial sales milestones for each of the indications and other direct costs incurred by the NIH pursuant to the Second Amended and Restated Patent License Agreement. The Company anticipates making payments that could range from several hundred thousand dollars to the mid-single-digit millions of dollars in conjunction with certain development milestones, the approval of a BLA or its foreign equivalent, or the first U.S. and foreign commercial sales of any of our product candidates covered by the Second Amended

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

and Restated Patent License Agreement. The term of the Second Amended and Restated Patent License Agreement continues until the expiry of the last-to-expire patent rights licensed thereunder, and the agreement contains standard termination provisions.

Exclusive Patent License Agreement Related to TIL Selection

On February 10, 2015, the Company entered into an exclusive patent license agreement (the “Exclusive Patent License Agreement”) with the NIH under which the Company received an exclusive, worldwide license under the selected TIL patents. This license was superseded and replaced by the Second Amended and Restated Patent License Agreement.

H. Lee Moffitt Cancer Center

Research Collaboration and Clinical Grant Agreements with Moffitt

In June 2020, the Company entered into a Sponsored Research Agreement with the H. Lee Moffitt Cancer Center (“Moffitt”), with a term that ends either upon completion of the research thereunder or on July 1, 2022, whichever is sooner. In June 2022, this agreement was extended until the later of December 19, 2022, or a mutually acceptable completion of the Research Agreement, which is expected in mid-2023. The Company recorded research and development costs of \$0.6 million, \$0.3 million and \$0.2 million for each of the years ended December 31, 2022, 2021 and 2020, respectively.

In December 2016, the Company entered into a clinical grant agreement with Moffitt to support an ongoing clinical trial at Moffitt that combines TIL therapy with nivolumab for the treatment of patients with metastatic melanoma. In June 2017, the Company entered into a second clinical grant agreement with Moffitt to support a new clinical trial at Moffitt that combines TIL therapy with nivolumab for the treatment of patients with non-small cell lung cancer, under which the Company obtained a non-exclusive, royalty-free license to any new Moffitt inventions made in the performance of the agreement. Under both clinical grant agreements with Moffitt, the Company has non-exclusive rights to clinical data arising from the respective clinical trials. For the years ended December 31, 2022 and 2021 the Company recorded research and development costs of \$0.1 million, and for the year ended December 31, 2020 the company recorded \$0.4 million of research and development costs, in connection with the research collaboration and clinical grant agreements with Moffitt.

Exclusive License Agreements with Moffitt

The Company entered into a license agreement with Moffitt (the “First Moffitt License”), effective as of June 28, 2014, under which the Company received a worldwide license to Moffitt’s rights to patent-pending technologies related to methods for improving TIL for adoptive cell therapy using toll-like receptor agonists. Unless earlier terminated, the term of the license extends until the earlier of the expiration of the last issued patent related to the licensed technology or 20 years after the effective date of the license agreement.

Pursuant to the First Moffitt License, the Company paid an upfront licensing fee in the amount of \$0.1 million, which was recorded as research and development expense. A patent issuance fee will also be payable under the First Moffitt License, upon the issuance of the first U.S. patent covering the subject technology. In addition, the Company agreed to pay milestone license fees upon completion of specified milestones, customary royalties based on a specified percentage of net sales (which percentage is in the low single digits) and sublicensing payments, as applicable, and annual minimum royalties beginning with the first sale of products based on the licensed technologies, which minimum royalties will be credited against the percentage royalty payments otherwise payable in that year. The Company will also be responsible for all costs associated with the preparation, filing, maintenance and prosecution of the patent applications and patents covered by the First Moffitt License related to the treatment of any cancers in the U.S., Europe and Japan and in other countries designated by the Company in agreement with Moffitt. No expenses were recorded for the First Moffitt License for the year ended December 31, 2022, 2021, and 2020.

