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

FORM 10-Q

- QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the quarterly period ended **March 31, 2022**
- TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from __ to __.
- Commission File Number 001-36860

IOVANCE BIOTHERAPEUTICS, INC.

(Exact name of issuer as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

75-3254381
(I.R.S. employer
identification number)

825 Industrial Road, Suite 400, San Carlos, CA 94070

(Address of principal executive offices and zip code)

(650) 260-7120

(Registrant's telephone number, including area code)

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 pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) 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 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	IOVA	The Nasdaq Global Market

At April 25, 2022, the issuer had 157,168,321 shares of common stock, par value \$0.000041666 per share, outstanding.

IOVANCE BIOTHERAPEUTICS, INC.
FORM 10-Q
For the Quarter Ended March 31, 2022

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PART I. FINANCIAL INFORMATION

Item 1. Condensed Consolidated Financial Statements

**IOVANCE BIOTHERAPEUTICS, INC.
Condensed Consolidated Balance Sheets
(unaudited; in thousands, except share and per share information)**

	March 31, 2022	December 31, 2021
ASSETS		
Current Assets		
Cash and cash equivalents	\$ 92,360	\$ 78,229
Short-term investments	389,829	426,181
Prepaid expenses and other assets	7,779	3,546
Total Current Assets	489,968	507,956
Property and equipment, net	102,757	100,938
Operating lease right-of-use assets	73,475	68,983
Long-term investments	27,701	91,588
Restricted cash	6,084	6,084
Long-term assets	1,266	1,784
Total Assets	\$ 701,251	\$ 777,333
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current Liabilities		
Accounts payable	\$ 20,454	\$ 27,377
Accrued expenses	48,911	56,766
Operating lease liabilities	7,710	5,057
Total Current Liabilities	77,075	89,200
Non-Current Liabilities		
Operating lease liabilities – noncurrent	71,184	65,474
Long-term note payable	1,000	1,000
Total Non-Current Liabilities	72,184	66,474
Total Liabilities	149,259	155,674
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 March 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 March 31, 2022 and December 31, 2021	3	3
Common stock, \$0.000041666 par value; 300,000,000 shares authorized, 157,168,321 and 157,004,742 shares issued and outstanding as of March 31, 2022 and December 31, 2021, respectively	7	7
Accumulated other comprehensive loss	(2,343)	(601)
Additional paid-in capital	1,818,377	1,794,695
Accumulated deficit	(1,264,052)	(1,172,445)
Total Stockholders' Equity	551,992	621,659
Total Liabilities and Stockholders' Equity	\$ 701,251	\$ 777,333

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

IOVANCE BIOTHERAPEUTICS, INC.
Condensed Consolidated Statements of Operations
(unaudited; in thousands, except per share information)

	Three Months Ended March 31,	
	2022	2021
Costs and expenses		
Research and development	68,300	55,949
General and administrative	23,413	19,621
Total costs and expenses	91,713	75,570
Loss from operations	(91,713)	(75,570)
Other income		
Interest income, net	106	121
Net Loss	<u>\$ (91,607)</u>	<u>\$ (75,449)</u>
Net Loss Per Share of Common Stock, Basic and Diluted	<u>\$ (0.58)</u>	<u>\$ (0.51)</u>
Weighted Average Shares of Common Stock Outstanding, Basic and Diluted	<u>157,113</u>	<u>147,370</u>

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

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

	Three Months Ended March 31,	
	2022	2021
Net Loss	\$ (91,607)	\$ (75,449)
Other comprehensive (loss) income:		
Unrealized (loss) gain on investments	(1,742)	77
Comprehensive Loss	<u>\$ (93,349)</u>	<u>\$ (75,372)</u>

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

IOVANCE BIOTHERAPEUTICS, INC.
Condensed Consolidated Statements of Stockholders' Equity
For the Three Months Ended March 31, 2022 and 2021
(unaudited; 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 (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount	Shares	Amount				
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	—	—	—	—	—	—	22,265	—	—	22,265
Common stock issued upon exercise of stock options	—	—	—	—	163,579	—	1,417	—	—	1,417
Unrealized loss on investments	—	—	—	—	—	—	—	(1,742)	—	(1,742)
Net loss	—	—	—	—	—	—	—	—	(91,607)	(91,607)
Balance - March 31, 2022	<u>194</u>	<u>\$ —</u>	<u>2,842,158</u>	<u>\$ 3</u>	<u>157,168,321</u>	<u>\$ 7</u>	<u>\$1,818,377</u>	<u>\$ (2,343)</u>	<u>\$ (1,264,052)</u>	<u>\$ 551,992</u>
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	—	—	—	—	—	—	16,941	—	—	16,941
Common stock issued upon exercise of stock options	—	—	—	—	423,178	—	6,479	—	—	6,479
Common stock sold in public offering, net of offering costs	—	—	—	—	1,278,243	—	42,885	—	—	42,885
Common stock issued from preferred stock conversion	—	—	(738,961)	(1)	738,961	—	1	—	—	—
Unrealized gain on investments	—	—	—	—	—	—	—	77	—	77
Net loss	—	—	—	—	—	—	—	—	(75,449)	(75,449)
Balance - March 31, 2021	<u>194</u>	<u>\$ —</u>	<u>2,842,158</u>	<u>\$ 3</u>	<u>149,315,299</u>	<u>\$ 6</u>	<u>\$1,552,968</u>	<u>\$ 96</u>	<u>\$ (905,642)</u>	<u>\$ 647,431</u>

IOVANCE BIOTHERAPEUTICS, INC.
Condensed Consolidated Statements of Cash Flows
(unaudited; in thousands)

	Three Months Ended March 31,	
	2022	2021
Cash Flows from Operating Activities		
Net loss	\$ (91,607)	\$ (75,449)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	22,265	16,941
Amortization of right of use asset	3,181	2,402
Depreciation and amortization	1,797	372
Accretion (amortization) of discounts and premiums on investments	541	2,066
Loss on write-off of fixed assets	314	—
Changes in assets and liabilities:		
Prepaid expenses, other assets and long-term assets	(3,715)	(4,067)
Operating lease liabilities	690	(1,374)
Accounts payable	(2,104)	(15)
Accrued expenses and other liabilities	(5,164)	(3,267)
Net cash used in operating activities	<u>(73,802)</u>	<u>(62,391)</u>
Cash Flows from Investing Activities		
Maturities of investments	143,508	158,286
Purchase of investments	(45,552)	(70,370)
Purchase of property and equipment	(11,440)	(10,705)
Net cash provided by investing activities	<u>86,516</u>	<u>77,211</u>
Cash Flows from Financing Activities		
Proceeds from the issuance of common stock upon exercise of options	1,417	6,479
Proceeds from the issuance of common stock, net	—	42,885
Proceeds from the issuance of debt	—	1,000
Net cash provided by financing activities	<u>1,417</u>	<u>50,364</u>
Net increase in cash, cash equivalents and restricted cash	14,131	65,184
Cash, Cash Equivalents and Restricted Cash Beginning of Period	84,313	72,854
Cash, Cash Equivalents and Restricted Cash End of Period	<u>\$ 98,444</u>	<u>\$ 138,038</u>
Supplemental disclosure of non-cash investing and financing activities:		
Net unrealized (loss) gain on short-term investments	\$ (1,742)	\$ 77
Acquisition of property and equipment included in accounts payable and accrued expenses	4,900	8,352
Conversion of convertible preferred stock to common stock	—	(1)
Lease liabilities arising from obtaining right-of-use asset from lease modifications	7,673	—

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

IOVANCE BIOTHERAPEUTICS, INC.
NOTES TO THE CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
(unaudited)

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 cure cancer by harnessing the human immune system’s ability to recognize and destroy diverse cancer cells in each patient. Tumor infiltrating lymphocyte (“TIL”) therapy is an autologous cell therapy platform technology that was originally developed by the National Cancer Institute (“NCI”), which conducted initial clinical trials in diseases such as metastatic melanoma and cervical cancer, as well as non-small cell lung cancer. The Company’s mission is to be the global leader in innovating, developing and delivering TIL therapy for patients with cancer. The Company has developed a new, shorter proprietary TIL manufacturing process known as Generation 2 (“Gen 2”), which yields a cryopreserved TIL product. This centralized, proprietary, and scalable manufacturing method is being investigated in multiple indications. The Company’s lead product candidates include lifileucel for metastatic melanoma and metastatic cervical cancer, as well as LN-145 for metastatic non-small cell lung cancer (“NSCLC”). In addition, the Company is investigating the effectiveness and safety of combinations of TIL therapy with immune checkpoint inhibitors (“ICI”), in metastatic melanoma, cervical cancer, NSCLC, and head and neck squamous cell carcinoma (“HNSCC”). The Company is investigating peripheral blood lymphocyte (“PBL”) therapy for patients with relapsed or refractory chronic lymphocytic leukemia (“CLL”) and small lymphocytic lymphoma (“SLL”) through its sponsored trials. The Company is also investigating the potential for TIL therapy in other oncology indications through academic collaborations with leading cancer research centers. On June 1, 2017, the Company reincorporated from a Nevada corporation to a Delaware corporation.

