ZIOPHARM ONCOLOGY INC
Form 10-K
February 16, 2017
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

ANNUAL REPORT UNDER SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

OR

TRANSITION REPORT UNDER SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from _____ to _____

Commission File Number 001-33038

ZIOPHARM Oncology, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**84-1475642**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**
One First Avenue, Parris Building 34, Navy Yard Plaza	
Boston, Massachusetts	**02129**
(Address of Principal Executive Offices)	**(Zip Code)**

(617) 259-1970

(Registrant s Telephone Number, Including Area Code)

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

Common Stock (par value $0.001 per share)

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the past 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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definition of large accelerated filer, accelerate filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large Accelerated Filer	Accelerated Filer
Non-Accelerated Filer	Smaller Reporting Company

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

The aggregate market value of the registrant s common stock held by non-affiliates was $659,304,778 as of June 30, 2016 (the last business day of the registrant s most recently completed second fiscal quarter), based on a total of 120,091,945 shares of common stock held by non-affiliates and a closing price of $5.49 as reported on the NASDAQ Capital Market on June 30, 2016.

As of February 6, 2017, there were 132,376,670 shares of the registrant s common stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the definitive proxy statement for the registrant s 2017 annual meeting of stockholders, which is to be filed within 120 days after the end of the fiscal year ended December 31, 2016, are incorporated by reference into Part III of this Form 10-K, to the extent described in Part III.

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ZIOPHARM Oncology, Inc.

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Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements that are based on our current beliefs and expectations. These forward-looking statements may be accompanied by such words as anticipate, believe, estimate, expect, forecast, intend, may, plan, project, target, will and other words and terms of similar meaning. I made in particular to forward-looking statements regarding:

our ability to finance our operations and business initiatives;

the sufficiency of our cash and investments and our expected uses of cash;

the progress, timing and results of preclinical and clinical trials involving our product candidates;

the progress of our research and development programs;

the costs and timing of the development and commercialization of our products;

additional planned regulatory filings for the approval and commercialization of our immuno-oncology product candidates;

whether any of our other therapeutic discovery and development efforts will advance further in pre-clinical research or in the clinical trial process and whether and when, if at all, our product candidates will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications;

whether any other therapeutic products we develop will be successfully marketed if approved;

the risk that final trial data may not support interim analysis of the viability of our product candidates;

our ability to achieve the results contemplated by our collaboration agreements and the benefits to be derived from relationships with collaborators;

competition from other pharmaceutical and biotechnology companies;

the development of, and our ability to take advantage of, the market for our product candidates;

the anticipated amount, timing and accounting of deferred revenues, milestone and other payments under licensing, collaboration or acquisition agreements, research and development costs and other expenses;

the strength and enforceability of our intellectual property rights;

our assessment of the potential impact on our future revenues of healthcare reform legislation in the United States;

the timing and impact of measures worldwide designed to reduce healthcare costs;

the uncertainty of economic conditions in certain countries in Europe and Asia such as related to the United Kingdom s referendum in June 2016 in which voters approved an exit from the European Union, commonly referred to as Brexit ; and general economic conditions.

These forward-looking statements involve risks and uncertainties, including those that are described in the *Risk Factors* section of this report and elsewhere within this report that could cause actual results to differ materially from those reflected in such statements. You should not place undue reliance on these statements. Forward-looking statements speak only as of the date of this report. We do not undertake any obligation to publicly update any forward-looking statements.

Throughout this Annual Report on Form 10-K, ZIOPHARM, the Company, we, us and our refer to ZIOPHARM Oncology, Inc.

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PART I

Item 1. Business

General

ZIOPHARM Oncology, Inc. is a biopharmaceutical company seeking to develop, acquire and commercialize, on its own or with partners, a diverse portfolio of cancer therapies that address unmet medical needs. We are currently focused on developing products in immuno-oncology that employ novel gene expression, control and cell technologies to deliver safe, effective and scalable cell- and viral-based therapies for the treatment of cancer and graft-versus-host-disease (GvHD). Pursuant to two exclusive channel partner agreements, or Channel Agreements with Intrexon Corporation, or Intrexon, we obtained certain exclusive rights to Intrexon s technologies for use in the fields of oncology and graft-versus-host disease.

The technologies represent an industrialized engineering approach for molecular and cell biology and gene control. They employ an inducible gene-delivery system, or switch, that enables controlled in vivo expression of genes that produce therapeutic proteins to treat cancer. We and Intrexon refer to this switch as the RheoSwitch Therapeutic System®, or RTS®, platform. Our initial product candidate being developed using the immuno-oncology platform is Ad-RTS-IL-12 + veledimex, a clinical stage product that we license from Intrexon under the Channel Agreement.

Ad-RTS-IL-12 + veledimex uses our gene delivery system to produce interleukin-12, or IL-12, a potent, naturally occurring anti-cancer protein. IL-12 is a potent pro-inflammatory cytokine capable of reversing immune escape mechanisms and improving the function of tumor fighting natural killer, or NK, and T cells. Additionally, expression of functional IL-12 in human subjects by direct intratumoral injection of Ad-RTS-hIL-12 + veledimex is further demonstrated by the generation of downstream interferon gamma, or IFN-g. We have completed two Phase 2 studies evaluating Ad-RTS-IL-12 + veledimex, the first for the treatment of metastatic melanoma, and the second for the treatment of metastatic breast cancer. We are conducting a single-center Phase 1b/2 study, following standard chemotherapy, for the treatment of patients with locally advanced or metastatic breast cancer, and a multi-center Phase 1 study in patients with recurrent or progressive glioblastoma, or GBM, or Grade III malignant glioma, a form of brain cancer. We have concluded enrollment in the Phase 1b/2 breast cancer study and enrollment is ongoing in the Phase 1 GBM study. Early clinical data from the GBM study was presented at the Society for Neuro-Oncology (SNO) meeting in November 2015, and on February 24, 2016, we announced the successful completion of the initial dosing phase of the study and the dosing of the first patient in the next succeeding cohort of the study. On June 27, 2016, we announced the successful completion of enrollment in the first and second cohorts and the opening of a third cohort, which has now completed. Updated clinical data from this trial occurred during the 2016 SNO meeting. In addition, we presented nonclinical data in a pontine mouse model at SNO; we believe these data will support initiation of a pediatric brain tumor clinical trial during the first half of 2017. We also presented information about the Phase 1b/2 breast cancer study at the San Antonio Breast Cancer Symposium in December 2015. We presented updated information on the GBM and breast cancer studies at the 2016 American Society of Clinical Oncology (ASCO) meeting in June and on the GBM study at the 2016 American Society of Hematology Workshop on Genome Editing in July. We also presented additional breast cancer clinical study results at the European Society for Medical Oncology (ESMO) 2016 Congress in October.

