

ZIOPHARM ONCOLOGY INC

Form S-3

November 07, 2011

As filed with the Securities and Exchange Commission November 7, 2011

Registration No. 333-

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

FORM S-3
REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

ZIOPHARM Oncology, Inc.
(Exact name of registrant as specified in its charter)

Delaware
(State or jurisdiction
of incorporation or organization)

84-1475642
(I.R.S. Employer
Identification No.)

1180 Avenue of the Americas, 19th Floor
New York, NY 10036
(646) 214-0700

(Address and telephone number of registrant's principal executive offices and principal place of business)

Caesar Belbel
Chief Legal Officer
ZIOPHARM Oncology, Inc.
One First Avenue, Building 34
Boston, Massachusetts 02129
(617) 259-1970

(Name, address and telephone number of agent for
service)

Copies to:
Marc Recht, Esq.
Cooley LLP
500 Boylston Street, 14th Floor
Boston, Massachusetts 02116
(617) 937-2300

Approximate date of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box:

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. "

If this form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. "

If this form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. "

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

Large accelerated filer "

Accelerated filer

Non-accelerated filer "

Smaller reporting company "

(Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title Of Each Class Of Securities To Be Registered	Amount To Be Registered (1)	Proposed Maximum Offering Price Per Security (2)	Proposed Maximum Aggregate Offering Price (2)	Amount Of Registration Fee (3)
Common stock, par value \$0.001 per share				
Preferred Stock, par value \$0.001 per share				
Warrants				
Debt Securities				
Total			\$ 150,000,000	\$ 17,190(4)

- (1) An indeterminate number of shares of common stock and preferred stock, an indeterminate number of warrants to purchase common stock, preferred stock and/or debt securities, and an indeterminate principal amount of debt securities are being registered hereunder, which together shall have an aggregate initial offering price not to exceed \$150,000,000. If any debt securities are issued at an original issue discount, then the offering price of such debt securities shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed \$150,000,000, less the aggregate dollar amount of all securities previously issued hereunder. Any securities registered hereunder may be sold separately or as units with other securities registered hereunder. The proposed maximum offering price per unit will be determined, from time to time, by the registrant in connection with the issuance by the registrant of the securities registered hereunder. The securities registered hereunder also include such indeterminate number of shares of common stock and preferred stock and amount of debt securities as may be issued upon conversion of or exchange for preferred stock or debt securities that provide for conversion or exchange, upon exercise of warrants or pursuant to the antidilution provisions of any of such securities. In addition, pursuant to Rule 416 under the Securities Act, there are also being registered hereunder an indeterminate number of shares of common stock and preferred stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends or similar transactions.
- (2) The proposed maximum aggregate offering price per class of security will be determined from time to time by the registrant in connection with the issuance by the registrant of the securities registered hereunder and is not specified as to each class of security pursuant to General Instruction II.D. of Form S-3 under the Securities Act.
- (3) Calculated pursuant to Rule 457(o) under the Securities Act.
- (4) In accordance with Rule 415(a)(6) and Rule 457(p) under the Securities Act of 1933, the registrant hereby offsets from the total registration fee due under this registration statement the amount of the filing fee paid for the unsold securities registered by the registrant's registration statement on Form S-3, filed with the Securities and Exchange Commission, or the Commission, on April 30, 2010, as amended by Form S-3/A, filed with the Commission on May 10, 2010 (File No. 333-166444), registering securities for a maximum aggregate offering price of \$150,000,000 (collectively, the "Prior Registration Statement"). Of that amount, the registrant sold certain of its securities having an aggregate offering price of \$98,480,000, leaving a balance of unsold securities with an aggregate offering price of \$1,520,000. The associated filing fee of \$176.47 paid for such unsold securities, calculated under Rule 457(o), is hereby used to offset the current registration fee due. Accordingly, the full amount of the \$17,190.00 registration fee currently due for this registration statement has been partially paid by offset against the balance of the fee paid for the Prior Registration Statement and the registrant is paying \$17,013.53 in filing fees for this registration statement. Pursuant to Rule 415(a)(6), the offering of the unsold securities registered under the Prior Registration Statement will be deemed terminated as of the date of effectiveness of this registration

statement.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated November 7, 2011

PROSPECTUS

\$150,000,000

ZIOPHARM Oncology, Inc.

Common Stock
Preferred Stock
Warrants
Debt Securities

From time to time, we may offer and sell any combination of common stock, preferred stock, warrants and debt securities, with a total initial offering price of up to \$150,000,000. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants.

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

Our common stock is listed on the NASDAQ Capital Market under the symbol "ZIOP." On November 4, 2011, the closing price of our common stock, as reported on the NASDAQ Capital Market, was \$4.68.