Basis of Presentation of Unaudited Condensed Consolidated Financial Information

The accompanying unaudited condensed consolidated financial statements of the Company for the three months ended March 31, 2022 and 2021 have been prepared in accordance with accounting principles generally accepted in the United States of America (“GAAP”) for interim financial information and pursuant to the requirements for reporting on Form 10-Q and Regulation S-X. Accordingly, they do not include all the information and footnotes required by GAAP for audited financial statements. However, such information reflects all adjustments (consisting solely of normal recurring adjustments), which are, in the opinion of management, necessary for the fair presentation of the Company’s financial position and results of operations. Results shown for interim periods are not necessarily indicative of the results that may be expected for the year ended December 31, 2022 or for any other period. The condensed consolidated balance sheet as of December 31, 2021 was derived from the audited consolidated financial statements included in the Company’s Annual Report on Form 10-K filed with the Securities and Exchange Commission (the “SEC”) on February 24, 2022. These interim financial statements should be read in conjunction with that report. Certain prior period amounts reported in our condensed consolidated financial statements and accompanying notes have been reclassified to conform to the current period presentation.

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 financial statements are issued. The Company has incurred a net loss of \$91.6 million for the three months ended March 31, 2022 and used \$73.8 million of cash in its operating activities during the three months ended March 31, 2022. As of March 31, 2022, the Company had \$516.0 million in cash, cash equivalents, investments, and restricted cash (\$92.4 million of cash and cash equivalents, \$389.8 million in short-term investments, \$27.7 million in long-term investments, and \$6.1 million in restricted cash).

The Company expects to continue its research and development activities, increase pre-commercial activities and complete construction of the remaining tenant improvements for the Iovance Cell Therapy Center (the “iCTC”), which are expected to increase the amount of cash used during the remainder of 2022 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 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 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.

NOTE 2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

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 Condensed 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 three months ended March 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 Condensed 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 Condensed 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 three letters of credit, one for \$5.45 million for the benefit of the landlord for the iCTC used as a security deposit for the lease (See Note 8 - Leases), one for \$0.1 million for the benefit of a utilities service provider to cover the use of certain minimum established levels of utilities, and one for \$0.6 million for the benefit of the landlord for the Company’s current headquarters’ lease. The total amount is classified as Restricted Cash on the Condensed Consolidated Balance Sheets. The first 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 second letter of credit for \$0.1 million expired on March 9, 2021, however, it automatically extends, without written agreement, to the expiration date of December 1, 2022, or until such established minimum service levels are achieved, whichever is earlier. The third letter of credit for \$0.6 million 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 March 31, 2022 and December 31, 2021, restricted cash totaled \$6.1 million and has been classified as a non-current asset on the Company’s Condensed Consolidated Balance Sheets.

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

	March 31,	
	2022	2021
Cash and cash equivalents	\$ 92,360	\$ 131,954
Restricted cash	6,084	6,084
Total cash, cash equivalents and restricted cash	<u>\$ 98,444</u>	<u>\$ 138,038</u>

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 equivalents 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 (iv) conversion of preferred stock, are only included in the calculation of diluted net loss per share when their effect is dilutive.

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

	March 31,	
	2022	2021
Stock options	14,101,526	15,419,226
Employee Stock Purchase Plan	86,448	55,963
Restricted stock units	3,095,177	—
Series A Convertible Preferred Stock*	97,000	97,000
Series B Convertible Preferred Stock*	2,842,158	2,842,158
	<u>20,222,309</u>	<u>18,414,347</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.

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.

Principles of Consolidation

The accompanying condensed 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 Condensed Consolidated Balance Sheets as Operating lease right-of-use assets and Operating lease liabilities as of March 31, 2022 and December 31, 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 Condensed 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.

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 estimates of 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 estimates of services received and efforts expended pursuant to agreements established with CROs, CMOs and other outside service providers. The Company determines its estimates 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 study 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 study 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 study, 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 study treatment. The Company accrues for 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 Condensed Consolidated Balance Sheets and subsequently recognized as research and development expense in the Condensed 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. Changes in these estimates that result in material changes to the Company’s accruals could materially affect its results of operations. The Company’s historical estimates have not been materially different from actual amounts recorded.

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, INVESTMENTS AND FAIR VALUE MEASUREMENTS

The amortized cost, fair value measurements, and fair value of cash equivalents and investments as of March 31, 2022 and December 31, 2021 were as follows (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
As of March 31, 2022				
U.S. treasury securities	\$ 248,546	\$ —	\$ (2,062)	\$ 246,484
U.S. government agency securities	5,067	—	(21)	5,046
Corporate securities	34,408	—	(79)	34,329
Commercial paper	158,276	1	(182)	158,095
Money market funds	45,249	—	—	45,249
Total investments	<u>\$ 491,546</u>	<u>\$ 1</u>	<u>\$ (2,344)</u>	<u>\$ 489,203</u>
As of December 31, 2021				
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>

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The fair value of cash equivalents and investments as of March 31, 2022 and December 31, 2021 are classified as follows in the Company's Consolidated Balance Sheets (in thousands):

Classified as:	March 31,	December 31,
	2022	2021
Cash equivalents	\$ 71,673	\$ 61,249
Short-term investments	389,829	426,181
Long-term investments	27,701	91,588
Total investments	<u>\$ 489,203</u>	<u>\$ 579,018</u>

Cash equivalents in the tables above exclude cash demand deposits of \$20.7 million and \$17.0 million as of March 31, 2022 and December 31, 2021, respectively. Unrealized gains and losses are included in accumulated other comprehensive loss, and as of March 31, 2022 and December 31, 2021 no unrealized losses on available-for-sale securities have resulted from credit risk. All available-for-sale securities held as of March 31, 2022 and December 31, 2021 had contractual maturities of less than two years. No 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.

The following table summarizes the Company's cash equivalents and available-for-sale investments by contractual maturity (in thousands):

	March 31, 2022	
	Amortized Cost	Fair Value
Within one year	\$ 463,385	\$ 461,502
One year to two years	28,161	27,701
Total investments	<u>\$ 491,546</u>	<u>\$ 489,203</u>

Recurring Fair Value Measurements

As of March 31, 2022 and December 31, 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 March 31, 2022			
	Level 1	Level 2	Level 3	Total
U.S. treasury securities	\$ 246,484	\$ —	\$ —	\$ 246,484
U.S. government agency securities	—	5,046	—	5,046
Corporate securities	—	34,329	—	34,329
Commercial paper	—	158,095	—	158,095
Money market funds	45,249	—	—	45,249
Total	<u>\$ 291,733</u>	<u>\$ 197,470</u>	<u>\$ —</u>	<u>\$ 489,203</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.

NOTE 4. PROPERTY AND EQUIPMENT, NET

Property and equipment, net consists of the following (in thousands):

	March 31, 2022	December 31, 2021
Leasehold improvements	\$ 65,767	\$ 57,817
Lab, process, and validation equipment	9,173	8,686
Utility equipment	4,179	4,179
Office furniture and equipment	2,136	1,244
Computer software	6,264	1,163
Computer equipment	674	674
Machinery and equipment	82	82
Construction in progress	23,732	35,782
Total Property and equipment, cost	112,007	109,627
Less: Accumulated depreciation and amortization	(9,250)	(8,689)
Property and equipment, net	\$ 102,757	\$ 100,938

Depreciation expense for the three months ended March 31, 2022 and 2021, was \$1.8 million and \$0.4 million, respectively.

