

ZIOPHARM ONCOLOGY INC

Form 424B7

April 01, 2015

Table of Contents

Filed pursuant to Rule 424(b)(7)

Registration No. 333-201826

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities To Be Registered	Amount to be Registered⁽¹⁾	Proposed Maximum Offering Price Per Share⁽²⁾	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee⁽³⁾
Common stock, par value \$0.001 per share	11,722,163	\$10.97	\$128,592,128.11	\$14,942.41

- (1) There is also being registered hereunder an indeterminate number of additional shares of common stock as shall be issuable pursuant to Rule 416 to prevent dilution resulting from stock splits, stock dividends or similar transactions.
- (2) Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457 of the Securities Act based upon a \$10.97 per share average of high and low prices of the registrant's common stock on the Nasdaq Capital Market on March 26, 2015.
- (3) Calculated in accordance with Rule 456(b) and Rule 457(r) of the Securities Act. This Calculation of Registration Fee table shall be deemed to update the Calculation of Registration Fee table in the registrant's Registration Statement on Form S-3 (File No. 333-201826).

Table of Contents

Prospectus supplement

(To prospectus dated February 2, 2015)

11,722,163 Shares

Common stock

This prospectus supplement relates to the possible resale from time to time of up to 11,722,163 shares of our common stock, by the selling stockholder set forth in this prospectus supplement under the caption "Selling Stockholder", or its donees, pledgees, transferees or other successors-in-interest. We will not receive any proceeds from the disposition of such shares.

The selling stockholder identified in this prospectus supplement or its donees, pledgees, transferees or other successors-in-interest may, from time to time, offer and sell the shares of common stock in public transactions or in privately negotiated transactions, without limitation, at market prices prevailing at the time of sale or at negotiated prices. The timing and amount of any sale are within the sole discretion of the selling stockholder. The selling stockholder may offer and sell the shares of common stock held directly by it or through underwriters, broker-dealers or agents, who may receive compensation in the form of discounts, commissions or concessions. The selling stockholder will pay all underwriting discounts, brokerage fees or selling commissions, if any, applicable to the sale of the shares of our common stock. We are paying certain other expenses relating to this offering and the registration of the shares of common stock with the Securities and Exchange Commission (the "SEC"). For further information regarding the possible methods by which shares of common stock may be distributed, see "Plan of Distribution" of this prospectus supplement.

Our common stock is listed on the Nasdaq Capital Market under the symbol "ZIOP". On March 30, 2015, the closing price of our common stock, as reported on the Nasdaq Capital Market, was \$11.61. We urge prospective purchasers of our common stock to obtain current information about the market prices of our common stock.

Investing in our common stock involves risk. Before buying any shares, you should read the discussion of material risks of investing in our common stock in Risk Factors beginning on page S-11 of this prospectus supplement, and in the risks discussed in the documents incorporated by reference in this prospectus supplement, as they may be amended, updated or modified periodically in our reports filed with the SEC.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus supplement is April 1, 2015.

Table of Contents

Table of Contents

	Page
Prospectus supplement	
<u>About this Prospectus Supplement</u>	S-1
<u>Prospectus Supplement Summary</u>	S-2
<u>Risk Factors</u>	S-11
<u>Cautionary Note Regarding Forward-Looking Statements</u>	S-11
<u>Use of Proceeds</u>	S-13
<u>Selling Stockholder</u>	S-13
<u>Plan of Distribution</u>	S-15
<u>Disclosure of Commission Position on Indemnification for Securities Act Liabilities</u>	S-16
<u>Where You Can Find More Information</u>	S-17
<u>Incorporation of Certain information by Reference</u>	S-17
<u>Legal Matters</u>	S-17
<u>Experts</u>	S-18
	Page
Prospectus	
<u>About This Prospectus</u>	i
<u>Prospectus Summary</u>	1
<u>Risk Factors</u>	10
<u>Special Note Regarding Forward-Looking Statements</u>	11
<u>Ratio Of Earnings To Fixed Charges And To Combined Fixed Charges And Preference Dividends</u>	12
<u>Use Of Proceeds</u>	13
<u>Dilution</u>	13
<u>Description Of Capital Stock</u>	14
<u>Description Of Debt Securities</u>	17
<u>Description Of Warrants</u>	24
<u>Certain Provisions Of Delaware Law, The Certificate Of Incorporation And Bylaws</u>	26
<u>Plan Of Distribution</u>	28
<u>Legal Matters</u>	30
<u>Experts</u>	30
<u>Where You Can Find More Information</u>	30
<u>Incorporation Of Information By Reference</u>	31

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date specified in the relevant agreement. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

You should rely only on the information contained in this prospectus supplement, the accompanying prospectus, or any free writing prospectus authorized by us, or incorporated by reference herein. We have not authorized, and the selling stockholder has not authorized, anyone to provide you with information that is different. The information contained in this prospectus supplement, the accompanying prospectus, or any free writing prospectus authorized by us, or incorporated by reference herein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement, the accompanying prospectus, and any free writing prospectus authorized by us or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement, the accompanying prospectus, and any free writing prospectus authorized by us, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled *Where You Can Find More Information* and *Incorporation of Information by Reference* in this prospectus supplement and in the accompanying prospectus.

The selling stockholder will offer to sell, and seek offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Investors Outside the United States. No action is being taken in any jurisdiction outside the United States to permit a public offering of our common stock or possession or distribution of this prospectus in that jurisdiction. Persons who come into possession of this prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus applicable to that

jurisdiction.

Unless otherwise stated, all references in this prospectus to we, us, our, ZIOPHARM, the Company and similar designations refer to ZIOPHARM Oncology, Inc.

S-1

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference in this prospectus supplement. Because it is only a summary, it does not contain all of the detailed information contained elsewhere in this prospectus supplement or in the documents incorporated by reference into this prospectus supplement or included as exhibits to the registration statement of which this prospectus supplement is a part. Accordingly, you should carefully review this prospectus supplement, including all documents incorporated by reference into this prospectus supplement, in its entirety. Unless otherwise indicated, ZIOPHARM, the Company, we, us, our and similar terms refer to ZIOPHARM Oncology, Inc.

Our Company

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that seeks to acquire, develop and commercialize, on its own or with commercial partners, a diverse portfolio of cancer therapies that can address unmet medical needs through synthetic biology. Pursuant to an exclusive channel collaboration agreement, or Channel Agreement, with Intrexon Corporation, or Intrexon, we obtained rights to Intrexon's synthetic biology platform for use in the field of oncology, which included a clinical stage product candidate, Ad-RTS-IL-12 used with the oral activator veledimex. The synthetic biology platform is an industrialized engineering approach for molecular and cell biology and gene control. It employs an inducible gene-delivery system that enables controlled in vivo expression of genes that produce therapeutic proteins to treat cancer. Ad-RTS-IL-12 + veledimex uses this gene delivery system to produce Interleukin-12, or IL-12, a potent, naturally occurring anti-cancer protein. 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; data from these Phase 2 studies was presented in December 2014. We are continuing to pursue intratumoral injection of Ad-RTS-IL-12 + veledimex in breast cancer and brain cancer.

In addition to our synthetic biology programs, Intrexon (and we, through our Channel Agreement with Intrexon) recently obtained an exclusive, worldwide license to certain immuno-oncology technologies owned and licensed by The University of Texas M.D. Anderson Cancer Center, or MD Anderson, including technologies relating to novel chimeric antigen receptors, or CARs, natural killer, or NK cells and T cell receptors, or TCRs. Combining these technologies with Intrexon's technology suite and clinically tested RheoSwitch Therapeutic System[®], or RTS[®], IL-12 modules, we plan to develop CAR-T and other immune cells that will target and kill cancer cells. We plan to leverage the synergy between the platforms to accelerate a promising synthetic immuno-oncology pipeline, with up to five CAR-T therapies expected to enter the clinic in 2015 and programs for the development of allogeneic CAR-T therapies that can be used off-the-shelf expected to be initiated in 2016.

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.

More detailed descriptions of the product candidates and clinical development plans described in this prospectus supplement summary are set forth in our Annual Report on Form 10-K for the fiscal year ended December 31, 2014 and in the other reports that we file from time to time with the Securities and Exchange Commission that are incorporated herein by reference.

Enabling Technology

Synthetic biology 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. Synthetic biology 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. Synthetic biology 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.

On January 6, 2011, we entered into the Channel Partner Agreement with Intrexon to develop and commercialize novel DNA-based therapeutics in the field of cancer treatment by combining Intrexon's synthetic biology platform with our

S-2

Table of Contents

capabilities to translate science to the patient. As a result, our DNA synthetic biology 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 (and on and off repeatedly) 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 drug candidate being developed using the synthetic biology platform is Ad-RTS-IL-12 + veledimex.

Immuno-oncology

Immuno-oncology, which 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. A central player in immune surveillance is a type of white blood cell known as the T cell. In healthy individuals, T cells 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 last five years, there has been substantial scientific progress in countering these evasion mechanisms using immunotherapies, or therapies that activate the immune system.

License Agreement with The University of Texas M. D. Anderson Cancer Center and Related Transactions

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., professor of pediatrics at MD Anderson, 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 rapidly and efficiently reprogram T cells to express a particular CAR or TCR construct that will enable the T cell to recognize and target cancer cells. CAR-T cells target cell surface tumor antigens, such as CD-19, that exist on cancer cells and that are independent of human leukocyte antigens, or HLAs, and which we refer to as public antigens. TCR+ cells target tumor antigens that are dependent on HLAs and which we refer to as private antigens. Natural killer cells target tumors with loss of HLAs, or tumors with no antigens. Most CAR-T cell and TCR products currently being developed by competitors are autologous, or derived from the patient's own blood, and gene engineered with viral technology. As a result, the patient's blood must be harvested, shipped to a manufacturing facility where it is modified using a retrovirus to express the CAR or TCR, and then shipped back to be infused into the patient. The process can take several weeks to a month and is very labor intensive and costly. Currently, this complex technique can only be done in very sophisticated laboratories. We believe we will be able to manufacture our CAR-T cells and TCRs using non-viral methods, which we expect will enable a simpler process requiring only days or hours and result in a lower cost of manufacturing. Our non-viral methods could also potentially enable autologous point of care treatment, where a patient's own T cells would be modified at or near the point of care, for example, utilizing a local blood bank, to express the CAR-T or TCR construct and then infused back into the patient, potentially during the same visit. In addition, we intend to use our non-viral methods to develop allogeneic treatments that can be used off-the-shelf. An allogeneic off-the-shelf treatment would enable a patient to be treated with a CAR-T or TCR construct that is created from a separate healthy donor, personalized for that patient, and then distributed to the point of care. Our non-viral methods, which we believe are nimble, fast and less costly than other 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, Intrexon's proprietary RheoSwitch Therapeutic System® may give us the ability to control in vivo gene expression (on-off-on-off etc.) in CAR-T or TCR cells, which we believe could result in significantly lower toxicity compared to other products currently in development.

Pursuant to the terms of the MD Anderson License, MD Anderson received consideration of \$50 million in shares of our common stock (or 10,124,561 shares) and \$50 million in shares of Intrexon's common stock, in each case based on a trailing 20-day volume-weighted average of the closing price of the Company's and Intrexon's common stock, respectively, ending on the date prior to the announcement of the entry into the MD Anderson License, collectively referred to as the License Shares, pursuant to the terms of the License Shares Securities Issuance Agreement described below. We and Intrexon also agreed to reimburse MD Anderson for out of pocket expenses for maintaining patents covering the licensed technologies.

In addition, pursuant to the MD Anderson License, MD Anderson has agreed to transfer to us certain existing research programs described in the MD Anderson License and to grant to Intrexon and us certain additional technology rights related

Table of Contents

thereto. In connection with such transfer, the terms of the MD Anderson License also require us and Intrexon to enter into a research and development agreement with MD Anderson pursuant to which we will provide funding for certain research and development activities of MD Anderson for a period of three years, in an amount between \$15 and \$20 million per year. The first quarterly payment of \$3.75 million due under this arrangement was required to be made by us within 90 days of the date of the MD Anderson License.

