ZIOPHARM ONCOLOGY INC
Form S-3
August 20, 2009

**As filed with the Securities and Exchange Commission August 19, 2009**

## 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 | 84-1475642 |
|---|---|
| (State or Jurisdiction of Incorporation or Organization) | (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)

Dr. Jonathan Lewis
Chief Executive Officer
ZIOPHARM Oncology, Inc.
1180 Avenue of the Americas, 19th Floor
New York, NY 10036
Telephone: (646) 214-0700
Facsimile: (646) 214-0711
(Name, Address and Telephone Number of Agent for Service)

Copies to:
Alan M. Gilbert, Esq.
Maslon Edelman Borman & Brand, LLP
90 South 7th Street, Suite 3300
Minneapolis, Minnesota 55402
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Facsimile: (612) 642-8381

**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. o

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: x

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. o

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. o

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. o

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. o

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 o Accelerated filer o Non-accelerated filer o Smaller reporting company x
(Do not check if a smaller reporting company)

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**CALCULATION OF REGISTRATION FEE**

| Title Of Each Class Of Securities To Be Registered | Amount To Be Registered[1] | Proposed Maximum Aggregate Offering Price[1] | Amount Of Registration Fee[2] |
|---|---|---|---|
| Common stock, par value $.001 per share | $ 75,000,000 | $ 75,000,000 | $ 4,185.00 |

(1) The Registrant is registering an indeterminate number of securities as may be issued at various times and at indeterminate prices, with a total public offering price not to exceed $75,000,000. Pursuant to Rule 416 under the Securities Act, there are also being registered hereunder an indeterminate number of shares of common stock as shall be issuable as a result of stock splits, stock dividends or other adjustments to or changes in the outstanding shares of common stock.

(2) Calculated pursuant to Rule 457(o) under the Securities Act.

**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.**

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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 August 19, 2009

# PROSPECTUS

# $75,000,000

# ZIOPHARM Oncology, Inc.

# Common Stock

We may offer and sell, from time to time, shares of our common stock. We will provide the specific terms of these offerings in one or more supplements to this prospectus. You should read the information contained or incorporated by reference in this prospectus and any prospectus supplement carefully before you invest.

We may offer our common stock in one or more offerings in amounts, at prices, and on terms determined at the time of the offering. We may sell our common stock directly to purchasers, through agents we select or through underwriters and dealers we select. If we use agents, underwriters or dealers, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on the Nasdaq Capital Market under the symbol ZIOP. On August 19, 2009, the closing price of our common stock, as reported on the Nasdaq Capital Market, was $1.80. We urge prospective purchasers of our common stock to obtain current information about the market prices of our common stock.

**The securities offered by this prospectus involve a high degree of risk. See Risk Factors beginning on page 5.**

**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 , 2009.

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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 SEC, using a shelf registration process. Under the shelf registration process, we may sell common stock in one or more offerings up to a total dollar amount of $75,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer and sell common stock under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of the applicable offering. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. This prospectus, together with the applicable prospectus supplement(s) and the documents incorporated by reference into this prospectus and such supplement(s), includes all material information relating to this offering. Please carefully read both this prospectus and any prospectus supplement, together with the additional information described below under Where You Can Find More Information, before buying securities in this offering.

You should rely only on the information contained or incorporated by reference in this prospectus or a prospectus supplement. We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus or any prospectus supplement, as well as information we have previously filed with the SEC and incorporated by reference into this prospectus or any prospectus supplement, is accurate as of the date on the front of those documents only. Our business, financial condition, results of operations and prospectus may have changed since those dates.