NOTE 5. ACCRUED EXPENSES

Accrued expenses consist of the following (in thousands):

	March 31, 2022	December 31, 2021
Accrued payroll and employee related expenses	\$ 18,204	\$ 21,513
Clinical related	17,910	18,167
Manufacturing related	6,295	6,566
Facilities related	2,077	4,857
Legal and related services	1,654	1,907
Other accrued expenses	2,771	3,756
Total accrued expenses	\$ 48,911	\$ 56,766

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 March 31, 2022, 157,168,321 shares of the Company's common stock were issued and outstanding.

At the Market Offering Program

On February 8, 2021, the Company entered into an Open Market Sale Agreement (the "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"). The issuance and sale, if any, of the Common Shares by the Company under the Sales Agreement will be made pursuant to a prospectus supplement, dated February 8, 2021, 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 Agreement, 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 Agreement.

The Company is not obligated to make any sales of Common Shares under the Sales Agreement. 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 Agreement in accordance with its terms.

No sales were made pursuant to the Sales Agreement during the three months ended March 31, 2022. For the three months ended March 31, 2021, the Company received approximately \$42.9 million in net proceeds, net of offering costs, through the sale of 1,278,243 shares of its common stock through the Sales Agreement at a weighted average price per share of \$34.67.

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 March 31, 2022, 17,000 shares were designated as Series A Convertible Preferred Stock (“Series A Convertible Preferred Stock”) and 11,500,000 shares were designated as Series B Convertible Preferred Stock (“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 during the three months ended March 31, 2022 or 2021. As of March 31, 2022, and December 31, 2021, 194 shares of Series A Convertible Preferred Stock (that are convertible into 97,000 shares of common stock) remained outstanding.

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 shares 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.

During the three months ended March 31, 2022, no shares of Series B Convertible Preferred Stock were converted into shares of common stock. During the three months ended March 31, 2021, a total of 738,961 of Series B Convertible Preferred Stock were converted into 738,961 shares of common stock. As of March 31, 2022, and December 31, 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 March 31, 2022, there are 79,465 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. As of March 31, 2022, 1,058,461 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.

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 March 31, 2022, 552,925 shares of common stock were available for grant under the 2021 Inducement Plan.

Stock Options

A summary of the stock option activity during the three months ended March 31, 2022, 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 December 31, 2021	12,520,865	\$ 25.05		
Issued	1,887,052	14.69		
Exercised	(163,579)	8.65		
Expired/Cancelled	(142,812)	29.52		
Outstanding at March 31, 2022	<u>14,101,526</u>	<u>\$ 23.81</u>	<u>7.83</u>	<u>\$ 27,587</u>
Ending vested and expected to vest at March 31, 2022	<u>14,101,526</u>	<u>\$ 23.81</u>	<u>7.83</u>	<u>\$ 27,587</u>
Options exercisable at March 31, 2022	<u>7,543,738</u>	<u>\$ 20.50</u>	<u>6.74</u>	<u>\$ 23,859</u>

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As of March 31, 2022, there was \$94.1 million of total unrecognized compensation expense related to the options that is expected to be recognized over a weighted average period of 1.97 years.

The weighted average grant date fair value for employee options granted under the Company's stock option plans during the three months ended March 31, 2022 and 2021 was \$8.81 and \$26.42 per option, respectively.

The aggregate intrinsic value in the table above reflects the total pre-tax intrinsic value (calculated as the difference between the Company's closing stock price on the last trading day of the quarter ended March 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 March 31, 2022. The intrinsic value of the Company's stock options changes based on the closing price of the Company's common stock.

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.

Under the 2020 ESPP, employees of the Company can purchase shares of its 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 three months ended March 31, 2022 and 2021 was \$0.2 million and \$0.3 million, respectively. As of March 31, 2022, 94,148 shares had been issued to date under the 2020 ESPP and there was \$0.2 million of unrecognized compensation cost associated with the 2020 ESPP, which is expected to be recognized over the remaining 2.3 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.

Activity for RSUs and PRSUs units during the three months ended March 31, 2022 is presented in the following table:

	Number of RSUs and PRSUs	Weighted Average Grant Date Fair Value
Outstanding, non-vested as of December 31, 2021	1,110,010	\$ 23.87
Granted	2,027,774	15.18
Canceled/Forfeited	(42,607)	19.43
Outstanding, non-vested as of March 31, 2022	<u>3,095,177</u>	<u>\$ 18.24</u>

As of March 31, 2022, there was \$37.0 million of unrecognized stock-based compensation expense associated with unvested RSU and PRSUs, which the Company expects to recognize over a remaining weighted-average period of 1.88 years. The aggregate intrinsic value of the unvested RSUs and PRSUs outstanding as of March 31, 2022 was \$51.5 million.

Stock-Based Compensation

Total stock-based compensation expense related to all of the Company's stock-based awards was recorded on the Condensed Consolidated Statements of Operations as follows (in thousands):

	Three Months Ended March 31,	
	2022	2021
Research and development	\$ 13,651	\$ 9,202
General and administrative	8,614	7,739
Total stock-based compensation expense	<u>\$ 22,265</u>	<u>\$ 16,941</u>

Total stock-based compensation expense by type of award was as follows (in thousands):

	Three Months Ended March 31,	
	2022	2021
Stock option expense	\$ 14,867	\$ 16,660
Restricted stock expense	7,162	—
ESPP expense	236	281
Total stock-based compensation expense	<u>\$ 22,265</u>	<u>\$ 16,941</u>

NOTE 7. 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 \$0.5 million for each of the three months ended March 31, 2022 and 2021, respectively, as research and development expenses.

Patent License Agreement Related to the Development and Manufacture of TIL

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 (the “Amended and Restated Patent License Agreement”), which includes the grant of additional exclusive, worldwide patent rights in the Indications to cytokine-tethered TIL technology, and expands the non-exclusive, worldwide field of use to all cancers. The 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 Amended and Restated Patent License Agreement. The Company anticipates making milestone payments, including a payment in the low-single-digit millions of dollars in conjunction with the approval of a Biologics License Application for any of its product candidates covered by the Amended and Restated Patent License Agreement. The term of the 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 license to the NIH’s rights to patent-pending technologies related to methods for improving adoptive cell therapy through more potent and efficient production of TIL from melanoma tumors by selecting for T cell populations that express various inhibitory receptors. Unless terminated sooner, the license shall remain in effect until the last licensed patent right expires.

Under the Exclusive Patent License Agreement, the Company agreed to pay customary royalties based on a percentage of net sales of a licensed product (which percentage is in the mid-single digits), a percentage of revenues from sublicensing arrangements, and lump sum benchmark payments upon the successful completion of clinical studies involving licensed technologies, the receipt of the first Food and Drug Administration (the “FDA”) approval or foreign equivalent for a licensed product or process resulting from the licensed technologies, the first commercial sale of a licensed product or process in the U.S., and the first commercial sale of a licensed product or process in any foreign country.

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, and under which immaterial payments will be made to Moffitt in connection with the research services thereunder.

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. The Company recorded \$0.1 million and \$0.2 million of research and development expense for the three months ended March 31, 2022 and 2021 respectively, 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 world-wide 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 three months ended March 31, 2022 and 2021.

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. In addition, 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 a de minimis amount for the three months ended March 31, 2022 and 2021 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 antagonists 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 \$7.0 million has been funded cumulatively through March 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 a de minimis amount associated with the SAA for the three months ended March 31, 2022 and 2021, respectively, as research and development expenses.

WuXi Advanced Therapies, Inc.

In November 2016, the Company entered into a three-year manufacturing and services agreement (“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 MSA, the Company entered into two statements of work for two cGMP manufacturing suites to be established and operated by WuXi for the Company, both of the suites are expected to be capable of being used for the commercial manufacture of its products. The terms of the two statements of work were both extended to December 2022. The Company recorded costs associated with agreements with WuXi of \$3.9 million and \$3.4 million for the three months ended March 31, 2022 and 2021, respectively, as research and development expenses.

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. Financial terms of the license include 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 \$0.1 million for each of the three months ended March 31, 2022 and 2021, respectively, as research and development expense.