The term of the MD Anderson License expires on the last to occur of (a) the expiration of all patents licensed thereunder, or (b) the twentieth anniversary of the date of the MD Anderson License; provided, however, that following the expiration of the term, we and Intrexon shall then have a fully-paid up, royalty free, perpetual, irrevocable and sublicensable license to use the licensed intellectual property thereunder. After ten years from the date of the MD Anderson License and subject to a 90-day cure period, MD Anderson will have the right to convert the MD Anderson License into a non-exclusive license if we and Intrexon are not using commercially reasonable efforts to commercialize the licensed intellectual property on a case-by-case basis. After five years from the date of the MD Anderson License and subject to a 180-day cure period, MD Anderson will have the right to terminate the MD Anderson License with respect to specific technology(ies) funded by the government or subject to a third party contract if we and Intrexon are not meeting the diligence requirements in such funding agreement or contract, as applicable. MD Anderson may also terminate the MD Anderson License with written notice upon material breach by us and Intrexon, if such breach has not been cured within 60 days of receiving such notice. In addition, the MD Anderson License will terminate upon the occurrence of certain insolvency events for both us and Intrexon and may be terminated by the mutual written agreement of us, Intrexon and MD Anderson.

On January 9, 2015, in order to induce MD Anderson to enter into the MD Anderson License on an accelerated schedule, we and Intrexon entered into a letter agreement, or the MD Anderson Letter Agreement, pursuant to which MD Anderson received consideration of \$7.5 million in shares of our common stock (or 1,597,602 shares) and \$7.5 million in shares of Intrexon's common stock, in each case based on a trailing 20-day volume-weighted average of the closing price of our and Intrexon's common stock, respectively, ending on the date prior to the MD Anderson Letter Agreement, collectively referred to as the Incentive Shares, if the MD Anderson License was entered into on or prior to 8:00 am Pacific time on January 14, 2015, referred to as the Accelerated Closing Deadline. The Incentive Shares were issued to MD Anderson within sixty days of the date of the MD Anderson License pursuant to the terms of the Incentive Shares Securities Issuance Agreement described below.

In connection with the entry into the MD Anderson License, on January 13, 2015, we entered into a Securities Issuance Agreement with MD Anderson, or the License Shares Securities Issuance Agreement, pursuant to which we agreed to issue and sell the License Shares to MD Anderson in consideration for the License. The License Shares were issued to MD Anderson on March 11, 2015.

In connection with the entry into the MD Anderson Letter Agreement, on January 13, 2015, we entered into another Securities Issuance Agreement with MD Anderson, or the Incentive Shares Securities Issuance Agreement, pursuant to which we agreed to issue and sell the Incentive Shares to MD Anderson in consideration for the execution and delivery of the MD Anderson License on or prior to the Accelerated Closing Deadline in connection with the MD Anderson Letter Agreement. The Incentive Shares were issued to MD Anderson on March 11, 2015.

Also in connection with the MD Anderson License and the issuance of the License Shares and the Incentive Shares, on January 13, 2015, we and MD Anderson entered into a Registration Rights Agreement, or the Registration Rights Agreement, pursuant to which we agreed to file a resale registration statement, or the Registration Statement, registering the resale of the License Shares, the Incentive Shares and any other shares of our common stock held by MD Anderson on the date that the Registration Statement is filed, within 15 business days of the closing under the License Shares Securities Issuance Agreement. Under the Registration Rights Agreement, we are obligated to use our

reasonable best efforts to cause the Registration Statement to be declared effective as promptly as practicable after filing and in no event later than 120 days of the closing under the License Shares Securities Issuance Agreement and to maintain the effectiveness of the Registration Statement until all securities therein are sold or are otherwise can be sold pursuant to Rule 144, without any restrictions.

The shares being offered pursuant to this prospectus supplement consist of the License Shares and the Incentive Shares. We are filing this prospectus supplement to fulfill our obligations to MD Anderson under the Registration Rights Agreement.

Cancer Overview

Cancer is a group of diseases characterized by either the runaway growth of cells or the failure of cells to die normally.

Table of Contents

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, or STS, 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.

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 was estimated that about 1,658,370 new cases of cancer are expected to be diagnosed in 2015 and about 589,430 Americans are expected to die from cancer in 2015. The cost of treating cancer is significant. The Agency for Healthcare Research and Quality estimates that the direct medical cost of cancer in 2011 was \$88.7 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. Other treatment for cancer may involve supportive care. While there are many experimental treatments under investigation, including DNA and other immunological based therapies, we believe cancer treatment will remain a significant unmet medical need.

Product Candidates

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

Synthetic Biology 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. Ad-RTS-IL-12 + veledimex is our lead product candidate, which 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. Intratumoral administration of Ad-RTS-IL-12 + veledimex, which allows for adjustment of IL-12 gene expression upon varying the dose of veledimex, is designed to reduce the toxicity elicited by systemic delivery of IL-12, and increase efficacy through high intratumoral expression.

S-5

Table of Contents

We reported the controlled local expression of IL-12 as an immunotherapeutic treatment of glioma (brain cancer) in animal models through the use of the RTS® at the October 2013 AACR-NCI-EORTC conference. Veledimex brain penetration was demonstrated in normal mice and monkeys with intact blood brain barriers. Treatment with Ad-RTS-IL-12 + veledimex and DC-RTS-IL-12 + veledimex both demonstrated dose-related increase in survival in the mouse GL-261 glioma model with no adverse clinical signs observed. In December 2013, we announced the unanimous approval of the Recombinant DNA Advisory Committee of the National Institutes of Health, or the RAC/NIH, for the initiation of a Phase 1 study of Ad-RTS-IL-12 + veledimex, in subjects with recurrent or progressive high grade gliomas. The U.S Food and Drug Administration, or FDA, has requested additional nonclinical information to support the Phase 1 study and this data has been generated. Subject to reaching agreement with the FDA, we anticipate initiation of the Phase 1 study during the first half of 2015. Glioblastoma is by far the most frequent malignant brain tumor and is associated with a particularly aggressive course and dismal prognosis. The current standard of care is based on surgical resection to the maximum feasible extent, followed by radiotherapy and concomitant adjuvant temozolomide. Such aggressive treatment, however, is associated with only modest improvements in survival resulting in a very high unmet medical need.

At the American Association for Cancer Research, or AACR, 2014 Annual Meeting, in April 2014, we presented data from a preclinical study conducted jointly by us and Intrexon demonstrating the anti-tumor effects and tolerability of Ad-RTS-mIL-12 in a glioblastoma murine model. Veledimex was found to effectively cross the blood brain barrier, with dose-related increases in plasma and brain tissue exposure, and no accumulation in brain tissue following repeat dosing. The study data demonstrated that administration of Ad-RTS-mIL-12 + veledimex resulted in dose-related increases in survival of four- to five-fold, without exhibiting an adverse safety profile, when compared to median survival in vehicle control groups.

At the 17th Annual Meeting of the American Society of Gene and Cell Therapy, or ASGCT, in May 2014, we presented results demonstrating the potent anti-tumor and anti-cancer stem cell effects of Ad-RTS-IL-12 in a preclinical glioma model. Results from human and laboratory studies of Ad-RTS-IL-12 demonstrated that precise control of IL-12 gene expression levels can be achieved using Intrexon's RTS®. Rapid, tight modulation of in vivo expression of IL-12 using the activator ligand, veledimex, was demonstrated across these studies. When IL-12 expression was switched on it rapidly led to expression and an immune response. This immune response was characterized by an increase in tumor infiltrating lymphocytes with system wide immune activation. The data presented in May 2014 further demonstrated that Ad-RTS-IL-12 has potent anti-cancer effects in a glioma model, showing both a reduction in tumor mass and prolonged survival when compared to existing treatment standards. The data also showed a significant reduction in cancer stem cells, as measured by dramatically reduced nestin levels. Cancer stem cells are thought to play a critical role in recurrence and metastasis.

At the AACR 2014 Immunology and Immunotherapy Meeting in December 2014, together with Intrexon, we presented clinical results from the Ad-RTS-hIL-12 + veledimex studies in patients with advanced breast cancer and melanoma demonstrating local and systemic IL-12-mediated anti-cancer activity, as well as safety and control of both immune- and IL-12-mediated toxicity with use of the RTS® gene switch. In two open-label Phase 2 clinical studies, twelve patients with metastatic advanced stage breast cancer and twenty-six patients with metastatic melanoma were administered Ad-RTS-hIL-12. Following intra-tumoral injection of Ad-RTS-hIL-12, expression of IL-12 within patients was controlled by the RTS® gene switch using the oral activator ligand, veledimex, at doses ranging from 5mg to 160mg. All subjects had heavy tumor burden and disease progression at the time of enrollment, with mean number of prior therapies at 14 and 10 for breast cancer and melanoma patients, respectively. Treatment with Ad-RTS-hIL-12 + veledimex resulted in an increase in the immune cytokine IL-12 and downstream cytokines, IFN-g, IP-10 and IL-10, resulting in a significant increase in the number of CD8+ T-cells. Among seven evaluable subjects in the Phase 2 clinical study of Ad-RTS-IL-12 + veledimex in patients with recurrent or metastatic breast cancer, three had stable disease, including one triple negative breast cancer subject who crossed the primary endpoint of 16 week

progression free survival, for a disease control rate (stable disease or better) of 43%. Target lesions and tumor burden were significantly reduced in approximately 40% of patients. In the Phase 1/2 study of Ad-RTS-hIL-12 + veledimex in subjects with unresectable stage III/IV melanoma, of eighteen evaluable subjects, one had a partial response and six had stable disease, for a disease control rate of 39%. In melanoma patients for whom a response was observed, there was evidence of local and systemic anti-cancer activity. The adverse event profile of Ad-RTS-hIL-12 + veledimex in both melanoma and breast cancer was predictable, reversible and characteristic of immune activation. The most common ³ Grade 3 treatment emergent adverse events, or TEAEs, in breast cancer and melanoma included neutropenia and electrolyte abnormalities (21%) each, LFTs increased (16%), leukopenia (13%) and pyrexia, hypotension, lymphopenia, anemia, and cytokine release syndrome (11%) each. Importantly, all TEAEs and SAEs ³ Grade 3 reversed rapidly upon discontinuation of veledimex oral dosing.

Also at the AACR 2014 Immunology and Immunotherapy Meeting in December 2014, together with Intrexon, we

Table of Contents

presented preclinical data supporting the potential for cytolytic activity against solid tumor targets with allogeneic, genetically-modified stem cells enabled for controlled release of cell-linking moieties, or CLMs, within the tumor micro-environment and preclinical data describing the development of a novel, high-throughput screening technology for rapidly identifying bi-specific antibodies capable of inducing targeted immunologic activity through the activation of T-cells or other immune cells against tumors. CLMs are small bi-specific antibody fragments capable of directing potent T-cell mediated tumor lysis by bridging the immunologic synapses of T-cells and surface targets on tumor cells. Previous studies have shown that the systemic distribution and pharmacokinetic profile of bi-specific antibodies limit their utility for many target/effector combinations. In two preclinical studies, Intrexon and Ziopharm researchers interrogated a large number of CLM-based effectors for their ability to activate white blood cells from peripheral blood and lyse receptor target-positive tumor cells. Allogeneic, tumor targeting stem cells were then genetically modified to express CLMs within the tumor microenvironment using the RTS[®] platform as a mechanism for providing spatial and temporal control. The first study demonstrated the ability of Intrexon's proprietary image-based screening systems and rapid DNA assembly to screen a large number of EGFR and HER2 receptor-targeted CLM variants for their ability to recruit CD3+ T-cells and mediate selective cell killing against target positive cells in peripheral blood co-cultures. The image-based screening platform allowed for real time target cell killing information to be obtained, as well as kinetic cell morphologic analyses to understand the dynamics of killing activity, thereby shortening the developmental timeline to lead candidate selection. The second study validated these CLM candidates in scalable, allogeneic endometrial regenerative cells, or ERCs, genetically modified to express an anti-CD3-anti-EGFR CLM under RTS[®] ligand inducible control. Expression of CLMs under the RTS[®] inducible promoter provided effective control of CLM secretion and modulation of killing activity, with vedimex-dependent cytotoxicity of greater than 80% against an EGFR+ KRAS mutant lung cancer cell model. CLM-expressing ERCs were found to be effective in co-culture killing assays at cellular doses as low as 1% of target cells. These data supported the feasibility of localized cytolytic activity of CLM-secreting allogeneic cell therapy products against EGFR+ KRAS mutant solid tumor malignancies.