The Company entered into a second license agreement with Moffitt effective as of May 7, 2018 (the “Second Moffitt License”), under which the Company received a license to Moffitt’s rights to patent-pending technologies related to the use of 4-1BB agonists in conjunction with TIL manufacturing processes and therapies. Pursuant to the Second Moffitt License, the Company paid an upfront licensing fee in the amount of \$0.1 million in 2018. An annual license maintenance fee is also payable commencing on the first anniversary of the effective date. The Company agreed to pay an annual commercial use payment for each indication for which a first sale has occurred, which in the aggregate amounts to up to \$0.4 million a year. The Company recorded \$0.2 million for the year ended

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2022, and \$0.1 million for each of the years ended December 31, 2021 and 2020, respectively, as research and development expenses in connection with this agreement.

The Company subsequently exercised an option to exclusively license Moffitt's rights to patent pending technologies related to the use of tumor digests in conjunction with TIL manufacturing processes and therapies and entered into an amended and restated Second Moffitt License in October 2021 (the "Amended & Restated Second Moffitt License"), to include these rights. Pursuant to the Amended & Restated Second Moffitt License, the Company paid an upfront licensing fee in the amount of \$0.2 million in 2021, which was recorded as research and development expense. In addition, the Company agreed to pay an annual commercial use payment for each indication for which a first sale has occurred for products relating to the use of 4-1BB agonists and for products relating to the use of tumor digests covered by the license.

The University of Texas M.D. Anderson Cancer Center

Strategic Alliance Agreement

On April 17, 2017, the Company entered into a Strategic Alliance Agreement (the "SAA") with The University of Texas M.D. Anderson Cancer Center ("MDACC") under which the Company and MDACC agreed to conduct clinical and preclinical research studies. The Company agreed in the SAA to provide total funding not to exceed approximately \$14.2 million for the performance of the multi-year studies under the SAA, of which approximately \$5.3 million has been funded cumulatively through December 31, 2022 and has been recorded as research and development expense. In return, the Company acquired all rights to inventions resulting from the studies and has been granted a non-exclusive, sub-licensable, royalty-free, and perpetual license to specified background intellectual property of MDACC reasonably necessary to exploit, including the commercialization thereof. The Company has also been granted certain rights in clinical data generated by MDACC outside of the clinical trials to be performed under the SAA. The SAA's term shall continue in effect until the later of the fourth anniversary of the SAA or the completion or termination of the research and receipt by the Company of all deliverables due from MDACC thereunder. The Company recorded \$0.2 million, \$0.5 million and \$1.1 million associated with the SAA for the year ended December 31, 2022, 2021 and 2020 as research and development expenses, respectively.

WuXi Advanced Therapies, Inc.

First WuXi Manufacturing and Services Agreement

In November 2016, the Company entered into a three-year manufacturing and services agreement (the "First WuXi MSA") with WuXi Advanced Therapies, Inc. ("WuXi") pursuant to which WuXi agreed to provide manufacturing and other services, which has since been amended and assigned to its subsidiary Iovance Biotherapeutics Manufacturing LLC. Under the First WuXi MSA, the Company entered into two statements of work for two cGMP manufacturing suites to be operated by WuXi for the Company. Both of the suites are expected to be capable of being used for the commercial manufacture of the Company's products. The terms of one of these statements of work was extended to December 2022. The Company recorded costs associated with agreements with WuXi of \$14.2 million, \$17.5 million, and \$20.6 million for the years ended December 31, 2022, 2021, and 2020 respectively, as research and development expenses.

Second WuXi Manufacturing and Services Agreement

In October 2022, the Company's subsidiary Iovance Biotherapeutics Manufacturing LLC entered into an additional three-year manufacturing and services agreement (the "Second WuXi MSA") with WuXi and its parent company WuXi Apptec, Co, Ltd pursuant to which WuXi agreed to provide commercial and clinical manufacturing services and related testing services. Under the Second WuXi MSA, the Company entered into a statement of work for the two cGMP manufacturing suites to be operated by WuXi for the Company. Both suites are expected to be capable of being used for the commercial and clinical manufacture of the Company's products. The Second WuXi MSA and its related statement of work will supersede the statements of work under the First WuXi MSA with respect to commercial and clinical manufacturing and the two manufacturing suites. Certain other statements of work for related services will also be covered by the Second WuXi MSA. The First WuXi MSA will continue to address development services provided by WuXi to the Company. Prior to regulatory approval, or if the Company experiences a material adverse event, the Company may unilaterally terminate the statement of work for commercial and clinical manufacturing under the Second WuXi MSA at any time by providing written notice of at least 120 days. Post regulatory approval, the Company may unilaterally terminate the statement of work for commercial and clinical manufacturing with written notice of 15 month in year 1 of the term, written notice of 9