Novartis Pharma AG

On January 12, 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 has 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 during the fiscal year ended December 31, 2020. No expenses were recorded for the three months ended March 31, 2022 or 2021.

NOTE 8. 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 iCTC, 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 of 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.

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 an 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):

	March 31, 2022	December 31, 2021
Operating lease right-of-use assets	\$ 73,475	\$ 68,983
Operating lease liabilities		
Current portion included in current liabilities	7,710	5,057
Long-term portion included in non-current liabilities	71,184	65,474
Total operating lease liabilities	\$ 78,894	\$ 70,531

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The following table summarizes components of lease expenses, which were included in Total costs and expenses in the Company's Condensed Consolidated Statements of Operations, and other information related to its operating leases as follows (in thousands except weighted-average remaining lease terms and discount rates):

	Three Months Ended March 31,	
	2022	2021
Operating lease cost	\$ 4,555	\$ 3,398
Variable lease cost	980	710
Short-term lease cost	42	36
Total lease cost	<u>\$ 5,577</u>	<u>\$ 4,144</u>
<i>Other information</i>		
Cash paid for amounts included in the measurement of lease liabilities included in Operating cash flows	\$ 3,811	\$ 2,466
Tenant improvement allowance received for amounts included in the measurement of lease liabilities included in Operating cash flows	\$ 3,115	\$ 144
Right-of-use assets obtained from entering new leases	\$ —	\$ 618
Increase in right-of-use assets from lease modifications	\$ 7,673	\$ 2,159
Weighted-average remaining lease terms (years)	14.13	17.55
Weighted-average discount rates	7.2%	7.4%

As of March 31, 2022, the maturities of the Company's operating lease liabilities were as follows (in thousands):

Year Ending December 31,	Facility leases	CMO embedded leases	Total
2022	\$ 4,332	\$ 6,317	\$ 10,648
2023	8,015	3,120	11,135
2024	8,215	—	8,215
2025	8,116	—	8,116
2026	7,989	—	7,989
Thereafter	92,013	—	92,013
Total lease payments	<u>\$ 128,678</u>	<u>\$ 9,437</u>	<u>\$ 138,115</u>
Less: Present value adjustment	(55,300)	(425)	(55,725)
Future tenant improvement reimbursement	(3,496)	—	(3,496)
Operating lease liabilities	<u>\$ 69,883</u>	<u>\$ 9,012</u>	<u>\$ 78,894</u>

For its corporate headquarters' office, the lease agreement includes a tenant improvement allowance of \$8.2 million. As of March 31, 2022, the Company has received total reimbursements associated with this tenant improvement allowance of \$4.7 million, of which \$3.1 million was received during the three months ended March 31, 2022.

NOTE 9. 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 its current directors, as defendants, in the Court of Chancery in the State of Delaware. 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 defendants intend to vigorously defend against the foregoing complaints. Based on the early stage of the litigation, it is not possible to estimate the amount or range of possible loss that might result from these matters.

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 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 to 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 judgement on the pleadings, dismissing the second and third claims against the Company and dismissing all claims against Singh.

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.

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 10. INCOME TAXES

The Company did not record income tax expense for the three months ended March 31, 2022 and 2021, respectively as the Company expected to be in a taxable loss position in 2022 and 2021, and the net deferred tax assets are fully offset by a valuation allowance as it is not more likely than not that the benefit will be realized. As of March 31, 2022, the Company remains in a cumulative book loss position and does not have sufficient positive evidence to realize its net deferred tax assets. As such, the Company continues to maintain a full valuation allowance against its net deferred tax assets.

Item 2. Management’s Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of our financial condition as of March 31, 2022 and results of operations for the three months ended March 31, 2022, should be read in conjunction with management’s discussion and analysis of financial condition and results of operations included in our Annual Report on Form 10-K for the year ended December 31, 2021 which was filed with the Securities and Exchange Commission (the “SEC”) on February 24, 2022. 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 of our Annual Report on Form 10-K and elsewhere in this Quarterly Report on Form 10-Q and other reports we file with the SEC. 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. Unless the context requires otherwise, references in this Quarterly Report on Form 10-Q to “Iovance,” “we,” “us” and “our” refer to Iovance Biotherapeutics, Inc. and our subsidiaries.

Overview

We are a clinical-stage biopharmaceutical company 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. TIL therapy is an autologous, polyclonal cell therapy platform technology that was originally developed by the National Cancer Institute, or NCI, which conducted initial clinical trials of this therapy in diseases such as metastatic melanoma and cervical cancer. Our mission is to be the global leader in innovating, developing and delivering TIL therapies for patients with cancer. We have developed a new, shorter TIL manufacturing process known as Gen 2, which yields a cryopreserved TIL product. This centralized, proprietary, and scalable manufacturing method is being investigated in multiple indications. Our lead product candidates include lifileucel for metastatic melanoma and metastatic cervical cancer, as well as LN-145 for metastatic non-small cell lung cancer, or NSCLC. In addition, we are investigating the effectiveness and safety of combinations of TIL therapy with immune checkpoint inhibitors, or ICIs, in metastatic melanoma, cervical cancer, NSCLC, and head and neck squamous cell carcinoma, or HNSCC. We are investigating peripheral blood lymphocyte, or PBL, therapy for patients with relapsed or refractory chronic lymphocytic leukemia, or CLL, and small lymphocytic lymphoma, or SLL, through our sponsored trials. We are developing first-in-class genetically edited TIL products based on the inactivation of genes that encode immune checkpoint proteins and other proteins, as well as the insertion of genes that encode immunomodulatory proteins. We are also developing an alternative interleukin-2, or IL-2, co-therapy for use with TIL therapies. Finally, we are investigating the potential for TIL therapy in other oncology indications and treatment settings through academic collaborations with leading cancer research centers.

Our current product candidate pipeline is summarized in the figure below:

Iovance Immuno-Oncology Pipeline

	PRODUCT CANDIDATE	INDICATION(S)	IND-ENABLING	PHASE 1	PHASE 2	PIVOTAL
TIL	Lifileucel/LN-144	Melanoma (post-anti-PD-1)	C-144-01 Study, Cohorts 2 & 4			FDA RMAT designation
	Lifileucel	Cervical cancer (post-chemo, post-chemo & post-anti-PD-1)	C-145-04 Study, Cohorts 1 & 2			FDA BTD
	LN-145	NSCLC (2L post-chemo & post-anti-PD-1)	IOV-LUN-202 Study, Cohorts 1 & 2			
	LN-145	NSCLC (2-4L, incl. post-anti-PD-1)	IOV-COM-202 Study, Cohort 3B			
	LN-145	HNSCC (post-anti-PD-1)	C-145-03 Study, Cohort 2			
TIL Combinations	Lifileucel + pembro	Melanoma (anti-PD-1 naive)	IOV-COM-202 Study, Cohort 1A			
	Lifileucel + pembro	Cervical cancer (1L, chemo & anti-PD-1 naive)	C-145-04 Study, Cohort 3			
	LN-145 + pembro	NSCLC (anti-PD-1 naive)	IOV-COM-202 Study, Cohort 3A			
	LN-145 + ipi/nivo	NSCLC (post-anti-PD-1)	IOV-COM-202 Study, Cohort 3C			
	LN-145 + pembro	HNSCC (anti-PD-1 naive)	IOV-COM-202 Study, Cohort 2A			
PD-1 Selected TIL	LN-145-S1	Melanoma (post-anti-PD-1)	IOV-COM-202 Study, Cohort 1B			
	LN-145-S1	HNSCC (post-anti-PD-1)	C-145-03 Study, Cohort 4			
Third-Generation (Gen 3) TIL 16-day manufacturing	LN-145 Gen 3 + core biopsy	NSCLC (2L post-chemo & post-anti-PD-1)	IOV-LUN-202 Study, Cohort 3			
	LN-144 Gen 3	Melanoma (post-anti-PD-1)	IOV-COM-202 Study, Cohort 1C			
	LN-145 Gen 3	HNSCC (post-anti-PD-1)	C-145-03 Study, Cohort 3			
PBL Therapy	IOV-2001	CLL/SLL (post-BTK)	IOV-CLL-01 Study			
PD-1 Inactivated TIL	IOV-4001	Multiple	IND Allowance			
IL-2 Analog	IOV-3001	Multiple				