In addition to Ad-RTS-IL-12 + veledimex as monotherapy, we have undertaken pre-clinical studies that suggest we may be able to combine this viral-based immunotherapy with an immune checkpoint inhibitor, or iCPI, to improve the anti-tumor effect for GBM. These pre-clinical data were presented at the 2016 Annual Meeting of the American Society of Gene and Cell Therapy, or ASGCT, in May, and we believe the data will lend support to the first-in-human application of combining Ad-RTS-IL-12 + veledimex with an iCPI for investigational treatment of GBM.

Pursuant to our Channel Agreement for the cancer program, we and Intrexon obtained an exclusive, worldwide license to certain additional immuno-oncology technologies owned and licensed by The University of Texas MD

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Anderson Cancer Center, or MD Anderson, including technologies relating to novel chimeric antigen receptors, or CARs, NK cells and TCRs. We refer to this as the MD Anderson License. We plan to develop genetically modified T cells and other immune cells that will target and kill cancer cells using viral and non-viral approaches to gene transfer. Regarding our non-viral approach, we are using the *Sleeping Beauty* (SB) transposon/transposase system under the MD Anderson license to express CAR in clinical trials to render T cells specific for CD19. The initial associated trials using the first generation CAR with a four-week manufacturing process showed favorable progression free survival, or PFS, and/or overall survival when patient- and donor-derived CAR+ T cells were infused after hematopoietic stem-cell transplantation. All patients receiving autologous SB-modified T cells had non-Hodgkin lymphoma and most patients receiving allogeneic CAR+ T cells had acute lymphoblastic leukemia. In addition to survival of the recipients, these trials demonstrated that the infused T cells persisted for length of times that compared favorably with T cells genetically modified with virus to express CAR. An update was provided in publication (J Clin Invest. 2016 Sep 1;126(9):3363-76.).

We are currently enrolling an investigator-led Phase 1 study using second generation CD19-specific CAR+ T cells with a revised CAR structure in patients with advanced lymphoid malignancies at MD Anderson. A patient with multiple-relapsed B-cell ALL received CD19-specific CAR+ T cells produced with a 3-week manufacturing process and achieved a complete remission with normalization of PET/CT tumor imaging. Steps were taken in 2016 to further decrease the T-cell culture time in the manufacturing process, which advances our efforts to address the challenges of cost and manufacturing time associated with these therapies. Preclinical data in a mouse tumor model showing improved survival with treatment using CAR+ T cells with reduced time in culture (approximately 2 weeks versus 4 weeks for previous first generation CAR+ T process) were presented at the 2016 annual meeting of American Society of Gene & Cell Therapy (ASGCT). The second generation CD19 trial underway is now employing the shortened 2-week manufacturing process advancement. On January 31, 2017, the Company announced a patient with triple-hit NHL treated in January 2017 was the first to receive *Sleeping Beauty*-modified CD19-specific CAR+ T cells with the manufacturing time reduced to 2 weeks.

In the pre-clinical setting, the time to administration of third generation *Sleeping Beauty* CAR+ T cells co-expressing a membrane-bound version of IL-15 (mbIL15) has been reduced to less than two days. This shortened process delivers genetically modified T cells with superior proliferative potential. Data presented at the 58th American Society of Hematology (ASH) Annual Meeting in December 2016, supported by an earlier publication in the Proceedings of the National Academy of Sciences (2016 Nov 29;113(48):E7788-E7797), revealed promising results: Third generation *Sleeping Beauty* CAR+ T cells demonstrated that a single low-dose of T cells co-expressing a CD19-specific CAR and mbIL15 resulted in sustained *in vivo* persistence that produced potent anti-tumor effects and superior leukemia-free survival. These clinical and pre-clinical data support the Company s point-of-care (POC) plans to rapidly infuse *Sleeping Beauty* CAR+ T cells in a Phase I trial expected to be opened later this year. With the intent to administer clinical-grade *Sleeping Beauty* CAR+ T cells in less than 48 hours, this non-viral CAR-T approach has the potential to outpace viral-based methods.

We expect to enter the clinic with an additional CAR+ T therapy specific for CD33 for treatment of relapsed or refractory acute myeloid leukemia or AML during the first half of 2017. An update on the pre-clinical data for the CD33 program was provided at the 2016 annual meeting of ASH. We successfully completed an application to the National Institute of Health s Office of Biotechnical Activities in June 2016 and expect to file an IND with the FDA in the first half of 2017. Genetic modification will use lentivirus and enrollment to the CD33 CAR+ T trial will occur in 2017. Together with Intrexon, we currently have research programs evaluating additional CAR targets and CARs co-expressed with cytokines, in particular mbIL15. Control systems are also being developed such as the RTS® for receptor and/or cytokine expression as well as for the conditional ablation of genetically modified cells using a kill switch. We anticipate future CAR+ T programs will also utilize the POC manufacturing approach.

Only a minority of tumor antigens are on the surface and thus can be targeted by CARs, while most tumor-derived antigens are within the cell and will likely need to be targeted by TCRs. Therefore, we are developing approaches to target solid tumors using T cells genetically modified with the SB system to express TCRs for

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recognition of neoantigens. An update was provided in publication (Molecular Therapy (2016); 24(6), 1078 1089) and further pre-clinical information regarding the targeting of solid tumors was presented at the annual meeting of ASH in December 2016. On January 10, 2017, the Company announced the signing of a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) for the development of adoptive cell transfer (ACT)-based immunotherapies genetically modified using the *Sleeping Beauty* (SB) transposon/transposase system to express T cell receptors (TCRs) for the treatment of solid tumors. The principal goal of the CRADA is to develop and evaluate ACT for patients with advanced cancers using autologous peripheral blood lymphocytes (PBL) genetically modified using the non-viral SB system to express TCRs that recognize specific immunogenic mutations, or neoantigens, expressed within a patient s cancer. Clinical evaluations of the ability of these SB-engineered PBL to express TCRs reactive against cancer mutations to mediate cancer regression in patients with metastatic disease will be performed. Research conducted under the CRADA will be at the direction of Steven A. Rosenberg, M.D., Ph.D., Chief of the Surgery Branch at the NCI, in collaboration with researchers at the Company and Intrexon.