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

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

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free

writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus.

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

The date of this Prospectus is _____, 2011.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the Commission, using a “shelf” registration process. Under this shelf registration process, from time to time, we may sell any combination of the securities described in this prospectus in one or more offerings, up to a total dollar amount of \$150,000,000. 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 authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement, and any related free writing prospectus that we may authorize to be provided to you, may also add, update or change the information contained in this prospectus or in the documents incorporated by reference into this prospectus. We urge you to carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the headings “Where You Can Find More Information” and “Incorporation of Information by Reference” before buying any of the securities being offered. **THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.**

You should rely only on the information contained in, or incorporated by reference into, this prospectus or any applicable prospectus supplement, along with the information contained in any related free writing prospectus that we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different information. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus that we may authorize to be provided to you. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document, and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

PROSPECTUS SUMMARY

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

Our Company

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that is seeking to develop and commercialize a diverse portfolio of in-licensed cancer drugs that can address unmet medical needs. Our principal focus has been 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, or IV, and/or oral dosing. Our clinical programs for our small molecule candidates include palifosfamide (Zymafos™ or ZIO-201) darinaparsin (Zinapar™ or ZIO-101) and indibulin (Zybulin™ or ZIO-301). We are also pursuing the development of novel DNA-based biotherapeutics in the field of cancer pursuant to a partnering arrangement with Intrexon Corporation, or Intrexon. Under the arrangement, we obtained rights to Intrexon’s effector platform for use in the field of oncology, which includes two existing clinical stage product candidates, ZIN-CTI-001 (or DC-RTS-IL-12 + AL) and ZIN-ATI-001 (or Ad-RTS-IL-12 + AL). We plan to leverage Intrexon’s synthetic biology platform to develop products to stimulate key pathways used by the body’s immune system to inhibit the growth and metastasis of cancers, adding significantly to our small molecule drug development portfolio utilizing our global capabilities to translate science to the patient setting. Descriptions of our current clinical development plans for palifosfamide, darinaparsin, indibulin, ZIN-CTI-001 and ZIN-ATI-001 are set forth below. More detailed descriptions of these product candidates and our clinical development plans for each are also set forth in the our Annual Report on Form 10-K for the fiscal year ended December 31, 2010, incorporated by reference herein, and in other reports that we file from time to time with the Securities and Exchange Commission, or the Commission.

We believe that our strategy will result in expedited drug development programs for product candidates with a cost of manufacturing that, upon successful commercialization, would help to address changing worldwide product reimbursement requirements. We are currently in Phase 1, 2, and/or Phase 3 studies for our product candidates with a particular emphasis on completing a global palifosfamide pivotal Phase 3 trial to support registration in combination with doxorubicin in the front-line setting of metastatic soft tissue sarcoma.

Product Candidates

ZIO-101, Darinaparsin, Zinapar™

Darinaparsin is a novel mitochondrial-targeted agent (organic arsenic) in development with IV and oral administrations. Phase 1 testing of the IV form of darinaparsin in solid tumors and hematological cancers was completed and we reported clinical activity and, importantly, a safety profile from these studies as predicted by preclinical results. We subsequently completed Phase 2 studies in advanced myeloma, primary liver cancer and in certain other hematological cancers. 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, or PTCL. With focus on the relapsed setting, a Phase 1 study of darinaparsin in

combination with the treatment regimen called “CHOP” in the front-line setting of PTCL was ended. A Phase 1 trial with an oral form of darinaparsin is currently in progress in a solid tumor Phase 1 study. Data from the completion of this study will guide further study in solid tumors and/or PTCL. We have obtained Orphan Drug Designation for darinaparsin in the United States and Europe for the treatment of PTCL.