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

months in year 2 of the term, and written notice of 6 months in year 3 of the term. If WuXi fails a Pre-Licensing Inspection and does not address any related issues within 90 days of receipt of the FDA response letter, the Company may either terminate the statement of work for commercial and clinical manufacturing under the Second WuXi MSA immediately or shorten the term of this statement of work to June 30, 2024.

Collectis S.A.

On December 31, 2019, the Company entered into a research collaboration and exclusive worldwide license agreement whereby the Company will license gene-editing technology from Collectis S.A. (“Collectis”), a clinical-stage biopharmaceutical company, to develop TIL therapies that have been genetically edited, including a PD-1 inactivated product that the Company refers to as IOV-4001. Financial terms of the license include annual license payments and development, regulatory and sales milestone payments from the Company to Collectis, as well as royalty payments based on net sales of TALEN®-modified TIL products. The Company recorded costs associated with the license agreement with Collectis of \$0.4 million for each of the years ended December 31, 2022, 2021 and 2020 respectively as research and development expense.

Novartis Pharma AG

On January 9, 2020, the Company obtained a license from Novartis Pharma AG (“Novartis”) to develop and commercialize an antibody cytokine engrafted protein, which the Company refers to as IOV-3001. Under the agreement, the Company paid an upfront payment to Novartis and may pay future milestones related to initiation of patient dosing in various phases of clinical development for IOV-3001 and approval of the product in the U.S., EU and Japan. Novartis is also entitled to low-to-mid single digit percentage royalties from commercial sales of the product. The Company recorded costs associated with the license agreement from Novartis of \$10.0 million as research and development expenses for the year ended December 31, 2020. No expenses were recorded for the years ended December 31, 2022 and 2021.

NOTE 10. LEASES

Operating Leases

The Company leases corporate office space in California, including 49,918 square feet for its current corporate headquarters’ office space in San Carlos, California, manufacturing, research and development lab facilities and office space in Philadelphia, Pennsylvania, including 136,000 square feet of commercial manufacturing and lab space at the *i*CTC, and research and development lab facilities in Tampa, Florida. The determination if an arrangement is a lease occurs at inception, and for leases with terms greater than 12 months, the Company records a related right-of-use asset and lease liability at the present value of lease payments over the term. Many leases include fixed rental escalation clauses, renewal options and/or termination options that are factored into the determination of lease payments when appropriate. The Company’s leases do not provide an implicit rate, and thus the Company estimated the incremental borrowing rate in calculating the present value of the lease payments.

The Company’s leases have remaining lease terms that range from less than one year to approximately 20 years. Some of our leases include one or more options to renew with renewal terms that can extend the lease for additional years, or options to terminate the leases, both at the Company’s discretion. The Company’s leases may include options to extend or terminate the lease, which is considered in the lease term when it is reasonably certain that the Company will exercise any such options. Lease expense for minimum lease payments is recognized on a straight-line basis based on the fixed components of a lease arrangement.

Variable lease cost is determined based on performance or usage in accordance with the contractual agreements, and not based on an index or rate. Such costs that are not fixed in nature are recognized as incurred.

The Company also leases certain furniture and equipment that has a lease term of 12 months or less. Since the lease agreement do not include an option to purchase the underlying asset, the Company elected not to apply the recognition requirements of Topic 842 for short-term leases, however, the lease costs that pertain to the short-term leases are disclosed in the components of lease costs table below.

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

Manufacturing Contracts

The Company uses contract manufacturing organizations (collectively the “CMOs” and each a “CMO”) to manufacture and supply TILs for clinical and commercial purposes. The CMO contractual obligations consist of the use of manufacturing facilities and minimum fixed commitment fees, such as personnel, general support fees, and minimum production or material fees. In addition to the minimum fixed commitment fees, the CMO contractual obligations include variable costs such as production and material costs in excess of the minimum quantity specified in each CMO agreement. During the term of each CMO agreement, the Company has access to and control of the use of a dedicated suite in each of the CMOs’ facilities for manufacturing activities. The contracts with CMOs generally contain embedded operating leases based on the fact that the suites are used for the Company’s production are implicitly identified, are used exclusively by the Company during the contractual term of the arrangements, and the CMOs have no substantive contractual rights to substitute the facilities used by the Company.