We plan to leverage the synergy between the platforms to accelerate an immuno-oncology pipeline and programs for the development of allogeneic CAR+ T and/or NK cells that can be used as off-the-shelf, or OTS, therapies. For example, NK cells do not have endogenous TCRs, so do not require genetic editing to eliminate TCRs, and may be used as an OTS therapy. Further, cytokines such as IL- 12 are fuel for NK cells. In addition to developing T cells, we expect to initiate an investigator led trial of OTS primary NK cells for AML after completing regulatory review during 2017. We have additional interest in OTS products such as the development of an allogenic CAR+ T therapy.

We plan to continue to combine Intrexon s technology suite with our capabilities to translate science to the patient, and to identify and develop additional products to stimulate or inhibit key pathways, including those used by the body s immune system, to treat cancer.

On March 27, 2015, we entered into a global collaboration with Intrexon focused exclusively on CAR T cell, or CAR+ T, products with Ares Trading, or Ares, a biopharmaceutical division of Merck KGaA, which we refer to as the Ares Trading Agreement. Intrexon will share the economic provisions of this collaboration equally with us, including an upfront payment of $115.0 million that was received in July 2015, milestones and royalties. Under this collaboration, Ares already selected two CAR+ T targets for which we will perform certain research activities that will, in part, be funded by Ares. Pursuant to the terms of an amendment to our Channel Agreement with Intrexon, or ECP Amendment, that we entered into at the time of the Ares Trading Agreement, we will be responsible for any additional research and development expenditures. Once these candidates reach investigational new drug stage, the programs will be transferred to Ares for clinical development and commercialization. We, together with Intrexon, will also independently conduct research and development on other CAR+ T candidates, with Ares Trading having the opportunity during clinical development to opt-in to these candidates for additional payments to us and Intrexon.

On September 28, 2015, we entered into a new Exclusive Channel Collaboration Agreement, or the GvHD Agreement, with Intrexon to develop therapies for the treatment and/or prevention of graft-versus-host disease, or GvHD, a major complication of allogeneic hematopoietic stem-cell transplantation, or HSCT, which significantly impairs the quality of life and survival of many recipients. Allogeneic HSCT is used for the treatment of various diseases including hematological malignancies, immunological deficiencies as well as non-malignant conditions. Human studies have shown that administration of low-dose subcutaneous interleukin-2, or IL-2, a cytokine critical for modulation of the immune system, in patients with steroid-refractory GvHD acts via regulatory T cells, or Tregs, to ameliorate its manifestations.

We believe that the combined expertise and knowledge gained from our research programs with Intrexon in adoptive T-cell therapies and cytokine modulation for the treatment of cancer positions us well to develop and implement therapeutic approaches addressing an area of high unmet medical need for patients with GvHD. Through the GvHD

Agreement, we, together with Intrexon, plan to pursue engineered cell therapy strategies,

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used either separately or in combination, for targeted prevention and/or treatment of GvHD. The first approach is expected to utilize the infusion of Tregs, such as those conditionally expressing IL-2, such as utilizing the RTS® platform. The second approach is expected to utilize the deployment of Intrexon s orally-delivered microbe-based ActoBiotics® therapeutics, based on *Lactococcus lactis*, such as to express IL-2 to modulate immune function.

Enabling Technology

Our approach to immuno-oncology and GvHD entails the application of engineering principles to biological systems for the purpose of designing and constructing new biological systems or redesigning/modifying existing biological systems. Biological systems are governed by DNA, the building block of gene programs, which control cellular processes by coding for the production of proteins and other molecules that have a functional purpose and by regulating the activities of these molecules. This regulation occurs via complex biochemical and cellular reactions working through intricate cell signaling pathways, and control over these molecules modifies the output of biological systems. Our approach to immuno-oncology and GvHD has been enabled by the application of information technology and advanced statistical analysis, also known as bioinformatics, to genetic engineering, as well as by improvements in DNA synthesis. This approach aims to engineer gene-based programs or codes to modify cellular function to achieve a desired biological outcome. Its application is intended to allow more precise control of drug concentration and dose, thereby improving the therapeutic index associated with the resulting drug. A further embodiment of this technology is the ability to eliminate genetically modified immune cells after infusion.

On January 6, 2011, we entered into the Channel Agreement with Intrexon, to develop and commercialize novel DNA-based therapeutics in the field of cancer treatment by combining Intrexon s technological platform with our capabilities to translate science to the patient. As a result, our bioengineered DNA platform employs an inducible gene-delivery system that enables regulated and controlled delivery of genes that produce therapeutic proteins to treat cancer. The first example of this regulated controlled delivery is achieved by producing IL-12, a potent, naturally occurring anti-cancer protein, under the control of Intrexon s proprietary biological switch to turn on and off the therapeutic protein expression at the tumor site. We and Intrexon refer to this switch as the RheoSwitch Therapeutic System® or RTS®, platform. Our initial product candidate being developed using the immuno-oncology platform is Ad-RTS-IL-12 + veledimex.

On September 28, 2015, we entered into the GvHD Agreement with Intrexon to develop therapies for the treatment and/or prevention of GvHD, a major complication of allogeneic HSCT, which significantly impairs the quality of life and survival of many recipients. Some of the technologies used to generate product candidates for immuno-oncology have potential application for GvHD. These include the ability to genetically modify cells using viral and non-viral approaches and the application of RTS® to control gene expression, such as cytokines. Some of these methodologies as well as our expertise in bioprocessing are being investigated to generate regulatory T cells, or Tregs. In addition, we are generating genetically modified *L lactis* to alter the inflammatory milieu of patients with GvHD, especially of the gastrointestinal tract. These modifications are facilitated though collaboration with ActoBiotics®, a division of Intrexon.

