ZIOPHARM ONCOLOGY INC
Form 424B5
May 26, 2010

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MAY 26, 2010

Prospectus Supplement
(To Prospectus dated May 10, 2010)

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-166444

Shares

Common Stock

We are offering shares of our common stock. Our common stock is listed on The NASDAQ Capital Market under the symbol ZIOP. On May 25, 2010, the last reported sale price of our common stock on The NASDAQ Capital Market was $5.58 per share.

Investing in our common stock involves a high degree of risk. Please read Risk Factors beginning on page S-6 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement.

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

	PER SHARE	TOTAL
Public Offering Price	$	$
Underwriting Discounts and Commissions	$	$
Proceeds to ZIOPHARM (Before Expenses)	$	$

Delivery of the shares of common stock is expected to be made on or about , 2010. We have granted the underwriters an option for a period of 30 days to purchase up to an additional shares of our common stock solely to cover over allotments. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $, and the total proceeds to us, before expenses, will be $.

Sole Book-Running Manager

Jefferies & Company

Co-Manager

JMP Securities

Prospectus Supplement dated , 2010

TABLE OF CONTENTS

ZIOPHARM ONCOLOGY INC.

TABLE OF CONTENTS

Prospectus Supplement

Prospectus

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the underwriters have not, authorized anyone to provide you with different information. If

anyone provides you with different or inconsistent information, you should not rely on it. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus supplement entitled Where You Can Find More Information and Information Incorporated by Reference.

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated May 10, 2010, including the documents incorporated by reference therein, provides more general information. 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, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. 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.

All references in this prospectus supplement and the accompanying prospectus to ZIOPHARM Oncology, ZIOPHARM, the Company, we, us, our, or similar references refer to ZIOPHARM Oncology, Inc., except whe context otherwise requires or as otherwise indicated.

This prospectus supplement, the accompanying prospectus, and the information incorporated herein and therein by reference, include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement or the accompanying prospectus are the property of their respective owners.

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 into 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 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, including the information referred to under the heading Risk Factors in this prospectus supplement beginning on page S-6.

Company Overview

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that is seeking to develop and commercialize a diverse, risk-sensitive portfolio of in-licensed cancer drugs that can address unmet medical needs through enhanced efficacy and/or safety and quality of life. Our principal focus is on the licensing and development of proprietary small molecule drug candidates that are related to cancer therapeutics already on the market or in development and that can be administered by intravenous and/or oral capsule dosing. We believe this strategy will result in lower risk and expedited drug development programs with product candidates having a low cost of manufacturing to address changing reimbursement requirements around the world. While we may endeavor to commercialize our products on our own in North America, we recognize that favorable clinical trial results can be better addressed by partnering with companies with the requisite financial resources. With partnering, we could also negotiate the right to complete development and marketing in certain geographies, especially for certain limited (niche) indications. Although we are currently in phase I and/or II studies for three product candidates identified as darinaparsin (Zinapar™, ZIO-101), palifosfamide (Zymafos™, ZIO-201), and indibulin (Zybulin™, ZIO-301), our primary focus has been and remains on palifosfamide development and more specifically on completing the ongoing randomized phase II trial with palifosfamide to support a registration trial for palifosfamide in combination with doxorubicin in the front- and second-line setting of soft tissue sarcoma. We anticipate the initiation of such a registration trial as early as the first half of 2010.

ZIO-101 or darinaparsin (Zinapar™) is an anti-mitochondrial (organic arsenic) compound. Issued patents and pending patent applications covering proprietary forms of darinaparsin for pharmaceutical compositions and methods of use have been filed in the U.S. and in foreign countries. A form of commercially available inorganic arsenic (arsenic trioxide [Trisenox®] or ATO) has been approved in the United States and the European Union and Japan for the treatment of acute promyelocytic leukemia, a precancerous condition. In the United States, ATO is on the compendia listing for the therapy of multiple myeloma, and has been studied for the treatment of various other cancers. Nevertheless, ATO has been shown to be toxic to the heart, liver, and brain, which limits its use as an anti-cancer agent. ATO carries a black box warning for ECG abnormalities since arsenic trioxide has been shown to cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. Inorganic arsenic has also been shown to cause cancer of the skin and lung in humans. The toxicity of arsenic is generally correlated to its accumulation in organs and tissues. Our preclinical and clinical studies to date have demonstrated that darinaparsin is considerably less toxic than ATO, particularly with regard to cardiac toxicity. In vitro testing of darinaparsin using the National Cancer Institute s human cancer cell panel demonstrated activity against a series of tumor cell lines including lung, colon, brain, melanoma, ovarian, and kidney cancer. Moderate activity was shown against breast and prostate cancer tumor cell

TABLE OF CONTENTS

lines. In addition to solid tumors, in vitro testing in both the National Cancer Institute s cancer cell panel and in vivo testing in a leukemia animal model demonstrated substantial activity against hematological cancers (cancers of the blood and blood-forming tissues) such as leukemia, lymphoma, myelodysplastic syndromes, and multiple myeloma. Results indicate significant activity against the HuT 78 cutaneous T-cell lymphoma, the NK-G2MI natural killer-cell NHL, KARPAS-299 T-cell NHL, SU-DHL-8 B-cell NHL, SU-DHL-10 B-cell NHL and SU-DHL-16 B-cell NHL cell lines. Preclinical studies have also established anti-angiogenic properties of darinaparsin and provided support for the development of an oral capsule form of the drug, and established synergy of darinaparsin in combination with other approved anti-cancer agents.

Phase I testing of the intravenous (IV) form of darinaparsin in solid tumors and hematological cancers has been completed. We reported clinical activity and, importantly, a safety profile from these studies as predicted by preclinical results. We subsequently completed Phase II studies in advanced myeloma and primary liver cancer and are nearing completion of a Phase II study in certain other hematological cancers. In addition, we are completing two Phase I studies with an oral capsule form of darinaparsin. At the May 2009 annual meeting of the American Society of Clinical Oncology, or ASCO, we reported favorable results from the trial with IV-administered darinaparsin in lymphoma, particularly peripheral T-cell lymphoma. In the ongoing Phase I trials, also reported at the ASCO annual meeting, preliminary data primarily in solid tumors indicate the oral form is active and well tolerated. We are completing data collection from the IV Phase II trial to address a registration and other trials with the United States Food and Drug Administration. The oral Phase I program will be progressed to establish a dose for further clinical testing.

ZIO-201 or palifosfamide (Zymafos™), comprises the active metabolite of ifosfamide, a compound chemically related to cyclophosphamide. Patent applications covering proprietary forms of palifosfamide for pharmaceutical composition and method of use have been filed in the United States and internationally and in the United States we recently received a patent covering pharmaceutical composition. Like cyclophosphamide, ifosfamide and bendamustine, palifosfamide is a DNA alkylating agent, a form of cancer therapy to treat a wide range of solid tumors and hematological malignancies. We believe that cyclophosphamide is the most widely used alkylating agent in cancer therapy, with significant use in the treatment of breast cancer and non-Hodgkin s lymphoma. Bendamustine has been recently approved and successfully launched by Cephalon Oncology in the United States and Europe to treat certain hematological malignancies. Ifosfamide has been shown to be effective in the treatment of sarcoma and lymphoma, either by itself or in combination with other anti-cancer agents. Ifosfamide is approved by the FDA as a treatment for testicular cancer while ifosfamide-based treatment is a standard of care for sarcoma, although it is not licensed for this indication by the FDA. Preclinical studies have shown that palifosfamide has activity against leukemia and solid tumors. These studies also indicate that palifosfamide may have a better safety profile than ifosfamide or cyclophosphamide because it does not appear to produce known toxic metabolites of ifosfamide, such as acrolein and chloroacetaldehyde. Acrolein, which is toxic to the kidneys and bladder, can mandate the administration of a protective agent called mesna, which is inconvenient and expensive. Chloroacetaldehyde is toxic to the central nervous system, causing fuzzy brain syndrome for which there is currently no protective measure. Similar toxicity concerns pertain to high-dose cyclophosphamide, which is widely used in bone marrow and blood cell transplantation. Palifosfamide has evidenced preclinical activity against ifosfamide- and/or cyclophosphamide-resistant cancer cell lines. Also in preclinical cancer models, palifosfamide was shown to be orally active and encouraging results have been obtained with palifosfamide in combination with doxorubicin, an agent approved to treat sarcoma.

TABLE OF CONTENTS

Following completion of Phase I study, we completed Phase II testing of the intravenous form of palifosfamide as a single agent to treat advanced sarcoma. In both Phase I and Phase II testing, palifosfamide has been administered without the uroprotectant mesna, and the toxicities associated with acrolein and chloroacetaldehyde have not been observed. We reported clinical activity of palifosfamide when used alone in the Phase II study addressing advanced sarcoma. Following review of preclinical combination studies, clinical data, and discussion with sarcoma experts, we initiated a Phase I dose escalation study of palifosfamide in combination with doxorubicin primarily in patients with soft tissue sarcoma. We reported favorable results and a favorable safety profile from this study at the ASCO 2009 annual meeting. In light of reported favorable Phase II clinical activity data and with the combination of palifosfamide with doxorubicin well-tolerated and evidencing activity in the Phase I trial, we initiated a Phase II randomized controlled trial in the second half of 2008 to compare doxorubicin plus palifosfamide to doxorubicin alone in patients with front and second-line metastatic or unresectable soft tissue sarcoma, or the PICASSO study. The PICASSO study generated positive top line interim data in 2009. Upon reaching a pre-specified efficacy milestone and following safety and efficacy data review by the Data Committee, sarcoma experts, and our Medical Advisory Board, we elected to suspend enrollment in the trial in October 2009. Subsequently, we presented positive interim data from the trial at the 15th Annual Connective Tissue Oncology Society meeting held in November 2009 and have disclosed further interim data in connection with the release of a PICASSO trial study abstract that will be presented at the ASCO 2010 annual meeting in June 2010. We currently plan to initiate a registration trial following regulatory review of the palifosfamide program to date. We are also developing an oral capsule form of palifosfamide to be studied clinically following receipt of further data from the IV trials and subject to obtaining sufficient additional sources of funding, either from potential partnering arrangements or from other sources. To date we have no such partnering arrangements or other sources of such financing in place. We are also considering additional Phase II trials in other solid tumors as funding becomes available. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of soft tissue sarcomas.