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

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# PROSPECTUS SUMMARY

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

## Our Company

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

ZIO-101, or darinaparsin (ZinaparTM), is an anti-mitochondrial (organic arsenic) compound covered by issued patents and pending patent applications in the U.S. and in foreign countries. A form of commercially available inorganic arsenic (arsenic trioxide [Trisenox ®]; ATO ) has been approved in the United States and the European Union for the treatment of acute promyelocytic leukemia ( APL ), a precancerous condition. ATO is on the compendia listing for the therapy of multiple myeloma, and has been studied for the treatment of various other cancers. Nevertheless, ATO has been shown to be toxic to the heart, liver, and brain, which limits its use as an anti-cancer agent. ATO carries a black box warning for ECG abnormalities since arsenic trioxide has been shown to cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. Inorganic arsenic has also been shown to cause cancer of the skin and lung in humans. The toxicity of arsenic is generally correlated to its accumulation in organs and tissues. Our preclinical and clinical studies to date have demonstrated that darinaparsin is considerably less toxic than inorganic arsenic, particularly with regard to cardiac toxicity. In vitro testing of darinaparsin using the National Cancer Institute s human cancer cell panel detected activity against a series of tumor cell lines including lung, colon, brain, melanoma, ovarian, and kidney cancer. Moderate activity was detected against breast and prostate cancer. In addition to solid tumors, in vitro testing in both the National Cancer Institute s cancer cell panel and in vivo testing in a leukemia animal model demonstrated substantial activity against hematological cancers (cancers of the blood and blood-forming tissues) such as leukemia, lymphoma, myelodysplastic syndromes, and multiple myeloma. Results indicate significant activity against the HuT 78 cutaneous T-cell lymphoma, the NK-G2MI natural killer-cell NHL, KARPAS-299 T-cell NHL, SU-DHL-8 B-cell NHL, SU-DHL-10 B-cell NHL and SU-DHL-16 B-cell NHL cell lines. Preclinical studies have

also established anti-angiogenic properties of darinaparsin and provided support for the development of an oral capsule form of the drug, and established synergy of darinaparsin in combination with other approved anti-cancer agents.

Phase I testing of the intravenous form of darinaparsin in solid tumors and hematological cancers has been completed. The Company reported clinical activity and, importantly, a safety profile from these studies as predicted by preclinical results. The Company subsequently completed Phase II

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studies in advanced myeloma and primary liver cancer and is nearing completion of a Phase II study in certain other hematological cancers. In addition, the Company is completing two Phase I studies with an oral capsule form of darinaparsin. At the May 2009 annual meeting of the American Society of Clinical Oncology ( ASCO ), the Company reported favorable results from the trial with IV-administered darinaparsin in lymphoma, particularly peripheral T-cell lymphoma ( PTCL ). In the ongoing Phase I trials, also reported at the ASCO annual meeting, preliminary data primarily in solid tumors indicate the oral form is active and well tolerated. The Company is actively seeking a partner or other sources of funding to progress the IV program into a potentially pivotal trial in PTCL as early as the first half of 2010 as well as to complete the oral Phase I program. If we cannot find a partner or otherwise raise the capital for continuing the darinaparsin programs, our intent is to complete the ongoing studies included in the Company s current estimate of expenses and then place the development program for darinaparsin on hold.

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

Following Phase I study, Phase II testing of the intravenous form of palifosfamide as a single agent to treat advanced sarcoma has been completed. In both Phase I and Phase II testing, palifosfamide has been administered without the uroprotectant mesna, and the toxicities associated with acrolein and chloroacetaldehyde have not been observed. The Company reported clinical activity of palifosfamide when used alone in the Phase II study addressing advanced sarcoma. Following review of the preclinical combination studies, clinical data, and discussion with sarcoma experts, the Company initiated a Phase I dose escalation study of palifosfamide in combination with doxorubicin in patients with metastatic or unresectable soft tissue sarcoma. The Company reported favorable results and safety profile from this study at the 2009 ASCO annual meeting. In light of reported favorable Phase II clinical activity data and with the combination of palifosfamide with doxorubicin well tolerated in the Phase I trial and evidencing activity, the Company initiated a Phase II randomized controlled trial in the second half of last year to compare doxorubicin plus palifosfamide to doxorubicin alone in patients with front and second-line metastatic or unresectable soft tissue sarcoma. Data from the initial patients in this trial are expected to shape a registration trial in the same setting which is expected to initiate as early as the first half of 2010. The study is currently actively enrolling and, in conjunction with ASCO, the initial drug safety monitoring committee meeting concluded to continue enrollment as planned. The Company is also developing an oral capsule form of palifosfamide to be studied clinically following further data from

the IV trials and partnering or other sources of funding. The Company is also considering additional Phase II trials in other solid tumors

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as funding becomes available. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of soft tissue sarcomas.