Abbreviations: BTD=breakthrough therapy designation; BTK=Bruton's tyrosine kinase inhibitor; CLL/SLL=chronic lymphocytic leukemia and small lymphocytic lymphoma; HNSCC=head and neck squamous cell carcinoma; IL-2=interleukin 2; ipi/nivo=ipilimumab/nivolumab; NSCLC=non-small cell lung cancer; PBL=peripheral blood lymphocytes; RMAT=Regenerative Medicines Advanced Therapy; TIL=tumor infiltrating lymphocytes

TIL Monotherapy in Metastatic Solid Tumor Cancers

We have investigated TIL monotherapy in metastatic melanoma, cervical cancer, NSCLC and HNSCC. We are conducting a Phase 2 clinical trial, C-144-01, of our lead TIL product candidate, lifileucel, for the treatment of metastatic melanoma. This multicenter pivotal trial enrolled melanoma patients with disease progression following treatment with at least one systemic therapy, including a PD-1 inhibitor and, if BRAF mutated, a BRAF inhibitor, or a combination of BRAF and MEK inhibitors. Cohort 4 of the C-144-01 clinical trial is a single-arm cohort intended to support the submission of a Biologics License Application, or BLA, to the Food and Drug Administration, or the FDA, for lifileucel. Cohorts 2 and 4 of the C-144-01 trial use our Gen 2 manufacturing process. We completed and closed enrollment of patients into Cohort 2 of the C-144-01 trial in 2018. Results from Cohort 2 of the C-144-01 clinical trial were initially reported at the American Society of Clinical Oncology annual meeting, or ASCO, in June 2019 and subsequently updated at ASCO in June 2021. In addition, detailed Cohort 2 data was published in the *Journal of Clinical Oncology* in May 2021.

Pivotal Cohort 4 of the C-144-01 trial was enrolled to evaluate Overall Response Rate, or ORR, as read out by an Independent Review Committee, or IRC, as the primary endpoint based on our interpretation of discussions with the FDA as part of an End of Phase 2, or EOP2, meeting held with the FDA in the third quarter of 2018. In October 2018, based on the data provided to the FDA during the EOP2 meeting, we announced that lifileucel had received a Regenerative Medicines Advanced Therapy, or RMAT, designation from the FDA. Enrollment in Cohort 4 of the C-144-01 trial commenced in March 2019 and patient dosing was completed in January 2020.

Previously, 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 have continued our ongoing work developing and validating our potency assays and have engaged in discussions with the FDA during the second half of 2021 and the first quarter of 2022. Based on feedback received from these discussions, we expect to request a pre-BLA meeting in July 2022 and to complete a BLA submission for lifileucel in metastatic melanoma by August 2022. In connection with this BLA submission, the IRC is expected to independently assess responses for Cohort 4 patients through the data cut date, which must be completed prior to BLA submission or disclosure of IRC-read data.

We are also conducting a Phase 2 clinical trial, C-145-04, which is a multicenter pivotal trial to assess the safety and efficacy of our lead product candidate lifileucel for the treatment of patients with recurrent, metastatic, or persistent cervical cancer. In February 2019, lifileucel received Fast Track designation from the FDA for development in the treatment of cervical cancer with disease progression on or after chemotherapy. In March 2019, the protocol for this trial was amended to modify the primary endpoint of ORR to be determined by IRC. In May 2019, lifileucel received Breakthrough Therapy Designation, or BT, from the FDA for development in the treatment of cervical cancer. Results from the C-145-04 clinical trial were reported at ASCO in June 2019. In November 2019, we amended the C-145-04 trial to collect additional data on early-line patients as well as late-line patients by adding additional cohorts, in anticipation of a changing landscape in this indication, including Cohort 2 for patients that had previously received chemotherapy and anti-PD-1/anti-PD-L1 therapy. In January 2021, we announced that Cohort 2 of the C-145-04 trial had completed enrollment and that data from this cohort may be supportive of registration because of the expected changing landscape of care for cervical cancer patients. For example, because of recent regulatory approvals for pembrolizumab, there may be a potential shift from chemotherapy in front-line cervical cancer followed by pembrolizumab in second-line cervical cancer. We intend to execute our strategy based on dialog and feedback on these cohorts and continue to plan for a potential BLA submission for lifileucel in cervical cancer.

In November 2020, we announced that we had finalized the protocol for our potential registrational clinical trial in NSCLC, IOV-LUN-202, to investigate LN-145 in patients with metastatic NSCLC, without driver mutations, who previously received a single line of approved systemic therapy of combined checkpoint inhibitor and chemotherapy. The IOV-LUN-202 clinical trial includes three cohorts. Cohorts 1 and 3 of the IOV-LUN-202 clinical trial are enrolling patients with a PD-L1 TPS of less than one percent at the time they started front-line therapy, and Cohort 2 will enroll patients with a PD-L1 TPS of greater than or equal to one percent at the time they started front-line therapy. Cohort 3 will also explore manufacturing TIL extracted from core biopsies using our third-generation, or Gen 3, manufacturing process. In June 2021, we reported that the first patient was dosed in the IOV-LUN-202 clinical trial. We intend to continue to enroll patients in the IOV-LUN-202 clinical trial throughout 2022. We are engaged in regulatory discussions with the FDA on IOV-LUN-202 and intend to incorporate FDA feedback to optimize this clinical trial to support further registration in NSCLC.

In June 2021, we reported initial data for LN-145 in Cohort 3B of our IOV-COM-202 clinical trial in metastatic NSCLC. IOV-COM-202 is a Phase 2, multicenter trial for that is composed of seven cohorts. Cohort 3B of IOV-COM-202 enrolled patients with metastatic NSCLC that had progressed on prior ICI therapy, including patients with oncogene-driven tumors who received prior tyrosine kinase inhibitor therapy. Patients were treated with LN-145 monotherapy. All patients treated in Cohort 3B of the IOV-COM-202 trial received prior anti-PD-1/L1 therapy and all six responding patients also received prior chemotherapy. We also provided an update on Cohort 3B in November 2021, at the Society for Immunotherapy in Cancer Annual Meeting, or SITC.

C-145-03 is our Phase 2, multicenter trial to assess the safety and efficacy of our product candidate LN-145 for the treatment of patients with metastatic HNSCC. We redesigned our C-145-03 trial to include multiple cohorts, in order to allow for dosing of TIL therapies produced by multiple manufacturing methods, including our Gen 2 manufacturing process, our Gen 3 manufacturing process, and our PD-1 selected TIL manufacturing process. Our PD-1 selected TIL manufacturing process results in a product that we refer to as LN-145-S1. In January 2021, we announced that we are closing the C-145-03 clinical trial after the trial reached its pre-specified enrollment target.

TIL Combinations in Earlier Treatment Settings for Solid Tumors

We are also investigating the potential of our TIL therapies in earlier lines of treatment in combination with pembrolizumab or other ICIs in cancer patients who are naïve to anti-PD-1 therapy, including in four cohorts in our IOV-COM-202 study in solid tumors as well as in one cohort in our C-145-04 clinical study in cervical cancer. In addition to its ongoing enrollment in the U.S., the IOV-COM-202 trial has also received regulatory approval in Canada and in certain European countries.

In Cohort 1A of the IOV-COM-202 trial, we are enrolling advanced unresectable or metastatic melanoma patients who are naïve to anti-PD-1 therapy. In Cohort 2A of the IOV-COM-202 trial, we are enrolling advanced, recurrent, or metastatic HNSCC patients who are naïve to prior immunotherapy including anti-PD-1/anti-PD-L1 therapy. The patients receive LN-145 in combination with pembrolizumab. In Cohort 3, which is our C-145-04 cervical cancer study, patients receive TIL plus pembrolizumab. We reported results from ongoing Cohort 1A of the IOV-COM-202 trial at ASCO in June 2021, as well as provided updated results in November 2021 at SITC. Our oral presentation at SITC in November 2021 also included initial results for TIL therapy plus pembrolizumab for patients enrolled in Cohort 3 of our C-145-04 cervical cancer study.