ZIO-301 or indibulin (Zybulin™), is a novel, orally available small molecular-weight inhibitor of tubulin polymerization that we acquired from Baxter Healthcare Corporation in 2006 and is the subject of numerous patents worldwide, including the United States, Europe and Japan. The microtubule component, tubulin, is one of the more well established drug targets in cancer. Microtubule inhibitors interfere with the dynamics of tubulin polymerization, resulting in inhibition of chromosome segregation during mitosis and consequently inhibition of cell division. A number of marketed IV anti-cancer drugs target tubulin, such as the taxane family members, paclitaxel (Taxol®), docetaxel (Taxotere®), the Vinca alkaloid family members, vincristine and vinorelbine, and the new class of epothilones with Ixempra® marketed. This class of agents is typically the mainstay of therapy in a wide variety of indications. In spite of their effectiveness, the use of these drugs is associated with significant toxicities, notably peripheral neurotoxicity.

Preclinical studies with indibulin demonstrate significant and broad antitumor activity, including activity against taxane-refractory cell lines. The cytotoxic activity of indibulin was demonstrated in several rodent and human tumor cell lines derived from prostate, brain, breast, pancreas, lung, ovary and cervical tumor tissues and in rodent tumor and human tumor xenograft models. In addition, indibulin was effective against multidrug resistant tumor cell lines (breast, lung and leukemia) both in vitro and in vivo. Indibulin is potentially safer than other tubulin inhibitors. No neurotoxicity has

TABLE OF CONTENTS

been observed at therapeutic doses in rodents and in the Phase I trials. Indibulin has also demonstrated synergy with approved anti-cancer agents in preclinical studies. The availability of an oral capsule formulation of indibulin creates significant commercial opportunity because no oral capsule formulations of the taxane family are currently on the market in the United States.

Indibulin, as a single agent, has completed Phase I trials in patients with advanced solid tumors. We have reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging results obtained with indibulin in combination with erlotinib, and 5-FU in preclinical models, two Phase I combination studies were initiated with Tarceva® and Xeloda®, respectively. Favorable activity and safety profile of oral indibulin with oral Xeloda® were reported at ASCO s annual meeting in May 2009. Preclinical work with our consultant, Dr. Larry Norton, to explore dose scheduling for the clinical setting has been completed, with results supporting the recently initiated Phase I safety trial necessary for a Phase I/II breast cancer trial and using the mathematical dose schedule/frequency established preclinically.

We intend to continue with clinical development of IV palifosfamide for soft tissue sarcoma by both completing the ongoing PICASSO trial and in a planned registration trial. Depending on the availability of additional resources, we intend to initiate a clinical study with the oral form and/or in additional indications beyond soft tissue sarcoma. For darinaparsin, we will complete the ongoing Phase I oral trial and will address peripheral T-cell lymphoma, or PTCL, registration and other trials for the IV formulation, in part dependent on additional funding. For oral indibulin, we will complete the Phase I breast cancer safety trial and initiate the subsequent Phase I/II trial and, with additional funding, other trials. However, the successful development of our product candidates is highly uncertain. Product development costs and timelines can vary significantly for each product candidate, are difficult to accurately predict, and will require us to obtain additional funding, either alone or in connection with partnering arrangements. Various statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of each product. The lengthy process of seeking approval and the subsequent compliance with applicable statutes and regulations require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could materially, adversely affect our business. To date, we have not received approval for the sale of any drug candidates in any market and, therefore, have not generated any revenues from our drug candidates.

Corporate Information

We were 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 were 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. 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 SEC and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our executive offices are located at 1180 Avenue of the Americas, 19th Floor, New York, NY 10036, and our telephone number is (646) 214-0700. Our internet site is *www.ziopharm.com.* None of the information on our internet site is part of this prospectus.

TABLE OF CONTENTS

The Offering

Common stock offered by us

shares

Common stock to be outstanding immediately after this offering

shares

Use of Proceeds

We intend to use the net proceeds from this public offering for the overall development of our drug candidates, including to further expand the clinical trial programs, and for general corporate and working capital purposes. See Use of Proceeds on page S-9 of this prospectus supplement.

Risk Factors

You should carefully read and consider the information set forth under Risk Factors on page S-6 of this prospectus supplement, together with all of the other information set forth or incorporated by reference in this prospectus supplement and the accompanying prospectus, before deciding to invest in our common stock.

NASDAQ Capital Market Listing

Our common stock is listed on The NASDAQ Capital Market under the symbol ZIOP.

Outstanding Shares

The number of shares of our common stock to be outstanding immediately after this offering is based on 41,836,655 shares of common stock outstanding as of May 25, 2010 and excludes:

3,527,685 shares of our common stock issuable upon the exercise of stock options outstanding as of May 25, 2010, having a weighted average exercise price of $2.94 per share;
3,145,484 shares of our common stock available as of May 25, 2010 for future issuance pursuant to our 2003 Stock Option Plan, and 3,000,000 additional shares of our common stock that will be reserved for issuance pursuant to our 2003 Stock Option Plan if a proposed amendment to our 2003 Stock Option Plan is approved by our stockholders at our annual stockholders meeting schedule for June 23, 2010; and
15,931,642 shares of our common stock issuable upon the exercise of outstanding warrants as of May 25, 2010 with a weighted-average exercise price of $4.11 per share.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their over allotment option.

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 March 31, 2010, 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 this Offering

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the price of our common stock to decline.

You will experience immediate and substantial dilution in the net tangible book value per share of the common stock you purchase.

Since the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on the public offering price of $ per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and based on a net tangible book value of our common stock of $0.27 per share as of March 31, 2010, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of $ per share in the net tangible book value of the common stock. See the section entitled Dilution below for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

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

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per

share in this offering. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders, including investors who purchase shares of common stock in this offering. The price per share at which we sell additional shares of our common stock or securities convertible into common stock in future transactions may be higher or lower than the price per share in this offering.

You will not be able to vote the shares of our common stock on matters to be brought before our 2010 annual stockholders meeting.

Our 2010 annual stockholders meeting is scheduled to take place on June 23, 2010. As set forth in the proxy statement for our annual meeting filed with the SEC on April 30, 2010, the meeting has been called for the purpose of considering and taking appropriate action with respect to (i) the election eight directors, (ii) the approval of an amendment to our 2003 Stock Option Plan to increase the number of shares of common stock reserved for issuance thereunder from 6,002,436 shares to 9,002,436 shares, (iii) the ratification of the appointment of Caturano and Company, P.C. as our independent registered public

TABLE OF CONTENTS

accounting firm for fiscal 2010, and (iv) the transaction of any other business as may properly come before the meeting or any adjournments thereof. The record date for the meeting has been established as May 10, 2010. Because only holders of record of our common stock at the close of business on that record date were entitled to notice of and are entitled to vote at the annual meeting, you will not be able to vote the shares of our common stock that you purchase in this offering for the proposals brought before such meeting.

You will not be able to vote the shares of our common stock onmatters to be brought before our 2010 annual stockh

TABLE OF CONTENTS

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus contain, the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering 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. These statements relate to future events or to our future operating or 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; and
our estimates regarding our capital requirements, our ability to control our costs and our need for additional funding.

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 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 beginning on page S-6 of this prospectus supplement and in our SEC filings. 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 supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated by reference and any 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.

You should rely only on the information contained, or incorporated by reference, in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering. We and the underwriters for this offering have not authorized anyone to provide you with different information. The common stock offered under this prospectus is not being

TABLE OF CONTENTS

offered in any state where the offer is not permitted. You should not assume that the information contained in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the date on the front of this prospectus supplement or the accompanying prospectus, as applicable, or that any information incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the date of the document so incorporated by reference. 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.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of the shares of common stock that we are offering will be approximately $ million, or approximately $ million if the underwriters exercise in full their option to purchase an additional shares of common stock, based on the public offering price of $ per share and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this public offering for the overall development of our drug candidates, including to further expand the clinical trial programs, and for general corporate and working capital purposes.

The amounts and timing of these expenditures will depend on a number of factors, such as the timing and progress of our research and development efforts, the timing and progress of any partnering efforts, technological advances and the competitive environment for our product candidates. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, our management will have broad discretion in the application of these proceeds. Pending application of the net proceeds as described above, we intend to invest the proceeds in investment grade interest bearing instruments.

TABLE OF CONTENTS

DILUTION

Our net tangible book value as of March 31, 2010 was approximately $11.4 million, or $0.27 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2010. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this public offering and the net tangible book value per share of our common stock immediately after this public offering.

After giving effect to the sale of shares of our common stock in this offering at the public offering price of $ per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2010 would have been approximately $ million, or $ per share. This represents an immediate increase in net tangible book value of $ per share to existing stockholders and immediate dilution in net tangible book value of $ per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Assumed public offering price per share		$
Net tangible book value per share as of March 31, 2010	$ 0.27	
Increase per share attributable to investors purchasing our common stock in this offering		
As adjusted net tangible book value per share as of March 31, 2010, after giving effect to this offering		
Dilution in net tangible book value per share to investors purchasing our common stock in this offering		$

If the underwriters exercise in full their option to purchase additional shares of common stock at the public offering price of $ per share, the as adjusted net tangible book value after this offering would be $ per share, representing an increase in net tangible book value of $ per share to existing stockholders and immediate dilution in net tangible book value of $ per share to investors purchasing our common stock in this offering at the public offering price.

The amounts above are based on 41,710,778 shares of common stock outstanding as of March 31, 2010 and assume no exercise of outstanding options or warrants since that date. The number of common stock expected to be outstanding after this offering excludes:

- 3,569,352 shares of our common stock issuable upon the exercise of outstanding stock options as of March 31, 2010, including those issued under our 2003 Stock Option Plan, having a weighted average exercise price of $2.90 per share;
- 196,734 shares of our common stock reserved for future issuance as of March 31, 2010 under our 2003 Stock Option Plan, and 3,000,000 additional shares of our common stock that will be reserved for issuance under our 2003 Stock Option Plan if a proposed amendment to our 2003 Stock Option Plan is approved by our stockholders at our annual stockholders meeting schedule for June 23, 2010; and
- 16,011,588 shares of our common stock issuable upon the exercise of outstanding warrants as of March 31, 2010 with a weighted-average exercise price of $4.11 per share.