More detailed descriptions of our clinical development plans for each of these programs are set forth below under the caption *Product Candidates.*

Immuno-oncology and GvHD

Immuno-oncology, which typically utilizes a patient s own immune system to treat cancer, is one of the most actively pursued areas of research by biotechnology and pharmaceutical companies today. Cancer cells contain mutated proteins and may overexpress other proteins usually found in the body at low levels. The immune system typically

recognizes unusual or aberrant cell protein expression and eliminates these cells in a highly efficient process known as immune surveillance. Central players in immune surveillance are types of white blood

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cell known as the T cells and NK cells. In healthy individuals, T cells and NK cells can identify and kill infected or abnormal cells, including cancer cells. Cancer cells develop the ability to evade immune surveillance, which is a key factor in their growth, spread, and persistence. In the recent past, there has been substantial scientific progress in countering these evasion mechanisms using immunotherapies, or therapies that activate the immune system.

On January 13, 2015, we, together with Intrexon, entered into a license agreement with MD Anderson, which we refer to as the MD Anderson License. Pursuant to the MD Anderson License, we and Intrexon hold an exclusive, worldwide license to certain technologies owned and licensed by MD Anderson including technologies relating to novel CAR+ T cell therapies arising from the laboratory of Laurence Cooper, M.D., Ph.D., who was then a tenured professor at MD Anderson and is now our current Chief Executive Officer, as well as either co-exclusive or non-exclusive licenses under certain related technologies.

Combining the non-viral genetic engineering technologies, we licensed from MD Anderson together with Intrexon s industrialized approach to gene engineering and cell control, we believe we can reprogram T cells to express a particular CAR or TCR construct that will enable the T cell and/or NK cell to recognize and target cancer cells. CAR+ T cells target cell surface tumor antigens, such as CD19, that exist on cancer cells and that are independent of human leukocyte antigens, or HLAs, and which we refer to as public antigens. TCR-expressing T cells target tumor antigens that are dependent on HLAs and which we refer to as private antigens and include neo-antigens. NK cells target tumors with loss or differences of HLAs, or tumors with no defined antigens. Most CAR+ T cell and TCR products currently being developed by competitors are autologous, or derived from the patient s own mononuclear white blood cells, and gene engineered with viral technology. As a result, the patient s blood must be harvested, shipped to a manufacturing facility where the isolated mononuclear white blood cells are modified using a virus to express the CAR or TCR, and then shipped back to the hospital and infused into the patient. The process can take weeks and is labor intensive and costly. Currently, this complex technique can only be done in sophisticated laboratories. We believe we will be able to manufacture genetically modified cells using viral and non-viral methods. The latter may result in a reduced cost of manufacturing, particularly as we develop processes to eliminate the requirements for cell propagation and activation, thereby facilitating a shortened manufacturing process which can be implemented at multiple points-of-care. We intend to use our gene transfer methods to develop allogeneic treatments that can be used as an OTS treatment. An allogeneic OTS (also referred to as universal donor) treatment would enable a patient to be treated with a CAR+ T and/or NK-cell products that are created in advance of need from one or more separate healthy donor(s), possibly genetically modified for a tumor type, and then distributed to multiple points of care. Our non-viral methods, which we believe are customizable, fast, and less costly than other gene transfer approaches, together with our industrialized, scalable engineering approach are expected to enable highly efficient and less costly manufacturing approaches to gene engineered cell-based therapy. In addition, our proprietary RTS® and/or kill switches may give us the ability to control *in vivo* gene expression of CAR or TCR or cytokine on T cells and/or NK cells, which we believe could result in significantly lower toxicity compared to other products currently in development.

Cancer Overview

Cancer is a group of diseases characterized by either the runaway growth of cells or the failure of cells to die normally. Often, cancer cells spread to distant parts of the body, where they can form new tumors. Cancer can arise in any organ of the body and, according to the American Cancer Society, strikes slightly less than one of every two American men and a little more than one of every three American women at some point in their lives.

It is reported that there are more than 100 different varieties of cancer. Carcinomas, the most common type of cancer, originate in tissues that cover a surface or line a cavity of the body. Lymphomas are cancers of the lymph system, which is a circulatory system that bathes and cleanses the body s cells. Leukemias involve blood-forming tissues and blood cells. As their name indicates, brain tumors are cancers that begin in the brain, skin cancers, including

melanomas, originate in the skin, while soft tissue sarcoma arises in soft tissue. Cancers are considered metastatic if they spread through the blood or lymphatic system to other parts of the body to form secondary tumors.

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Cancer is caused by a series of mutations (alterations) in genes that control cells ability to grow and divide. Some mutations are inherited; others arise from environmental factors such as smoking or exposure to chemicals, radiation, or viruses that damage cells DNA. The mutations cause cells to divide relentlessly or lose their normal ability to die.

According to the American Cancer Society, it is estimated that about 1,685,210 new cases of cancer are expected to be diagnosed in 2016 and about 595,690 Americans are expected to die from cancer in 2016. The cost of treating cancer is significant. The Agency for Healthcare Research and Quality estimates that the direct medical cost of cancer in 2013 was $74.8 billion.

Cancer Treatments

Major treatments for cancer include surgery, radiotherapy, chemotherapy and immunotherapy. Newer approaches such as anti-angiogenic and targeted therapies are rapidly evolving. While there are many experimental treatments under investigation, including DNA and other immunological-based therapies, we believe the prevalence of cancer will remain a significant unmet medical need. Many therapies, including combination approaches, with different mechanisms of action may be needed to overcome tumor escape. In addition to monotherapy treatment in GBM, our approach to cancer treatment includes applying multiple modality and multi-delivery approaches that encompasses viral and non-viral mechanisms, differentiating us from many other companies in the field of adoptive cellular therapy today.

Market Opportunities

Glioblastoma is an aggressive primary brain tumor affecting approximately 74,000 people worldwide each year. Recurrent glioblastoma is an aggressive cancer with one of the lowest 3-year survival rates, at 3%, among all cancers. For patients who have experienced multiple recurrences the prognosis is particularly poor, with a median overall survival (OS) of 6-7 months, while OS in patients that have failed temozolomide and bevacizumab, or equivalent salvage chemotherapy, is approximately 3-5 months. Given the poor overall prognosis and lack of effective treatments, new therapeutic approaches for malignant gliomas are needed.