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

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

Indibulin, as a single agent, has completed a Phase I trial in Europe and additional Phase I trials are nearing completion in the U.S. in patients with advanced solid tumors and the Company has reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging results obtained with indibulin in combination with erlotinib, and 5-FU in preclinical models, two Phase I combination studies were initiated with Tarceva® in one and Xeloda® in another and are reaching completion. Favorable activity and safety profile of oral indibulin with oral Xeloda® were reported at ASCO s annual meeting in May 2009. Preclinical work with consultant Dr. Larry Norton to explore dose scheduling for the clinical setting have been completed and were also reported at the ASCO meeting, supporting the Company s plan, subject to the availability of additional funding, to initiate a Phase I/II breast cancer trial using a dose schedule established preclinically.

Subject to obtaining appropriate funding, we intend to continue with clinical development of IV palifosfamide for soft tissue sarcoma and to initiate a clinical study with the oral form following the United States Food and Drug Administration approval; with IV darinaparsin, for PTCL and with the further development of the oral form; and with oral indibulin, for solid tumors and in particular breast cancer. However, the successful development of our product candidates is highly uncertain. Product development costs and timelines can vary significantly for each product candidate, are difficult to accurately predict, and will require us to obtain additional funding, either alone or in connection with partnering arrangements. Various statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of each product. The lengthy process of seeking approval and the subsequent compliance with applicable statutes and regulations require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could materially, adversely affect our business. To date, we have not received approval for the sale of any drug candidates in any market and, therefore, have not generated any revenues from our drug candidates.

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# Corporate Information

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

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

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# RISK FACTORS

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

# SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

the progress of preclinical and clinical trials involving our drug candidates;
the progress of our research and development programs;
the benefits to be derived from relationships with our collaborators;
the receipt or anticipated receipt of regulatory clearances and approvals;
our estimates of future revenues and profitability; and
our estimates regarding our capital requirements and our need for additional financing.

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

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

# USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of our common stock offered by this prospectus. Unless we indicate otherwise in the applicable prospectus supplement, we anticipate that any net proceeds will be used for working capital and general corporate purposes. We will set forth in the applicable prospectus supplement our intended use for the net proceeds received from the sale of any common stock sold pursuant to that prospectus supplement.

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# PLAN OF DISTRIBUTION

We may sell the common stock covered by this prospectus:

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

We may distribute the common stock offered hereby:

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

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

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

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers (as their agents in connection with the sale of the common stock). In addition, underwriters may sell common stock to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they act as agent. These underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions, or profits on resale received by the underwriters, dealers or agents may be treated as underwriting discounts and commissions. Each applicable prospectus supplement will identify any such underwriter, dealer or agent, and describe any compensation received by them from us. Any initial public offering price and any discounts or concessions allowed or re-allowed or paid to dealers may be changed from time to time.

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

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

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

The underwriters in an offering of the common stock may also create a short position for their account by selling more common stock in connection with the offering than they are committed to purchase from us. In that case, the

underwriters could cover all or a portion of the short position by either purchasing common stock in the open market or by exercising any over-allotment option granted to them by us. In addition, any managing underwriter may impose penalty bids under contractual arrangements with other underwriters, which means that they can reclaim from an underwriter (or any selling group member participating in the offering) for the account of the other underwriters, the selling concession for the common stock that are distributed in the offering but subsequently purchased for the account of the underwriters in the open market.

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Any of the transactions described in this paragraph or comparable transactions that are described in any accompanying prospectus supplement may result in the maintenance of the price of the common stock at a level above that which might otherwise prevail in the open market. None of the transactions described in this paragraph or in an accompanying prospectus supplement are required to be taken by any underwriters and, if they are undertaken, may be discontinued at any time.

# WHERE YOU CAN FIND MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference room at 100 F. Street, N.E., Washington, D.C. 20549 or at the SEC s other public reference facilities. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. You can request copies of these documents by writing to the SEC and paying a fee for the copying costs. In addition, the SEC maintains an Internet site at *http://www.sec.gov* that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. Our SEC filings are available on the SEC's Internet site.

# INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

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

We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (other than any Current on Reports on Form 8-K filed under Item 12):

Annual Report on Form 10-K for the fiscal year ended December 31, 2008, filed on March 23, 2009;
Quarterly Reports on Form 10-Q for the quarters ended March 31, 2009 and June 30, 2009, filed on May 15, 2009 and August 14, 2009, respectively;
Current Reports on Form 8-K filed on June 1, 2009 and June 4, 2009; and
The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the SEC on September 20, 2006.

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

ZIOPHARM Oncology, Inc.
1180 Avenue of the Americas, 19th Floor

New York, NY 10036
Attention: President
Telephone: (646) 214-0700

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

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# LEGAL MATTERS

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

# EXPERTS

The balance sheets of ZIOPHARM Oncology, Inc. as of December 31, 2008 and 2007 and the related statements of operations, changes in convertible preferred stock and stockholders equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2008 and for the period from September 9, 2003 (date of inception) through December 31, 2008, included in this prospectus, have been included herein in reliance on the report, dated March 16, 2009, of Vitale, Caturano & Company, P.C., (whose name has been changed to Caturano and Company, P.C. effective May 1, 2009) independent registered public accounting firm, given on the authority of that firm as experts in auditing and accounting.

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# 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 SEC 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.

| | |
|---|---|
| SEC registration fee | $ 4,185 |
| Legal fees and expenses | $ 150,000 |
| Accounting fees and expenses | $ 100,000 |
| Printing and engraving expenses | $ 25,000 |
| Miscellaneous expenses | $ 25,000 |
| Blue sky fees and expenses | $ 25,000 |
| | $ 329,185 |

## 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 the 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 arising by or in the right of the corporation) by reason of the fact that he 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 him in connection with such action, suit or proceeding if he acted in good faith and in a manner he 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 his 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 he 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 his conduct was unlawful.

(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 he 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

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of another corporation, partnership, joint venture, trust, or other enterprise against expenses (including attorneys fees) actually and reasonably incurred by him in connection with the defense or settlement of such action or suit if he acted in good faith and in a manner he 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 to 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 expense which the Court of Chancery or such other court shall deem proper.

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* |
| 5.1 | Legal opinion of Maslon Edelman Borman & Brand, LLP. |
| 23.1 | Consent of Independent Registered Public Accounting Firm - Caturano and Company, P.C. |
| 23.2 | Consent of Maslon Edelman Borman & Brand, LLP (included as part of Exhibit 5.1). |
| 24.1 | Power of Attorney (included on signature page). |

*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.

# Item 17. Undertakings.

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 Commission 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

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(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

(A) the undertakings set forth in paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the registration statement is on Form S-8, and the information required to be included in a post-effective amendment by those paragraphs is contained in reports field 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; and

(B) the undertakings set forth in paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the registration statement is on Form S-3 or Form F-3 and 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.

(C) *provided further, however,* that paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the registration statement is for an offering of asset-backed securities on From S-1 or Form S-3, and the information required to be included in a post-effective amendment is proved pursuant to Item 1100(c) of Regulation AB.

(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.

(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,

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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.

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.

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.

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# 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 New York, State of New York, on August 19, 2009.

**ZIOPHARM Oncology, Inc.**

By: /s/ Jonathan Lewis
Jonathan Lewis
Chief Executive 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) 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.

| Name | Position | Date |
|---|---|---|
| /s/ Jonathan Lewis<br>Jonathan Lewis | Director and Chief Executive Officer (Principal Executive Officer) | August 19, 2009 |
| /s/ Richard Bagley<br>Richard E. Bagley | Director, President, Treasurer and Chief Operating Officer (Principal Accounting and Financial Officer) | August 19, 2009 |
| /s/ Murray Brennan<br>Murray Brennan | Director | August 19, 2009 |
| James Cannon | Director | August 19, 2009 |
| /s/ Timothy McInerney<br>Timothy McInerney | Director | August 19, 2009 |
| Wyche Fowler, Jr. | Director | August 19, 2009 |
| Gary S. Fragin | Director | August 19, 2009 |
| /s/ Michael Weiser<br>Michael Weiser | Director | August 19, 2009 |

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