The Cohort 1A and Cohort 2A results from the IOV-COM-202 study as well as Cohort 3 from the C-145-04 study demonstrated that lifileucel or LN-145 can be safely combined with pembrolizumab. The treatment emergent adverse event, or TEAE, profile in all Cohorts was consistent with the underlying advanced disease and the known adverse event profiles of pembrolizumab, lymphodepletion, and IL-2 regimens. Two additional cohorts, Cohort 3A and 3C in the IOV-COM-202 study, explore LN-145/ICI combination therapies in NSCLC patients. Cohort 3A is evaluating LN-145 in combination with pembrolizumab in patients with recurrent or metastatic NSCLC who have not received prior immunotherapy, including checkpoint inhibitors. Cohort 3C is investigating LN-145 therapy in combination with ipilimumab and nivolumab in patients with recurrent or metastatic NSCLC who have previously received one line of approved checkpoint inhibitor monotherapy as the only prior line of systemic therapy.

In September 2021, we announced that our Iovance Cell Therapy Center, or the iCTC, had successfully manufactured and delivered its first clinical batch of LN-145 for the IOV-COM-202 trial, representing our first internally manufactured TIL product. We continue to supply the IOV-COM-202 trial, and other ongoing trials, with both internally manufactured and externally manufactured TIL products.

Next-Generation Product Candidates

Our clinical pipeline also includes next generation TIL product candidates and manufacturing processes, as well as a cytokine-engrafted protein. Our TIL candidate LN-145-S1, in which TIL are selected for PD-1 expression, is being investigated in post-anti-PD-1 melanoma in Cohort 1B of our IOV-COM-202 basket study as well as in post-anti-PD-1 HNSCC in Cohort 4 of our C-145-03 trial.

We are using our Gen 3 manufacturing process in Cohort 1C of the IOV-COM-202 clinical trial in melanoma and in Cohort 3 of the IOV-LUN-202 clinical trial in NSCLC and have previously used it in the C-145-03 clinical trial in HNSCC.

In November 2019, we announced that our Investigational New Drug, or IND, application for our PBL therapy, IOV-2001, was authorized by the FDA. Our sponsored clinical trial using this therapy, IOV-CLL-01, was cleared to proceed and patient dosing began in 2020. IOV-2001 is a non-genetically modified, polyclonal T cell product that is manufactured using a nine-day process starting from 50 mL of patient's blood. IOV-CLL-01 is a Phase 1/2 clinical trial evaluating the safety and efficacy of IOV-2001 in patients with relapsed or refractory CLL or SLL.

In January 2020, we announced a research collaboration and exclusive worldwide licensing agreement with Cellectis S.A., or Cellectis, a clinical-stage biopharmaceutical company focused on developing immunotherapies based on gene-edited allogeneic chimeric antigen receptor modified T cells. The worldwide exclusive license enables us to use certain TALEN® technology addressing multiple gene targets to develop TIL that have been genetically modified to create potentially more potent cancer therapeutics for use in several cancer indications. Financial terms of the license include development, regulatory and sales milestone payments from us to Cellectis, as well as royalty payments based on net sales of TALEN-modified TIL products. In March 2022, we announced the FDA allowed an IND to proceed for our first genetically modified TIL therapy, IOV-4001, for the treatment of previously treated advanced melanoma or metastatic NSCLC. We expect to initiate our first clinical trial of IOV-4001 in 2022. In addition to IOV-4001, we are currently developing additional targets for genetic modification using the TALEN technology, including double-knock out programs in preclinical development.

We continue to explore additional transient and permanent genetic modifications of TILs. For example, under the amended and restated patent license agreement we entered into May 2021 with National Institutes of Health, or NIH, an agency of the U.S. Public Health Service within the Department of Health and Human Services, we license a patent family related to cytokine-tethered TILs, which are intended to potentially expand and activate TILs to achieve better efficacy while avoiding systemic side effects of cytokines. We are currently developing cytokine-tethered TIL products in preclinical studies.

In addition, in January 2020, we obtained a license from Novartis Pharma AG, or Novartis, to develop and commercialize an antibody cytokine-engrafted protein, which we refer to as IOV-3001. Under the agreement, we paid an upfront payment to Novartis and may pay milestones involved in initiation of patient dosing in various phases of clinical development for IOV-3001 and approval of a potential product in the U.S., EU, and Japan. We are currently conducting IND enabling studies of this novel IL-2 analog. Novartis is also entitled to low-to-mid single digit percentage royalties from commercial sales of IOV-3001.

Investigator-Sponsored Trials

Through our academic collaborators, we are also exploring the potential for TIL therapies in additional indications. As part of our collaboration program with The University of Texas M.D. Anderson Cancer Center, or MDACC, two Phase 2 trials were initiated in 2018. Both trials are sponsored by MDACC. The first trial, NCT03449108, investigates LN-145 manufactured by us, using our manufacturing processes, to treat patients with soft tissue sarcoma, osteosarcoma, platinum resistant ovarian cancer, and thyroid cancer. A second trial under the collaboration with MDACC, NCT03610490, was previously active. This trial treated patients with platinum resistant ovarian cancer, pancreatic and colorectal cancer with TIL manufactured by MDACC. The data obtained using this manufacturing process may not be representative of our data using our Gen 2 manufacturing process. We also collaborate with many other academic institutions using our TIL therapies. For example, a trial in collaboration with The Ohio State University, NCT05176470, began recruiting in April 2022, and will explore the use of lifileucel in high-risk melanoma in the neoadjuvant setting.

Intellectual Property

We have developed our own patent portfolio based on internal research and development activities. As a result, we now own a number of pending patent applications and granted patents in the fields of TIL therapy, MIL therapy, and PBL therapy, TIL, MIL, and PBL manufacturing processes, and TIL, MIL, and PBL expansion methods. For example, we currently own more than 40 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; and 11,273,181. More than 30 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 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 treatment of a broad range of cancers using TIL therapies; methods of manufacturing TIL, MIL, and PBL therapies; the use of costimulatory molecules in TIL therapy and manufacturing; stable and transient genetically-modified 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 three months ended March 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 through this crisis as it continues to unfold. 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 Results of Operations

Revenues

We have not yet generated any revenues since our formation, and we currently do not anticipate that we will generate any significant revenues from the sale or licensing of our product candidates during the 12 months from the date these financial statements are issued. 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, accounting, 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 Three Months Ended March 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).

	Three Months Ended March 31,		Increase (Decrease)	
	2022	2021	\$	%
Research and development expense	\$ 68,300	\$ 55,949	12,351	22
Stock-based compensation expense included in research and development expense	13,651	9,202	4,449	48

Research and development expense for the three months ended March 31, 2022 increased by \$12.4 million, or 22%, compared to the same period in 2021. The increase was primarily attributable to (i) a \$6.5 million increase in payroll and related expenses and a \$4.4 million increase in stock-based compensation expenses, both driven by increased hiring of research and development employees to support our ongoing and planned clinical development activities, (ii) a \$5.7 million increase in facility and related costs, including depreciation expenses, associated with the *i*CTC and the build-out of our new corporate headquarters office, and (iii) a \$1.6 million increase in other costs, including lab consumables, manufacturing, insurance, and travel expenses. These expenses were partially offset by a \$5.8 million decrease in clinical trial costs due to completion of enrollment in pivotal cohorts for melanoma and cervical cancer, as well as our head and neck clinical trials.

General and administrative expense (in thousands).

	Three Months Ended March 31,		Increase (Decrease)	
	2022	2021	\$	%
General and administrative expense	\$ 23,413	\$ 19,621	3,792	19
Stock-based compensation expense included in general and administrative expense	8,614	7,739	875	11

General and administrative expenses for the three months ended March 31, 2022 increased by \$3.8 million, or 19%, compared to the same period in 2021. The increase was primarily attributable to (i) a \$1.4 million increase in payroll and related expenses and a \$0.9 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, and (ii) a \$1.5 million increase in other costs, including marketing, intellectual property and legal expenses, costs associated with the build-out of our new corporate headquarters, and increased costs to enhance and expand our information technology infrastructure to support our pre-commercialization activities as well as the continued growth in the overall company.

[Table of Contents](#)Interest income, net (in thousands)

	Three Months Ended March 31,		Increase (Decrease)	
	2022	2021	\$	%
Interest income, net	\$ 106	\$ 121	(15)	(12)

Interest income, net for the three months ended March 31, 2022 and 2021 decreased by less than \$0.1 million, or 12%, primarily due to declining interest rates and lower interest received on our cash, cash equivalents and investment portfolio.