Further, the Company controls the use of the facilities by obtaining all of the economic benefits from the use of the facilities and direct the use of the facilities throughout the period of use. The terms of the CMO contracts include options to terminate the lease with advance notice of five to six months. The termination clauses and extension clauses are included in the calculation of the lease term for each of the CMOs when it is reasonably certain that it will not exercise such options.

For contracts with multiple deliverables, Topic 842 requires the Company to first identify a lease deliverable and non-lease deliverable included in the arrangements, and then allocate the fixed contractual consideration to the lease deliverable(s) and the non-lease deliverable(s) on a relative standalone selling price basis to determine the amount of operating lease right-of-use assets and liabilities. The Company identified the use of a dedicated suite as a single lease deliverable, and related labor services as a single non-lease deliverable in each of the CMO arrangements. Judgment is required to determine the relative standalone selling price of each deliverable as the observable standalone selling prices are not readily available. Therefore, management uses estimates and assumptions in determining relative standalone selling price of lease of a suite and labor service using information that includes market and other observable inputs to the extent possible.

The balance sheet classification of the Company’s right-of-use asset and lease liabilities was as follows (in thousands):

	December 31, 2022	December 31, 2021
Operating lease right-of-use assets	\$ 73,015	\$ 68,983
Operating lease liabilities		
Current portion included in current liabilities	12,587	5,057
Long-term portion included in non-current liabilities	71,859	65,474
Total operating lease liabilities	\$ 84,446	\$ 70,531

IOVANCE BIOTHERAPEUTICS, INC.
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The following table summarizes components of lease expenses, which were included in Total expenses in the Company's Consolidated Statements of Operations, and other information related to our operating leases as follows (in thousands, except weighted-average remaining lease terms and discount rates):

	For the Year Ended December 31, 2022	For the Year Ended December 31, 2021
Operating lease cost	\$ 17,657	\$ 15,341
Variable lease cost	5,447	4,649
Short-term lease cost	154	119
Total lease cost	<u>\$ 23,258</u>	<u>\$ 20,109</u>
<i>Other information</i>		
Cash paid for amounts included in the measurement of lease liabilities included in cash flows from operations	\$ 14,209	\$ 12,316
Tenant improvement allowance received for amounts included in the measurement of lease liabilities included in cash flows from operations	6,432	—
Right-of-use assets obtained from entering new leases	\$ 553	\$ 17,617
Increase in right-of-use assets from lease modifications	\$ 15,304	\$ 7,796
Weighted-average remaining lease terms (years)	12.90	15.38
Weighted-average discount rates	7.5 %	7.3 %

As of December 31, 2022, maturities of the Company's operating lease liabilities were as follows (in thousands):

Year Ending December 31,	Facility leases	CMO embedded leases	Total
2023	\$ 8,304	\$ 10,235	\$ 18,539
2024	8,424	1,454	9,878
2025	8,240	—	8,240
2026	7,989	—	7,989
2027	8,186	—	8,186
Thereafter	83,827	—	83,827
Total lease payments	<u>\$ 124,970</u>	<u>\$ 11,689</u>	<u>\$ 136,659</u>
Less: Present value adjustment	(51,468)	(745)	(52,213)
Operating lease liabilities	<u>\$ 73,502</u>	<u>\$ 10,944</u>	<u>\$ 84,446</u>

For its corporate headquarters' office, the lease agreement includes a tenant improvement allowance of \$8.2 million. For the years ended December 31, 2022, and 2021, the Company has received reimbursement associated with this tenant improvement allowance of \$6.4 million and \$1.6 million, respectively. The Company does not expect to receive additional reimbursements associated with this tenant improvement allowance.