To the extent options or warrants outstanding as of March 31, 2010 have been or may be exercised or other shares have been issued, there may be further dilution to investors.

TABLE OF CONTENTS

MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSEQUENCES FOR CERTAIN NON-U.S. HOLDERS

The following summary describes the material U.S. federal income and estate tax consequences of the acquisition, ownership and disposition of common stock acquired in this offering by certain Non-U.S. Holders (as defined below). This discussion does not address all aspects of U.S. federal income and estate taxes and does not deal with foreign, state and local consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances, nor U.S. federal tax consequences other than income and estate taxes. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or the Code, such as financial institutions, insurance companies, tax-exempt organizations, broker-dealers and traders in securities, U.S. expatriates, regulated investment companies, real estate investment trusts, controlled foreign corporations, passive foreign investment companies, corporations that accumulate earnings to avoid U.S. federal income tax, persons that hold our common stock as part of a straddle, hedge, conversion transaction, synthet security or integrated investment or other risk reduction strategy, partnerships and other pass-through entities, and investors in such pass-through entities. Such Non-U.S. Holders are urged to consult their own tax advisors to determine the United States. federal, state, local and other tax consequences that may be relevant to them. Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in United States. federal income and estate tax consequences different from those discussed below. We have not requested any ruling from the U.S. Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions. This discussion assumes that the Non-U.S. Holder holds our common stock as a capital asset.

The following discussion is for general information only and is not tax advice. **Persons considering the purchase of common stock pursuant to this offering should consult their own tax advisors concerning the U.S. federal income and estate tax consequences in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local or foreign tax consequences.**

For purposes of this discussion, a Non-U.S. Holder is a beneficial owner of common stock that is not a U.S. Holder, for U.S. federal income tax purposes. A U.S. Holder means a beneficial owner of common stock that is, for U.S. federal income tax purposes, (i) an individual who is a citizen or resident of the United States, (ii) a corporation or other entity treated as a corporation created or organized in or under the laws of the United States or any political subdivision thereof, (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source or (iv) a trust if it (x) is subject to the primary supervision of a court within the United States and one or more U.S. persons have the authority to control all substantial decisions of the trust or (y) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person. The test for whether an individual is a resident of the United States for federal estate tax purposes differs from the test used for federal income tax purposes.

Distributions

Subject to the discussion below, distributions, if any, made on our common stock to a Non-U.S. Holder of our common stock to the extent made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to

withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder

TABLE OF CONTENTS

generally will be required to provide us with a properly-executed IRS Form W-8BEN, or other appropriate form, certifying the Non-U.S. Holder s entitlement to benefits under that treaty. In the case of a Non-U.S. Holder that is an entity, Treasury Regulations and the relevant tax treaty provide rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends will be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder s behalf, the holder will be required to provide appropriate documentation to such agent. The holder s agent will then be required to provide certification to us or our paying agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty, you may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that you maintain in the United States) if a properly-executed IRS Form W-8ECI, stating that the dividends are so connected, is filed with us (or, if stock is held through a financial institution or other agent, with such agent). In general, such effectively connected dividends will be subject to regular U.S. federal income tax, as if the Non-U.S. Holder were a U.S. person, unless a specific treaty exemption applies. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional branch profits tax, which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder s effectively connected earnings and profits, subject to certain adjustments.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will constitute a non-taxable return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

Gain on Disposition of Common Stock

A Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (i) the gain is effectively connected with a trade or business of such holder in the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that you maintain in the United States), (ii) in the case of a Non-U.S. Holder who is a nonresident alien individual and holds our common stock as a capital asset, such individual is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (iii) we are or have been a United States real property holding corporation within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder s holding period. In general, we would be a United States real property holding corporation if interests in U.S. real estate comprised at least half of our business assets. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation. Even if we are treated as a United States real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (a) the five year period preceding the disposition or (b) the holder s holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

TABLE OF CONTENTS

If you are a Non-U.S. Holder described in (i) above, you will be required to pay tax on the net gain derived from the sale in the same manner applicable to U.S. persons, unless a specific treaty exemption applies, and corporate Non-U.S. Holders described in (i) above may be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (ii) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by U.S. source capital losses (even though you are not considered a resident of the United States). If gain realized by you on the sale of our common stock is taxable because we are a United States real property holding corporation and your ownership of our common stock exceeded the 5% threshold in the period noted above, you will be taxed on such disposition generally in the manner applicable to U.S. persons.

Information Reporting Requirements and Backup Withholding

Generally, we must report information to the IRS with respect to any dividends we pay on our stock including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient s country of residence.

Proceeds from a disposition of our stock and dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly-executed IRS Form W-8BEN or otherwise establishes an exemption. The current backup withholding rate is 28%. Notwithstanding the foregoing, backup withholding may apply if either we or our paying agent has actual knowledge, or reason to know, that the holder of our common stock is a U.S. person that is not an exempt recipient.

Backup withholding is not an additional tax. Rather, the tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund may generally be obtained, provided that the required information is timely furnished to the IRS.

Federal Estate Tax

An individual who is treated as the owner of, or has made certain lifetime transfers of, an interest in our common stock will be required to include the value thereof in his or her gross estate for U.S. federal estate tax purposes, and may be subject to U.S. federal estate tax unless an applicable estate tax treaty provides otherwise, even though such individual was not a citizen or resident of the United States at the time of his or her death.

New Legislation Relating to Foreign Accounts

Newly enacted legislation may impose withholding taxes on certain types of payments made to foreign financial institutions and certain other non-U.S. entities. Under this legislation, the failure to comply with additional certification, information reporting and other specified requirements could result in withholding tax being imposed on payments of dividends and sales proceeds to foreign intermediaries and certain non-U.S. Holders. The legislation imposes a 30% withholding tax on dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to a foreign financial institution or to a foreign non-financial entity, unless (i) the foreign financial institution undertakes certain diligence and reporting obligations or (ii) the foreign non-financial entity either certifies it does not have any substantial U.S. owners or furnishes identifying information regarding each substantial U.S. owner. If the payee is a foreign financial institution, it must enter into an agreement with the U.S. Treasury requiring,

among other

TABLE OF CONTENTS

things, that it undertake to identify accounts held by certain U.S. persons or U.S.-owned foreign entities, annually report certain information about such accounts and withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. The legislation applies to payments made after December 31, 2012. Prospective investors should consult their tax advisors regarding this legislation.

THE PRECEDING DISCUSSION OF U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS IS FOR GENERAL INFORMATION ONLY. IT IS NOT TAX ADVICE. EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW.

TABLE OF CONTENTS

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement to be dated on or about May , 2010, between us and Jefferies & Company, Inc. and JMP Securities LLC, as underwriters, we have agreed to sell to the underwriters and the underwriters have severally agreed to purchase from us, the number of shares of common stock indicated in the table below:

Underwriter	Number of Shares
Jefferies & Company, Inc.	
JMP Securities LLC	
Total	

Jefferies & Company, Inc. is acting as sole book-running manager of this offering and as representative of the underwriters named above.

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the shares if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters have advised us that they currently intend to make a market in the common stock. However, the underwriters are not obligated to do so and may discontinue any market-making activities at any time without notice. No assurance can be given as to the liquidity of the trading market for the common stock.

The underwriters are offering the common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part. In addition, the underwriters have advised us that they do not intend to confirm sales to any account over which they exercise discretionary authority.

Commission and Expenses

The underwriters have advised us that they propose to offer the common stock to the public at the public offering price set forth on the cover page of this prospectus supplement and to certain dealers at that price less a concession not in excess of per common share. The underwriters may allow, and certain dealers may reallow, a discount from the concession not in excess of $ per common share to certain brokers and dealers. After the offering, the public offering price, concession and reallowance to dealers may be reduced by the representative. No such reduction will change the amount of proceeds to be received by us as set forth on the cover page of this prospectus supplement.

TABLE OF CONTENTS

The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters option to purchase additional shares.

	Per Share		Total	
	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares
Public offering price	$	$	$	$
Underwriting discounts and commissions paid by us	$	$	$	$
Proceeds to us, before expenses	$	$	$	$

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $.

Listing

Our common stock is listed on The NASDAQ Capital Market under the trading symbol ZIOP .

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to an aggregate of additional shares of common stock at the public offering price set forth on the cover page of this prospectus supplement, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional shares proportionate to that underwriter s initial purchase commitment as indicated in the table above. This option may be exercised only if the underwriters sell more shares than the total number set forth in the table above.

No Sales of Similar Securities

Subject to specified exceptions, we, our officers and directors have agreed not to directly or indirectly:

sell, offer, contract or grant any option to sell (including any short sale), pledge, transfer, establish an open put equivalent position within the meaning of Rule 16a-l(h) under the Exchange Act, or

otherwise dispose of any common stock, options or warrants to acquire common stock, or securities exchangeable or exercisable for or convertible into common stock currently or hereafter owned either of record or beneficially, or publicly announce an intention to do any of the foregoing for a period of 90 days after the date of this prospectus without the prior written consent of Jefferies & Company, Inc.

This restriction terminates after the close of trading of the common stock on and including the 90 days after the date of this prospectus supplement. However, subject to certain exceptions, in the event that either:

during the last 17 days of the 90-day restricted period, we issue an earnings release or material news or a material event relating to us occurs, or

prior to the expiration of the 90-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 90-day restricted period,

then in either case the expiration of the 90-day restricted period will be extended until the expiration of the 18-day period beginning on the date of the issuance of an earnings release or the occurrence of the material news or event, as applicable, unless Jefferies & Company, Inc. waives, in writing, such an extension.

TABLE OF CONTENTS

Jefferies & Company, Inc. may, in its sole discretion and at any time or from time to time before the termination of the 90-day period, without public notice, release all or any portion of the securities subject to lock-up agreements. There are no existing agreements between the underwriters and any of our shareholders who will execute a lock-up agreement, providing consent to the sale of shares prior to the expiration of the lock-up period.