ZIO-201, Palifosfamide, Zymafos™

Palifosfamide is a novel DNA cross-linker (stabilized active metabolite of ifosfamide) in class with bendamustine, ifosfamide, and cyclophosphamide and currently in development with IV administration (oral in late preclinical). Following Phase 1 study, we completed Phase 2 testing of the IV form of palifosfamide as a single agent to treat advanced sarcoma. In both Phase 1 and Phase 2 testing, palifosfamide has been administered without the “uroprotectant” mesna as is required with ifosfamide, and the toxicities associated with other ifosfamide metabolites, acrolein and chloroacetaldehyde, have not been observed. We reported clinical activity of palifosfamide when used alone in the Phase 2 study addressing advanced sarcoma. Following review of preclinical combination studies, we initiated a Phase 1 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 2 single agent clinical activity data and with the combination being well tolerated in the Phase 1 trial, we initiated a Phase 2 randomized controlled trial, entitled PICASSO, 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 generated positive top line interim data in 2009. Upon successfully 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 and again at the 2010 ASCO annual meeting in June 2010, where the presentation was selected for “Best of ASCO.” In July 2010, we announced the initiation of a worldwide registration trial on a protocol design developed through a FDA End-of-Phase 2 meeting and the Special Protocol Assessment, or SPA, process. Although we did engage in the SPA process, we, with guidance from the U.S. Food and Drug Administration, or FDA, elected to initiate the trial without having obtained SPA agreement from the FDA. The Phase 3 trial is in front-line metastatic soft tissue sarcoma, entitled PICASSO 3, and is an international, randomized, double-blinded, placebo-controlled trial with a targeted enrollment of 424 patients. The study is designed to evaluate the safety and efficacy of palifosfamide administered with doxorubicin compared with doxorubicin administered with placebo, with no cross-over between the arms. Progression-free survival is the primary endpoint for accelerated approval, with overall survival as the primary endpoint for full approval PICASSO 3 has no interim data analysis, although the trial is monitored by a Data Monitoring Committee, or DMC, of outside, independent experts. The DMC has met twice to review trial data for safety and futility and on both occasions has recommended trial continuation. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of soft tissue sarcomas.

A Phase 1 trial is also ongoing with palifosfamide in combination with etoposide and carboplatin to determine appropriate safety for initiating a potentially pivotal, adaptive trial in front-line small-cell lung cancer, or SCLC. An oral form of palifosfamide has been the subject of preclinical studies necessary for an Investigational New Drug, or IND, application to support commencing Phase 1 study. Based on an initial review, the FDA has requested that we repeat an animal study, that is currently underway, in order to support the planned Phase 1 protocol.

ZIO-301, Indibulin, Zybulin™

Indibulin is a novel orally administered tubulin binding agent. Phase 1 study as a single agent in patients with advanced solid tumors has been completed. We have reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging preclinical results obtained with indibulin in combination with other chemotherapies, two Phase 1 combination studies were initiated with Tarceva™ and Xeloda™, respectively. The favorable activity and safety profile of oral indibulin with oral Xeloda™ was reported at ASCO’s annual meeting in May 2009. In all studies, a maximum tolerated dose, or MTD, was not established. Preclinical work with our consultant, Dr. Larry Norton, established a dosing schedule to enhance activity and reduce toxicity, which is presently five days on drug and nine

days off in a Phase 1 study in late stage metastatic breast cancer. In light of the lack of establishing an MTD and the need to administer many capsules several times a day, we have recently modified the dosage form to administer once a day dosing in the Phase 1 trial.

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ZIN-CTI-001 (or DC-RTS-IL-12 + AL) and ZIN-ATI-001 (or Ad-RTS-IL-12 + AL)

We are also pursuing the development of novel DNA-based therapeutics in the field of cancer pursuant to an exclusive channel partnership with Intrexon. The partnership includes two existing clinical-stage product candidates. ZIN-CTI-001 is in a Phase 1b trial in the United States and employs intratumoral injection of modified dendritic cells from each patient and oral dosing of an activator ligand to turn on in vivo expression of interleukin-12, or IL-12. ZIN-CTI-001 uses a RheoSwitch Therapeutic System® (RTS) to control the timing and level of transgene expression for gene and cell therapy. The RTS technology functions as a “gene switch” for the regulated expression of human IL-12 in the patients’ dendritic cells, which are transduced with a replication deficient adenoviral vector carrying the IL-12 gene under the control of the RTS and in this study injected intratumorally for the treatment of patients with stage III or IV melanoma. The binding of the small molecule activator to the fusion proteins of RTS is intended to regulate the timing and level of IL-12 expression. In the absence of the activator ligand, the level of IL-12 is below detectable levels.

The activator ligand has been the subject of a number of preclinical, safety and pharmacology studies under FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. Preclinical studies in the B16 mouse melanoma model consistently induced regression of established melanoma lesions, both in those directly injected and those elsewhere in the body. Preclinical studies have shown DC-RTS-IL-12, in combination with an activator ligand, to have strong activity against a broad array of cancers, including brain, colon, renal, and pancreatic cancers and melanoma.

A Phase 1a clinical study of the activator ligand was conducted in 65 healthy volunteers, with the two most common side effects being dysgeusia (impairment of taste) and throat irritation. A subsequent Phase 1b trial, which is ongoing in patients with advanced melanoma, has been amended to study efficacy and immunological and biological effects in addition to safety with cohort-based dose escalation of the activator ligand during repeated treatment cycles. Initial positive clinical results from the Phase 1b trial were presented at the June 2011 ASCO annual meeting. The trial enrolled ten patients (median age 61) with unresectable Stage III or IV melanoma. Among eight evaluable patients, partial or complete regression of injected and some uninjected lesions was observed by computed axial tomography scans in three patients, with one patient having a RECIST PR of >11 months and three patients demonstrating stable disease by RECIST, for an overall disease control rate of 50%. Treatment was generally well tolerated, and maximum tolerated dose has not yet been reached. Adverse events were mild to moderate, with one to two patients each experiencing nausea, vomiting, anorexia, arthralgia, fever or chills. One severe adverse event was reported 18 hours after treatment onset with 60 mg AL + ZIN-CTI-001, and included diarrhea, followed by hypotension and reversible acute renal failure, which completely resolved.

