ZIOPHARM ONCOLOGY INC
Form 424B5
February 04, 2015
Table of Contents

Filed pursuant to Rule 424(b)(5)

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	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee[2]
Common stock, par value $0.001 per share	11,500,000	$8.75	$100,625,000	$11,692.63

(1) Includes shares of common stock that may be purchased by the underwriters pursuant to their option to purchase additional shares of common stock.

(2) 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)

10,000,000 Shares

Common stock

We are offering 10,000,000 shares of our common stock.

Shares of our common stock trade on the NASDAQ Capital Market under the symbol ZIOP. The last reported sale price on February 2, 2015 was $8.95 per share.

	Per share	Total
Public offering price	$ 8.750	$ 87,500,000
Underwriting discounts and commissions	$ 0.525	$ 5,250,000
Proceeds, before expenses, to us	$ 8.225	$ 82,250,000

We have granted the underwriters an option for a period of up to 30 days from the date of this prospectus supplement to purchase up to 1,500,000 additional shares of common stock at the public offering price less the underwriting discounts and commissions.

INVESTING IN OUR COMMON STOCK INVOLVES RISK. SEE RISK FACTORS BEGINNING ON PAGE S-14.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

Intrexon Corporation, or Intrexon, which is affiliated with Randal J. Kirk, who serves as one of our directors, has agreed to purchase 1,440,000 shares of our common stock in this offering at the public offering price. The underwriters will receive the same discount from the sale of these shares of our common stock as they will from the sale of shares of our common stock to the public in this offering.

The underwriters expect to deliver the shares on or about February 9, 2015.

Book-running manager

J.P. Morgan

Senior lead manager

BMO Capital Markets

Co-managers

Griffin Securities **Maxim Group** **Mizuho Securities**

February 3, 2015

Table of Contents

This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

Table of contents

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 underwriters have 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.

We are offering to sell, and seeking 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

Table of Contents

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.

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. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the information referred to under the heading Risk factors in this prospectus supplement beginning on page S-14 the information incorporated by reference in this prospectus supplement and the accompanying prospectus, and the information included in any free writing prospectus that we have authorized for use in connection with this offering.

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.

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.

Table of Contents

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, 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.

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.

Table of Contents

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 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

Table of Contents

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 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.

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 ab 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 a or b 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:

Table of Contents

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 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 isophosphoramide 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.

Table of Contents

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 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 this 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.

Table of Contents

Risk factors

An investment in our common stock is subject to a number of risks and uncertainties. Before investing in our common stock, you should carefully consider the following, as well as the more detailed discussion of risk factors and other information included in this prospectus supplement.

Our plans to develop and commercialize, pursuant to the MD Anderson License with MD Anderson and Intrexon and our Channel Agreement with Intrexon, non-viral adoptive cellular therapies based on designer cytokines and novel CAR-T cell therapies are new approaches to cancer treatment that present significant challenges in a competitive landscape.

We will require additional financial resources in order to continue on-going development of our product candidates; if we are unable to obtain these additional resources, we may be forced to delay or discontinue clinical testing of our product candidates.

We need to raise additional capital to fund our operations. The manner in which we raise any additional funds may affect the value of your investment in our common stock.

Clinical trials are very expensive, time-consuming, and difficult to design and implement, and may not support our product candidate claims.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following any potential marketing approval.

We may not be able to obtain the necessary U.S. or worldwide regulatory approvals, commercialize any products, generate significant revenues, or attain profitability.

The technology underlying our Channel Arrangement with Intrexon is based in part on early stage technology in the field of human oncologic therapeutics, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval.

Currently, no gene therapy products have been approved in the United States and only one product has been approved in Europe.

Our use of synthetic biology to develop product candidates may become subject to increasing regulation, or may be limited by ethical, legal and social concerns about synthetic biologically engineered products.

Because we currently neither have nor intend to establish internal research capabilities, we are dependent upon pharmaceutical and biotechnology companies and academic and other researchers to sell or license us their product candidates and technology.

We are dependent on third parties for clinical testing, research and development activities and the formulation and manufacture of our product candidates, which exposes us to risks that may delay the development, regulatory approval and commercialization of our products or result in higher product costs.

If we or our licensors fail to adequately protect or enforce our intellectual property rights or secure rights to patents of others, the value of our intellectual property rights would diminish and our ability to successfully commercialize our products may be impaired.

We have a limited operating history upon which to base an investment decision.

Table of Contents

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 supplement or the accompanying prospectus, and you should not consider it part of this prospectus supplement or part of the accompanying prospectus.