We have completed the Phase 2 monotherapy studies in melanoma and breast cancer using Ad-RTS-IL-12 + vedimex. Additionally, we expect a future trial with IL-12 in combination therapies with standard of care for breast cancer. As the treatment of advanced melanoma has undergone and continues to undergo a rapid evolution with the introduction and approval of highly promising new single and combination agents, the standard of care in this indication has become uncertain, resulting in a much more competitive and commercially unpredictable environment. As a result, we are pursuing intratumoral injection of Ad-RTS-IL-12 + vedimex in brain cancer and breast cancer, and will pause further development of Ad-RTS-IL-12 + vedimex in melanoma with intratumoral injection. However, through current strategic initiatives, we expect to utilize RTS-IL-12 + vedimex in cell based immunotherapy of melanoma and other cancers. We plan to initiate a Phase 1 trial to evaluate Ad-RTS-IL-12 + vedimex as a single agent in the treatment of patients with brain cancer in the first half of 2015.

CAR-T Cells

We are actively pursuing non-viral, genetic engineering technologies to develop novel CAR-T, NK and TCR cells. Combining this technology with Intrexon's industrialized synthetic biologic engineering and clinically tested and validated RTS IL-12 modules, represents a differentiated approach to genetically modified CAR-T cell and other immune cells. Employing novel cell engineering techniques and multigenic gene programs, we expect to implement next-generation non-viral adoptive cellular therapies based on designer cytokines and CARs under control of RTS[®] technology targeting both hematologic malignancies and solid tumors. We plan to leverage the synergy between the platforms to accelerate a promising synthetic immuno-oncology pipeline, with up to five CAR-T therapies expected to enter the clinic in 2015 and programs for the development of allogeneic CAR-T therapies that can be used off-the-shelf expected to be initiated in 2016.

Research suggests that T cells can be re-programmed to have a very strong anti-cancer therapeutic effect through the expression of CARs to redirect specificity to tumors without HLA restrictions. The signature event within this field has resulted from the infusion of T cells expressing CARs into patients with B cells leukemias and lymphomas. Many of these patients have responded to these new therapies with a durable and dramatic anti-tumor effect after infusing CD19-specific T cells. Despite the highly promising results that have been demonstrated by early researchers in the field, current technologies and approaches have shown a number of serious drawbacks, including toxicity, manufacturing complexity and expense. A particular problem is that infusions of T cells into patients with large amounts of disease have invariably led to significant issues of toxicity for recipient patients. These toxicities primarily involve three major, potentially catastrophic side-effects:

The rapid killing of tumor cells releases a large number intracellular constituents that are very toxic to various organs and is called tumor lysis syndrome that can be fatal,

the supra-physiologic release of cytokines (cytokine storm) that causes fever, instability of blood pressure, mental status changes and on occasion, death, and

on-target, and off-tissue toxicity represented by the concomitant damage of normal B cells and loss of humoral (antibody) immunity.

S-7

Table of Contents

We expect to be able to tightly control expansion and activation of CAR-T cells in the body, which has the potential to alleviate or abrogate these toxicities.

MD Anderson's platform, which uses the exclusive Sleeping Beauty system, or SB system, generates and characterizes new CAR-T designs, which enables a high throughput approach to evaluate the CAR-T. This EZ-CAR-T non-viral system is used to fashion immuno-receptors that differ in specificity and ability to activate T cells. These CAR-T molecules are evaluated in a go/no go system based on serial killing and protection of T cells from activation-induced cell death. Non-viral gene transfer using the SB system is unique in the field of oncology. Examples of cell engineering techniques that we expect to employ with the SB system are induced pluripotent stem cell (iPSC) processing technologies combined with Laser-enabled Analysis and Processing, or LEAP®, which consists of computerized image-based selection and laser processing for very rapid cell identification and purification as well as AttSite® Recombinases, which involves stable, targeted gene integration and expression with proprietary serine recombinases. We believe the advanced DNA vectors derived from SB can be used to avoid the expense and manufacturing difficulty associated with creating CAR-T cells using viral vectors. After electroporation, the transposon/transposase improves the efficiency of integration of plasmids used to express CAR and other transgenes in T cells. Propagation of genetically modified T cells on activating and propagating cells, or AaPC, provide a competitive advantage over other non-viral methods of modification. The SB system combined with artificial antigen-presenting cells can selectively propagate and thus retrieve CAR+ T cells suitable for human application. T cells can also be genetically modified using these technologies to target a panel (several) cancer antigen targets. We are on the verge of implementing technology to manufacture minimally-manipulated T cells within days of gene transfer by electroporation.

We expect this platform will rapidly integrate with Intrexon's RTS® and multigenic control gene programs. The programs are also designed and built for rapid transition to universal donor products or minimally manipulated point of care products. Dr. Laurence Cooper and colleagues at MD Anderson recently published research which demonstrated that transformed, primary, and pluripotent stem cells can be permanently modified to eliminate HLA-A expression, demonstrating how to generate a priori cells from one allogeneic donor for infusion into multiple recipients representing a significant step towards our goal of on-demand therapy that can be pre-deployed at multiple sites and infused when needed. The primary factor limiting the development of a universal donor product is the existence of graft-vs-host response, or GVHD. GVHD occurs because the newly transplanted cells regard the recipient's body as foreign. When this happens, the newly transplanted cells attack the recipient's body. Additional research from Dr. Cooper and colleagues at MD Anderson suggests that universal allogeneic T cells generated from one donor could be administered to multiple recipients. This is achieved by genetically editing CD19-specific CAR+ T cells to eliminate expression of the endogenous $\alpha\beta$ TCR, the gene responsible for triggering GVHD, without compromising CAR-dependent effector functions. Genetically modified T cells are generated using the SB system to stably introduce the CD19-specific CAR with subsequent permanent deletion of α or β TCR chains with nucleases. The translation of the SB system and AaPC for use in clinical trials highlights how a nimble and cost-effective approach to developing genetically modified T cells can be used to implement clinical trials infusing next-generation T cells with improved therapeutic potential. We are expanding our initial trials targeting CD19 and planning to conduct additional trials with re-designed CAR-Ts expanding beyond CD19+ tumor cells.

Anticipated Milestones

We expect the following milestones to occur in 2015 and 2016:

Intra-tumoral IL-12 RheoSwitch® programs:

Early data is expected in the fourth quarter of 2015 for our Phase 1/2 study in Breast Cancer with standard of care.

Early data is expected in the fourth quarter of 2015 for our Phase 1 study of Glioblastoma multiforme (GBM).

CAR-T programs:

We expect to initiate two Phase 1 studies of next-generation CD19 CARs in the second quarter of 2015.

We expect to initiate a Phase 1 study of next-generation CAR with an inducible cytokine in the fourth quarter of 2015.

We expect to initiate a novel CAR for myeloid malignancies in the fourth quarter of 2015.

We expect to receive interim data on two Phase 1 CARs studies in advanced leukemia and lymphomas in the fourth quarter of 2015.

We expect to initiate other leukemia and solid tumor CAR-T cell studies in 2016.

We expect to initiate allogeneic, off-the-shelf T-cell studies in 2016.

Data from all programs is expected in 2015 and 2016. We are also evaluating additional potential preclinical candidates

Table of Contents

and continuing discovery efforts aimed at identifying other potential product candidates under our Channel Agreement with Intrexon. In addition, we may seek to enhance our pipeline in synthetic biology through focused strategic transactions, which may include acquisitions, partnerships and in-licensing activities. We are actively seeking to out-license some or all of our small molecule programs to further support our synthetic biology efforts.

Small Molecule Programs

In addition to our synthetic biology programs discussed above, we have certain rights to three small molecule programs, palifosfamide (or isophosphoramidate mustard), darinafarsin and indibulin, all of which we are no longer actively pursuing. With respect to palifosfamide, in March 2013, we announced that the pivotal Phase 3 study, PICASSO 3, did not meet its primary endpoint of progression-free survival, and that we would terminate our development program in metastatic soft tissue sarcoma. In addition, we recently received the overall survival endpoint data from our study of palifosfamide in combination with carboplatin and etoposide chemotherapy versus carboplatin and etoposide alone in chemotherapy naïve patients with metastatic small cell lung cancer, which we refer to as MATISSE. This data will be submitted for presentation at a scientific forum during the first half of 2015.

We are seeking transactions with third parties for the possible out-license of palifosfamide. With respect to darinafarsin, we have 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 darinafarsin, 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 darinafarsin, once commercialized, and a percentage of any sublicense revenues generated by Solasia. During 2014, we determined to no longer pursue clinical development of indibulin.

Recent Developments

On March 27, 2015, we, together with Intrexon, entered into a worldwide License and Collaboration Agreement with a subsidiary of Merck Serono S.A. which is the biopharmaceutical business of Merck KGaA, through which the parties established a collaboration for the research and development and commercialization of products for the prophylactic, therapeutic, palliative or diagnostic use for cancer in humans. Pursuant to the agreement and the Exclusive Channel Partner Agreement amendment described below, we and Intrexon will receive an aggregate of \$115 million in cash in upfront consideration, potential payments for development and commercial milestones on products produced under the agreement (up to \$826 million of such milestones for the first two products), and potential royalty payments based on net sales of products produced under the agreement.

On March 27, 2015, we and Intrexon entered into a Second Amendment to Exclusive Channel Partner Agreement amending their existing Exclusive Channel Partner Agreement. The amendment modifies the scope of the parties collaboration under the existing Exclusive Channel Partner Agreement in connection with the license and collaboration agreement with Merck, described above. The amendment provides that Intrexon will pay to ZIOPHARM fifty percent of all payments Intrexon receives for upfronts, milestones and royalties under the Merck agreement, described above.

Corporate Information

We originally incorporated in Colorado in September 1998 (under the name Net Escapes, Inc.) and later changed our name to EasyWeb, Inc. in February 1999. We re-incorporated in Delaware on May 16, 2005 under the same name. On September 13, 2005, we completed a reverse acquisition of privately held ZIOPHARM, Inc., a Delaware corporation. To effect this transaction, we caused ZIO Acquisition Corp., our wholly-owned subsidiary, to merge with and into

ZIOPHARM, Inc., with ZIOPHARM, Inc. surviving as our wholly owned subsidiary. In accordance with the terms of the merger, the outstanding common stock of ZIOPHARM, Inc. automatically converted into the right to receive an aggregate of approximately 97.3% of our outstanding common stock (after giving effect to the transaction). Following the merger, we caused ZIOPHARM, Inc. to merge with and into us and we changed our name to ZIOPHARM Oncology, Inc. Although EasyWeb, Inc. was the legal acquirer in the transaction, we accounted for the transaction as a reverse acquisition under generally accepted accounting principles. As a result, ZIOPHARM, Inc. became the registrant with the Commission and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our principal executive offices are located at One First Avenue, Parris Building 34, Navy Yard Plaza, Boston, Massachusetts 02129, and our telephone number is (617) 259-1970. Our internet site is www.ziopharm.com. None of the information on our internet site is part of this prospectus supplement or part of the accompanying prospectus, unless expressly noted.

Risk Factors

An investment in our common stock involves a number of risks. Before deciding to invest in our common stock, you should carefully consider the risk factors and all of the other information included under the section entitled Risk Factors beginning on page S-11 of this prospectus supplement, including the information incorporated by reference to the reports that we file with the Securities and Exchange Commission.

Table of Contents

The Offering

Common stock offered by the selling stockholder 11,722,163 of shares of our common stock

Common stock outstanding immediately prior to the offering 128,268,758 shares

Common stock to be outstanding immediately after the offering 128,268,758 shares

Use of proceeds The selling stockholder will receive all of the proceeds from the sale or other disposition of the shares of common stock offered by this prospectus. We will not receive any of the proceeds from the sale or other disposition of the shares of common stock offered hereby. See Use of Proceeds.