The FDA has recently accepted our IND application to begin clinical study of ZIN-ATI-001 in oncology and patient enrollment is underway. The Phase 1 study will evaluate safety in addition to immunological and biological effects of the therapeutic candidate in patients with melanoma.

We intend to evaluate both ZIN-CTI-001 and ZIN-ATI-001 with the intent either to further develop both candidates or to select one of the two candidates for further study. ZIN-ATI-001 is identical to ZIN-CTI-001 except that the autologous dendritic cell component is omitted. Both product candidates are targeted for further development in different indications.

Development Plans

We are currently pursuing several clinical programs which include:

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palifosfamide (Zymafos™ or ZIO-201) – completing our Phase 3 pivotal trial in front-line metastatic soft tissue sarcoma, entitled PICASSO 3, and completing our recently initiated Phase 1 trial with palifosfamide in combination with etoposide and carboplatin to determine appropriate safety for initiating a subsequent randomized trial in front-line small-cell lung cancer.

- darinaparsin (Zinapar™ or ZIO-101) – completing an ongoing Phase 1 study with an oral form.

indibulin (Zybulin™ or ZIO-301) – entering the Phase 2 portion of the Phase 1/2 trial having established the MTD in Phase 1 with once daily dosing.

ZIN-CTI-001 - completing a Phase 1b trial in patients with advanced melanoma that is on-going in the United States.

ZIN-ATI-001 – completing the Phase 1 trial treatment of patients with late-stage malignant melanoma that is the subject of an IND application recently accepted by FDA.

We are also in late preclinical evaluation with respect to several additional potential product candidates under our channel partnership with Intrexon and we anticipate continuing evaluation to select product candidates for clinical study, which could commence as early as 2012. We also anticipate continuing discovery efforts aimed at identifying additional potential product candidates under the Intrexon channel partnership for study thereafter.

Our current plans involve using internal financial resources to develop palifosfamide and pursue the clinical work outlined above, with the intention of ultimately partnering or otherwise raising additional resources to support further development activities for all of our product candidates. 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 product candidates in any market and, therefore, have not generated any revenues from our product candidates.

Corporate Information

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

Our principal executive offices are located at 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. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement.

RISK FACTORS

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

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

- the progress, timing and results of preclinical and clinical trials involving our drug candidates;
 - the progress of our research and development programs;
- our plans or others’ plans to conduct future clinical trials or research and development efforts;
- the risk that final trial data may not support interim analysis of the viability of our drug candidates;
 - our plans and expectations regarding partnering our drug candidates;
 - the benefits to be derived from relationships with our collaborators;
 - the receipt or anticipated receipt of regulatory clearances and approvals;
 - estimates of the potential markets for our drug candidates;
 - our ability to adequately protect our intellectual property rights;
 - the use of proceeds from this offering;
 - our estimates of future revenues and profitability; 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”, “expect”, “plans”, “anticipates”, “believes”, “estimates”, “projects”, “predicts”, “potential” and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on

assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading “Risk Factors” in the applicable prospectus supplement or free writing prospectus and in our reports filed from time to time under the Securities Act and/or the Exchange Act. We encourage you to read these filings as they are made. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

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

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

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

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

	Year Ended December 31,					Nine Months Ended September 30, 2011
	2006	2007	2008	2009	2010	
Ratio of earnings to fixed charges	—	—	—	—	—	—
Ratio of earnings to combined fixed charges and preference dividends	—	—	—	—	—	—

For purposes of computing the ratio of earnings to fixed charges and the ratio of earnings to our combined fixed charges and preference dividends, earnings consist of our net income (loss) before tax benefit (provision) for the period plus fixed charges. Fixed charges consist of interest expense and amortized premiums, discounts and capitalized expenses related to indebtedness. The ratio of earnings to fixed charges and the ratio of earnings to combined fixed charges and preference dividends were less than one-to-one for each of the periods presented. Earnings were insufficient to cover fixed charges by \$17.9 million in 2006, \$26.6 million in 2007, \$25.2 million in 2008, \$7.6 million in 2009, \$32.7 million in 2010 and \$50.5 million in the nine months ended September 30, 2011.