It is estimated that there are nearly 3 million women living in the United States with a history of invasive breast cancer, and an additional 226,870 women were diagnosed in 2012. Approximately 50% of women diagnosed with primary breast cancer will eventually relapse and develop metastatic or advanced disease. In addition, around 10% of patients present with metastatic disease at first diagnosis. The 5-year relative survival rate for women diagnosed with localized breast cancer is 98.6%; survival declines to 83.8% for regional stage and to 23.3% for distant stage. In addition to stage, factors that influence survival include tumor grade, hormone receptor status, and human epidermal growth factor receptor 2 (HER2) status.

According the Leukemia and Lymphoma Society, an estimated 1,237,824 people in the US are living with, or are in remission from, leukemia, lymphoma, or myeloma. New diagnoses for such hematologic malignancies in the US are expected to reach 171,500 people in 2016. These new diagnoses are expected to account for approximately 10% of the new cancer cases in the US in 2016.

GvHD Overview

GvHD is a major complication of allogeneic HSCT, which significantly impairs the quality of life and survival of many recipients. Allogeneic HSCT is an increasingly important treatment of various diseases including hematological malignancies, immunological deficiencies as well as non-malignant conditions, and is considered to be the most effective form of tumor immunotherapy available to date. However, GvHD, when immune (graft) cells in a transplant

patient recognize their engrafted host as foreign and attack the patient s (host) cells, remains a major source of morbidity and mortality following allogeneic HSCT. During development of GvHD, activation of various immune cells, especially donor T cells, leads to damage of target organs including skin, liver, hematopoietic system, and of particular importance, gut.

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There were approximately 23,000 allogeneic HSCT procedures in the US and Europe in 2013. Approximately 40% to 60% of HSCT recipients develop GvHD, either acute or chronic. Immunosuppressive agents and systemic steroids routinely used to treat GvHD have limited efficacy and toxicity; patients with steroid-resistant acute GvHD have a dismal prognosis, with mortality rates in excess of 90%, defining the need for safer, more effective therapies. New ways of treating and preventing GvHD have the potential to increase the market opportunity through (1) broadening of patient eligibility to receive allogeneic HSCT and (2) increasing the number of effective donor/recipient combinations.

Product Candidates

The following chart identifies our immuno-oncology product candidates and their current stage of development, each of which are described in more detail below.

Immuno-oncology programs:

Ad-RTS-IL-12 + veledimex

Ad-RTS-IL-12 + veledimex has been evaluated in two Phase 2 studies, the first for the treatment of metastatic melanoma, and the second for the treatment of unresectable recurrent or metastatic breast cancer. We are continuing to evaluate Ad-RTS-IL-12 + veledimex, in brain cancer and breast cancer. Ad-RTS-IL-12 + veledimex, our most advanced product candidate, uses our gene delivery system to produce IL-12, a potent, naturally occurring anti-cancer protein.

More specifically, IL-12 is a potent immunostimulatory cytokine which activates and recruits dendritic cells that facilitate the cross-priming of tumor antigen-specific T cells. We have developed an adenoviral vector, Ad-RTS-IL-12, administered intra-tumorally under the control of the RheoSwitch Therapeutic System® (RTS®) expression platform. Gene expression and subsequent IL-12 protein production is tightly controlled by the activator ligand veledimex.

Ad-RTS-IL-12 + veledimex for malignant glioma

We initiated a multi-center Phase 1 study in patients with recurrent or progressive GBM or Grade III malignant glioma, a form of brain cancer, in June 2015. We reported biologic data from this study in our presentation titled Intra-tumoral regulated expression of IL-12 as a gene therapy approach to treatment of glioma at the Society

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for Neuro-Oncology (SNO) 20th Annual Scientific Meeting, November 19-22, 2015 in San Antonio, TX, and on February 24, 2016, we announced the successful completion of the initial dosing cohort and that the first patient has been dosed in the next succeeding cohort of the GBM study.

Our ongoing Phase 1, multi-center dose-escalation study of the gene therapy candidate Ad-RTS-hIL-12 + orally-administered veledimex in patients with recurrent or progressive GBM was presented at the ASCO Annual Meeting in June 2016. Ad-RTS-hIL-12 + veledimex is a novel viral gene therapy candidate for the controlled expression of IL-12.

On June 27, 2016, we announced the successful completion of enrollment in the first and second dosing cohorts as well as the initiation of enrollment in a third cohort of our ongoing multi-center Phase 1 study of Ad-RTS-hIL-12 + orally administered veledimex to treat recurrent or progressive glioblastoma (GBM) or grade III malignant glioma.

The primary objective of the study is to determine the safety and tolerability of a single intratumoral Ad-RTS-hIL-12 injection activated upon dosing with oral veledimex. Secondary objectives are to determine the maximum tolerated dose, the immune responses elicited, and assessment of biologic response. The first cohort of seven patients received 20 mg doses of veledimex, the second cohort of six patients received 40 mg doses of veledimex, and the third cohort of four patients received 30 mg doses of veledimex to refine the effect of activating the immune response within the tumor. The resultant immunologic activity that followed IL-12 expression from the brain tumor suggested that no further dose escalation would be necessary and the optimal dosing may be reached sooner than initially anticipated. An expansion cohort to enroll additional patients at 20 mg has also been completed

Data from 11 patients with recurrent high-grade gliomas were presented at the 2016 ASCO Annual Meeting in June 2016. All of these patients had failed at least two prior lines of therapy and underwent partial resection leaving residual tumors, in certain cases with significant tumor burden. Ad-RTS-hIL-12 was administered through direct injection into the brain tumor at the time of surgery and veledimex was taken orally to activate the production of IL-12 from the tumor site and stimulate an immune response. No enrollment restrictions were imposed for tumor size or location within the supratentorial space.

As of May 18th, the date of data collection for the ASCO presentation, overall median follow up was 6.2 months, with 10 of 11 patients alive. IL-12 in the bloodstream was measured and was found to be proportional to the amount of veledimex administered, demonstrating that this orally-delivered activator crossed the blood brain barrier to turn on the RheoSwitch® technology in a dose-dependent manner.