Risk factors See Risk factors beginning on page S-11 for a discussion of some of the factors you should carefully consider before deciding to invest in shares of our common stock.

NASDAQ Capital Market symbol ZIOP

The number of shares of common stock to be outstanding immediately after this offering is based on 128,268,758 shares of common stock outstanding as of March 30, 2015. This number of shares excludes:

5,963,964 shares of our common stock issuable upon the exercise of stock options outstanding as of March 30, 2015, having a weighted average exercise price of \$4.09 per share; and

4,538,935 shares of our common stock available as of March 30, 2015 for future issuance pursuant to our 2012 Equity Incentive Plan

Table of Contents

RISK FACTORS

An investment in our common stock involves a number of risks. Before deciding to invest in our common stock, you should carefully consider the risks related to our Company and an investment in our common stock, including risks associated with delays in or discontinuance of development of our pharmaceutical product candidates, our inability to obtain necessary regulatory approvals to market products, unforeseen safety issues relating to the products, dependence on third-party collaborators and our ability to obtain financing sufficient to maintain our operations. Because we are a company with a limited history of operations, we are also subject to many risks associated with early-stage companies. These and other risks could materially harm our business, financial condition or future results. If any such risks materialize, the value of our common stock could decline, and you could lose all or part of your investment. For a more detailed discussion of the risks you should consider before purchasing shares of our common stock, you are urged to carefully review and consider the information detailed in Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2014 and in the other reports that we file from time to time with the Securities and Exchange Commission, which are incorporated herein by reference and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future, together with information in this prospectus and any other information incorporated by reference into this prospectus.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, including the documents that we incorporate by reference, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 (the Securities Act) and Section 21E of the Securities Exchange Act of 1934 (the Exchange Act). Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- the progress, timing and results of preclinical and clinical trials involving our drug candidates;
- the progress of our research and development programs;
- our plans or others' plans to conduct future clinical trials or research and development efforts;
- the risk that final trial data may not support interim analysis of the viability of our drug candidates;
- our plans and expectations regarding partnering our drug candidates;
- the benefits to be derived from relationships with our collaborators;

the receipt or anticipated receipt of regulatory clearances and approvals;

estimates of the potential markets for our drug candidates;

our ability to adequately protect our intellectual property rights;

our estimates of future revenues and profitability;

completive risks in our industry;

our estimates regarding our capital requirements and our ability to control costs; and

our need for additional funding and the period through which we anticipate our resources will sufficient to fund operations.

These statements are often, but not always, made through the use of words or phrases such as anticipate, estimate, plan, project, continuing, ongoing, expect, management believes, we believe, we intend and similar words or phrases. Accordingly, these statements involve estimates, assumptions and uncertainties that could cause actual results to differ materially from those expressed. Any forward-looking statements are qualified in their entirety by reference to the factors discussed in this prospectus supplement or incorporated by reference.

Because the factors discussed in this prospectus supplement or the accompanying prospectus, or incorporated herein by reference could cause actual results or outcomes to differ materially from those expressed in any forward-looking statements made by us or on our behalf, you should not place undue reliance on any such forward-looking statements. These statements are subject to risks and uncertainties both known and unknown which could cause actual results and developments to differ materially from those expressed or implied in such statements. Such risks and uncertainties relate to, among other factors: the development of our drug candidates; the regulatory approval of our drug candidates; our use of clinical research centers and other contractors; our ability to find collaborative partners for research, development and commercialization of potential products; acceptance of our products by doctors, patients or payors; our ability to market any of our products; our history of operating losses; our ability to compete against other companies and research institutions; our ability to secure adequate protection for our intellectual property; our ability to attract and retain key personnel; availability of reimbursement for our

Table of Contents

product candidates; the effect of potential strategic transactions on our business; our ability to obtain adequate financing; and the volatility of our stock price. These and other risks are detailed in Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2014 and in the other reports that we file from time to time under the Securities Act or the Exchange Act, which are incorporated herein by reference and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future, together with information in this prospectus supplement, the accompanying prospectus, and any other information incorporated by reference herein. You are encouraged to read these filings as they are made.

Finally, any forward-looking statement speaks only as of the date on which it is made, and we undertake no obligation to update any forward-looking statement or statements to reflect events or circumstances after the date on which such statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

S-12

Table of Contents**USE OF PROCEEDS**

We will not receive any proceeds from the disposition by the selling stockholder of any of the shares covered by this prospectus supplement.

SELLING STOCKHOLDER

This prospectus supplement covers the disposition by the selling stockholder identified below, or its donees, pledgees, transferees or other successors-in-interest, of a total of 11,722,163 shares of our common stock. All of these shares were issued in connection with our January 2015 licensing transaction with MD Anderson described beginning on page S-3 above under the caption Prospectus supplement Summary Immuno-oncology License Agreement with The University of Texas M. D. Anderson Cancer Center and Related Transactions .

The following table sets forth the number of shares of the common stock owned by the selling stockholder as of March 30 2015 and after giving effect to this offering assuming all of the shares covered hereby are sold by the selling stockholder. The percentage of beneficial ownership is based on 128,268,758 shares of our common stock outstanding as of March 30, 2015.

To our knowledge, the selling stockholder is not a broker-dealer or an affiliate of any broker-dealers, nor at the time of the selling stockholder's acquisition of the shares of our common stock listed below, did the selling stockholder have direct or indirect agreements or understandings with any person to distribute their shares. Information about the selling shareholder may change from time to time. Any changed information will be set forth in prospectus supplements, if required by applicable law.

	Shares Beneficially Owned Before Offering⁽¹⁾	Percentage of Beneficial Ownership Before Offering⁽¹⁾	Total Shares Offered By Selling Stockholder	Percentage of Shares Beneficial Ownership Owned After Offering⁽¹⁾ ⁽²⁾	Percentage of Beneficial Ownership After Offering⁽¹⁾ ⁽²⁾
Selling Stockholder The Board of Regents of the University of Texas System ⁽³⁾	11,722,163	9.1%	11,722,163		%

- (1) Beneficial ownership is determined in accordance with SEC rules, beneficial ownership includes any shares as to which the security or stockholder has sole or shared voting power or investment power, and also any shares which the security or stockholder has the right to acquire within 60 days of the date hereof, whether through the exercise or conversion of any stock option, convertible security, warrant or other right. The indication herein that shares are beneficially owned is not an admission on the part of the security or stockholder that he, she or it is a direct or indirect beneficial owner of those shares.
- (2) Assumes the sale of all shares offered under this prospectus supplement by the selling stockholder.
- (3) The shares held by the selling stockholder were issued to the selling stockholder as consideration for the licensing of certain technology to the Company pursuant to the MD Anderson License among the Company, Intrexon Corporation and the selling stockholder. Pursuant to an Investment Management Services Agreement with the selling stockholder, the University of Texas Investment Management Co. (UTIMCO), an institutional investment advisor, holds the shares on behalf of the selling stockholder and is authorized to exercise investment discretion

and voting power with respect to such shares on behalf of the selling stockholder. Accordingly, the selling stockholder and UTIMCO share beneficial ownership of the shares. The selling stockholder on behalf of MD Anderson has entered into the MD Anderson License with the Company and Intrexon, pursuant to which the Company and Intrexon obtained 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., professor of pediatrics at MD Anderson as well as either co-exclusive or non-exclusive licenses under certain related technologies. In addition, pursuant to the MD Anderson License, MD Anderson has agreed to transfer to us certain existing research programs described in the MD Anderson License and to grant to Intrexon and us certain additional technology rights related thereto. In connection with such transfer, the terms of the MD Anderson License also require us and Intrexon to enter into a research and development agreement with MD Anderson pursuant to which we will provide funding for certain research and development activities of MD Anderson for a period of three years, in an amount between \$15 and \$20 million per year. The first quarterly payment of \$3.75 million due under this arrangement was required to be made by us within 90 days of the date of the MD Anderson License. Further details regarding our material relationships with MD Anderson and the selling stockholder can be found beginning on page S-3 above under the caption

S-13

Table of Contents

Prospectus supplement Summary Immuno-oncology License Agreement with The University of Texas M. D. Anderson Cancer Center and Related Transactions , in our Annual Report on Form 10-K for the fiscal year ended December 31, 2014 and in the other reports that we file from time to time with the SEC that are incorporated herein by reference.

S-14

Table of Contents

PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes donees, pledgees, transferees or other successors-in-interest selling shares of common stock or interests in shares of common stock received after the date of this prospectus supplement from the selling stockholder identified on page S-13 as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of common stock or interests in shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. The selling stockholders may sell their shares of our common stock pursuant to this prospectus supplement at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling stockholders may use any one or more of the following methods when disposing of shares or interests therein:

ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;

block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;

purchases by a broker-dealer as principal and resale by the broker-dealer for its account;

an exchange distribution in accordance with the rules of the applicable exchange;

privately negotiated transactions;

short sales;

through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;

broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;

a combination of any such methods of sale; and

any other method permitted pursuant to applicable law.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock, from time to time, under this prospectus supplement, or under an amendment to this prospectus supplement under Rule 424(b)(7), Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus supplement. The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus supplement.

In connection with the sale of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the common stock in the course of hedging the positions they assume. The selling stockholders may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge the common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus supplement, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus supplement (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling stockholders from the sale of the common stock offered by them will be the purchase price of the common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the common stock or interests therein may be underwriters within the meaning of Section 2(a)(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. Selling stockholders who are underwriters within the meaning of Section 2(a)(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act.

To the extent required, the shares of our common stock to be sold, the names of the selling stockholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus supplement and the accompanying prospectus.

Table of Contents

In order to comply with the securities laws of some states, if applicable, the common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the common stock may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus supplement and the accompanying prospectus (as they may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

We have agreed to indemnify the selling stockholders against liabilities, including liabilities under the Securities Act and state securities laws, relating to the registration of the shares offered by this prospectus supplement.

We have agreed with the selling stockholders to keep the registration statement of which this prospectus supplement constitutes a part effective until such time as the shares offered by the selling stockholders have been effectively registered under the Securities Act and disposed of in accordance with such registration statement, the shares offered by the selling stockholders have been disposed of pursuant to Rule 144 under the Securities Act or the shares offered by the selling stockholders may be resold pursuant to Rule 144 without restriction or limitation (including without the requirement to be in compliance with Rule 144(c)(1)) or another similar exemption under the Securities Act.

DISCLOSURE OF COMMISSION POSITION ON INDEMNIFICATION FOR SECURITIES ACT LIABILITIES

Pursuant to our certificate of incorporation and bylaws, we may indemnify an officer or director who is made a party to any proceeding, because of his position as such, to the fullest extent authorized by Delaware General Corporation Law, as the same exists or may hereafter be amended. In certain cases, we may advance expenses incurred in defending any such proceeding.

To the extent that indemnification for liabilities arising under the Securities Act may be permitted to directors, officers or persons controlling our company pursuant to the foregoing provisions, or otherwise, we have been advised that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable. If a claim for indemnification against such liabilities (other than the payment by us of expenses incurred or paid by a director, officer or controlling person of our company in the successful defense of any action, suit or proceeding) is asserted by any of our directors, officers or controlling persons in connection with the securities being registered, we will, unless in the opinion of our counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by us is against public policy as expressed in the Securities Act and will be governed by the final adjudication of that issue.

Table of Contents

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-3 (including exhibits to such registration statement) under the Securities Act, with respect to the shares of our common stock offered by this prospectus. This prospectus does not contain all the information set forth in the registration statement. For further information with respect to our Company and the shares of our common stock to be sold under this prospectus, we refer you to the registration statement (SEC File No. 333-201826). Statements contained in this prospectus supplement as to the contents of any contract, agreement or other document to which we make reference are not necessarily complete. In each instance, we refer you to the copy of such contract, agreement or other document filed as an exhibit to the registration statement, each such statement being qualified in all respects by the more complete description of the matter involved.