USE OF PROCEEDS

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

DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus, our authorized capital stock consists of 280,000,000 shares, comprised of 250,000,000 shares of common stock, par value \$.001 per share, and 30,000,000 shares of preferred stock, par value \$.001 per share. As of October 28, 2011, there were 68,451,324 shares of common stock and no shares of preferred stock issued and outstanding. Our common stock is traded on the NASDAQ Capital Market under the symbol "ZIOP".

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

Common Stock

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

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

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

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

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

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

Preferred Stock

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

designation, powers, preferences and rights of the shares of each series and any qualifications, limitations or restrictions thereof, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

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

- the title and stated value;
- the number of shares offered;
- the liquidation preference per share;
- the purchase price per share;
- the dividend rate(s), period(s) and/or payment date(s) or method(s) of calculation for dividends;
- whether dividends are cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- our right, if any, to defer payment of dividends and the maximum length of any such deferral period;
 - the procedures for any auction and remarketing, if any;
 - the provisions for a sinking fund, if any;
- the provision for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
 - any listing of the preferred stock on any securities exchange or market;
- the terms and conditions, if applicable, upon which the preferred stock will be convertible into common stock, including the conversion price (or manner of calculation) and conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;
 - voting rights, if any, of the preferred stock;
 - preemptive rights, if any;
 - restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material and/or special U.S. federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights upon the liquidation, dissolution or winding up of our affairs;

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

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

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

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

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

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. 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. The particular terms of each series of debt securities will be described in more detail in the applicable prospectus supplement or any related free writing prospectus. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below.

Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

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

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

General

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

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

- 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 applicable subordination provisions for any subordinated debt securities;
- 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.

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 indenture.

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. Except as described in the prospectus supplement, the corporate trust office of the trustee 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 each series.

All moneys paid by us to a paying agent for payment on any debt security that 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 applicable 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 sell, convey, transfer or lease all or substantially all of our assets 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.

Events of Default

Unless we inform you otherwise in the applicable 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 applicable 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.

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 indenture, or for the appointment of a receiver or a trustee, or for any other remedy under the indenture, 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 indenture (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;
- 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 indenture:

- to cure any ambiguity, defect or inconsistency;
- 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 materially adversely affect the legal rights under the indenture of any such holder;
- to comply with requirements of the SEC in order to effect or maintain the qualification of the indenture under the Trust Indenture Act of 1939; 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 indenture 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.

The 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 certain 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.

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.

Subordinated Debt Securities

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.

Notices

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

Governing Law

The indenture and the debt securities will be governed by, and construed under, the law of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

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 or free writing prospectus 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 or free writing prospectus for that series of warrants and the warrant agreement for that particular series. The terms of any warrants we offer under a prospectus supplement or free writing prospectus may differ from the terms we describe below.

Debt Warrants

The prospectus supplement or free writing prospectus 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.

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 or free writing prospectus.

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 or to enforce covenants in the indenture.

Equity Warrants

The prospectus supplement or free writing prospectus 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.

Exercise of Warrants

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

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

Governing Law

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

Enforceability of Rights by Holders of Warrants

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

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

Limitations on Directors' Liability

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

- the benefits to be derived from relationships with our collaborators;
- any breach of his or her duty of loyalty to the registrant or its stockholders;
- acts or omissions not in good faith which involve intentional misconduct or a knowing violation of law;
- the payment of dividends or the redemption or purchase of stock in violation of Delaware law; or
- any transaction from which the director derived an improper personal benefit.

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

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

Provisions that May Have an Anti-Takeover Effect

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

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

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

Delaware Takeover Statute.

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

- prior to such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- on consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding those shares owned (x) by persons who are directors and also officers and (y) by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or subsequent to such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 $\frac{2}{3}$ % of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 of the DGCL defines “business combination” to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

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

PLAN OF DISTRIBUTION

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

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the times of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

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

- the name or names of the underwriters, if any;
- the purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;
 - any over-allotment options under which underwriters may purchase additional securities from us;
 - any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;
 - any public offering price;
 - any discounts or concessions allowed or reallocated or paid to dealers; and
 - any securities exchange or market on which the securities may be listed.

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

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

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus

supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

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

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

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

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

LEGAL MATTERS

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

EXPERTS

The financial statements as of and for the year ended December 31, 2010 and for the period from September 9, 2003 (date of inception) through December 31, 2010, incorporated by reference into this prospectus and registration statement, and the effectiveness of internal control over financial reporting as of December 31, 2010, have been audited by McGladrey & Pullen, LLP, an independent registered public accounting firm, as stated in their report incorporated by reference herein, and are included in reliance upon such reports and upon the authority of such firm as experts in accounting and auditing.