Net loss (in thousands)

	Three Months Ended March 31,		Increase (Decrease)	
	2022	2021	\$	%
Net loss	\$ (91,607)	\$ (75,449)	(16,158)	21

Net loss for the three months ended March 31, 2022 increased by \$16.2 million or 21% compared to the same period in 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.

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. We currently do not anticipate that we will generate any significant revenues from the sale or licensing of any products during the 12 months from the date these financial statements are issued. We expect to further increase our research and development activities, especially continuing pre-commercial activities and completing the construction of our tenant improvements to the iCTC facility, which will increase the amount of cash we will use during the remainder of 2022 and beyond. Specifically, we expect increased spending on clinical trials, research and development activities, higher payroll expenses as we increase our professional and scientific staff and continue our expansion of manufacturing activities, including completion of the iCTC.

Corporate Capitalization

As of March 31, 2022, we had outstanding 157,168,321 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 May 27, 2020, we filed an automatic shelf registration statement with the SEC for the issuance of an indeterminate amount of Shelf Securities (the “2020 Automatic Shelf Registration Statement”), 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 (the “June 2020 Public Offering”). We received gross proceeds of \$603.7 million and net proceeds of \$567.0 million, after deducting underwriting discounts and offering expenses. Following the 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 Sale Agreement (the “Sales Agreement”), with Jefferies LLC (“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. The issuance and sale, if any, of shares of our common stock under the Sales Agreement will be made pursuant to a prospectus supplement, dated February 8, 2021, to the 2020 Automatic Shelf Registration Statement. There were no sales of our common stock through the Sales Agreement during the three months ended March 31, 2022.

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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

The following table summarizes our cash flows for the periods indicated (in thousands):

	Three Months Ended March 31,	
	2022	2021
Net cash (used in) provided by:		
Operating activities	\$ (73,802)	\$ (62,391)
Investing activities	86,516	77,211
Financing activities	1,417	50,364
Net increase in cash, cash equivalents and restricted cash	<u>\$ 14,131</u>	<u>\$ 65,184</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 three months ended March 31, 2022 was \$73.8 million as compared to \$62.4 million for the same period in 2021. The increase of \$11.4 million in cash used in operating activities was 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 \$6.3 million primarily driven by higher stock-based compensation expenses, as well as depreciation expenses and the amortization of operating right-of-use assets associated with our leased facilities. We also had an increase in cash used by assets and liabilities driven primarily by changes in accruals and accounts payable resulting from the increased size of our 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 associated with receipts of tenant improvement allowances for our new corporate headquarters office, offset by payments on lease arrangements.

Investing Activities

Net cash provided by investing activities for the periods presented primarily relates to the purchase and maturity of investments and capital expenditures. Net cash provided by investing activities for the three months ended March 31, 2022 was \$86.5 million compared to net cash provided by investing activities of \$77.2 million for the same period in 2021. The increase in cash provided by investing activities of \$9.3 million was primarily due to the timing of maturities and purchases of investments.

Financing Activities

Net cash provided by financing activities for the three months ended March 31, 2022 was \$1.4 million compared to \$50.4 million for the same period in 2021. The net cash provided by financing activities for the three months ended March 31, 2022 related to the cash proceeds from issuance of common stock upon exercise of stock options during the period. The net cash provided by financing activities for the same period in 2021 primarily related to net proceeds of \$42.9 million received from sales of common shares through the “at the market” offering program and \$6.5 million received from issuance of common stock upon exercise of stock options.

Off-Balance Sheet Arrangements

As of March 31, 2022, we had no obligations that would require disclosure as off-balance sheet arrangements.

Significant Accounting Policies and Recent Accounting Standards

See Note 2 of the condensed consolidated financial statements for a discussion of our significant accounting policies. There were no recently issued accounting standards applicable to us and we did not adopt any accounting standards during the three months ended March 31, 2022.

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 3. Quantitative and Qualitative Disclosures About Market 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 March 31, 2022, we had \$489.2 million invested in marketable securities with a maturity date of less than two years. As such, we believe that we are not exposed to any material market risk. If interest rates had varied by 1% as of March 31, 2022, the fair value of our investment portfolio would increase or decrease by approximately \$2.0 million.

Item 4. Controls and Procedures

Conclusion Regarding the Effectiveness of Disclosure Controls and Procedures

Under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of our disclosure controls and procedures, as such term is defined under Rule 13a-15(e) promulgated under the Exchange Act as of the end of the period covered by this Quarterly Report on Form 10-Q. Based on this evaluation, our principal executive officer and our principal financial officer concluded that our disclosure controls and procedures were effective as of the end of the period covered by this Quarterly Report on Form 10-Q.

Changes in Internal Controls Over Financial Reporting

There have not been any changes in our internal control over financial reporting (as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended March 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1. Legal Proceedings

The information in Note 9 to the Condensed Consolidated Financial Statements contained in Part I, Item 1 of this Quarterly Report on Form 10-Q 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 9 to our Condensed Consolidated Financial Statements for the quarter ended March 31, 2022 contained in this Quarterly Report on Form 10-Q.

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 Quarterly Report on Form 10-Q, 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

We have marked with an asterisk () those risk factors below that reflect a substantive change from the risk factors included in our Annual Report on Form 10-K filed with the SEC on February 24, 2022.*

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.

- *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 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;*

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- *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 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;*
- *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.*

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 March 31, 2022, we had an accumulated deficit of \$1.3 billion. In addition, during the three months ended March 31, 2022, we incurred a net loss of \$91.6 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 2022. 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-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.

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 do not expect to submit 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 and metastatic cervical cancer. 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 study 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. We rely on CMOs in the U.S. and Europe to manufacture TIL for use in our trials. 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 does 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 trial and for ensuring that our preclinical trials 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 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 trial sponsors, clinical investigators, 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 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 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 studies 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 May 2020, we disclosed interim results for Cohort 4 of the C-144-01 clinical trial. The interim results speak only to data available as of March 16, 2020, and although such data have been reviewed by the investigators, they have not been reviewed by an IRC. In addition, differences in patient population may affect the clinical results of Cohort 4 as compared to Cohort 2. We plan to initiate trials in new indications, and new cohorts in existing trials. Even as these 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 studies 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 trial site, or amend 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 study design;
- the FDA or comparable foreign regulatory authorities may disagree with our intended indications, study 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;

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- 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 studies;
- delays in or failure to reach an agreement on acceptable terms with prospective CROs and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical study sites;
- delays in obtaining required IRB approval at each clinical study 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 studies;
- delay in adding new investigators or clinical trial sites, or withdrawal of clinical trial sites from a study;
- 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 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 study 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 study or clinical trial, increase the needed enrollment size for the study or clinical trial or extend the study's or clinical trial's duration;
- patients dropping out of a study;
- 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 trials;
- the cost of clinical studies 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 studies 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 studies, or preclinical studies, or abandon product development programs;
- early results from our clinical studies 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;

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- 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 studies 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 trials, contract negotiations, the need to obtain agreement from multiple parties, and the necessity of obtaining additional approvals for therapeutics used in the combination 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 or preclinical studies. For example, while we currently intend to file our first BLA using 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 and preclinical studies, or results in a refusal to file or non-approval of a BLA.

Clinical study 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 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 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 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 trials.

For example, our studies of our TIL therapy lifileucel in patients with metastatic cervical cancer and metastatic melanoma 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 of TIL therapy lifileucel in patients with metastatic cervical cancer and metastatic melanoma, the investigators have significant discretion over the selection of patient participants. Although preliminary data from these trials was 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 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 trials and replaced by patients with less advanced forms of cancer. This opportunity for investigator selection bias in our 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 study 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 trials may instead opt to enroll in a trial being conducted by one of our competitors. Accordingly, we cannot guarantee that the 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 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 manufacture 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 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 trials, and the number of 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 study 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 studies may not be representative of the final study 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 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 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 trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials could be required before we submit our product candidates for approval. To the extent that the results of the 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 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 studies 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 in the pivotal program to the Phase 2, who remain in the 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 study population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the design of the 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 study 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 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 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 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 pre-clinical 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 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 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 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 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 have not been 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 have continued ongoing work developing and validating our potency assays and have engaged in discussions with the FDA during the second half of 2021 and first quarter of 2022. We expect to request a pre-BLA meeting in July 2022 and to complete a BLA submission for lifileucel by August 2022.. 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.