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the Commission. You may read and copy these reports, proxy statements and other information at the Commission's public reference room at 100 F Street, N.E., Washington, D.C. 20549 or at the Commission's other public reference facilities. Please call the Commission at 1-800-SEC-0330 for more information about the operation of the public reference rooms. You can request copies of these documents by writing to the Commission and paying a fee for the copying costs. In addition, the Commission maintains an Internet site at <http://www.sec.gov> that contains reports, proxy and information statements and other information regarding issuers that file electronically with the Commission. Our Commission filings are available on the Commission's Internet site. We maintain a website at <http://www.ziopharm.com>. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus supplement, and you should not consider it part of this prospectus supplement or the accompanying prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We are allowed to incorporate by reference information contained in documents that we file with the SEC. This means that we can disclose important information to you by referring you to those documents and that the information in this prospectus supplement is not complete and you should read the information incorporated by reference for more detail. We incorporate by reference in two ways. First, we list certain documents that we have already filed with the SEC. The information in these documents is considered part of this prospectus supplement. Second, the information in documents that we file in the future will update and supersede the current information in, and incorporated by reference in, this prospectus supplement.

We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than information furnished in Current Reports on Form 8-K filed under Item 2.02 or 7.01 of such form), including filings made after the date of the initial registration statement of which this prospectus supplement is a part and prior to the effective date of such registration statement:

Annual Report on Form 10-K for the fiscal year ended December 31, 2014, filed on February 6, 2015;

Current Reports on Form 8-K filed on January 14, 2015, a second filing on January 14, 2015 (excluding Item 7.01), January 28, 2015, February 2, 2015 (excluding Items 2.02 and 7.01), February 4, 2015 (excluding Item 7.01), a second filing on February 4, 2015, February 12, 2015 (excluding Item 7.01), February 26, 2015 (excluding Item 2.02), and March 30, 2015 (excluding Item 7.01); and

The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the Commission on September 20, 2006, including any amendments or reports filed for purposes of updating such description. We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus but not delivered with this prospectus. You may request a copy of this information at no cost, by writing or telephoning us at the following address or telephone number:

ZIOPHARM Oncology, Inc.

One First Avenue, Parris Building 34, Navy Yard Plaza

Boston, Massachusetts 02129

Attention: Chief Legal Officer

(617) 259-1970

LEGAL MATTERS

The validity of the securities offered hereby will be passed upon by Cooley LLP, Boston, Massachusetts.

S-17

Table of Contents

EXPERTS

The financial statements and the effectiveness of internal control over financial reporting incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2014, have been audited by McGladrey LLP, an independent registered public accounting firm, as stated in their report incorporated by reference herein and have been so incorporated in reliance upon such reports and upon the authority of such firm as experts in accounting and auditing.

S-18

Table of Contents

PROSPECTUS

Common Stock

Preferred Stock

Warrants

Debt Securities

From time to time, we may offer and sell any combination of common stock, preferred stock, warrants and debt securities, in one or more offerings. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants. We may offer these securities separately or as units, which may include combinations of the securities.

This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these offerings and securities in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the securities being offered.

Our common stock is listed on the NASDAQ Capital Market under the symbol ZIOP. On January 30, 2015, the closing price of our common stock, as reported on the NASDAQ Capital Market, was \$8.95.

This prospectus may not be used to consummate a sale of any securities unless accompanied by a prospectus supplement.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section entitled Plan of Distribution in this prospectus. If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and options to purchase additional securities will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus is truthful or complete. A representation to the contrary is a criminal offense.

The date of this Prospectus is February 2, 2015.

Table of Contents

TABLE OF CONTENTS

	Page
<u>About This Prospectus</u>	i
<u>Prospectus Summary</u>	1
<u>Risk Factors</u>	10
<u>Special Note Regarding Forward-Looking Statements</u>	11
<u>Ratio Of Earnings To Fixed Charges And To Combined Fixed Charges And Preference Dividends</u>	12
<u>Use Of Proceeds</u>	13
<u>Dilution</u>	13
<u>Description Of Capital Stock</u>	14
<u>Description Of Debt Securities</u>	17
<u>Description Of Warrants</u>	24
<u>Certain Provisions Of Delaware Law, The Certificate Of Incorporation And Bylaws</u>	26
<u>Plan Of Distribution</u>	28
<u>Legal Matters</u>	30
<u>Experts</u>	30
<u>Where You Can Find More Information</u>	30
<u>Incorporation Of Information By Reference</u>	31

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the Commission, using a shelf registration process. Under this shelf registration process, from time to time, we may sell any combination of the securities described in this prospectus in one or more offerings. This prospectus provides you with a general description of the securities we may offer. Each time we offer and sell securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of the applicable offering. The prospectus supplement may include a discussion of risks or other special considerations applicable to us or the offered securities. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement, and any related free writing prospectus that we may authorize to be provided to you, may also add, update or change the information contained in this prospectus or in the documents incorporated by reference into this prospectus. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you must rely on the information in the prospectus supplement. We urge you to carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the headings Where You Can Find More Information and Incorporation of Information by Reference before buying any of the securities being offered. **THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.**

You should rely only on the information contained in, or incorporated by reference into, this prospectus or any applicable prospectus supplement, along with the information contained in any related free writing prospectus that we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different information. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus that we may authorize to be provided to you. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions

where it is lawful to do so. The information in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document, and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

i.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference into this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading Risk Factors contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part. Unless otherwise indicated, ZIOPHARM, our Company, we, us, our and similar terms refer to ZIOPHARM Oncology, Inc.

Company overview

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that seeks to acquire, develop and commercialize, on its own or with commercial partners, a diverse portfolio of cancer therapies that can address unmet medical needs through synthetic biology. Pursuant to an exclusive channel agreement with Intrexon Corporation, or Intrexon, we obtained rights to Intrexon's synthetic biology platform for use in the field of oncology, which included a clinical stage product candidate, Ad-RTS-IL-12 used with the oral activator veledimex. The synthetic biology platform is an industrialized engineering approach for molecular and cell biology and gene control. It employs an inducible gene-delivery system that enables controlled in vivo expression of genes that produce therapeutic proteins to treat cancer. Ad-RTS-IL-12 + veledimex uses this gene delivery system to produce Interleukin-12, or IL-12, a potent, naturally occurring anti-cancer protein. 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; data from these Phase 2 studies was presented in December 2014. We are continuing to pursue intratumoral injection of Ad-RTS-IL-12 + veledimex in breast cancer and brain cancer.

In addition to our synthetic biology programs, we recently obtained an exclusive, worldwide license to certain immuno-oncology technologies owned and licensed by The University of Texas M.D. Anderson Cancer Center, or MD Anderson, including technologies relating to novel chimeric antigen receptors, or CARs, natural killer, or NK cells and T cell receptors, or TCRs. Combining these technologies with Intrexon's technology suite and clinically tested RheoSwitch Therapeutic System®, or RTS®, IL-12 modules, we plan to develop CAR-T and other immune cells that will target and kill cancer cells. We plan to leverage the synergy between the platforms to accelerate a promising synthetic immuno-oncology pipeline, with up to five CAR-T therapies expected to enter the clinic in 2015 and programs for the development of allogeneic CAR-T therapies that can be used off-the-shelf expected to be initiated in 2016.

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

We also have a portfolio of small molecule drug candidates, which are no longer a strategic focus of our development activities and for some of which we are seeking partners to pursue further development and potential commercialization.

1.

Table of Contents***Enabling technologies******Synthetic biology***

Synthetic biology 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. Synthetic biology 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. Synthetic biology 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.

On January 6, 2011, we entered into an Exclusive Channel Partner Agreement with Intrexon, which we refer to as the Channel Agreement, to develop and commercialize novel DNA-based therapeutics in the field of cancer treatment by combining Intrexon's synthetic biology platform with our capabilities to translate science to the patient. As a result, our DNA synthetic biology 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 (and on and off repeatedly) 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 drug candidate being developed using the synthetic biology platform is Ad-RTS-IL-12 + veledimex.

More detailed descriptions of our clinical development for each are set forth in this report under the caption Product candidates below.

Immuno-oncology

Immuno-oncology, which 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. A central player in immune surveillance is a type of white blood cell known as the T cell. In healthy individuals, T cells 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 last five years, 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., professor of pediatrics at MD Anderson, 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 rapidly and efficiently reprogram T cells to express a particular CAR or TCR construct that will enable the T cell to recognize and target

2.

Table of Contents

cancer cells. CAR-T cells target cell surface tumor antigens, such as CD-19, that exist on cancer cells and that are independent of human leukocyte antigens, or HLAs, and which we refer to as public antigens. TCRs target tumor antigens that are dependent on HLAs and which we refer to as private antigens. Natural killer cells target tumors with loss of HLAs, or tumors with no antigens. Most CAR-T cell and TCR products currently being developed by competitors are autologous, or derived from the patient's own blood, and gene engineered with viral technology. As a result, the patient's blood must be harvested, shipped to a manufacturing facility where it is modified using a retrovirus to express the CAR or TCR, and then shipped back to be infused into the patient. The process can take several weeks to a month and is very labor intensive and costly. Currently, this complex technique can only be done in very sophisticated laboratories. We believe we will be able to manufacture our CAR-T cells and TCRs using non-viral methods, which we expect will enable a simpler process requiring only days or hours and result in a lower cost of manufacturing. Our non-viral methods could also potentially enable autologous point of care treatment, where a patient's own T cells would be modified at or near the point of care, for example, utilizing a local blood bank, to express the CAR-T or TCR construct and then infused back into the patient, potentially during the same visit. In addition, we intend to use our non-viral methods to develop allogeneic treatments that can be used off-the-shelf. An allogeneic off-the-shelf treatment would enable a patient to be treated with a CAR-T or TCR construct that is created from a separate healthy donor, personalized for that patient, and then distributed to the point of care. Our non-viral methods, which we believe are nimble, fast and less costly than other 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 RheoSwitch Therapeutic System[®] may give us the ability to control in vivo gene expression (on-off-on-off etc.) in CAR-T or TCR cells, which we believe could result in significantly lower toxicity compared to other products currently in development.

Product candidates

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

3.

Table of Contents

Synthetic biology 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. Ad-RTS-IL-12 + veledimex is our lead product candidate, which 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. Intratumoral administration of Ad-RTS-IL-12 + veledimex, which allows for adjustment of IL-12 gene expression upon varying the dose of veledimex, is designed to reduce the toxicity elicited by systemic delivery of IL-12, and increase efficacy through high intratumoral expression.

We reported the controlled local expression of IL-12 as an immunotherapeutic treatment of glioma (brain cancer) in animal models through the use of the RTS® at the October 2013 AACR-NCI-EORTC conference. Veledimex brain penetration was demonstrated in normal mice and monkeys with intact blood brain barriers. Treatment with Ad-RTS-IL-12 + veledimex and DC-RTS-IL-12 + veledimex both demonstrated dose-related increase in survival in the mouse GL-261 glioma model with no adverse clinical signs observed. In December 2013, we announced the unanimous approval of the Recombinant DNA Advisory Committee of the National Institutes of Health, or the RAC/NIH, for the initiation of a Phase 1 study of Ad-RTS-IL-12 + veledimex, in subjects with recurrent or progressive high grade gliomas. The U.S Food and Drug Administration, or FDA, has requested additional nonclinical information to support the Phase 1 study and this data has been generated. Subject to reaching agreement with the FDA, we anticipate initiation of the Phase 1 study during the first half of 2015. Glioblastoma is by far the most frequent malignant brain tumor and is associated with a particularly aggressive course and dismal prognosis. The current standard of care is based on surgical resection to the maximum feasible extent, followed by radiotherapy and concomitant adjuvant temozolomide. Such aggressive treatment, however, is associated with only modest improvements in survival resulting in a very high unmet medical need.

At the American Association for Cancer Research, or AACR, 2014 Annual Meeting, in April 2014, we presented data from a preclinical study conducted jointly by us and Intrexon demonstrating the anti-tumor effects and tolerability of Ad-RTS-mIL-12 in a glioblastoma murine model. Veledimex was found to effectively cross the blood brain barrier, with dose-related increases in plasma and brain tissue exposure, and no accumulation in brain tissue following repeat dosing. The study data demonstrated that administration of Ad-RTS-mIL-12 + veledimex resulted in dose-related increases in survival of four- to five-fold, without exhibiting an adverse safety profile, when compared to median survival in vehicle control groups.