NOTE 11. LEGAL PROCEEDINGS

Derivative Lawsuit. On December 11, 2020, a purported stockholder derivative complaint was filed by plaintiff Leo Shumacher against the Company, as nominal defendant, and then current directors, as defendants, in the Court of Chancery in the State of Delaware (the "Court"). The complaint alleges breach of fiduciary duty and a claim for unjust enrichment in connection with alleged excessive compensation of certain non-executive directors of the Company and seeks unspecified damages on behalf of the Company. The parties have agreed to a proposed settlement, which was submitted to the Court on June 15, 2022. After a hearing on November 17, 2022, the Court required the parties to take additional steps before it would approve the settlement. The Company, as nominal defendant, and its current directors, as defendants, answered the complaint on Feb. 3, 2023.

Solomon Capital, LLC. On April 8, 2016, a lawsuit ("the First Solomon Suit") titled *Solomon Capital, LLC, Solomon Capital 401(K) Trust, Solomon Sharbat and Shelhav Raff v. Lion Biotechnologies, Inc.* was filed by Solomon Capital, LLC, Solomon Capital

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

401(k) Trust, Solomon Sharbat and Shelhav Raff (“Solomon Plaintiffs”) against the Company in the Supreme Court of the State of New York, County of New York (index no. 651881/2016). The Solomon Plaintiffs allege that, between June and November 2012, they provided the Company \$0.1 million and that they advanced and paid on behalf of the Company an additional \$0.2 million.

The complaint further alleges that the Company agreed to (i) provide them with promissory notes totaling \$0.2 million, plus interest, (ii) issue a total of 1,110 shares to the Solomon Plaintiffs (after the 1-for-100 reverse split of the Company’s common stock effected in March 2013) (the “Equity Claim”), and (iii) allow the Solomon Plaintiffs to convert the foregoing funds into its securities in the next financing of the Company on the same terms offered to other investors, which Solomon Plaintiffs allege, should have given them the right to convert their advances and payments into shares of the Company’s common stock in the restructuring that took effect in May 2013. Based on the foregoing, the Solomon Plaintiffs allege causes for breach of contract and unjust enrichment and demand judgment against the Company in an unspecified amount exceeding \$1.5 million, plus interest. On June 3, 2016, the Company filed an answer and counterclaims in the lawsuits. The Company has asserted counterclaims for fraudulent inducement, fraudulent misrepresentation, fraudulent concealment, breach of fiduciary duty, and breach of contract, alleging principally that the counterclaim defendants misrepresented their qualifications and failed to disclose that Solomon Sharbat was the subject of an investigation by the Financial Industry Regulatory Authority (“FINRA”) that resulted in the loss of his FINRA license.

In its counterclaims, the Company is seeking damages in an amount exceeding \$0.5 million and an order rescinding any and all agreements that the Solomon Plaintiffs contend entitled them to obtain shares of Company stock. On May 12, 2020, the court granted the Company’s motion for summary judgment limiting the Solomon Plaintiffs’ damages for the Equity Claim to \$47,420. The Solomon Plaintiffs filed a notice of appeal of this summary judgment on June 9, 2020. On July 2, 2020, the court granted the Company’s motion to dismiss the First Solomon Suit for want of prosecution. On January 4, 2021, the court granted the Solomon Plaintiffs motion for reconsideration, and reinstated the case. On January 15, 2021, the Company filed a notice of appeal of the court’s grant of the Solomon Plaintiffs motion for reconsideration. On May 11, 2021, the Appellate Division upheld the court’s grant of the Solomon Plaintiffs’ motion for reconsideration of the dismissal of the First Solomon Suit for want of prosecution.