Table of Contents

The offering

Common stock offered by us in this offering	10,000,000 of shares of our Common Stock
Option to purchase additional shares	We have granted the underwriters an option for a period of up to 30 days from the date of this prospectus supplement to purchase up to 1,500,000 of additional shares of common stock at the public offering price less the underwriting discounts and commissions.
Common stock to be outstanding immediately after this offering	112,683,984 shares (or 114,183,984 shares if the underwriters exercise in full their option to purchase additional shares)
Use of proceeds	We intend to use the net proceeds from this offering for general corporate and working capital purposes, including clinical development of our pipeline and development of the technologies licensed from MD Anderson. See Use of Proceeds.
Risk factors	See Risk factors beginning on page S-14 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 102,683,984 shares of common stock outstanding as of September 30, 2014 and excludes:

- 5,792,428 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2014, having a weighted average exercise price of $3.94 per share;
- 5,555,864 shares of our common stock available as of September 30, 2014 for future issuance pursuant to our 2012 Equity Incentive Plan;
- 1,755,845 shares of our common stock issued upon the exercise of warrants since September 30, 2014; and
- 11,722,163 shares of our common stock to be issued to MD Anderson within sixty days of the execution of the MD Anderson License, pursuant to the terms of the MD Anderson License, a letter agreement that we and Intrexon entered into with MD Anderson on January 9, 2015, or the Letter Agreement, and the securities issuance agreements and registration rights agreement entered into in connection therewith, which we collectively refer to as the MD Anderson Equity Agreements.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares.

Table of Contents

Participation of Certain Stockholders

Intrexon Corporation, or Intrexon, which is affiliated with Randal J. Kirk, who serves as one of our directors, has agreed to purchase 1,440,000 shares of our common stock in this offering at the public offering price. The underwriters will receive the same discount from the sale of these shares of our common stock as they will from the sale of shares of our common stock to the public in this offering.

Table of Contents

Risk factors

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks described below and discussed under the section captioned Risk Factors contained in our Quarterly Report on Form 10-Q for the period ended September 30, 2014, which is incorporated by reference in this prospectus supplement and the accompanying prospectus, in its entirety, together with other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference, and in any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. The risks described below and in the documents referenced above are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business.

Risks related to our business

Our plans to develop and commercialize, through the MD Anderson License with MD Anderson and Intrexon and our Channel Agreement with Intrexon, nonviral adoptive cellular therapies based on designer cytokines and novel chimeric antigen receptor (CAR) T-cell therapies are new approaches to cancer treatment that present significant challenges in a competitive landscape and the success of our efforts depends in large part on our owned and licensed intellectual property, and our efforts may be affected by litigation and developments in intellectual property law outside of our control.

We intend to employ technologies licensed from MD Anderson pursuant to the MD Anderson License described above in *Summary Recent developments*, and from Intrexon, pursuant to our existing Channel Agreement with Intrexon, to pursue the development and commercialization of nonviral adoptive cellular therapies based on cytokines and CARs under control of the RTS® technology targeting both hematologic and solid tumor malignancies. Because this is a new approach to cancer immunotherapy and cancer treatment generally, developing and commercializing product candidates subjects us to a number of challenges, including:

- obtaining regulatory approval from the FDA and other regulatory authorities that have very limited experience with the commercial development of genetically modified T-cell therapies for cancer;
- developing and deploying consistent and reliable processes for engineering a patient s T-cells ex vivo and infusing the engineered T-cells back into the patient;
- possibly conditioning patients with chemotherapy in conjunction with delivering each of the potential products, which may increase the risk of adverse side effects of the potential products;
- educating medical personnel regarding the potential side effect profile of each of the potential products, such as the potential adverse side effects related to cytokine release;
- developing processes for the safe administration of these potential products, including long-term follow-up for all patients who receive the potential products;
- sourcing additional clinical and, if approved, commercial supplies for the materials used to manufacture and process the potential products;
- developing a manufacturing process and distribution network with a cost of goods that allows for an attractive return on investment;

establishing sales and marketing capabilities after obtaining any regulatory approval to gain market acceptance;

Table of Contents

developing therapies for types of cancers beyond those addressed by the current potential products; and

not infringing the intellectual property rights, in particular, the patent rights, of third parties, including competitors developing alternative CAR-T cell therapies.

We cannot be sure that T-cell immunotherapy technologies that we intend to develop in partnership with MD Anderson and Intrexon will yield satisfactory products that are safe and effective, scalable, or profitable. Moreover, public perception of therapy safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical trials, or if approved, of physicians to subscribe to the novel treatment mechanics. Physicians, hospitals and third-party payors often are slow to adopt new products, technologies and treatment practices that require additional upfront costs and training. Physicians may not be willing to undergo training to adopt this novel and personalized therapy, may decide the therapy is too complex to adopt without appropriate training and may choose not to administer the therapy. Based on these and other factors, hospitals and payors may decide that the benefits of this new therapy do not or will not outweigh its costs.

Our CAR-T product candidates are supported by limited clinical data, all of which has been generated through trials conducted by MD Anderson, not by us. We plan to assume control of the overall clinical and regulatory development of our CAR-T product candidates, and any failure to obtain, or delays in obtaining, sponsorship of investigational new drug applications, or INDs, or in filing new INDs sponsored by us for these or any other product candidates we determine to advance could negatively affect the timing of our potential future clinical trials. Such an impact on timing could increase researc