At the 17th Annual Meeting of the American Society of Gene and Cell Therapy, or ASGCT, in May 2014, we presented results demonstrating the potent anti-tumor and anti-cancer stem cell effects of Ad-RTS-IL-12 in a preclinical glioma model. Results from human and laboratory studies of Ad-RTS-IL-12 demonstrated that precise control of IL-12 gene expression levels can be achieved using Intrexon's RTS®. Rapid, tight modulation of in vivo expression of IL-12 using the activator ligand, veledimex, was demonstrated across these studies. When IL-12 expression was switched on it rapidly led to expression and an immune response. This immune response was characterized by an increase in tumor infiltrating lymphocytes with system wide immune activation. The data presented in May 2014 further demonstrated that Ad-RTS-IL-12 has potent anti-cancer effects in a glioma model, showing both a reduction in tumor mass and prolonged survival when compared to existing treatment standards. The data also showed a significant reduction in cancer stem cells, as measured by dramatically reduced nestin levels. Cancer stem cells are thought to play a critical role in recurrence and metastasis.

At the AACR 2014 Immunology and Immunotherapy Meeting in December 2014, together with Intrexon, we presented clinical results from the Ad-RTS-hIL-12 + veledimex studies in patients with advanced breast cancer and

4.

Table of Contents

melanoma demonstrating local and systemic IL-12-mediated anti-cancer activity, as well as safety and control of both immune- and IL-12-mediated toxicity with use of the RTS[®] gene switch. In two open-label Phase 2 clinical studies, twelve patients with metastatic advanced stage breast cancer and twenty-six patients with metastatic melanoma were administered Ad-RTS-hIL-12. Following intra-tumoral injection of Ad-RTS-hIL-12, expression of IL-12 within patients was controlled by the RTS[®] gene switch using the oral activator ligand, veledimex, at doses ranging from 5mg to 160mg. All subjects had heavy tumor burden and disease progression at the time of enrollment, with mean number of prior therapies at 14 and 10 for breast cancer and melanoma patients, respectively. Treatment with Ad-RTS-hIL-12 + veledimex resulted in an increase in the immune cytokine IL-12 and downstream cytokines, IFN-g, IP-10 and IL-10, resulting in a significant increase in the number of CD8+ T-cells. Among seven evaluable subjects in the Phase 2 clinical study of Ad-RTS-IL-12 + veledimex in patients with recurrent or metastatic breast cancer, three had stable disease, including one triple negative breast cancer subject who crossed the primary endpoint of 16 week progression free survival, for a disease control rate (stable disease or better) of 43%. Target lesions and tumor burden were significantly reduced in approximately 40% of patients. In the Phase 1/2 study of Ad-RTS-hIL-12 + veledimex in subjects with unresectable stage III/IV melanoma, of eighteen evaluable subjects, one had a partial response and six had stable disease, for a disease control rate of 39%. In melanoma patients for whom a response was observed, there was evidence of local and systemic anti-cancer activity. The adverse event profile of Ad-RTS-hIL-12 + veledimex in both melanoma and breast cancer was predictable, reversible and characteristic of immune activation. The most common³ Grade 3 treatment emergent adverse events, or TEAEs, in breast cancer and melanoma included neutropenia and electrolyte abnormalities (21%) each, LFTs increased (16%), leukopenia (13%) and pyrexia, hypotension, lymphopenia, anemia, and cytokine release syndrome (11%) each. Importantly, all TEAEs and SAEs³ Grade 3 reversed rapidly upon discontinuation of veledimex oral dosing.

Also at the AACR 2014 Immunology and Immunotherapy Meeting in December 2014, together with Intrexon, we presented preclinical data supporting the potential for cytolytic activity against solid tumor targets with allogeneic, genetically-modified stem cells enabled for controlled release of cell-linking moieties, or CLMs, within the tumor micro-environment and preclinical data describing the development of a novel, high-throughput screening technology for rapidly identifying bi-specific antibodies capable of inducing targeted immunologic activity through the activation of T-cells or other immune cells against tumors. CLMs are small bi-specific antibody fragments capable of directing potent T-cell mediated tumor lysis by bridging the immunologic synapses of T-cells and surface targets on tumor cells. Previous studies have shown that the systemic distribution and pharmacokinetic profile of bi-specific antibodies limit their utility for many target/effector combinations. In two preclinical studies, Intrexon and Ziopharm researchers interrogated a large number of CLM-based effectors for their ability to activate white blood cells from peripheral blood and lyse receptor target-positive tumor cells. Allogeneic, tumor targeting stem cells were then genetically modified to express CLMs within the tumor microenvironment using the RTS[®] platform as a mechanism for providing spatial and temporal control. The first study demonstrated the ability of Intrexon's proprietary image-based screening systems and rapid DNA assembly to screen a large number of EGFR and HER2 receptor-targeted CLM variants for their ability to recruit CD3+ T-cells and mediate selective cell killing against target positive cells in peripheral blood co-cultures. The image-based screening platform allowed for real time target cell killing information to be obtained, as well as kinetic cell morphologic analyses to understand the dynamics of killing activity, thereby shortening the developmental timeline to lead candidate selection. The second study validated these CLM candidates in scalable, allogeneic endometrial regenerative cells, or ERCs, genetically modified to express an anti-CD3-anti-EGFR CLM under RTS[®] ligand inducible control. Expression of CLMs under the RTS[®] inducible promoter provided effective control of CLM secretion and modulation of killing activity, with veledimex-dependent cytotoxicity of greater than 80% against an EGFR+ KRAS mutant lung cancer cell model. CLM-expressing ERCs were found to be effective in co-culture killing assays at cellular doses as low as 1% of target cells. These data supported the feasibility of localized cytolytic activity of CLM-secreting allogeneic cell therapy products against EGFR+ KRAS mutant solid tumor malignancies.

We have completed the Phase 2 monotherapy studies in melanoma and breast cancer using Ad-RTS-IL-12 + veledimex. Additionally, we expect a future trial with IL-12 in combination therapies with standard of care for

5.

Table of Contents

breast cancer. As the treatment of advanced melanoma has undergone and continues to undergo a rapid evolution with the introduction and approval of highly promising new single and combination agents, the standard of care in this indication has become uncertain, resulting in a much more competitive and commercially unpredictable environment. As a result, we are pursuing intratumoral injection of Ad-RTS-IL-12 + veledimex in brain cancer and breast cancer, and will pause further development of Ad-RTS-IL-12 + veledimex in melanoma with intratumoral injection. However, through current strategic initiatives, we expect to utilize RTS-IL-12 + veledimex in cell based immunotherapy of melanoma and other cancers. We plan to initiate a Phase 1 trial to evaluate Ad-RTS-IL-12 + veledimex as a single agent in the treatment of patients with brain cancer in the first half of 2015.

CAR-T/cytokine programs

We are actively pursuing non-viral, genetic engineering technologies to develop novel CAR-T, NK and TCR cells. Combining this technology with Intrexon's industrialized synthetic biologic engineering and clinically tested and validated RTS IL-12 modules, represents a differentiated approach to genetically modified CAR-T cell and other immune cells. Employing novel cell engineering techniques and multigenic gene programs, we expect to implement next-generation non-viral adoptive cellular therapies based on designer cytokines and CARs under

control of RTS® technology targeting both hematologic malignancies and solid tumors. We plan to leverage the synergy between the platforms to accelerate a promising synthetic immuno-oncology pipeline, with up to five CAR-T therapies expected to enter the clinic in 2015 and programs for the development of allogeneic CAR-T therapies that can be used off-the-shelf expected to be initiated in 2016.

Research suggests that T cells can be re-programmed to have a very strong anti-cancer therapeutic effect through the expression of CARs to redirect specificity to tumors without HLA restrictions. The signature event within this field has resulted from the infusion of T cells expressing CARs into patients with B cells leukemias and lymphomas. Many of these patients have responded to these new therapies with a durable and dramatic anti-tumor effect after infusing CD19-specific T cells. Despite the highly promising results that have been demonstrated by early researchers in the field, current technologies and approaches have shown a number of serious drawbacks, including toxicity, manufacturing complexity and expense. A particular problem is that infusions of T cells into patients with large amounts of disease have invariably led to significant issues of toxicity for recipient patients. These toxicities primarily involve three major, potentially catastrophic side-effects:

1. The rapid killing of tumor cells releases a large number intracellular constituents that are very toxic to various organs and is called tumor lysis syndrome that can be fatal,
2. the supra-physiologic release of cytokines (cytokine storm) that causes fever, instability of blood pressure, mental status changes and on occasion, death, and
3. on-target, and off-tissue toxicity represented by the concomitant damage of normal B cells and loss of humoral (antibody) immunity.

We expect to be able to tightly control expansion and activation of CAR-T cells in the body, which has the potential to alleviate or abrogate these toxicities.

MD Anderson's platform, which uses the exclusive Sleeping Beauty system, or SB system, generates and characterizes new CAR-T designs, which enables a high throughput approach to evaluate the CAR-T. This EZ-CAR-T non-viral system is used to fashion immuno-receptors that differ in specificity and ability to activate T cells. These CAR-T molecules are evaluated in a go/no go system based on serial killing and protection of T cells from activation-induced cell death. Non-viral gene transfer using the SB system is unique in the field of oncology. Examples of cell engineering techniques that we expect to employ with the SB system are induced pluripotent stem cell (iPSC) processing technologies combined with Laser-enabled Analysis and Processing, or LEAP[®], which consists of computerized image-based selection and laser processing for very rapid cell identification and purification as well as AttSite[®] Recombinases, which involves stable, targeted gene integration

6.

Table of Contents

and expression with proprietary serine recombinases. We believe the advanced DNA vectors derived from SB can be used to avoid the expense and manufacturing difficulty associated with creating CAR-T cells using viral vectors. After electroporation, the transposon/transposase improves the efficiency of integration of plasmids used to express CAR and other transgenes in T cells. Propagation of genetically modified T cells on activating and propagating cells, or AaPC, provide a competitive advantage over other non-viral methods of modification. The SB system combined with artificial antigen-presenting cells can selectively propagate and thus retrieve CAR+ T cells suitable for human application. T cells can also be genetically modified using these technologies to target a panel (several) cancer antigen targets. We are on the verge of implementing technology to manufacture minimally-manipulated T cells within days of gene transfer by electroporation.

We expect this platform will rapidly integrate with Intrexon's RTS® and multigenic control gene programs. The programs are also designed and built for rapid transition to universal donor products or minimally manipulated point of care products. Dr. Laurence Cooper and colleagues at MD Anderson recently published research which demonstrated that transformed, primary, and pluripotent stem cells can be permanently modified to eliminate HLA-A expression, demonstrating how to generate *a priori* cells from one allogeneic donor for infusion into multiple recipients representing a significant step towards our goal of on-demand therapy that can be pre-deployed at multiple sites and infused when needed. The primary factor limiting the development of a universal donor product is the existence of graft-vs-host response, or GVHD. GVHD occurs because the newly transplanted cells regard the recipient's body as foreign. When this happens, the newly transplanted cells attack the recipient's body. Additional research from Dr. Cooper and colleagues at MD Anderson suggests that universal allogeneic T cells generated from one donor could be administered to multiple recipients. This is achieved by genetically editing CD19-specific CAR+ T cells to eliminate expression of the endogenous $\alpha\beta$ TCR, the gene responsible for triggering GVHD, without compromising CAR-dependent effector functions. Genetically modified T cells are generated using the SB system to stably introduce the CD19-specific CAR with subsequent permanent deletion of α or β TCR chains with nucleases. The translation of the SB system and AaPC for use in clinical trials highlights how a nimble and cost-effective approach to developing genetically modified T cells can be used to implement clinical trials infusing next-generation T cells with improved therapeutic potential. We are expanding our initial trials targeting CD19 and planning to conduct additional trials with re-designed CAR-Ts expanding beyond CD19+ tumor cells.

Anticipated Milestones

We expect the following milestones to occur in 2015 and 2016:

Intra-tumoral IL-12 RheoSwitch® programs:

Early data is expected in the fourth quarter of 2015 for our Phase 1/2 study in Breast Cancer with standard of care.

Early data is expected in the fourth quarter of 2015 for our Phase 1 study of Glioblastoma multiforme (GBM).