Our current manufacturing strategy involves the use of CMOs. Currently our product candidates are manufactured by WuXi, Lonza, and Moffitt. 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 May 2019 we entered into a lease agreement to build a commercial-scale manufacturing facility in Philadelphia, Pennsylvania for commercial and clinical production of autologous TIL products, including our product candidate lifileucel. We expect that development of our own 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. However, we have no experience as a company in developing a manufacturing facility and 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.

Moreover, 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.

In addition, the manufacturing process and facilities for any products that we may develop 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 studies, 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 for metastatic melanoma and metastatic cervical cancer, our research and development programs are 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 studying 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 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 March 31, 2022, we have an accumulated deficit of \$1.3 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 Sales Agreement, with Jefferies LLC, which provides for the sale of up to \$350.0 million of our common stock from time to time. As of March 31, 2022, we had \$516.0 million in cash, cash equivalents and investments (\$92.4 million of cash and cash equivalents, \$389.8 million in short-term investments, \$27.7 million of long-term investments, and restricted cash of \$6.1 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 Quarterly Report on Form 10-Q 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, 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 Sales Agreement with Jefferies LLC, which provides for the sale of up to \$350.0 million of our common stock from time to time, 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, 2021, we had U.S. federal net operating loss carryforwards of approximately \$945.3 million. 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, 2020, 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 iCTC 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 not yet sought FDA approval for any 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 violate 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 trial period, the number of patients the FDA will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of immunotherapy products, or that the data generated in these 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 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, Idera Pharmaceuticals, Checkmate Pharmaceuticals, Daiichi Sankyo, Eisai, Exelixis, 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, Immatic, 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, 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, and Roche. We may also face competition from novel interleukin-2 (IL-2) treatments in development by 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 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. 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, 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 studying 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 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. We were granted BT, 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, when the FDA approved Novartis' Kymriah in August 2017, a CAR-T cell therapy for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia, or ALL, that is refractory or in second or later relapse, the FDA required significant post-marketing commitments, including a Phase 4 trial, revalidation of a test method, and a substantial REMS program that included, among other requirements, the certification of hospitals and their associated clinics that dispense Kymriah, which certification includes a number of requirements, the implementation of a Kymriah training program, and limited distribution only to certified hospitals and their associated clinics. 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 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 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 security 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. 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 related breaches.

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, 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. Similar executive orders have been issued by state and local governments in Pennsylvania, Florida, and elsewhere, and states of emergency have 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 in the U.S. have been rescinded, however the Company remains vigilant and continues to monitor the situation 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. 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.

We are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by geopolitical instability due to the ongoing military conflict between Russia and Ukraine. 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 or any other geopolitical tensions.*

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. We are continuing to monitor the situation in Ukraine and globally and assessing its potential impact on our business.

Additionally, the recent military conflict in Ukraine has led to sanctions and other penalties being levied by the United States, European Union and other countries against Russia. Additional potential sanctions and penalties have also been proposed and/or threatened. Russian military actions and the resulting sanctions could 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.

Although our business has not been materially impacted by the ongoing military conflict between Russia and Ukraine 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 military action, 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.

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 not previously submitted a BLA to the FDA, or similar approval filings to comparable foreign authorities. 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. For example, following our End of Phase 2 meeting with the FDA, 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 is 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. 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 study may support a BLA submission also assume that our as-adjusted study has addressed the additional requests by the FDA that were raised at our End of Phase 2 meeting. Further, enrollment in this study may need to be further adjusted based on future feedback from the FDA, changes in the competitive environment, or other regulatory agency input. The revised protocol which further defines the patient population to include more advanced patients in the study, 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 study 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 our product candidate or prevent its approval entirely. Similarly, our current beliefs for our lifileucel product candidate for the treatment of melanoma are based on our interpretation of communications received from the FDA to date regarding this product candidate and our ongoing C-144-01 clinical trial, and may also be incorrect.

A BLA must also include significant information regarding the chemistry, manufacturing and controls for the product. Additionally, 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 BTM 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 announced that we and the FDA have not been 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 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 have continued ongoing work developing and validating our potency assays and have engaged in discussions with the FDA during the second half of 2021 and first quarter of 2022. We expect to request a pre-BLA meeting in July 2022 and to complete a BLA submission for lifileucel by August 2022. Accordingly, 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 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 trial sites;
- obtaining approval at each clinical trial site by an independent IRB, or central IRB;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical trial sites deviating from trial protocol or dropping out of a 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 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 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 and pre-clinical trials 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 studies 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 Quarterly Report on Form 10-Q

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 March 31, 2022, we had 157,168,321 shares of common stock outstanding. In addition, we had 20,222,309 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 our current directors, as defendants, in the Court of Chancery in the State of Delaware. 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. While we intend to vigorously defend against the foregoing complaint, it is not possible to estimate the amount or range of possible loss that might result from these matters.

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 2. Unregistered Sales of Securities and Use of Proceeds.

Nothing to report.

Item 3. Defaults Upon Senior Securities.

Nothing to report.

Item 4. Mine Safety Disclosures

Nothing to report.

Item 5. Other Information.

Nothing to report.

Item 6. Exhibits

EXHIBIT INDEX

Exhibit	Description
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.INS++	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document).
101.SCH++	Inline XBRL Taxonomy Schema Linkbase Document.
101.CAL++	Inline XBRL Taxonomy Calculation Linkbase Document.
101.DEF++	Inline XBRL Taxonomy Definition Linkbase Document.
101.LAB++	Inline XBRL Taxonomy Labels Linkbase Document.
101.PRE++	Inline XBRL Taxonomy Presentation Linkbase Document.
104	Cover Page Interactive Data File (the cover page interactive data file does not appear in the Interactive Date File because its XBRL tags are embedded within the Inline XBRL document).
++	Filed herewith (unless otherwise noted as being furnished herewith).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Iovance Biotherapeutics, Inc.

May 5, 2022

By: /s/ Frederick G. Vogt, Ph.D., J.D.
Frederick G. Vogt, Ph.D., J.D.
Interim Chief Executive Officer and President, and General
Counsel (Principal Executive Officer)

May 5, 2022

By: /s/ Jean-Marc Bellemin
Jean-Marc Bellemin
Chief Financial Officer and Treasurer (Principal Financial and
Accounting Officer)

CERTIFICATION

I, Frederick G. Vogt, PhD., J.D, Interim Chief Executive Officer and President, and General Counsel of Iovance Biotherapeutics, Inc., certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Iovance Biotherapeutics, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. I am responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under my supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under my supervision, 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;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report my conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. I have disclosed, based on my most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 5, 2022

By: /s/ Frederick G. Vogt, PhD., J.D.

Frederick G. Vogt, PhD., J.D.

Interim Chief Executive Officer and President, and General Counsel (Principal Executive Officer)

CERTIFICATION

I, Jean-Marc Bellemin, Chief Financial Officer of Iovance Biotherapeutics, Inc., certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Iovance Biotherapeutics, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. I am responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under my supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under my supervision, 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;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report my conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. I have disclosed, based on my most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 5, 2022

By: /s/ Jean-Marc Bellemin

Jean-Marc Bellemin

Chief Financial Officer

(Principal Financial Officer & Principal Accounting Officer)

**CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Quarterly Report on Form 10-Q of Iovance Biotherapeutics, Inc. (the "Company") for the quarter ended March 31, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Frederick G. Vogt, PhD., J.D., Interim Chief Executive Officer and President, and General Counsel, hereby certifies, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: May 5, 2022

By: /s/ Frederick G. Vogt, PhD., J.D.

Frederick G. Vogt, PhD., J.D.

Interim Chief Executive Officer and President, and General
Counsel (Principal Executive Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

**CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Quarterly Report on Form 10-Q of Iovance Biotherapeutics, Inc. (the "Company") for the quarter ended March 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Jean-Marc Bellemin, Chief Financial Officer, hereby certifies, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: May 5, 2022

By: /s/ Jean-Marc Bellemin
Jean-Marc Bellemin
Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.