It is increasingly recognized that the measurement of progression free survival, or PFS, with immunotherapy may not correlate directly with overall survival, or OS. For purposes of the data that we presented at the ASCO Annual Meeting, all pseudoprogression/progression were assumed to trigger progressive disease for PFS analysis by Response Assessment for Neuro-Oncology, or RANO. However, clinical benefit, including long term survival and tumor regression, can still occur after initial disease progression or after the appearance of new lesions in the Immunotherapy Response Assessment for Neuro-Oncology, or iRANO.

Overall, Ad-RTS-hIL-12 + veledimex was well tolerated, with a higher incidence of grade 3 or greater adverse events in the 40 mg cohort. All serious adverse events and Grade 3 related toxicities were rapidly reversible upon discontinuation of veledimex. The most common related adverse events included headache, nausea/vomiting, fever, white blood cell/leukocyte count decrease, platelet count decrease, liver function test increase and cytokine release syndrome. Five subjects had related serious adverse events. As of July 8, 2016, we received a report of one additional death occurring approximately 3.9 months after completing veledimex therapy and subsequently receiving additional salvage therapy. The death is unrelated to Ad-RTS-hIL-12 + veledimex.

On July 15, 2016 the Company issued a statement with regard to a third death that had been recently reported to us. In our statement we announced that we were collecting and analyzing information concerning this death to

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determine appropriate and timely reporting to the FDA. The cause of death was an intracranial hemorrhage, which occurred sometime after the patient had been discharged from the treating center. We have determined that this is an isolated case, and there have been no other reported related instances of brain hemorrhage in any pervious cohort or prior studies with Ad-RTS-hIL-12 + veledimex. On July 19th, we announced that the Safety Review Committee for the GBM trial concluded that this third patient death was unrelated to study drug. The GBM trial remained open to enrollment and we have subsequently completed the 30 mg cohort. For patients who have experienced multiple recurrences of GBM, as the patients in our study have, prognoses are particularly poor. As of July 19th, median follow up in the first dose cohort from our study was 8 months, and the overall survival remains very encouraging in a population with an expected overall survival of 3 to 5 months for patients that have failed temozolomide and bevacizumab, or equivalent salvage chemotherapy.

We presented further interim updates on the progress of the Phase 1 GBM study, including longer-term survival follow up, at the SNO 21st Annual Scientific Meeting November 17-20, 2016 in Scottsdale, Arizona, in a poster entitled Phase 1 study of intratumoral viral delivery of Ad-RTS-hIL-12 + oral veledimex is well tolerated and suggests survival benefit in recurrent high grade glioma demonstrating median overall survival of 12.8 months, with 11 of 17 patients alive. Survival rates at 6, 9, and 12 months for patients with multiple recurrences prior to administration of Ad-RTS-hIL-12 were 100%, 86% and 71% respectively in the 20 mg cohort and 87%, 65% and 54% respectively for all subjects. In addition, a nonclinical poster was also presented at SNO in November entitled Local regulated IL-12 expression as an immunotherapy for the treatment of pontine glioma . We intend to initiate a pediatric brain tumor study in the first half of 2017.

At the 35th Annual J.P. Morgan Healthcare Conference on January 11th we presented further Phase 1 GBM study data. Based on tolerability and survival benefit (median OS=12.7 months, n=15), 20 mg was selected for an expansion cohort and we are following patients overall survival data. Ad-RTS-hIL-12 + veledimex is well tolerated and suggests a survival benefit over historical controls at 6, 9, and 12 months (median OS=9.6 months, n=25). Toxicities were tolerable, predictable and reversible upon discontinuing veledimex. There is a strong correlation between veledimex dose, BBB penetration, and IL-12 production. These data demonstrate that the RTS® gene switch works in humans toggling not only as a switch to turn on and off the production of IL-12, but also as a rheostat to control the level of IL-12.

The company is meeting with the FDA and European regulators in Q1 2017 to discuss the design and commencement of a multi-national pivotal trial in recurrent or progressive glioblastoma patients.

We reported pre-clinical data on combining Ad-RTS-IL-12 + veledimex with iCPI at ASGCT May 6, 2016 The combination of controlled expression of IL-12 with multiple immune checkpoint inhibitors in a GBM mice model showed superior results than either treatment alone, with a combination with anti-PD1 demonstrating 100% survival. These data provide a strong scientific rationale for evaluating this combination in human GBM; ZIOPHARM plans to initiate a combination study in the first half of 2017 in recurrent GBM.

On July 23, 2015, the FDA granted orphan drug designation for Ad-RTS-IL-12 + veledimex for the treatment of malignant glioma. Orphan drug designation provides eligibility for a seven-year period of market exclusivity in the United States after product approval, an accelerated review process, accelerated approval where appropriate, grant funding, tax benefits and an exemption from user fees.

Ad-RTS-IL-12 + veledimex for metastatic breast cancer

On April 27, 2015, we announced the initiation of a Phase 1b/2 study of Ad-RTS-hIL-12 + veledimex following standard chemotherapy for the treatment of patients with locally advanced or metastatic breast cancer. The study was

conducted at the Memorial Sloan Kettering Cancer Center in New York and evaluated improving the patient s response at 12-weeks. A poster presentation of this study titled Phase 1b/2 study of intra-tumoral Ad-RTS-hIL-12 + veledimex in patients with chemotherapy-responsive locally advanced or metastatic breast cancer was presented at the San Antonio Breast Cancer Symposium, in San Antonio, Texas in December 2015. We also presented updated information on the study at the 2016 ASCO meeting in June 2016.

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We presented an update of the study at the European Society for Medical Oncology (ESMO) 2016 Congress, October 7th -11th in Copenhagen, Denmark. As of August 30, 2016, a total of nine patients were available for initial assessment. Results show that Ad-RTS-hIL-12 + 7 days of veledimex consistently elicited production of IL-12 which in turn produced IFNg. It was notable that the intratumoral influx of CD8+ T cells and IFNg were present six weeks after completion of veledimex consistent with the ability of Ad-RTS-hIL-12 to favorably impact the tumor environment over the long term. In two patients, Ad-RTS-hIL-12 + veledimex provided a meaningful drug holiday, with durable responses for 18 and 35 weeks. In all patients, disease control rate (DCR) was 44% at Week 6 and 22% at Week 12. Overall response rate (ORR), defined as achieving a partial response (PR) or better, was 11% at Week 12. Most toxicities promptly reversed upon discontinuation of veledimex, including cytokine release syndrome (grade 1-2 CRS), observed in six of nine patients. The higher than expected incidence of CRS was likely related to CYP-3A4 drug interactions with veledimex (80 mg) which resulted in enhanced peak cytokine expression.