CAR-T programs:

We expect to initiate two Phase 1 studies of next-generation CD19 CARs in the second quarter of 2015.

We expect to initiate a Phase 1 study of next-generation CAR with an inducible cytokine in the fourth quarter of 2015.

We expect to initiate a novel CAR for myeloid malignancies in the fourth quarter of 2015.

We expect to receive interim data on two Phase 1 CARs studies in advanced leukemia and lymphomas in the fourth quarter of 2015.

7.

Table of Contents

We expect to initiate other leukemia and solid tumor CAR-T cell studies in 2016.

We expect to initiate allogeneic, off-the-shelf T-cell studies in 2016.

Data from all programs is expected in 2015 and 2016. We are also evaluating additional potential preclinical candidates and continuing discovery efforts aimed at identifying other potential product candidates under our Channel Agreement with Intrexon. In addition, we may seek to enhance our pipeline in synthetic biology through focused strategic transactions, which may include acquisitions, partnerships and in-licensing activities. We are actively seeking to out-license some or all of our small molecule programs to further support our synthetic biology efforts.

Small molecule programs

In addition to our synthetic biology programs discussed above, we have certain rights to three small molecule programs, palifosfamide (or isophosphoramidate mustard), darinaparsin and indibulin, all of which we are no longer actively pursuing. With respect to palifosfamide, in March 2013, we announced that the pivotal Phase 3 study, PICASSO 3, did not meet its primary endpoint of progression-free survival, and that we would terminate our development program in metastatic soft tissue sarcoma. In addition, we recently received the overall survival endpoint data from our study of palifosfamide in combination with carboplatin and etoposide chemotherapy versus carboplatin and etoposide alone in chemotherapy naïve patients with metastatic small cell lung cancer, which we refer to as MATISSE, which data will be submitted for presentation at a scientific forum during the first half of 2015.

We are seeking transactions with third parties for the possible out-license of palifosfamide. With respect to darinaparsin, we have 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. During 2014, we determined to no longer pursue clinical development of indibulin.

Recent developments

Expected cash as of December 31, 2014

Based upon preliminary estimates, we expect to have approximately \$43 million in cash and cash equivalents as of December 31, 2014. We have not yet completed our year-end financial close process for the year ended December 31, 2014. This estimate of our cash and cash equivalents as of December 31, 2014 is based on preliminary estimates of our financial results that we expect to report for the period. These estimates are subject to completion of our financial closing procedures. Our independent registered public accounting firm, McGladrey LLP, has not audited, reviewed or compiled these estimates. These estimates are not a comprehensive statement of our financial results for the year ended December 31, 2014 and our actual results may differ materially from these estimates as a result of the completion of our financial closing procedures, final adjustments and other developments arising between now and the time that our financial results for this period are finalized.

Development plans

Our current plan is to raise additional capital to support further development activities for our strategic product candidates. Based upon our current plans and without taking into account the net proceeds of this offering, we anticipate that our cash resources will be sufficient to fund our operations into the third quarter of 2015. This forecast

of cash resources is forward-looking information that involves risks and uncertainties, and the actual

8.

Table of Contents

amount of our expenses could vary materially and adversely as a result of a number of factors, including the factors discussed in the Risk Factors section of the applicable prospectus supplement and the uncertainties applicable to our forecast for the overall sufficiency of our capital resources. 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. In particular, pursuant to the MD Anderson License, MD Anderson agreed to transfer to us certain existing research programs described in the MD Anderson License and we, together with Intrexon, agreed to enter into a research and development agreement pursuant to which we will provide funding for certain research and development activities of MD Anderson for a period of three years from the date of the MD Anderson License, in an amount between \$15 and \$20 million per year. In addition, we also expect to enter into additional collaboration and technology transfer agreements with MD Anderson and Intrexon to accelerate technology and clinical development of these product candidates. We expect to increase the level of our overall research and development expenses significantly going forward as a result of each of these items. Further, in light of our entry into the MD Anderson License, we expect to establish operations in Houston, Texas that will enable us to join and collaborate with the MD Anderson academic and medical community, which may require that we add headcount in the future, and which could add to our general and administrative expenses going forward. Although our forecasts for expenses and the sufficiency of our capital resources takes into account our plans to develop the technology licensed from MD Anderson and our obligations under the MD Anderson License, the MD Anderson License was entered into on January 13, 2015 and is only beginning to be implemented, therefore the actual costs associated therewith may be significantly in excess of forecasted amounts.

Corporate Information

We originally incorporated in Colorado in September 1998 (under the name Net Escapes, Inc.) and later changed our name to EasyWeb, Inc. in February 1999. We re-incorporated in Delaware on May 16, 2005 under the same name. On September 13, 2005, we completed a reverse acquisition of privately held ZIOPHARM, Inc., a Delaware corporation. To effect this transaction, we caused ZIO Acquisition Corp., our wholly-owned subsidiary, to merge with and into ZIOPHARM, Inc., with ZIOPHARM, Inc. surviving as our wholly owned subsidiary. In accordance with the terms of the merger, the outstanding common stock of ZIOPHARM, Inc. automatically converted into the right to receive an aggregate of approximately 97.3% of our outstanding common stock (after giving effect to the transaction). Following the merger, we caused ZIOPHARM, Inc. to merge with and into us and we changed our name to ZIOPHARM Oncology, Inc. Although EasyWeb, Inc. was the legal acquirer in the transaction, we accounted for the transaction as a reverse acquisition under generally accepted accounting principles. As a result, ZIOPHARM, Inc. became the registrant with the Commission and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our principal executive offices are located at One First Avenue, Parris Building 34, Navy Yard Plaza, Boston, Massachusetts 02129, and our telephone number is (617) 259-1970. Our internet site is www.ziopharm.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement.

Table of Contents

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully review the risks and uncertainties described under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus and the applicable prospectus supplement, before deciding whether to purchase any of the securities being offered. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Moreover, the risks described are not the only ones that we face. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations.

10.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference herein contain, and any prospectus supplement or free writing prospectus may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical facts contained in this prospectus and the documents incorporated by reference herein contain, and any prospectus supplement or free writing prospectus are forward-looking statements. These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to statements about:

- the progress, timing and results of preclinical and clinical trials involving our drug candidates;
- the progress of our research and development programs;
- our plans or others' plans to conduct future clinical trials or research and development efforts;
- the risk that final trial data may not support interim analysis of the viability of our drug candidates;
- our plans and expectations regarding partnering our drug candidates;
- the benefits to be derived from relationships with our collaborators;
- the receipt or anticipated receipt of regulatory clearances and approvals;
- estimates of the potential markets for our drug candidates;
- our ability to adequately protect our intellectual property rights;
- the use of proceeds from this offering;
- our estimates of future revenues and profitability;
- completive risks in our industry;

our estimates regarding our capital requirements and our ability to control costs; and

our need for additional funding and the period through which we anticipate our resources will sufficient to fund operations.

In some cases, you can identify forward-looking statements by terms such as may, will, should, could, would, plans, anticipates, believes, estimates, projects, predicts, potential and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading Risk Factors in the applicable prospectus supplement or free writing prospectus and in our reports filed from time to time under the Securities Act and/or the Exchange Act. We encourage you to read these filings as they are made. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

You should read this prospectus, the documents incorporated by reference herein, and any prospectus supplement or free writing prospectus that we have authorized for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

Table of Contents

**RATIO OF EARNINGS TO FIXED CHARGES AND TO
COMBINED FIXED CHARGES AND PREFERENCE DIVIDENDS**

The following table shows our ratio of earnings to fixed charges and the ratio of earnings to combined fixed charges and preference dividends for the periods indicated.

	Year Ended December 31,					Nine Months Ended September 30,
	2009	2010	2011	2012	2013	2014
Ratio of earnings to fixed charges						
Ratio of earnings to combined fixed charges and preference dividends						

For purposes of computing the ratio of earnings to fixed charges and the ratio of earnings to our combined fixed charges and preference dividends, earnings consist of our net income (loss) before tax benefit (provision) for the period plus fixed charges. Fixed charges consist of interest expense and amortized premiums, discounts and capitalized expenses related to indebtedness. The ratio of earnings to fixed charges and the ratio of earnings to combined fixed charges and preference dividends were less than one-to-one for each of the periods presented. Earnings were insufficient to cover fixed charges by \$7.6 million in 2009, \$32.7 million in 2010, \$63.8 million in 2011, \$96.1 million in 2012, \$57.1 million in 2013 and \$21.4 million in the nine months ended September 30, 2014.

Table of Contents

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of our securities offered by this prospectus. Unless we indicate otherwise in the applicable prospectus supplement or in any related free writing prospectus we have authorized for use in connection with a specific offering, we anticipate that any net proceeds will be used for working capital and general corporate purposes. We will set forth in the applicable prospectus supplement or free writing prospectus our intended use for the net proceeds received from the sale of securities sold pursuant to that prospectus supplement or free writing prospectus.

DILUTION

We will set forth in a prospectus supplement the following information regarding any material dilution of the equity interests of investors purchasing securities in an offering under this prospectus:

the net tangible book value per share of our equity securities before and after the offering;

the amount of the increase in such net tangible book value per share attributable to the cash payments made by purchasers in the offering; and

the amount of the immediate dilution from the public offering price which will be absorbed by such purchasers.

Table of Contents

DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus, our authorized capital stock consists of 280,000,000 shares, comprised of 250,000,000 shares of common stock, par value \$.001 per share, and 30,000,000 shares of preferred stock, par value \$.001 per share. As of January 30, 2015, there were 104,428,495 shares of common stock and no shares of preferred stock issued and outstanding. Our common stock is traded on the NASDAQ Capital Market under the symbol ZIOP .

The following description summarizes the material terms of our capital stock. This summary is, however, subject to the provisions of our certificate of incorporation and bylaws. For greater detail about our capital stock, please refer to our certificate of incorporation and bylaws.

Common Stock

Voting. The holders of our common stock are entitled to one vote for each outstanding share of common stock owned by such stockholder on every matter properly submitted to the stockholders for their vote. Stockholders are not entitled to vote cumulatively for the election of directors. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose. At any meeting of the stockholders, a quorum as to any matter shall consist of a majority of the votes entitled to be cast on the matter, except where a larger quorum is required by law, by our certificate of incorporation or by our bylaws.

Dividend Rights. Holders of our common stock are entitled to receive ratably dividends and other distributions of cash or any other right or property as may be declared by our board of directors out of our assets or funds legally available for such dividends or distributions. The dividend rights of holders of common stock are subject to the dividend rights of the holders of any series of preferred stock that may be issued and outstanding from time to time.

Liquidation Rights. In the event of any voluntary or involuntary liquidation, dissolution or winding up of our affairs, holders of our common stock would be entitled to share ratably in our assets that are legally available for distribution to stockholders after payment of liabilities. If we have any preferred stock outstanding at such time, the holders of such preferred stock may be entitled to distribution and/or liquidation preferences that require us to pay the applicable distribution to the holders of preferred stock before paying distributions to the holders of common stock.

Rights and Preferences. Holders of our common stock have no preemptive, conversion or subscription rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company.

See Certain Provisions of Delaware Law, the Certificate of Incorporation and Bylaws for a description of provisions of our certificate of incorporation and bylaws which may have the effect of delaying, deferring or preventing changes in the our control.

Preferred Stock

Pursuant to our amended and restated certificate of incorporation, our board of directors has the authority, without stockholder approval, subject to limitations prescribed by law, to provide for the issuance of up to 30,000,000 shares of preferred stock in one or more series, and by filing a certificate pursuant to the applicable law of the State of

Delaware, to establish from time to time the number of shares to be included in each such series, and to fix the designation, powers, preferences and rights of the shares of each series and any qualifications, limitations or restrictions thereof, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

14.