Stabilization

The underwriters have advised us that, pursuant to Regulation M under the Exchange Act, certain persons participating in the offering may engage in transactions, including overallotment, stabilizing bids, syndicate covering transactions or the imposition of penalty bids, which may have the effect of stabilizing or maintaining the market price of the common stock at a level above that which might otherwise prevail in the open market. Overallotment involves syndicate sales in excess of the offering size, which creates a syndicate short position. Covered short sales are sales made in an amount not greater than the underwriters option to purchase additional common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of common stock or purchasing common stock in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares. Naked short sales are sales in excess of the option to purchase additional shares of common stock. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. A stabilizing bid is a bid for the purchase of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the shares originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member. Neither we, nor any of the underwriters makes any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time by the underwriters.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Affiliations

The underwriters or their affiliates from time to time may in the future provide investment banking, commercial lending and financial advisory services to us and our affiliates in the ordinary course of business. The underwriters and their affiliates, as applicable, will receive customary compensation and reimbursement of expenses in connection with such services.

TABLE OF CONTENTS

NOTICE TO INVESTORS

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (as defined below) (each, a Relevant Member State), with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, or the Relevant Implementation Date, an offer of our common stock to the public may not be made in that Relevant Member State prior to the publication of a prospectus in relation to our common stock which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the competent authority in that Relevant Member State, all in accordance with the Prospectus Directive, except that an offer to the public in that Relevant Member State of any shares of our common stock may be made at any time under the following exemptions under the Prospectus Directive if they have been implemented in the Relevant Member State:

(a) to legal entities which are authorized or regulated to operate in the financial markets or, if not so authorized or regulated, whose corporate purpose is solely to invest in securities;

(b) to any legal entity which has two or more of (1) an average of at least 250 employees during the last financial year; (2) a total balance sheet of more than €43,000,000 and (3) an annual net turnover of more than €50,000,000, as shown in its last annual or consolidated accounts;

(c) to fewer than 100 natural or legal persons per Relevant Member State (other than qualified investors as defined in the Prospectus Directive); or

(d) in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an offer of our common stock to the public in relation to any shares of our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and our common stock to be offered so as to enable an investor to decide to purchase or subscribe our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State and the expression Prospectus Directive means Directive 2003/71/EC and includes any relevant implementing measure in each Relevant Member State.

United Kingdom

Shares of our common stock may not be offered or sold and will not be offered or sold to any persons in the United Kingdom other than to persons whose ordinary activities involve them in acquiring, holding, managing or disposing of investments (as principal or as agent) for the purposes of their businesses or otherwise in circumstances which have not resulted or will not result in an offer to the public in the United Kingdom within the meaning of the Financial Services and Markets Act 2000, or the FSMA.

In addition, any invitation or inducement to engage in investment activity (within the meaning of section 21 of the FSMA) in connection with the issue or sale of shares of our common stock may only be communicated or caused to be communicated in circumstances in which Section 21(1) of the FSMA does not apply to us. Without limitation to the other restrictions referred to herein, this prospectus supplement is directed only at (1) persons outside the United Kingdom or (2) persons who:

(a) are qualified investors as defined in section 86(7) of FSMA, being persons falling within the meaning of article 2.1(e)(i), (ii) or (iii) of the Prospectus Directive; and

TABLE OF CONTENTS

are either persons who fall within article 19(1) of the Financial Services and Markets Act 2000 (Financial
(b) Promotion) Order 2005, as amended, or Order, or are persons who fall within article 49(2)(a) to (d) (high net worth companies, unincorporated associations, etc.) of the Order; or

(c) to whom it may otherwise lawfully be communicated in circumstances in which Section 21(1) of the FSMA does not apply.

Without limitation to the other restrictions referred to herein, any investment or investment activity to which this offering circular relates is available only to, and will be engaged in only with, such persons, and persons within the United Kingdom who receive this communication (other than persons who fall within (2) above) should not rely or act upon this communication.

Germany

Any offer or solicitation of securities within Germany must be in full compliance with the German Securities Prospectus Act (Wertpapierprospektgesetz WpPG). The offer and solicitation of securities to the public in Germany requires the publication of a prospectus that has to be filed with and approved by the German Federal Financial Services Supervisory Authority (Bundesanstalt für Finanzdienstleistungsaufsicht BaFin). This prospectus supplement has not been and will not be submitted for filing and approval to the BaFin and, consequently, will not be published. Therefore, this prospectus supplement does not constitute a public offer under the German Securities Prospectus Act (Wertpapierprospektgesetz). This prospectus supplement and any other document relating to our common stock, as well as any information contained therein, must therefore not be supplied to the public in Germany or used in connection with any offer for subscription of our common stock to the public in Germany, any public marketing of our common stock or any public solicitation for offers to subscribe for or otherwise acquire our common stock. This prospectus supplement and other offering materials relating to the offer of our common stock are strictly confidential and may not be distributed to any person or entity other than the designated recipients hereof.

France

This prospectus has not been prepared in the context of a public offering of financial securities in France within the meaning of Article L.411-1 of the French Code Monétaire et Financier and Title I of Book II of the Reglement Général of the Autorité des marchés financiers (the AMF) and therefore has not been and will not be filed with the AMF for prior approval or submitted for clearance to the AMF. Consequently, the shares of our common stock may not be, directly or indirectly, offered or sold to the public in France and offers and sales of the shares of our common stock may only be made in France to qualified investors (investisseurs qualifiés) acting for their own, as defined in and in accordance with Articles L.411-2 and D.411-1 to D.411-4, D.734-1, D.744-1, D.754-1 and D.764-1 of the French Code Monétaire et Financier. Neither this prospectus nor any other offering material may be released, issued or distributed to the public in France or used in connection with any offer for subscription on sale of the shares of our common stock to the public in France. The subsequent direct or indirect retransfer of the shares of our common stock to the public in France may only be made in compliance with Articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French Code Monétaire et Financier.

Sweden

This is not a prospectus under, and has not been prepared in accordance with the prospectus requirements provided for in, the Swedish Financial Instruments Trading Act [lagen (1991:980) om handel med finasiella instrument] nor any other Swedish enactment. Neither the Swedish Financial Supervisory Authority nor any other Swedish public body has examined, approved, or registered this document.

TABLE OF CONTENTS

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon by our counsel, Maslon Edelman Borman & Brand, LLP, Minneapolis, Minnesota. The underwriters are represented in connection with this offering by Cooley LLP, Palo Alto, California.

EXPERTS

The balance sheets of ZIOPHARM Oncology, Inc. as of December 31, 2009 and 2008 and the related statements of operations, changes in convertible preferred stock and stockholders equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2009 and for the period from September 9, 2003 (date of inception) through December 31, 2009, included in this prospectus, have been included herein in reliance on the report, dated March 17, 2010, of Caturano and Company, P.C., independent registered public accounting firm, (which report expresses an unqualified opinion and includes an explanatory paragraph relating to the change in the manner in which the Company accounts for certain warrants), given on the authority of that firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus are part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and do not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement or the accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference in this prospectus supplement and the accompanying prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at *http://www.sec.gov*. You may also read and copy any document we file at the SEC s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

TABLE OF CONTENTS

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):

Annual Report on Form 10-K for the fiscal year ended December 31, 2009, filed on March 17, 2010, as amended by Amendment No. 1 to Annual Report on Form 10-K/A filed on April 30, 2010;

Quarterly Report on Form 10-Q for the quarter ended March 31, 2010, filed on April 30, 2010;

Current Reports on Form 8-K filed on January 27, 2010, April 6, 2010 and May 21, 2010; 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 SEC on September 20, 2006, including any amendments or reports filed for the purpose of updating such description.

We will provide to each person, including any beneficial owner, to whom a prospectus supplement is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus supplement but not delivered with this prospectus supplement. 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.
1180 Avenue of the Americas, 19th Floor
New York, NY 10036
Attention: President
Telephone: (646) 214-0700

You should rely only on the information incorporated by reference or provided in this prospectus supplement or the accompanying prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement is accurate as of any date other than the date on the front of this prospectus supplement.

TABLE OF CONTENTS

PROSPECTUS

$100,000,000

ZIOPHARM Oncology, Inc.

Common Stock, Preferred Stock, Warrants and Debt Securities

We may offer and sell any combination of common stock, preferred stock, warrants and debt securities, with a total initial offering price of up to $100,000,000.

This prospectus provides a general description of securities we may offer and sell from time to time. Each time we sell these securities, we will provide their specific terms in a supplement to this prospectus. This prospectus supplement may also add, update or change information contained in this prospectus. You should read this prospectus and the applicable prospectus supplement carefully before you invest in any securities. This prospectus may not be used to consummate a sale of securities unless accompanied by the applicable prospectus supplement.

We may offer and sell these securities, from time to time, to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis, at prices and on other terms to be determined at the time of offering. If we use agents, underwriters or dealers to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on the Nasdaq Capital Market under the symbol ZIOP. On May 7, 2010, the closing price of our common stock, as reported on the Nasdaq Capital Market, was $5.62. We urge prospective purchasers of our common stock to obtain current information about the market prices of our common stock.

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 May 10, 2010.

TABLE OF CONTENTS

ZIOPHARM ONCOLOGY, INC.

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, 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, up to a total dollar amount of $100,000,000. 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. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. This prospectus, together with the applicable prospectus supplement(s) and the documents incorporated by reference into this prospectus and such supplement(s), includes all material information relating to this offering. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the 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 this prospectus or any prospectus supplement the statement in the document having the later date modifies or supersedes the earlier statement. Please carefully read both this prospectus and any prospectus supplement, together with the additional information described below under Where You Can Find More Information, before buying securities in this offering.

You should rely only on the information contained or incorporated by reference in this prospectus or a prospectus supplement. We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus and the accompanying

supplement to this prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying supplement to this prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus and the accompanying prospectus supplement is accurate on any date subsequent to the date set forth on the front cover of this document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus and any accompanying prospectus supplement is delivered or securities sold on a later date.

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

TABLE OF CONTENTS

PROSPECTUS SUMMARY

The following is a summary of this prospectus. Because it is only a summary, it does not contain all of the detailed information contained elsewhere in this prospectus or in the documents incorporated by reference into this prospectus or included as exhibits to the registration statement that contains this prospectus. Accordingly, you are urged to carefully review this prospectus (including all documents incorporated by reference into this prospectus) in its entirety. Unless otherwise indicated, ZIOPHARM, our Company, we, us, our and similar terms refer to ZIOPHARM Oncology, Inc.