On September 27, 2019, the Solomon Plaintiffs filed a new lawsuit (through new legal counsel) (“the Second Solomon Suit”) titled *Solomon Capital, LLC, Solomon Capital 401(K) Trust, Solomon Sharbat and Shelhav Raff v. Iovance Biotherapeutics, Inc., f/k/a/ Lion Biotechnologies Inc. f/k/a/ Genesis Biopharma Inc., and Manish Singh* in the Supreme Court of the State of New York, County of New York (index no. 655668/2019). In the Second Solomon Suit, the Solomon Plaintiffs allege that they are third party beneficiaries of a “finder’s fee agreement” that prior management entered into with a third party unlicensed entity in 2012 in connection with seeking financing, that an agreement or understanding existed between the Company and the plaintiffs that the plaintiffs would be paid fees and commissions (in cash and stock) if they obtained financing for the Company, and that they directly and indirectly introduced investors to the Company who invested in the Company, or were willing to invest in the Company. Finally, the Solomon Plaintiffs allege that they were promised a license to use the Company’s technology in Israel. The plaintiffs claim that the Company breached the foregoing understandings, promises and agreements and, as a result, they are entitled to certain damages. The Solomon Plaintiffs also allege that Manish Singh, the Company’s former Chief Executive Officer, committed fraud and took shares belonging to them. On February 18, 2020, the Company filed a removal petition and removed the Second Solomon Suit to the U.S. District Court for the Southern District of New York, where the case has been assigned case no. 1:20-cv-1391. On May 22, 2020, the Company moved to dismiss the Second Solomon Suit for lack of personal jurisdiction. On March 26, 2021, the Court denied the Company’s motion to dismiss for lack of personal jurisdiction. The Company filed a response to the complaint in the Second Solomon Suit on April 30, 2021. On May 26, 2021, the Company and Singh filed motions for judgment on the pleadings with respect to the second and third claims asserted against the Company and all claims asserted against Singh, respectively, in the Second Solomon Suit. On January 5, 2022, the Court granted the Company’s motions for judgment on the pleadings, dismissing the second and third claims against the Company and dismissing all claims against Singh. On January 4, 2023, the Court granted in part the Company’s motion for sanctions against Plaintiffs for violating Rule 11 of the Federal Rules of Civil Procedure, in a decision and order that dismissed Plaintiffs’ first claim against the Company, denied Plaintiffs’ motion for leave to amend the complaint, and ordered Plaintiffs to pay the Company’s attorneys’ fees incurred in connection with the Rule 11 motion. Following the Court’s decision and order on the Rule 11 motion, only Plaintiffs’ fifth and sixth claims, for unjust enrichment and indemnification, respectively, remain pending against the Company.

The Company intends to vigorously defend these complaints and pursue its counterclaims, as applicable. At the current stage of the litigation, in both the First Solomon Suit and the Second Solomon Suit, it is not possible to estimate the amount or range of possible loss that might result from an adverse judgment or a settlement of these matters.

IOVANCE BIOTHERAPEUTICS, INC.
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The Company may be involved, from time to time, in legal proceedings and claims arising in the ordinary course of its business. Such matters are subject to many uncertainties and outcomes are not predictable with assurance. The Company accrues amounts, to the extent they can be reasonably estimated, that it believes are adequate to address any liabilities related to legal proceedings and other loss contingencies that it believes will result in a probable loss. While there can be no assurances as to the ultimate outcome of any legal proceeding or other loss contingency involving the Company, management does not believe any pending matter will be resolved in a manner that would have a material adverse effect on its financial position, results of operations or cash flows.

NOTE 12. LONG-TERM NOTE PAYABLE

On January 26, 2021, the Company entered into a Loan Note and accompanying Economic Stimulus Program Loan Agreement with PIDC – Local Development Corporation, a Pennsylvania nonprofit corporation (the “Lender”), pursuant to which the Lender agreed to make a loan (the “Job Creation Loan”) to the Company in a principal amount of \$1.0 million. The Job Creation Loan will be for a term of five years starting on February 18, 2021, the date of the issuance of a final certificate of occupancy for the Company’s leased premises in Philadelphia, Pennsylvania. The Job Creation Loan is unsecured, bears no interest, and will be forgiven by the Lender in the amount of \$2,000 per full-time or “full time equivalent” (defined as two or more part time employees whose working hours total at least 35 hours a week) employee with an average salary of at least \$80,000 (“FT Employees”), up to a maximum amount equal to the amount of the Job Creation Loan, as calculated based on the average number of FT Employees employed at the Company’s premises during the period of the 5-year term beginning on the date that is nine months prior to the maturity date and ending on the maturity date. If the Job Creation Loan is not forgiven in full by the maturity date, the remaining balance of the loan not forgiven will become payable on the maturity date. The Loan Note includes customary events of default. Upon the occurrence of an event of default, the Lender will have the right to exercise remedies against the Company, including the right to require immediate payment of all amounts due under the Loan Note.