Table of Contents

We will fix the designations, voting powers, preferences and rights of the preferred stock of each series, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the Commission, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. This description will include:

the title and stated value;

the number of shares offered;

the liquidation preference per share;

the purchase price per share;

the dividend rate(s), period(s) and/or payment date(s) or method(s) of calculation for dividends;

whether dividends are cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;

our right, if any, to defer payment of dividends and the maximum length of any such deferral period;

the procedures for any auction and remarketing, if any;

the provisions for a sinking fund, if any;

the provision for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;

any listing of the preferred stock on any securities exchange or market;

the terms and conditions, if applicable, upon which the preferred stock will be convertible into common stock, including the conversion price (or manner of calculation) and conversion period;

whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;

voting rights, if any, of the preferred stock;

preemptive rights, if any;

restrictions on transfer, sale or other assignment, if any;

whether interests in the preferred stock will be represented by depositary shares;

a discussion of any material and/or special U.S. federal income tax considerations applicable to the preferred stock;

the relative ranking and preferences of the preferred stock as to dividend rights and rights upon the liquidation, dissolution or winding up of our affairs;

any limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the class or series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs; and

any other specific terms, preferences, rights, limitations or restrictions of the preferred stock.

Our board of directors could authorize the issuance of shares of preferred stock with terms and conditions that could have the effect of discouraging a takeover or other transaction that might involve a premium price for holders of the shares or which holders might believe to be in their best interests. The issuance of preferred stock could adversely affect the voting power, conversion or other rights of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation.

Table of Contents

The laws of the state of Delaware, the state of our incorporation, provide that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of such preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The transfer agent and registrar for any series of preferred stock will be set forth in the applicable prospectus supplement.

Table of Contents

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as discount securities, which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with original issue discount, or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

the title of the series of debt securities;

any limit upon the aggregate principal amount that may be issued;

the maturity date or dates;

the form of the debt securities of the series;

the applicability of any guarantees;

whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

17.

Table of Contents

if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;

the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;

our right, if any, to defer payment of interest and the maximum length of any such deferral period;

if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;

the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;

the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;

any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;

whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities; and the depositary for such global security or securities;

if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;

if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;

additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;

additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;

additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;

additions to or changes in the provisions relating to satisfaction and discharge of the indenture;

additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;

the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;

Table of Contents

whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;

the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a United States person for federal tax purposes;

any restrictions on transfer, sale or assignment of the debt securities of the series; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than a subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;

if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any

indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;

if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and

if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate

Table of Contents

principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

the direction so given by the holder is not in conflict with any law or the applicable indenture; and

subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

the holder has given written notice to the trustee of a continuing event of default with respect to that series;

the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request,

such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and

the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;

to comply with the provisions described above under Description of Debt Securities Consolidation, Merger or Sale;

20.

Table of Contents

to provide for uncertificated debt securities in addition to or in place of certificated debt securities;

to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;

to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;

to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;

to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under Description of Debt Securities General to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;

to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or

to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

extending the fixed maturity of any debt securities of any series;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or

reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

provide for payment;

register the transfer or exchange of debt securities of the series;

replace stolen, lost or mutilated debt securities of the series;

pay principal of and premium and interest on any debt securities of the series;

maintain paying agencies;

hold monies for payment in trust;

recover excess money held by the trustee;

compensate and indemnify the trustee; and

appoint any successor trustee.

21.

Table of Contents

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depository named by us and identified in the applicable prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating to any book-entry securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or

register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an

indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

22.

Table of Contents

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the internal laws of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

Table of Contents

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements and in any related free writing prospectuses that we may authorize to be distributed to you, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may consist of warrants to purchase common stock, preferred stock or debt securities and be issued in one or more series. Warrants may be offered independently or in combination with common stock, preferred stock or debt securities offered by any prospectus supplement. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. The following description of warrants will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms.

We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that describe the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants. The following summaries of material terms and provisions of the warrants are subject to, and qualified in their entirety by reference to, all the provisions of the form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements applicable to a particular series of warrants that we may offer under this prospectus. We urge you to read the applicable prospectus supplement related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectuses, and the complete form of warrant and/or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements, that contain the terms of the warrants.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants being offered, including:

the offering price and aggregate number of warrants offered;

the currency for which the warrants may be purchased;

if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;

in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;

in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;

the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;

the terms of any rights to redeem or call the warrants;

any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;

the dates on which the right to exercise the warrants will commence and expire;

the manner in which the warrant agreements and warrants may be modified;

Table of Contents

a discussion of any material or special U.S. federal income tax considerations of holding or exercising the warrants;

the terms of the securities issuable upon exercise of the warrants; and

any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or

in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. The warrants may be exercised as set forth in the prospectus supplement relating to the warrants offered. Unless we otherwise specify in the applicable prospectus supplement, warrants may be exercised at any time up to the close of business on the expiration date set forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void.

Upon receipt of payment and the warrant or warrant certificate, as applicable, properly completed and duly executed at the corporate trust office of the warrant agent, if any, or any other office, including ours, indicated in the prospectus supplement, we will, as soon as practicable, issue and deliver the securities purchasable upon such exercise. If less than all of the warrants (or the warrants represented by such warrant certificate) are exercised, a new warrant or a new warrant certificate, as applicable, will be issued for the remaining warrants.

Governing Law

Unless we otherwise specify in the applicable prospectus supplement, the warrants and any warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent, if any, will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to

exercise, and receive the securities purchasable upon exercise of, its warrants.

25.

Table of Contents

**CERTAIN PROVISIONS OF DELAWARE LAW,
THE CERTIFICATE OF INCORPORATION AND BYLAWS**

Limitations on Directors' Liability

Our amended and restated certificate of incorporation and our bylaws contain provisions indemnifying our directors and officers to the fullest extent permitted by law. In addition, as permitted by Delaware law, our amended and restated certificate of incorporation provides that no director will be liable to us or our stockholders for monetary damages for breach of certain fiduciary duties as a director. The effect of this provision is to restrict our rights and the rights of our stockholders in derivative suits to recover monetary damages against a director for breach of certain fiduciary duties as a director, except that a director will be personally liable for:

the benefits to be derived from relationships with our collaborators;

any breach of his or her duty of loyalty to the registrant or its stockholders;

acts or omissions not in good faith which involve intentional misconduct or a knowing violation of law;

the payment of dividends or the redemption or purchase of stock in violation of Delaware law; or

any transaction from which the director derived an improper personal benefit.

This provision does not affect a director's liability under the federal securities laws.

To the extent that our directors, officers and controlling persons are indemnified under the provisions contained in our amended and restated certificate of incorporation, Delaware law or contractual arrangements against liabilities arising under the Securities Act, we have been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act, and is therefore unenforceable.

Provisions that May Have an Anti-Takeover Effect

Certain provisions set forth in our amended and restated certificate of incorporation, bylaws and in Delaware law, which are summarized below, are intended to enhance the likelihood of continuity and stability in the composition of our board of directors and in the policies formulated by our board of directors and to discourage certain types of transactions that may involve an actual or threatened change of control. In that regard, these provisions are designed to reduce our vulnerability to an unsolicited acquisition proposal. The provisions also are intended to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they also may inhibit fluctuations in the market price of our common stock that could result from actual or rumored takeover attempts. Such provisions also may have the effect of preventing changes in our management.

Blank Check Preferred Stock. Our amended and restated certificate of incorporation contains provisions that permit our board of directors to issue, without any further vote or action by the stockholders, up to 30,000,000 shares of preferred stock in one or more series and, with respect to each such series, to fix the number of shares constituting the series and the designation of the series, the voting powers (if any) of the shares of the series, and the preferences and relative, participating, optional and other special rights, if any, and any qualifications, limitations or restrictions, of the shares of such series. As a result, our board of directors could authorize the issuance of shares of preferred stock with terms and conditions that could have the effect of delaying, deferring or preventing a transaction or a change in control that might involve a premium price for holders of the registrant's common stock or otherwise be in their best interest.

Special Meetings of Stockholders. Our bylaws provide that special meetings of stockholders may be called only by the board of directors. Stockholders are not permitted to call a special meeting of stockholders or to require that the board of directors call such a special meeting.

Table of Contents

Delaware Takeover Statute.

We are subject to Section 203 of the Delaware General Corporation Law, or DGCL, which regulates acquisitions of some Delaware corporations. In general, Section 203 prohibits, with some exceptions, a Delaware corporation that is a public company from engaging in any business combination with any interested stockholder for a period of three years following the date that such stockholder became an interested stockholder, unless:

prior to such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

on consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding those shares owned (x) by persons who are directors and also officers and (y) by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 of the DGCL defines business combination to include:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested shareholder as an entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with such entity or person.

27.

Table of Contents

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the times of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;

any options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;

any public offering price;

any discounts or concessions allowed or reallowed or paid to dealers; and

any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any option to purchase additional securities. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

Table of Contents

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, either through exercise of the option to purchase additional securities or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Table of Contents

LEGAL MATTERS

The validity of the securities offered hereby will be passed upon by Cooley LLP, Boston, Massachusetts.

EXPERTS

The financial statements and the effectiveness of internal control over financial reporting incorporated in this Prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2013 and for the period from September 9, 2003 (date of inception) through December 31, 2013, have been audited by McGladrey LLP, an independent registered public accounting firm, as stated in their report incorporated by reference herein and have been so incorporated in reliance upon such reports and upon the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the Commission. You may read and copy these reports, proxy statements and other information at the Commission's public reference room at 100 F Street, N.E., Washington, D.C. 20549 or at the Commission's other public reference facilities. Please call the Commission at 1-800-SEC-0330 for more information about the operation of the public reference rooms. You can request copies of these documents by writing to the Commission and paying a fee for the copying costs. In addition, the Commission maintains an Internet site at <http://www.sec.gov> that contains reports, proxy and information statements and other information regarding issuers that file electronically with the Commission. Our Commission filings are available on the Commission's Internet site. We maintain a website at <http://www.ziopharm.com>. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement.

Table of Contents

INCORPORATION OF INFORMATION BY REFERENCE

We are allowed to incorporate by reference information contained in documents that we file with the Commission. This means that we can disclose important information to you by referring you to those documents and that the information in this prospectus is not complete and you should read the information incorporated by reference for more detail. Information in this prospectus supersedes information incorporated by reference that we filed with the Commission prior to the date of this prospectus, while information that we file later with the Commission will automatically update and supersede the information in this prospectus.

We incorporate by reference the documents listed below and any future filings we will make with the Commission under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (i) after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of such registration statement, and (ii) from the date of this prospectus but prior to the termination of the offering of the securities covered by this prospectus (other than Current Reports or portions thereof furnished under Item 2.02 or 7.01 of Form 8-K):

Annual Report on Form 10-K for the fiscal year ended December 31, 2013, filed on March 3, 2014;

The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2013 from our Definitive Proxy Statement on Schedule 14A, filed on April 30, 2014;

Quarterly Reports on Form 10-Q for the quarters ended March 31, 2014, June 30, 2014, and September 30, 2014, filed on May 8, 2014, August 7, 2014, and October 30, 2014, respectively;

Current Reports on Form 8-K filed on January 8, 2014, January 15, 2014, February 10, 2014, March 3, 2014 (excluding Item 2.02), March 28, 2014, April 8, 2014, May 8, 2014 (excluding Item 2.02), May 22, 2014 (excluding Item 7.01), June 19, 2014, July 31, 2014, August 7, 2014 (excluding Item 2.02), September 16, 2014, October 30, 2014 (excluding Item 2.02), December 3, 2014 (excluding Item 7.01), January 14, 2015, second filing on January 14, 2015 (excluding Item 7.01), and January 28, 2015; and

The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the Commission on September 20, 2006, including any amendments or reports filed for purposes of updating such description. We will provide to each person, including any beneficial owner, to whom a prospectus is delivered a copy of any or all of the documents that are incorporated by reference in this prospectus but not delivered with this prospectus, including exhibits that are specifically incorporated by reference in such documents. You may request a copy of such documents at no cost, by writing or telephoning us at the following address or telephone number:

ZIOPHARM Oncology, Inc.

One First Avenue, Parris Building 34, Navy Yard Plaza

Edgar Filing: ZIOPHARM ONCOLOGY INC - Form 424B7

Boston, Massachusetts 02129

Attention: Chief Legal Officer

(617) 259-1970

31.

Table of Contents

11,722,163 Shares

Common Stock

ZIOPHARM Oncology, Inc.

PROSPECTUS SUPPLEMENT

April 1, 2015