CAR, NK and TCR cells

We are actively pursuing viral and non-viral genetic engineering technologies and approaches to cell propagation to develop novel CAR+ T, NK and TCR therapies. Combining this technology with Intrexon s industrialized synthetic biologic engineering and clinically tested and validated RTS modules and/or kill switches, represents a differentiated approach to genetically modified T cells and other immune cells, such as NK cells. Employing novel cell engineering techniques and multigenic gene programs, we expect to implement next-generation non-viral and viral adoptive cellular therapies based on specialized cytokines, CARs and TCR s targeting both hematologic malignancies and solid tumors.

The platform we, together with Intrexon, exclusively licensed from MD Anderson uses the *Sleeping Beauty,* or SB, non-viral genetic modification system to generate and characterize new CAR+ T and TCR designs, which enables a high throughput approach to evaluate the genetically modified immune cells in oncology. In addition, we can rapidly assemble CARs and TCRs to fashion immuno-receptors that differ in specificity and ability to activate T cells. These CAR and TCR molecules are evaluated based on measurements of T cell function, phenotype, and genotype. We believe this non-viral gene transfer using the SB system is unique in the field of oncology and may avoid the expense and manufacturing difficulty associated with creating T cells engineered to express CAR and TCR using viral vectors. After electroporation, the transposon/transposase employed by *Sleeping Beauty* improves the efficiency of integration of donor plasmids used to express CAR and other transgenes in T cells. Propagation of genetically modified T cells on bio-engineered activating and propagating cells (AaPC) may provide a competitive advantage over other methods of modification. The SB system combined with AaPC can selectively propagate and thus retrieve CAR-expressing T cells suitable for human applications. The time in culture with or without AaPC may be shortened to manufacture minimally-manipulated T cells within days of gene transfer by electroporation. Associated pre-clinical data were presented at both the May 2016 ASGCT meeting and the December 2016 annual meeting of ASH. In the pre-clinical setting, the time to administration of third generation *Sleeping Beauty* CAR+ T cells co-expressing a membrane-bound version of IL-15 (mbIL15) has been reduced to less than two days through elimination of the need for *in vitro* T cell activation and propagation.

The ability to genetically modify immune cells using non-viral and viral-based technologies enables us to express other genes in addition to immunoreceptors (CARs and TCRs) to redirect specificity. The addition of mbIL15 described above in pre-clinical modeling endows CAR-expressing younger: T cells with an ability to be long-lived. The Company expects to build upon these data to co-express immunoreceptors with cytokines and to leverage its ability to control expression with RTS® and/or kill switches. The Company expects to build upon these data to co-express immunoreceptors with cytokines and to leverage its ability to control expression with RTS and/or kill switches. Using this unique set of genetic engineering tools, the company can employ a broad immunotherapy approach against cancer.

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CAR

Through the MD Anderson License, the Company was able to enter the clinic with three CAR+ T therapies in 2015 utilizing the non-viral genetic modification capabilities of the SB system. Two of these trials are with first generation technologies, the results from which were published in the Journal of Clinical Investigation August 2016.

We are currently enrolling an investigator-led Phase 1 study using second generation CD19-specific CAR+ T cells with a revised CAR structure in patients with advanced lymphoid malignancies at MD Anderson. A patient with multiple-relapsed B-cell ALL received CD19-specific CAR+ T cells produced with a 3-week manufacturing process and achieved a complete remission with normalization of PET/CT tumor imaging. Steps were taken in 2016 to further decrease the T cell culture time in the manufacturing process, which advances our efforts to address the challenges of cost and manufacturing time associated with these therapies. Preclinical data in a mouse tumor model showing improved survival with treatment using CAR+ T cells with reduced time in culture (approximately 2 weeks versus 4 weeks for previous first generation CAR+ T process) were presented at the 2016 annual meeting of American Society of Gene & Cell Therapy (ASGCT). The second generation CD19 trial underway is now employing the shortened 2-week manufacturing process advancement. On January 31, 2017, the Company announced a patient with triple-hit NHL treated in January 2017 was the first to receive *Sleeping Beauty*-modified CD19-specific CAR+ T cells with the manufacturing time reduced to 2 weeks.

In the pre-clinical setting, the time to administration of third generation *Sleeping Beauty* CAR+ T cells co-expressing a membrane-bound version of IL-15 (mbIL15) has been reduced to less than two days. This shortened process delivers genetically modified T cells with superior proliferative potential. Data presented at the 58th American Society of Hematology (ASH) Annual Meeting in December 2016, supported by an earlier publication in the Proceedings of the National Academy of Sciences (2016 Nov 29;113(48):E7788-E7797), revealed promising results: Third generation *Sleeping Beauty* CAR+ T cells demonstrated that a single low-dose of T cells co-expressing a CD19-specific CAR and mbIL15 resulted in sustained *in vivo* persistence that produced potent anti-tumor effects and superior leukemia-free survival. These clinical and pre-clinical data support the Company s point-of-care (POC) plans to rapidly infuse *Sleeping Beauty* CAR+ T cells in a Phase I trial expected to be opened this year. With the intent to administer clinical-grade *Sleeping Beauty* CAR+ T cells in less than 48 hours, this non-viral CAR-T approach has the potential to outpace viral-based methods.

On July 12, 2016, we announced that after receiving feedback from the U.S. National Institutes of Health Office of Biotechnology Activities Recombinant DNA Advisory Committee, we anticipated progressing plans for a Phase I adoptive cellular therapy clinical trial at MD Anderson infusing autologous T cells transduced with lentivirus to express a CD33-specific CAR co-expressed with a kill switch in patients with relapsed or refractory AML. Preclinical studies, presented at the 2016 annual meeting of ASH, demonstrated that lentiviral transduced CAR-T cells targeting CD33 exhibit specific cytotoxic activity for CD33+ AML cells. A proof-of-concept study utilizing an *in vivo* mouse model for AML showed that these CAR-T cells were able to eliminate disease burden and significantly enhance survival as compared to control groups. These positive preliminary results indicate biological activity and are suggestive of potential therapeutic effect for the treatment of AML. We plan to initiate this Phase 1 clinical trial at MD Anderson during the first half of 2017.