The balance sheet as of December 31, 2009 and the related statements of operations, changes in preferred stock and stockholders' equity (deficit) and cash flows for each of the years in the two-year period ended December 31, 2009, incorporated by reference into the registration statement of which this prospectus is a part, have been included herein in reliance on the report, dated March 17, 2010, of Caturano and Company, P.C. (whose name has since been changed to Caturano and Company, Inc.), independent registered public accounting firm, given on the authority of that firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the Commission. You may read and copy these reports, proxy statements and other information at the

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

INCORPORATION OF INFORMATION BY REFERENCE

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

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

- Annual Report on Form 10-K for the fiscal year ended December 31, 2010, filed on March 1, 2011;
- Quarterly Reports on Form 10-Q for the quarters ended March 31, 2011, June 30, 2011, and September 30, 2011, filed on May 5, 2011, August 1, 2011 (as amended by Amendment No. 1 on Form 10-Q/A filed on August 9, 2011), and November 3, 2011, respectively;
- Current Reports on Form 8-K filed on January 5, January 12, January 26, February 3 (excluding Item 2.02), February 7 (two filings), February 8, March 7, May 9, May 13, May 19, May 23, June 3, June 6, June 10, June 22, July 15, 2011, September 6, 2011, October 28, 2011 and November 3, 2011; and
- The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the Commission on September 20, 2006, including any amendments or reports filed for purposes of updating such description.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered a copy of any or all of the documents that are incorporated by reference in this prospectus but not delivered with this prospectus, including exhibits that are specifically incorporated by reference in such documents. You may request a copy of such documents at no cost, by writing or telephoning us at the following address or telephone number:

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

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses Of Issuance And Distribution.

The following table sets forth the fees and expenses, other than underwriting compensation, payable in connection with the registration of securities hereunder. All amounts are estimates except for the Commission registration fee. The assumed amount has been used to demonstrate the expenses of an offering and does not represent an estimate of the amount of securities that may be registered or distributed because such amount is unknown at this time.

Commission registration fee	\$ 17,190
Legal fees and expenses	\$ 75,000
Accounting fees and expenses	\$ 25,000
Printing and engraving expenses	\$ 25,000
Miscellaneous expenses	\$ 25,000
Blue sky fees and expenses	\$ 25,000
Total	\$ 192,190

Item 15. Indemnification of Directors and Officers.

Under Article 6 of the registrant's bylaws, each director and officer of the registrant will be indemnified to the fullest extent permitted by applicable law as it presently exists or may hereafter be amended, who was or is made or is threatened to be made a party or is otherwise involved in any action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that he or she, or a person for whom he or she is the legal representative, is or was a director or officer of the registrant or, while a director or officer of the registrant, is or was serving at the request of the registrant as a director, officer, employee or agent of another corporation or of a partnership, joint venture, trust, enterprise or nonprofit entity, including service with respect to employee benefit plans, against all liability and loss suffered and expenses (including attorneys' fees) reasonably incurred by such director or officer. However, the registrant shall be required to indemnify a director or officer in connection with a proceeding commenced by such director or officer only if the commencement of such proceeding (or part thereof) by the director or officer was authorized by the Board. The registrant's Amended and Restated Certificate of Incorporation also eliminates the liability of directors of the registrant for monetary damages to the fullest extent permissible under Delaware law.

Section 145 of the Delaware General Corporation Law states:

(a) A corporation shall have power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of the corporation) by reason of the fact that the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with such action, suit or proceeding if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe the person's conduct was unlawful. The termination of any action, suit or proceeding by judgment, order, settlement, conviction, or upon a plea of nolo contendere or its equivalent, shall not, of itself, create a presumption that the person did not act in good faith and in a manner which the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had reasonable cause to believe that the person's conduct was unlawful.

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(b) A corporation shall have power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor by reason of the fact that the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise against expenses (including attorneys' fees) actually and reasonably incurred by the person in connection with the defense or settlement of such action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation and except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

(c) To the extent that a present or former director or officer of a corporation has been successful on the merits or otherwise in defense of any action, suit or proceeding referred to in subsections (a) and (b) of this section, or in defense of any claim, issue or matter therein, such person shall be indemnified against expenses (including attorneys' fees) actually and reasonably incurred by such person in connection therewith.

(d) Any indemnification under subsections (a) and (b) of this section (unless ordered by a court) shall be made by the corporation only as authorized in the specific case upon a determination that indemnification of the present or former director, officer, employee or agent is proper in the circumstances because the person has met the applicable standard of conduct set forth in subsections (a) and (b) of this section. Such determination shall be made, with respect to a person who is a director or officer of the corporation at the time of such determination:

- (1) By a majority vote of the directors who are not parties to such action, suit or proceeding, even though less than a quorum; or
- (2) By a committee of such directors designated by majority vote of such directors, even though less than a quorum; or
- (3) If there are no such directors, or if such directors so direct, by independent legal counsel in a written opinion; or
- (4) By the stockholders.