Our Company

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that is seeking to develop and commercialize a diverse, risk-sensitive portfolio of in-licensed cancer drugs that can address unmet medical needs through enhanced efficacy and/or safety and quality of life. Our principal focus is on the licensing and development of proprietary small molecule drug candidates that are related to cancer therapeutics already on the market or in development and that can be administered by intravenous and/or oral capsule dosing. We believe this strategy will result in lower risk and expedited drug development programs with product candidates having a low cost of manufacturing to address changing reimbursement requirements around the world. While we may endeavor to commercialize our products on our own in North America, we recognize that favorable clinical trial results can be better addressed by partnering with companies with the requisite financial resources. With partnering, we could also negotiate the right to complete development and marketing in certain geographies, especially for certain limited (niche) indications. Although we are currently in phase I and/or II studies for three product candidates identified as darinaparsin (Zinapar™, ZIO-101), palifosfamide (Zymafos™, ZIO-201), and indibulin (Zybulin™, ZIO-301), our primary focus has been and remains on palifosfamide development and more specifically on completing the ongoing randomized phase II trial with palifosfamide to support a registration trial for palifosfamide in combination with doxorubicin in the front- and second-line setting of soft tissue sarcoma. We anticipate the initiation of such a registration trial as early as the first half of 2010.

ZIO-101 or darinaparsin (Zinapar™) is an anti-mitochondrial (organic arsenic) compound covered by issued patents and pending patent applications in the U.S. and in foreign countries. A form of commercially available inorganic arsenic (arsenic trioxide [Trisenox®] or ATO) has been approved in the United States and the European Union and Japan for the treatment of acute promyelocytic leukemia, a precancerous condition. In the United States, ATO is on the compendia listing for the therapy of multiple myeloma, and has been studied for the treatment of various other cancers. Nevertheless, ATO has been shown to be toxic to the heart, liver, and brain, which limits its use as an anti-cancer agent. ATO carries a black box warning for ECG abnormalities since arsenic trioxide has been shown to cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. Inorganic arsenic has also been shown to cause cancer of the skin and lung in humans. The toxicity of arsenic is generally correlated to its accumulation in organs and tissues. Our preclinical and clinical studies to date have demonstrated that darinaparsin is considerably less toxic than ATO, particularly with regard to cardiac toxicity. In vitro testing of darinaparsin using the National Cancer Institute s human cancer cell panel demonstrated activity against a series of tumor cell lines including lung, colon, brain, melanoma, ovarian, and kidney cancer. Moderate activity was shown against breast and prostate cancer tumor cell lines. In addition to solid tumors, in vitro testing in both the National Cancer Institute s cancer cell panel and in vivo testing in a leukemia animal model demonstrated substantial activity against hematological cancers (cancers of the blood and blood-forming tissues) such as leukemia, lymphoma, myelodysplastic syndromes, and multiple myeloma. Results indicate significant activity against the

1

TABLE OF CONTENTS

HuT 78 cutaneous T-cell lymphoma, the NK-G2MI natural killer-cell NHL, KARPAS-299 T-cell NHL, SU-DHL-8 B-cell NHL, SU-DHL-10 B-cell NHL and SU-DHL-16 B-cell NHL cell lines. Preclinical studies have also established anti-angiogenic properties of darinaparsin and provided support for the development of an oral capsule form of the drug, and established synergy of darinaparsin in combination with other approved anti-cancer agents.

Phase I testing of the intravenous (IV) form of darinaparsin in solid tumors and hematological cancers has been completed. We reported clinical activity and, importantly, a safety profile from these studies as predicted by preclinical results. We subsequently completed Phase II studies in advanced myeloma and primary liver cancer and are nearing completion of a Phase II study in certain other hematological cancers. In addition, we are completing two Phase I studies with an oral capsule form of darinaparsin. At the May 2009 annual meeting of the American Society of Clinical Oncology, we reported favorable results from the trial with IV-administered darinaparsin in lymphoma, particularly peripheral T-cell lymphoma. In the ongoing Phase I trials, also reported at the ASCO annual meeting, preliminary data primarily in solid tumors indicate the oral form is active and well tolerated. We are completing data collection from the IV Phase II trial to address a registration and other trials with the U.S. Food and Drug Administration. The oral Phase I program will be progressed to establish a dose for further clinical testing.

ZIO-201 or palifosfamide (Zymafos™), comprises the active metabolite of ifosfamide, a compound chemically related to cyclophosphamide. Patent applications covering proprietary forms of palifosfamide for pharmaceutical composition and method of use have been filed in the U.S. and internationally and in the U.S. we recently received a patent covering pharmaceutical composition. Like cyclophosphamide, ifosfamide and bendamustine, palifosfamide is a DNA alkylating agent, a form of cancer therapy to treat a wide range of solid tumors and hematological malignancies. We believe that cyclophosphamide is the most widely used alkylating agent in cancer therapy, with significant use in the treatment of breast cancer and non-Hodgkin s lymphoma. Bendamustine has been recently approved and successfully launched by Cephalon Oncology in the U.S. and Europe to treat certain hematological malignancies. Ifosfamide has been shown to be effective in the treatment of sarcoma and lymphoma, either by itself or in combination with other anticancer agents. Ifosfamide is approved by the FDA as a treatment for testicular cancer while ifosfamide-based treatment is a standard of care for sarcoma, although it is not licensed for this indication by the FDA. Preclinical studies have shown that palifosfamide has activity against leukemia and solid tumors. These studies also indicate that palifosfamide may have a better safety profile than ifosfamide or cyclophosphamide because it does not appear to produce known toxic metabolites of ifosfamide, such as acrolein and chloroacetaldehyde. Acrolein, which is toxic to the kidneys and bladder, can mandate the administration of a protective agent called mesna, which is inconvenient and expensive. Chloroacetaldehyde is toxic to the central nervous system, causing fuzzy brain syndrome for which there is currently no protective measure. Similar toxicity concerns pertain to high-dose cyclophosphamide, which is widely used in bone marrow and blood cell transplantation. Palifosfamide has evidenced activity against ifosfamide- and/or cyclophosphamide-resistant cancer cell lines. Also in preclinical cancer models, palifosfamide was shown to be orally active and encouraging results have been obtained with palifosfamide in combination with doxorubicin, an agent approved to treat sarcoma.

Following completion of Phase I study, we completed Phase II testing of the intravenous form of palifosfamide as a single agent to treat advanced sarcoma. In both Phase I and Phase II testing, palifosfamide has been administered without the uroprotectant mesna, and the toxicities associated with acrolein and chloroacetaldehyde have not been observed. We reported clinical activity of palifosfamide

TABLE OF CONTENTS

when used alone in the Phase II study addressing advanced sarcoma. Following review of preclinical combination studies, clinical data, and discussion with sarcoma experts, we initiated a Phase I dose escalation study of palifosfamide in combination with doxorubicin primarily in patients with soft tissue sarcoma. We reported favorable results and safety profile from this study at ASCO s 2009 annual meeting. In light of reported favorable Phase II clinical activity data and with the combination of palifosfamide with doxorubicin well tolerated in the Phase I trial and evidencing activity, we initiated a Phase II randomized controlled trial in the second half of 2008 to compare doxorubicin plus palifosfamide to doxorubicin alone in patients with front and second-line metastatic or unresectable soft tissue sarcoma. The study has generated positive top line interim data in 2009. Upon reaching a pre-specified efficacy milestone and following safety and efficacy data review by the Data Committee, sarcoma experts, and our Medical Advisory Board, we elected to suspend enrollment in the trial in October 2009. We subsequently presented further positive interim data from the trial at the 15th Annual Connective Tissue Oncology Society meeting held in November 2009. We currently plan to initiate a registration trial following regulatory review of the palifosfamide program to date. We are also developing an oral capsule form of palifosfamide to be studied clinically following receipt of further data from the IV trials and subject to obtaining sufficient additional sources of funding, either from potential partnering arrangements or from other sources. To date we have no such partnering arrangements or other sources of such financing in place. We are also considering additional Phase II trials in other solid tumors as funding becomes available. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of soft tissue sarcomas.

ZIO-301 or indibulin (Zybulin™), is a novel, orally available small molecular-weight inhibitor of tubulin polymerization that we acquired from Baxter Healthcare in 2006 and is the subject of numerous patents worldwide, including the United States, the European Union and Japan. The microtubule component, tubulin, is one of the more well established drug targets in cancer. Microtubule inhibitors interfere with the dynamics of tubulin polymerization, resulting in inhibition of chromosome segregation during mitosis and consequently inhibition of cell division. A number of marketed IV anticancer drugs target tubulin, such as the taxane family members, paclitaxel (Taxol®), docetaxel (Taxotere®), the Vinca alkaloid family members, vincristine and vinorelbine, and the new class of epothilones with Ixempra™ marketed. This class of agents is typically the mainstay of therapy in a wide variety of indications. In spite of their effectiveness, the use of these drugs is associated with significant toxicities, notably peripheral neurotoxicity.

Preclinical studies with indibulin demonstrate significant and broad antitumor activity, including activity against taxane-refractory cell lines. The cytotoxic activity of indibulin was demonstrated in several rodent and human tumor cell lines derived from prostate, brain, breast, pancreas, lung, ovary, and cervical tumor tissues and in rodent tumor and human tumor xenograft models. In addition, indibulin was effective against multidrug resistant tumor cell lines (breast, lung, and leukemia) both in vitro and in vivo. Indibulin is potentially safer than other tubulin inhibitors. No neurotoxicity has been observed at therapeutic doses in rodents and in the Phase I trials. Indibulin has also demonstrated synergy with approved anti-cancer agents in preclinical studies. The availability of an oral capsule formulation of indibulin creates significant commercial opportunity because no oral capsule formulations of the taxane family are currently on the market in the United States.