The Company concluded that it is not reasonably assured that all or a portion of the loan will be forgiven as of December 31, 2022, and therefore accounted for the Job Creation Loan as debt in accordance with ASC Topic 470, *Debt*, as opposed to an in-substance government grant, and classified as a long-term debt in its Consolidated Balance Sheets as of December 31, 2022 and 2021.

NOTE 13. SUBSEQUENT EVENTS

Acquisition of Proleukin®

Pursuant to that certain Option Agreement entered into on January 23, 2023 (the “Option Agreement”) between the Company and Clinigen Holdings Limited, Clinigen Healthcare Limited and Clinigen, Inc. (collectively, “Clinigen”), the Company will acquire worldwide rights to Proleukin® (aldesleukin) (the “Product”), an interleukin-2 product used to promote T-cell activity following TIL infusion.

Material terms of the Option Agreement include an upfront payment of £167.7 million, or approximately \$200 million, a £41.7 million, or approximately \$50 million, milestone payment upon first approval of lifileucel in advanced melanoma, and deferred consideration based on double-digit rates on global net sales of the Product payable from the Company to Clinigen following the completion of the transaction for the applicable deferred consideration term.

Subject to the terms and conditions of the Option Agreement, the Company will purchase (i) all issued and outstanding shares of Clinigen SP Limited (the “Target”), (ii) the business of the Target and Clinigen comprising the manufacturing, supply, commercialization and the generation of income from the Product rights and the undertaking of an active role in the development, maintenance and exploitation of those rights (the “Operations”), and (iii) certain specified assets identified in the Option Agreement.

The Option Agreement is subject to customary termination provisions, and the Company would be required to pay to Clinigen a reverse termination fee (less certain transaction fees and expenses incurred by the Company) upon certain events as described in the Option Agreement. The closing of the transaction is subject to required regulatory approvals and clearances and other customary closing conditions.

COMPANY INFORMATION

OFFICERS

FREDERICK G. VOGT, PH.D., J.D.

Interim CEO, President, and General Counsel

FRIEDRICH GRAF FINCKENSTEIN, M.D.

Chief Medical Officer

JEAN-MARC BELLEMIN, M.B.A.

Chief Financial Officer

IGOR BILINSKY, PH.D.

Chief Operating Officer

BOARD OF DIRECTORS

IAIN DUKES, D.PHIL.

Chairman of the Board
Venture Partner, OrbiMed Advisors LLC

ATHENA COUNTOURIOTIS, M.D.

President and Chief Executive Officer,
Avenzo Therapeutics

WENDY L. DIXON, PH.D.

Independent Director

RYAN MAYNARD

Chief Financial Officer,
Cara Therapeutics, Inc.

GENERAL MERRILL A. MCPEAK

Chief of Staff, U.S. Air Force (Ret.)

WAYNE ROTHBAUM

President, Quogue Capital LLC

MICHAEL WEISER, M.D., PH.D.

Principal, Actin Biomed LLC

WENDY L. YARNO

Independent Director

HEADQUARTERS

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2022 AUDITORS

Ernst & Young LLP
San Mateo, CA

SECURITIES COUNSEL

DLA Piper LLP (US)
New York, NY

COMMON STOCK

NASDAQ Symbol: IOVA

SEC FORM 10-K

A copy of the Company's annual report to the Securities and Exchange Commission on Form 10-K will be available without charge upon written request to Iovance Biotherapeutics at 825 Industrial Road, Suite 400, San Carlos, CA 94070 or via the Company's website at www.iovance.com.

ANNUAL MEETING

Iovance will hold its Annual Meeting of Stockholders virtually, via live webcast, at 11:00 a.m. EDT on Tuesday, June 6, 2023. Visit www.cstproxy.com/iovance/2023 to participate.

SAFE HARBOR

This annual report contains certain forward-looking statements. For a discussion of forward-looking statements, please see Part 1, Item 1 of our annual report on Form 10-K for 2022.

CORPORATE HEADQUARTERS

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