(e) Expenses (including attorneys' fees) incurred by an officer or director of the corporation in defending any civil, criminal, administrative or investigative action, suit or proceeding may be paid by the corporation in advance of the final disposition of such action, suit or proceeding upon receipt of an undertaking by or on behalf of such director or officer to repay such amount if it shall ultimately be determined that such person is not entitled to be indemnified by the corporation as authorized in this section. Such expenses (including attorneys' fees) incurred by former directors and officers or other employees and agents of the corporation or by persons serving at the request of the corporation as directors, officers, employees or agents of another corporation, partnership, joint venture, trust or other enterprise may be so paid upon such terms and conditions, if any, as the corporation deems appropriate.

(f) The indemnification and advancement of expenses provided by, or granted pursuant to, the other subsections of this section shall not be deemed exclusive of any other rights to which those seeking indemnification or advancement of expenses may be entitled under any bylaw, agreement, vote of stockholders or disinterested directors or otherwise, both as to action in such person's official capacity and as to action in another capacity while holding such office. A right to indemnification or to advancement of expenses arising under a provision of the certificate of incorporation or a bylaw shall not be eliminated or impaired by an amendment to such provision after the occurrence of the act or omission that is the subject of the civil, criminal, administrative or investigative action, suit or proceeding for which

indemnification or advancement of expenses is sought, unless the provision in effect at the time of such act or omission explicitly authorizes such elimination or impairment after such action or omission has occurred.

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(g) A corporation shall have power to purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise against any liability asserted against such person and incurred by such person in any such capacity, or arising out of such person's status as such, whether or not the corporation would have the power to indemnify such person against such liability under this section.

(h) For purposes of this section, references to "the corporation" shall include, in addition to the resulting corporation, any constituent corporation (including any constituent of a constituent) absorbed in a consolidation or merger which, if its separate existence had continued, would have had power and authority to indemnify its directors, officers, and employees or agents, so that any person who is or was a director, officer, employee or agent of such constituent corporation, or is or was serving at the request of such constituent corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, shall stand in the same position under this section with respect to the resulting or surviving corporation as such person would have with respect to such constituent corporation if its separate existence had continued.

(i) For purposes of this section, references to "other enterprises" shall include employee benefit plans; references to "fines" shall include any excise taxes assessed on a person with respect to any employee benefit plan; and references to "serving at the request of the corporation" shall include any service as a director, officer, employee or agent of the corporation which imposes duties on, or involves services by, such director, officer, employee or agent with respect to an employee benefit plan, its participants or beneficiaries; and a person who acted in good faith and in a manner such person reasonably believed to be in the interest of the participants and beneficiaries of an employee benefit plan shall be deemed to have acted in a manner "not opposed to the best interests of the corporation" as referred to in this section.

(j) The indemnification and advancement of expenses provided by, or granted pursuant to, this section shall, unless otherwise provided when authorized or ratified, continue as to a person who has ceased to be a director, officer, employee or agent and shall inure to the benefit of the heirs, executors and administrators of such a person.

(k) The Court of Chancery is hereby vested with exclusive jurisdiction to hear and determine all actions for advancement of expenses or indemnification brought under this section or under any bylaw, agreement, vote of stockholders or disinterested directors, or otherwise. The Court of Chancery may summarily determine a corporation's obligation to advance expenses (including attorneys' fees).

The registrant maintains insurance on behalf of its officers and directors, insuring them against liabilities that they may incur in such capacities or arising out of this status.

The above discussion of the registrant's Amended and Restated Certificate of Incorporation and Bylaws and of Section 145 of the Delaware General Corporation Law is not intended to be exhaustive and is respectively qualified in its entirety by such Amended and Restated Certificate of Incorporation, Bylaws and statute.

To the extent that our directors, officers and controlling persons are indemnified under the provisions contained in our amended and restated certificate of incorporation, Delaware law or contractual arrangements against liabilities arising under the Securities Act, we have been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933, as amended, and is therefore unenforceable.

Item 16. Exhibits.