Indibulin, as a single agent, has completed Phase I trials in patients with advanced solid tumors. We have reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging results obtained with

TABLE OF CONTENTS

indibulin in combination with erlotinib, and 5-FU in preclinical models, two Phase I combination studies were initiated with Tarceva™ and Xeloda™, respectively. Favorable activity and safety profile of oral indibulin with oral Xeloda™ were reported at ASCO s annual meeting in May 2009. Preclinical work with our consultant, Dr. Larry Norton, to explore dose scheduling for the clinical setting have been completed, with results supporting the recently initiated Phase I safety trial necessary for a Phase I/II breast cancer trial and using the mathematical dose schedule / frequency established preclinically.

We intend to continue with clinical development of IV palifosfamide for soft tissue sarcoma both completing the ongoing **P**hase II multicenter, parallel group, randomized study of pal**I**fosfamide tris plus doxorubicin versus doxorubi**C**in in subjects with unresect**A**ble or metastatic **S**oft tissue **S**arc**O**ma (PICASSO) trial and in a planned registration trial and, with additional resources, to initiate a clinical study with the oral form and/or in additional indications beyond STS. For IV darinaparsin, we will complete the ongoing Phase I oral trial and will address peripheral T-cell lymphoma (PTCL) registration and other trials, in part dependent on additional funding. For oral indibulin, we will complete the Phase I breast cancer safety trial and initiate the subsequent Phase I/II trial and, with additional funding, other trials. However, the successful development of our product candidates is highly uncertain. Product development costs and timelines can vary significantly for each product candidate, are difficult to accurately predict, and will require us to obtain additional funding, either alone or in connection with partnering arrangements. Various statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of each product. The lengthy process of seeking approval and the subsequent compliance with applicable statutes and regulations require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could materially, adversely affect our business. To date, we have not received approval for the sale of any drug candidates in any market and, therefore, have not generated any revenues from our drug candidates.

Corporate Information

We were 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 were 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 Securities and Exchange Commission and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our executive offices are located at 1180 Avenue of the Americas, 19th Floor, New York, NY 10036, and our telephone number is (646) 214-0700. Our internet site is *www.ziopharm.com*. None of the information on our internet site is part of this prospectus.

TABLE OF CONTENTS

RISK FACTORS

As with most pharmaceutical product candidates, the development of our product candidates is subject to numerous risks, including the risk of delays in or discontinuation of development from lack of financing, inability to obtain necessary regulatory approvals to market the products, unforeseen safety issues relating to the products and dependence on third party collaborators to conduct research and development of the products. Because we are a development stage company with a limited history of operations, we are also subject to many risks associated with early-stage companies. For a more detailed discussion of the risks you should consider before purchasing shares of our common stock, you should carefully consider the specific risks discussed under Risk Factors in the applicable prospectus supplement and in our filings with the Securities and Exchange Commission that are incorporated by reference in this prospectus and such prospectus supplement.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains, and the documents incorporated by reference herein and in any prospectus supplement hereto may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). 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 and timing of preclinical and clinical trials involving our drug candidates;
the progress and timing of our research and development programs;
the benefits to be derived from relationships with our collaborators;
the receipt or anticipated receipt of regulatory clearances and approvals;
our ability to enforce intellectual property rights;
our estimates of future revenues and profitability; and
our estimates regarding our capital requirements and our need for additional financing.

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 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 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.

Further, 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.

TABLE OF CONTENTS

RATIO OF EARNINGS TO FIXED CHARGES

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

	Fiscal Year Ended December 31,					Three Months Ended March 31,
$ In Thousands, Except Ratio	2005	2006	2007	2008	2009	2010
Ratio of earnings to fixed charges[1]						
Deficiency of earnings to fixed charges[2]	$(9,517)	$(17,857)	$(26,608)	$(25,231)	$(7,649)	$(17,653)

(1) In each of the periods presented, no earnings were sufficient to cover fixed charges.

(2) The deficiency of earnings is equivalent to net income (loss) before tax benefit (provision) and extraordinary gain.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds to us from the sale of our securities offered by this prospectus. Unless we indicate otherwise in the applicable prospectus supplement, 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 our intended use for the net proceeds received from the sale of securities sold pursuant to that prospectus supplement.

PLAN OF DISTRIBUTION

We may sell the securities covered by this prospectus:

to or through one or more underwriters or dealers;
directly to purchasers, or to purchasers through agents; or
through a combination of any of these methods of sale.

We may distribute the securities offered hereby:

from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time;
at market prices prevailing at the times of sale;
at prices related to such prevailing market prices; or
at negotiated prices.

We will describe the method of distribution of the securities in the applicable prospectus supplement.

We may determine the price or other terms of the securities offered under this prospectus by use of an electronic auction. We will describe how any auction will determine the price or any other terms, how potential investors may participate in the auction and the nature of the obligations of the underwriter, dealer or agent in the applicable prospectus supplement.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers (as their agents in connection with the sale of the securities). In addition, underwriters may sell securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they act as agent. These underwriters, dealers or agents may be considered to be

TABLE OF CONTENTS

underwriters under the Securities Act. As a result, discounts, commissions, or profits on resale received by the underwriters, dealers or agents may be treated as underwriting discounts and commissions. Each applicable prospectus supplement will identify any such underwriter, dealer or agent, and describe any compensation received by them from us. Any initial public offering price and any discounts or concessions allowed or re-allowed or paid to dealers may be changed from time to time.

We may enter into agreements that provide for indemnification against certain civil liabilities, including liabilities under the Securities Act, or for contribution with respect to payments made by the underwriters, dealers or agents and to reimburse these persons for certain expenses.

We may grant underwriters who participate in the distribution of the securities an option to purchase additional securities to cover over-allotments, if any, in connection with the distribution. Underwriters or agents and their associates may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

In connection with the offering of the securities, certain underwriters and selling group members and their respective affiliates, may engage in transactions that stabilize, maintain or otherwise affect the market price of the securities. These transactions may include stabilization transactions effected in accordance with Rule 104 of Regulation M promulgated by the SEC pursuant to which these persons may bid for or purchase securities for the purpose of stabilizing its market price.

The underwriters in the offering may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with rules and regulations under the Securities Exchange Act of 1934, as amended (the Exchange Act). Overallotment 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. Short covering transactions involve purchases of the securities 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 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 these activities at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

TABLE OF CONTENTS

DESCRIPTION OF CAPITAL STOCK

Pursuant to our certificate of incorporation, as amended and restated to date, 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 May 7, 2010, there were 41,824,732 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. 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 the registrant s 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.

Conversion, Redemption and Preemptive Rights. Holders of our common stock have no conversion, redemption, preemptive, subscription or similar rights.

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

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

Preferred Stock

The following description of preferred stock and the description of the terms of any particular series of preferred stock that we choose to issue hereunder and that will be set forth in the related prospectus supplement are not complete. These descriptions are qualified in their entirety by reference to the certificate of designation relating to that series. The rights, preferences, privileges and restrictions of the preferred stock of each series will be fixed by the certificate

of designation relating to that series.

The board of directors has the authority, without stockholder approval, subject to limitations prescribed by law, to provide for the issuance of the shares of preferred stock in one or more series, and by

TABLE OF CONTENTS

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 the qualifications, limitations or restrictions, including, but not limited to, the following:

the number of shares constituting that series;
dividend rights and rates;
voting rights;
conversion terms;
rights and terms of redemption (including sinking fund provisions); and
rights of the series in the event of liquidation, dissolution or winding up.

All shares of preferred stock offered hereby will, when issued, be fully paid and nonassessable and will not have any preemptive or similar rights. 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.

We will set forth in a prospectus supplement relating to the series of preferred stock being offered the following items:

the title and stated value of the preferred stock;
the number of shares of the preferred stock offered, the liquidation preference per share and the offering price of the preferred stock;
the dividend rate(s), period(s) and/or payment date(s) or method(s) of calculation applicable to the preferred stock;
whether dividends are cumulative or non-cumulative and, if cumulative, the date from which dividends on the preferred stock will accumulate;
the procedures for any auction and remarketing, if any, for the preferred stock;
the provisions for a sinking fund, if any, for the preferred stock;
the provision for redemption, if applicable, of the preferred stock;
any listing of the preferred stock on any securities exchange;
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;
voting rights, if any, of the preferred stock;
a discussion of any material and/or special United States 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;

TABLE OF CONTENTS

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.

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

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in an officers certificate or by a supplemental indenture. Debt securities may be issued in separate series without limitation as to aggregate principal amount. We may specify a maximum aggregate principal amount for the debt securities of any series. The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series, including any pricing supplement. The prospectus supplement will set forth specific terms relating to some or all of the following:

the offering price;
the title;
any limit on the aggregate principal amount;
the person who shall be entitled to receive interest, if other than the record holder on the record date;
the date the principal will be payable;
the interest rate, if any, the date interest will accrue, the interest payment dates and the regular record dates;
the place where payments may be made;
any mandatory or optional redemption provisions;
if applicable, the method for determining how the principal, premium, if any, or interest will be calculated by reference to an index or formula;
if other than U.S. currency, the currency or currency units in which principal, premium, if any, or interest will be payable and whether we or the holder may elect payment to be made in a different currency;
the portion of the principal amount that will be payable upon acceleration of stated maturity, if other than the entire principal amount;
any defeasance provisions if different from those described below under Satisfaction and Discharge; Defeasance ;
any conversion or exchange provisions;
any obligation to redeem or purchase the debt securities pursuant to a sinking fund;
whether the debt securities will be issuable in the form of a global security;
any subordination provisions, if different from those described below under Subordination ;
any deletions of, or changes or additions to, the events of default or covenants; and
any other specific terms of such debt securities.

Unless otherwise specified in the prospectus supplement, the debt securities will be registered debt securities. Debt securities may be sold at a substantial discount below their stated principal amount, bearing no interest or interest at a rate which at the time of issuance is below market rates.

TABLE OF CONTENTS

Exchange and Transfer

Debt securities may be transferred or exchanged at the office of the security registrar or at the office of any transfer agent designated by us.

We will not impose a service charge for any transfer or exchange, but we may require holders to pay any tax or other governmental charges associated with any transfer or exchange.

In the event of any potential redemption of debt securities of any series, we will not be required to:

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

register the transfer of or exchange any debt security of that series selected for redemption, in whole or in part, except the unredeemed portion being redeemed in part.