NK Cell

In addition to T cells, we are pursuing NK-cell therapies for the treatment of cancers. NK cells may have advantages over T-cell therapies in that killing is independent of a target antigen and the lack of expression of endogenous TCR obviates the need to genetically edit the associated genes. Initially, this OTS NK cell treatment will be tested in patients with AML in a clinical trial at MD Anderson which we expect to initiate in 2017.

Discovery programs are also underway to explore genetic modification of NK cells for increased tumor killing specificity. We expect to advance these and other exploratory NK-cell programs in preclinical studies in 2017.

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TCR

Many of these genetic engineering technologies can also be applied towards targeting intracellular antigens with one or more TCRs. This approach is particularly important for addressing the complexity of solid tumors. We believe that SB is ideally suited for targeting intracellular antigens by TCR as it may be more cost effective, should allow for rapid manufacturing and is customizable for individual patient therapies with the ability to include multiple TCRs in a single therapy. We are pursuing discovery programs in TCR therapies for neoantigen targets. The development of an approach to create a truly personalized therapy for each cancer patient based on his/her neoantigens is a strategic goal of our Company. On January 10, 2017, the Company announced the signing of a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) for the development of adoptive cell transfer (ACT)-based immunotherapies genetically modified using the *Sleeping Beauty* (SB) transposon/transposase system to express T cell receptors (TCRs) for the treatment of solid tumors. The principal goal of the CRADA is to develop and evaluate ACT for patients with advanced cancers using autologous peripheral blood lymphocytes (PBL) genetically modified using the non-viral SB system to express TCRs that recognize specific immunogenic mutations, or neoantigens, expressed within a patient s cancer. Clinical evaluations of the ability of these SB-engineered PBL to express TCRs reactive against cancer mutations to mediate cancer regression in patients with metastatic disease will be performed. Research conducted under the CRADA will be at the direction of Steven A. Rosenberg, M.D., Ph.D., Chief of the Surgery Branch at the NCI, in collaboration with researchers at the Company and Intrexon.

GvHD Program

GVHD may occur after a bone marrow or stem cell transplant in which someone receives bone marrow tissue or cells from a donor. The new, transplanted cells regard the recipient s body as foreign. When this happens, the newly transplanted cells attack the recipient s body. We, together with Intrexon, are initiating a research program focused on addressing the underlying pathologies of GvHD through its engineered cell platforms. The exclusive collaboration, or the GvHD Program, will focus on the pursuit of the following engineered cell therapy strategies, used either separately or in combination, for the targeted treatment of GvHD: (i) the infusion of regulatory T cell expressing membrane-bound and/or soluble interleukin-2 and (ii) the deployment of orally delivered, genetically modified *L. lactis* such as that express interleukin-2 to modulate immune function. We believe these strategies have the potential to broaden the number of patients eligible to receive allogeneic HCST and also increase the number of effective donor/recipient combinations.

Milestones

We achieved and expect to achieve the following milestones in 2017:

Intra-tumoral IL-12 RheoSwitch® programs:

Clinical data from Phase 1 of Ad-RTS-hIL-12 + veledimex for GBM to be presented at scientific meeting in 2017

Initiate pivotal clinical trial for GBM in 2017

Initiate combination study of Ad-RTS-hIL-12 + veledimex with iCPI (PD-1) during the first half of 2017

Initiate Phase 1 study in the treatment of brain tumors in children during the first half of 2017

CAR+ T programs:

Continue CD19 specific CAR+ T clinical study in 2017 enrolling patients under shortened manufacturing process towards point of care

Initiate a CD33 specific CAR+ T clinical study for relapsed or refractory AML in 2017

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Advance CAR+ T-cell preclinical studies for at least one hematological malignancy under a shortened manufacturing process towards point of care

TCR-T programs

Execute CRADA with NCI utilizing *Sleeping Beauty* to generate T cells targeting neoantigens

NK cell programs

Initiate a Phase 1 study of OTS NK cells for AML in 2017

GvHD programs

Advance preclinical studies in 2017

We are also evaluating additional potential preclinical candidates and continuing discovery efforts aimed at identifying other potential product candidates under our Channel Agreement and GvHD Agreement with Intrexon. In addition, we may seek to enhance our pipeline in immuno-oncology through focused strategic transactions, which may include acquisitions, partnerships and in-licensing activities.

Small molecule program

In addition to our immuno-oncology programs, we maintain certain rights to a small molecule program, darinaparsin which we are no longer developing directly. We entered into an amended and restated global licensing agreement with Solasia Pharma K.K., or Solasia, on July 31, 2014 granting Solasia an exclusive worldwide license to develop and commercialize darinaparsin, and related organoarsenic molecules, in both intravenous and oral forms in all indications for human use. In exchange, we will be eligible to receive from Solasia development-and sales-based milestones, a royalty on net sales of darinaparsin, once commercialized, and a percentage of any sublicense revenues generated by Solasia. On March 28, 2016, Solasia initiated a multi-center pivotal clinical trial intended to provide substantial evidence of efficacy necessary to support the filing of an application for a new drug approval in certain of the territories assigned to Solasia. The start of this trial triggered a $1.0 million milestone payment to us which was subsequently paid to MD Anderson under the terms of the MD Anderson License.

Development Plans

As of December 31, 2016, we have approximately $81.1 million of cash and cash equivalents. Given our development plans, we anticipate cash resources will be sufficient to fund our operations into the fourth quarter of 2017 and the Company has no committed sources of additional capital. The forecast of cash resources is forward-looking information that involves risks and uncertainties, and the actual amount of our expenses could vary materially and adversely as a result of a number of factors. We have based our estimates on assumptions that may prove to be wrong, and our expenses could prove to be significantly higher than we currently anticipate. Management does not know whether additional financing will be on terms favorable or acceptable to the Company when needed, if at all. If adequate additional funds are not available when required, or if the Company is unsuccessful in entering into

partnership agreements for further development of its products, management may need to curtail development efforts. Based on the forecast, management determined that there is substantial doubt regarding our ability to continue as a going concern. As a result, our independent registered accounting firm has expressed substantial doubt as to our ability to continue as a going concern in their report dated February 16, 2017 included elsewhere in the Form 10-K.