The following exhibits are filed as part of this Registration Statement:

Exhibit No.	Description of Document
1.1 *	Underwriting Agreement
4.1	Amended and Restated Certificate of Incorporation, as filed with the Delaware Secretary of State on April 26, 2006 (incorporated by reference to Exhibit 3.1 to the registrant's Current Report on Form 8-K filed April 26, 2006)
4.2	Bylaws, as amended to date (incorporated by reference to Exhibit 3.3 to the registrant's Current Report on Form 8-K filed September 19, 2005)
4.3	Specimen common stock certificate (incorporated by reference to Exhibit 4.1 to the registrant's Registration Statement on Form SB-2 (SEC File No. 333-129020) filed October 14, 2005)
4.4 *	Specimen preferred stock certificate
4.5 *	Form of Debt Security
4.6	Form of Indenture between the registrant and one or more trustees to be named
4.7 *	Form of Warrant
4.8 *	Form of Warrant Agreement
5.1	Legal opinion of Cooley LLP
12.1	Statement of Computation of Ratio of Earnings to Fixed Charges and Ratio of Combined Fixed Charges and Preferred Stock Dividends
23.1	Consent of Independent Registered Public Accounting Firm – McGladrey & Pullen, LLP
23.2	Consent of Independent Registered Public Accounting Firm – Caturano and Company, Inc.
23.3	Consent of Cooley LLP (included as part of Exhibit 5.1)
24.1	Power of Attorney (included on signature page)
25.1**	Statement of Eligibility of Trustee on Form T-1

* To be filed by amendment or as an exhibit to a report pursuant to Section 13(a), 13(c) or 15(d) of the Exchange Act.

** To be filed pursuant to Section 305(b)(2) of the Trust Indenture Act of 1939 at the time of an offering of debt securities.

Item 17. Undertakings.

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation

of Registration Fee” table in the effective registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that the undertakings set forth in paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement or is contained in a form of prospectus filed pursuant to Rule 424(b) that is a part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

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(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(i) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(5) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers, and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has 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. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

(d) The registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Securities and Exchange Commission under Section 305(b)(2) of the Trust Indenture Act.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Boston, Commonwealth of Massachusetts, on November 7, 2011.

ZIOPHARM Oncology, Inc.

By: /s/ Richard E. Bagley
Richard E. Bagley
President, Chief Financial Officer, Treasurer
and
Chief Operating Officer

POWER OF ATTORNEY

Each person whose signature appears below hereby constitutes and appoints Jonathan Lewis and Richard E. Bagley, and each of them, as his true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments and registration statements filed pursuant to Rule 462) to this registration statement, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent or his substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Jonathan Lewis Jonathan Lewis	Director and Chief Executive Officer (Principal Executive Officer)	November 7, 2011
/s/ Richard Bagley Richard Bagley	Director, President, Chief Financial Officer, Treasurer and Chief Operating Officer (Principal Accounting and Financial Officer)	November 7, 2011
/s/ Murray Brennan Murray Brennan	Director	November 7, 2011
/s/ James Cannon James Cannon	Director	November 7, 2011
/s/ Wyche Fowler, Jr. Wyche Fowler, Jr.	Director	November 7, 2011

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/s/ Randal J. Kirk Randal J. Kirk	Director	November 7, 2011
/s/ Timothy McInerney Timothy McInerney	Director	November 7, 2011
/s/ Michael Weiser Michael Weiser	Director	November 7, 2011

EXHIBIT INDEX

Exhibit No.	Description of Document
1.1 *	Underwriting Agreement
4.1	Amended and Restated Certificate of Incorporation, as filed with the Delaware Secretary of State on April 26, 2006 (incorporated by reference to Exhibit 3.1 to the registrant's Current Report on Form 8-K filed April 26, 2006)
4.2	Bylaws, as amended to date (incorporated by reference to Exhibit 3.3 to the registrant's Current Report on Form 8-K filed September 19, 2005)
4.3	Specimen common stock certificate (incorporated by reference to Exhibit 4.1 to the registrant's Registration Statement on Form SB-2 (SEC File No. 333-129020) filed October 14, 2005)
4.4 *	Specimen preferred stock certificate
4.5 *	Form of Debt Security
4.6	Form of Indenture between the registrant and one or more trustees to be named
4.7 *	Form of Warrant
4.8 *	Form of Warrant Agreement
5.1	Legal opinion of Cooley LLP
12.1	Statement of Computation of Ratio of Earnings to Fixed Charges and Ratio of Combined Fixed Charges and Preferred Stock Dividends
23.1	Consent of Independent Registered Public Accounting Firm – McGladrey & Pullen, LLP
23.2	Consent of Independent Registered Public Accounting Firm – Caturano and Company, Inc.
23.3	Consent of Cooley LLP (included as part of Exhibit 5.1)
24.1	Power of Attorney (included on signature page)
25.1**	Statement of Eligibility of Trustee on Form T-1

* To be filed by amendment or as an exhibit to a report pursuant to Section 13(a), 13(c) or 15(d) of the Exchange Act.

** To be filed pursuant to Section 305(b)(2) of the Trust Indenture Act of 1939 at the time of an offering of debt securities.