We may initially appoint the trustee as the security registrar. Any transfer agent, in addition to the security registrar, initially designated by us will be named in the prospectus supplement. We may designate additional transfer agents or change transfer agents or change the office of the transfer agent. However, we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

Global Securities

The debt securities of any series may be represented, in whole or in part, by one or more global securities. Each global security will:

be registered in the name of a depositary that we will identify in a prospectus supplement;

be deposited with the depositary or nominee or custodian; and

bear any required legends.

No global security may be exchanged in whole or in part for debt securities registered in the name of any person other than the depositary or any nominee unless:

the depositary has notified us that it is unwilling or unable to continue as depositary or has ceased to be qualified to act as depositary;

an event of default is continuing; or

the Company executes and delivers to the trustee an officers certificate stating that the global security is exchangeable.

As long as the depositary, or its nominee, is the registered owner of a global security, the depositary or nominee will be considered the sole owner and holder of the debt securities represented by the global security for all purposes under the indenture. Except in the above limited circumstances, owners of beneficial interests in a global security:

will not be entitled to have the debt securities registered in their names;

will not be entitled to physical delivery of certificated debt securities; and

will not be considered to be holders of those debt securities under the indentures.

TABLE OF CONTENTS

Payments on a global security will be made to the depositary or its nominee as the holder of the global security. Some jurisdictions have laws that require that certain purchasers of securities take physical delivery of such securities in definitive form. These laws may impair the ability to transfer beneficial interests in a global security.

Institutions that have accounts with the depositary or its nominee are referred to as participants. Ownership of beneficial interests in a global security will be limited to participants and to persons that may hold beneficial interests through participants. The depositary will credit, on its book-entry registration and transfer system, the respective principal amounts of debt securities represented by the global security to the accounts of its participants.

Ownership of beneficial interests in a global security will be shown on and effected through records maintained by the depositary, with respect to participants interests, or any participant, with respect to interests of persons held by participants on their behalf.

Payments, transfers and exchanges relating to beneficial interests in a global security will be subject to policies and procedures of the depositary.

The depositary policies and procedures may change from time to time. Neither we nor the trustee will have any responsibility or liability for the depositary s or any participant s records with respect to beneficial interests in a global security.

Payment and Paying Agent

The provisions of this paragraph will apply to the debt securities unless otherwise indicated in the prospectus supplement. Payment of interest on a debt security on any interest payment date will be made to the person in whose name the debt security is registered at the close of business on the regular record date. Payment on debt securities of a particular series will be payable at the office of a paying agent or paying agents designated by us. However, at our option, we may pay interest by mailing a check to the record holder. The corporate trust office will be designated as our sole paying agent.

We may also name any other paying agents in the prospectus supplement. We may designate additional paying agents, change paying agents or change the office of any paying agent. However, we will be required to maintain a paying agent in each place of payment for the debt securities of a particular series.

All moneys paid by us to a paying agent for payment on any debt security which remain unclaimed at the end of two years after such payment was due will be repaid to us. Thereafter, the holder may look only to us for such payment.

Consolidation, Merger and Sale of Assets

Except as otherwise set forth in the prospectus supplement, we may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to, any person, unless:

the successor, if any, is a U.S. corporation, limited liability company, partnership, trust or other entity;
the successor assumes our obligations on the debt securities and under the indenture;
immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and
certain other conditions are met.

13

TABLE OF CONTENTS

Events of Default

Unless we inform you otherwise in the prospectus supplement, the indenture will define an event of default with respect to any series of debt securities as one or more of the following events:

(1) failure to pay principal of or any premium on any debt security of that series when due;

(2) failure to pay any interest on any debt security of that series for 30 days when due;

(3) failure to deposit any sinking fund payment when due;

(4) failure to perform any other covenant in the indenture continued for 90 days after being given the notice required in the indenture;

(5) our bankruptcy, insolvency or reorganization; and

(6) any other event of default specified in the prospectus supplement.

An event of default of one series of debt securities is not necessarily an event of default for any other series of debt securities.

If an event of default, other than an event of default described in clause (5) above, shall occur and be continuing, either the trustee or the holders of at least 25% in aggregate principal amount of the outstanding securities of that series may declare the principal amount of the debt securities of that series to be due and payable immediately.

TABLE OF CONTENTS

If an event of default described in clause (5) above shall occur, the principal amount of all the debt securities of that series will automatically become immediately due and payable. Any payment by us on subordinated debt securities following any such acceleration will be subject to the subordination provisions described below under Subordinated Debt Securities.

After acceleration the holders of a majority in aggregate principal amount of the outstanding securities of that series may, under certain circumstances, rescind and annul such acceleration if all events of default, other than the non-payment of accelerated principal, or other specified amount, have been cured or waived.

Other than the duty to act with the required care during an event of default, the trustee will not be obligated to exercise any of its rights or powers at the request of the holders unless the holders shall have offered to the trustee reasonable indemnity. Generally, the holders of a majority in aggregate 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.

A holder will not have any right to institute any proceeding under the indentures, or for the appointment of a receiver or a trustee, or for any other remedy under the indentures, unless:

(1) the holder has previously given to the trustee written notice of a continuing event of default with respect to the debt securities of that series;

(2) the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made a written request and have offered reasonable indemnity to the trustee to institute the proceeding; and

(3) the trustee has failed to institute the proceeding and has not received direction inconsistent with the original request from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series within 90 days after the original request.

Holders may, however, sue to enforce the payment of principal or interest on any debt security on or after the due date without following the procedures listed in (1) through (3) above.

Modification and Waiver

Except as provided in the next two succeeding paragraphs, the applicable trustee and we may make modifications and amendments to the indentures (including, without limitation, through consents obtained in connection with a tender offer or exchange offer for, outstanding securities) and may waive any existing default or event of default (including, without limitation, through consents obtained in connection with a tender offer or exchange offer for, outstanding securities) with the consent of the holders of a majority in aggregate principal amount of the outstanding securities of each series affected by the modification or amendment.

However, neither we nor the trustee may make any amendment or waiver without the consent of the holder of each outstanding security of that series affected by the amendment or waiver if such amendment or waiver would, among other things:

change the amount of securities whose holders must consent to an amendment, supplement or waiver;

change the stated maturity of any debt security;

TABLE OF CONTENTS

reduce the principal on any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund;

reduce the principal of an original issue discount security on acceleration of maturity;

reduce the rate of interest or extend the time for payment of interest on any debt security;

make a principal or interest payment on any debt security in any currency other than that stated in the debt security;

impair the right to enforce any payment after the stated maturity or redemption date;

waive any default or event of default in payment of the principal of, premium or interest on any debt security (except certain rescissions of acceleration); or

waive a redemption payment or modify any of the redemption provisions of any debt security.

Notwithstanding the preceding, without the consent of any holder of outstanding securities, we and the trustee may amend or supplement the indentures:

to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;

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

to provide for the assumption of our obligations to holders of any debt security in the case of a merger, consolidation, transfer or sale of all or substantially all of our assets;

to make any change that does not adversely affect the legal rights under the indenture of any such holder;

to comply with requirements of the Commission in order to effect or maintain the qualification of an indenture under the Trust Indenture Act; or

to evidence and provide for the acceptance of appointment by a successor trustee with respect to the debt securities of one or more series and to add to or change any of the provisions of the indenture as shall be necessary to provide for or facilitate the administration of the trusts by more than one Trustee.

The consent of holders is not necessary under the indentures to approve the particular form of any proposed amendment. It is sufficient if such consent approves the substance of the proposed amendment.

Satisfaction and Discharge; Defeasance

We may be discharged from our obligations on the debt securities of any series that have matured or will mature or be redeemed within one year if we deposit with the trustee enough cash to pay all the principal, interest and any premium due to the stated maturity date or redemption date of the debt securities.

Each indenture contains a provision that permits us to elect:

to be discharged from all of our obligations, subject to limited exceptions, with respect to any series of debt securities then outstanding; and/or

to be released from our obligations under the following covenants and from the consequences of an event of default resulting from a breach of certain covenants, including covenants as to payment of taxes and maintenance of corporate existence.

TABLE OF CONTENTS

To make either of the above elections, we must deposit in trust with the trustee enough money to pay in full the principal and interest on the debt securities. This amount may be made in cash and/or U.S. government obligations. As a condition to either of the above elections, we must deliver to the trustee an opinion of counsel that the holders of the debt securities will not recognize income, gain or loss for federal income tax purposes as a result of the action.

If any of the above events occurs, the holders of the debt securities of the series will not be entitled to the benefits of the indenture, except for the rights of holders to receive payments on debt securities or the registration of transfer and exchange of debt securities and replacement of lost, stolen or mutilated debt securities.

Notices

Notices to holders will be given by mail to the addresses of the holders in the security register.

Governing Law

The indentures and the debt securities will be governed by, and construed under, the law of the State of New York.

Regarding the Trustee

The indenture limits the right of the trustee, should it become a creditor of us, to obtain payment of claims or secure its claims.

The trustee is permitted to engage in certain other transactions. However, if the trustee acquires any conflicting interest, and there is a default under the debt securities of any series for which they are trustee, the trustee must eliminate the conflict or resign.

Subordination

Payment on subordinated debt securities will, except as otherwise provided in the indenture, be subordinated in right of payment to the prior payment in full of all of our senior indebtedness (except that holders of the notes may receive and retain (i) permitted junior securities and (ii) payments made from the trust described under Satisfaction and Discharge; Defeasance). Any subordinated debt securities also are effectively subordinated to all debt and other liabilities, including lease obligations, if any.

Upon any distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of and interest on subordinated debt securities will be subordinated in right of payment to the prior payment in full in cash or other payment satisfactory to the holders of senior indebtedness. In the event of any acceleration of subordinated debt securities because of an event of default, the holders of any senior indebtedness would be entitled to payment in full in cash or other payment satisfactory to such holders of all senior indebtedness obligations before the holders of subordinated debt securities are entitled to receive any payment or distribution, except for certain payments made by the trust described under Satisfaction and Discharge; Defeasance. The indenture requires us or the trustee to promptly notify holders of designated senior indebtedness if payment of subordinated debt securities is accelerated because of an event of default.

We may not make any payment on subordinated debt securities, including upon redemption at the option of the holder of any subordinated debt securities or at our option, if:

a default in the payment of the principal, premium, if any, interest, rent or other obligations in respect of designated senior indebtedness occurs and is continuing beyond any applicable period of grace (called a payment default); or

17

TABLE OF CONTENTS

a default other than a payment default on any designated senior indebtedness occurs and is continuing that permits holders of designated senior indebtedness to accelerate its maturity, and the trustee receives notice of such default (called a payment blockage notice) from us or any other person permitted to give such notice under the indenture (called a non-payment default).

If the trustee or any holder of the notes receives any payment or distribution of our assets in contravention of the subordination provisions on subordinated debt securities before all senior indebtedness is paid in full in cash, property or securities, including by way of set-off, or other payment satisfactory to holders of senior indebtedness, then such payment or distribution will be held in trust for the benefit of holders of senior indebtedness or their representatives to the extent necessary to make payment in full in cash or payment satisfactory to the holders of senior indebtedness of all unpaid senior indebtedness.

In the event of our bankruptcy, dissolution or reorganization, holders of senior indebtedness may receive more, ratably, and holders of subordinated debt securities may receive less, ratably, than our other creditors (including our trade creditors). This subordination will not prevent the occurrence of any event of default under the indenture.

We are not prohibited from incurring debt, including senior indebtedness, under the indenture unless otherwise provided in the indenture. We may from time to time incur additional debt, including senior indebtedness.

We are obligated to pay reasonable compensation to the trustee and to indemnify the trustee against certain losses, liabilities or expenses incurred by the trustee in connection with its duties under the indenture. The trustee s claims for these payments will generally be senior to those of noteholders in respect of all funds collected or held by the trustee.

Certain Definitions

indebtedness means:

(1) all indebtedness, obligations and other liabilities for borrowed money, including overdrafts, foreign exchange contracts, currency exchange agreements, interest rate protection agreements, and any loans or advances from banks, or evidenced by bonds, debentures, notes or similar instruments, other than any account payable or other accrued current liability or obligation incurred in the ordinary course of business in connection with the obtaining of materials or services;

(2) all reimbursement obligations and other liabilities with respect to letters of credit, bank guarantees or bankers acceptances;

(3) all obligations and liabilities in respect of leases required in conformity with generally accepted accounting principles to be accounted for as capitalized lease obligations on our balance sheet;

(4) all obligations and other liabilities under any lease or related document in connection with the lease of real property which provides that we are contractually obligated to purchase or cause a third party to purchase the leased property and thereby guarantee a minimum residual value of the leased property to the lessor and our obligations under the lease or related document to purchase or to cause a third party to purchase the leased property;

(5) all obligations with respect to an interest rate or other swap, cap or collar agreement or other similar instrument or agreement or foreign currency hedge, exchange, purchase or other similar instrument or agreement;

TABLE OF CONTENTS

(6) all direct or indirect guaranties or similar agreements in respect of, and our obligations or liabilities to purchase, acquire or otherwise assure a creditor against loss in respect of, indebtedness, obligations or liabilities of others of the type described in (1) through (5) above;

(7) any indebtedness or other obligations described in (1) through (6) above secured by any mortgage, pledge, lien or other encumbrance existing on property which is owned or held by us; and

(8) any and all refinancings, replacements, deferrals, renewals, extensions and refundings of, or amendments, modifications or supplements to, any indebtedness, obligation or liability of the kind described in clauses (1) through (7) above.

permitted junior securities means (i) equity interests in the Company; or (ii) debt securities of the Company that are subordinated to all senior indebtedness and any debt securities issued in exchange for senior indebtedness to substantially the same extent as, or to a greater extent than the notes are subordinated to senior indebtedness under the indenture.

senior indebtedness means the principal, premium, if any, interest, including any interest accruing after bankruptcy, and rent or termination payment on or other amounts due on our current or future indebtedness, whether created, incurred, assumed, guaranteed or in effect guaranteed by us, including any deferrals, renewals, extensions, refundings, amendments, modifications or supplements to the above. However, senior indebtedness does not include:

indebtedness that expressly provides that it shall not be senior in right of payment to subordinated debt securities or expressly provides that it is on the same basis or junior to subordinated debt securities;

our indebtedness to any of our majority-owned subsidiaries; or

subordinated debt securities.

TABLE OF CONTENTS

DESCRIPTION OF WARRANTS

General

We may issue warrants for the purchase of our debt securities, preferred stock or common stock, or any combination thereof. Warrants may be issued independently or together with our debt securities, preferred stock or common stock and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement. We may enter into a warrant agreement with a bank or trust company, as warrant agent. We will indicate the name and address and other information regarding the warrant agent in the applicable prospectus supplement relating to a particular series of warrants. The warrant agent will act solely as our agent in connection with the warrants. The warrant agent will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants. This summary of certain provisions of the warrants is not complete. For the terms of a particular series of warrants, you should refer to the prospectus supplement for that series of warrants and the warrant agreement for that particular series.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to purchase debt securities will describe the terms of the debt warrants, including the following:

the title of the debt warrants;
the offering price for the debt warrants, if any;
the aggregate number of the debt warrants;
the designation and terms of the debt securities, including any conversion rights, purchasable upon exercise of the debt warrants;
if applicable, the date from and after which the debt warrants and any debt securities issued with them will be separately transferable;
the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
the dates on which the right to exercise the debt warrants will commence and expire;
if applicable, the minimum or maximum amount of the debt warrants that may be exercised at any one time;
whether the debt warrants represented by the debt warrant certificates or debt securities that may be issued upon exercise of the debt warrants will be issued in registered or bearer form;
information with respect to book-entry procedures, if any;
the currency or currency units in which the offering price, if any, and the exercise price are payable;
if applicable, a discussion of material U.S. federal income tax considerations;
the antidilution provisions of the debt warrants, if any;
the redemption or call provisions, if any, applicable to the debt warrants;
any provisions with respect to the holder s right to require us to repurchase the warrants upon a change in control or similar event; and
any additional terms of the debt warrants, including procedures, and limitations relating to the exchange, exercise and settlement of the debt warrants.

TABLE OF CONTENTS

Debt warrant certificates will be exchangeable for new debt warrant certificates of different denominations. Debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in the prospectus supplement. Prior to the exercise of their debt warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon exercise and will not be entitled to payment of principal or any premium, if any, or interest on the debt securities purchasable upon exercise.

Equity Warrants

The prospectus supplement relating to a particular series of warrants to purchase our common stock or preferred stock will describe the terms of the warrants, including the following:

the title of the warrants;
the offering price for the warrants, if any;
the aggregate number of warrants;
the designation and terms of the common stock or preferred stock that may be purchased upon exercise of the warrants;
if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each security;
if applicable, the date from and after which the warrants and any securities issued with the warrants will be separately transferable;
the number of shares of common stock or preferred stock that may be purchased upon exercise of a warrant and the exercise price for the warrants;
the dates on which the right to exercise the warrants shall commence and expire;
if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
the currency or currency units in which the offering price, if any, and the exercise price are payable;
if applicable, a discussion of material U.S. federal income tax considerations;
the antidilution provisions of the warrants, if any;
the redemption or call provisions, if any, applicable to the warrants;
any provisions with respect to holder s right to require us to repurchase the warrants upon a change in control or similar event; and
any additional terms of the warrants, including procedures, and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

to vote, consent or receive dividends;
to receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
to exercise any rights as stockholders of the Company.

TABLE OF CONTENTS

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

Limitations on Directors Liability

Our 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 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 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 Securities and Exchange 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 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 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.

TABLE OF CONTENTS

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.

Delaware Takeover Statute.

In general, Section 203 of the Delaware General Corporation Law prohibits a Delaware corporation that is a public company from engaging in any business combination (as defined below) with any interested stockholder (defined generally 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) for a period of three years following the date that such stockholder became an interested stockholder, unless: (1) 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; (2) 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 (3) 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 Delaware General Corporation Law defines business combination to include: (1) any merger or consolidation involving the corporation and the interested stockholder; (2) any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder; (3) 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; (4) 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 (5) 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.

TABLE OF CONTENTS

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 SEC. You may read and copy these reports, proxy statements and other information at the SEC s public reference room at 100 F. Street, N.E., Washington, D.C. 20549 or at the SEC s other public reference facilities. Please call the SEC 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 SEC and paying a fee for the copying costs. In addition, the SEC 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 SEC. Our SEC filings are available on the SEC s Internet site.

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 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. 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.

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 Securities Exchange Act of 1934, as amended, or 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 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, 2009, filed on March 17, 2010, as amended by Amendment No. 1 to Annual Report on Form 10-K/A filed on April 30, 2010;

Quarterly Report on Form 10-Q for the quarter ended March 31, 2010, filed on April 30, 2010;

Current Reports on Form 8-K filed on January 27, 2010 and April 6, 2010; 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 SEC on September 20, 2006.

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.
1180 Avenue of the Americas, 19th Floor
New York, NY 10036
Attention: President
Telephone: (646) 214-0700

You should rely only on the information incorporated by reference or provided in this prospectus or any supplement. We have not authorized anyone else to provide you with different information. The selling stockholders will not make an offer of these shares in any state where the offer is not permitted. You should not assume that the information in this prospectus or any supplement is accurate as of any date other than the date on the front of these documents.

TABLE OF CONTENTS

LEGAL MATTERS

The validity of the securities offered hereby will be passed upon by Maslon Edelman Borman & Brand, LLP, Minneapolis, Minnesota.

EXPERTS

The balance sheets of ZIOPHARM Oncology, Inc. as of December 31, 2009 and 2008 and the related statements of operations, changes in convertible preferred stock and stockholders equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2009 and for the period from September 9, 2003 (date of inception) through December 31, 2009, included in this prospectus, have been included herein in reliance on the report, dated March 17, 2010, of Caturano and Company, P.C., independent registered public accounting firm, (which report expresses an unqualified opinion and includes an explanatory paragraph relating to the change in the manner in which the Company accounts for certain warrants), given on the authority of that firm as experts in auditing and accounting.

TABLE OF CONTENTS

Shares

Common Stock

Prospectus Supplement

Sole Book-Running Manager

Jefferies & Company

Co-Manager

JMP Securities

2010