ZIOPHARM ONCOLOGY INC
Form 424B3
May 15, 2006

Prospectus Supplement No. 3
(To Prospectus dated April 14, 2006)

Filed Pursuant to Rule 424(b)(3)
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ZIOPHARM Oncology, Inc.

7,462,095 Shares

Common Stock

The information contained in this prospectus supplement amends and updates our prospectus dated April 14, 2006, as supplemented by Prospectus Supplement No. 1 dated April 26, 2006 and Prospectus No. 2 dated May 3, 2006 (collectively, the "Prospectus"), and should be read in conjunction therewith. Please keep this prospectus supplement with your Prospectus for future reference.

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

The date of this prospectus supplement is May 15, 2006

Note Regarding Forward-Looking Statements

This prospectus supplement contains statements that are not historical, but are forward-looking in nature, including statements regarding the expectations, beliefs, intentions or strategies regarding the future. In particular, the discussion contained in this prospectus supplement under the heading "Management's Discussion and Analysis or Plan of Operation" includes forward-looking statements that reflect our current views with respect to future events and financial performance. We use words such as we "expect," "anticipate," "believe," and "intend" and similar expressions to identify forward-looking statements. A number of important factors could, individually or in the aggregate, cause actual results to differ materially from those expressed or implied in any forward-looking statements. Such factors include, but are not limited to, the continued availability of our chief technology officer, our ability to obtain additional financing, our ability to develop and maintain customer relationships, regulatory developments relating to and the general success of our customers' products, and our ability to protect our proprietary technology. Other risks that may impact forward-looking statements contained in this prospectus supplement are described in the Prospectus under the heading "Risk Factors".

Interim Financial Statements - Quarter Ended March 31, 2006

Included in this prospectus supplement beginning at page F-1 are our interim financial statements as of and for the three month period ended March 31, 2006, including the accompanying footnotes thereto. These interim financial statements, which were included in our Quarterly Report on Form 10-QSB for the quarter ended March 31, 2006, should be read in conjunction with the audited financial statements as of and for the year ended December 31, 2005, which were included in the Prospectus.

Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion of our financial condition and results of operations should be read in conjunction with the financial statements and the notes to those statements included in this prospectus supplement and in the Prospectus. This discussion includes forward-looking statements that involve risks and uncertainties. As a result of many factors, such as those set forth under the heading "Risk Factors" in the Prospectus, our actual results may differ materially from those anticipated in these forward-looking statements.

Overview:

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that is seeking to develop and commercialize a diverse, risk-sensitive portfolio of in-licensed cancer drugs that address unmet medical needs. Our principal focus is on the licensing and development of proprietary drug candidate families that are related to cancer therapeutics that are already on the market or in development. We believe this strategy will result in lower risk and expedited drug development programs. We expect to commercialize our products on our own in North America but recognize that promising clinical trial results in cancers with a high incidence and prevalence might also be addressed in a commercial partnership with another company with the requisite financial resources. Currently, we are in U.S. phase I and I/II studies for two product candidates known as ZIO-101 and ZIO-201. We currently intend to continue with clinical development of ZIO-101 for advanced myeloma and ZIO-201 for advanced sarcoma and to study preclinically product candidates (ZIO-102, ZIO-202, etc.) in the same product families while licensing additional candidates.

We currently have two products in development:

- ZIO-101 is an organic arsenic compound covered by issued U.S. patents and applications internationally. A form of commercially available inorganic arsenic (arsenic trioxide (Trisenox®) or ATO) has been approved for the treatment of acute promyelocytic leukemia (APL), a precancerous condition, and is on the compendia listing for the therapy of multiple myeloma as well as having been studied for the treatment of various other cancers. Nevertheless, ATO has been shown to be toxic to the heart, liver, and

brain, limiting its use as an anti-cancer agent. Inorganic arsenic has also been shown to cause cancer of the skin and lung in humans. The toxicity of arsenic generally is correlated to its accumulation in organs and tissues. Our preclinical and phase I clinical studies to date have demonstrated that ZIO-101 (and organic arsenic in general) is considerably less toxic than inorganic arsenic, particularly with regard to heart toxicity. In vitro testing of ZIO-101 using the National Cancer Institute's human cancer cell panel detected activity against 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.

Phase I testing of ZIO-101 is ongoing with two safety and dose finding studies at The University of Texas M. D. Anderson Cancer Center ("MDACC"). The Company has seen encouraging signs of clinical activity in both of these studies including impact on blood and bone marrow blast cells in patients with acute myelogenous leukemia (AML) and including one patient with metastatic renal cell carcinoma where metastasis to the brain resolved. The Company recently initiated a phase I/II advanced multiple myeloma study to be conducted in the U.S., Canada and Europe designed to determine maximum tolerated dose and to assess clinical activity in this specific indication. The Company expects to pursue registration in the U.S. for the treatment of advanced multiple myeloma with a potentially pivotal trial to begin in 2007.

- ZIO-201, or isophosphoramide mustard (IPM), is a proprietary stabilized metabolite of ifosfamide that is also related to cyclophosphamide. A patent application for pharmaceutical composition has been filed. Cyclophosphamide and ifosfamide are alkylating agents. The Company believes cyclophosphamide is the most widely used alkylating agent in cancer therapy and is used to treat breast cancer and non-Hodgkin's lymphoma. Ifosfamide has been shown to be effective in high dose by itself, or in combination in treating sarcoma and lymphoma. Although ifosfamide-based treatment generally represents the standard of care for sarcoma, it is not licensed for this indication by the FDA. Our preclinical studies have shown that, in animal and laboratory models, IPM evidences activity against leukemia and solid tumors. These studies also indicate that ZIO-201 has a better pharmacokinetic and safety profile than ifosfamide or cyclophosphamide, offering the possibility of safer and more efficacious therapy with ZIO-201. Ifosfamide is metabolized to IPM. In addition to IPM, another metabolite of ifosfamide is acrolein, which is toxic to the kidneys and bladder. The presence of acrolein can mandate the administration of a protective agent called mesna, which is inconvenient and expensive. Chloroacetaldehyde is another metabolite of ifosfamide and 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. Because ZIO-201 is independently active without acrolein or chloroacetaldehyde metabolites, the Company believes that the administration of ZIO-201 may avoid many of the toxicities of ifosfamide and cyclophosphamide without compromising efficacy. In addition to anticipated lower toxicity, ZIO-201 (and without the co-administration of mesna) may have other advantages over ifosfamide. In preclinical studies ZIO-201 likely cross-links DNA differently than ifosfamide or cyclophosphamide metabolites, resulting in a different activity profile. Moreover, in some instances ZIO-201 appears to show activity in ifosfamide- and/or cyclophosphamide-resistant cancer cells.

Phase I testing of ZIO-201 is ongoing at two sites in the U.S. (Karmanos Cancer Center at Wayne State University in Detroit and Premiere Oncology in Los Angeles). IPM has been administered without the "uroprotectant" mesna and the toxicities associated with acrolein and chloroacetaldehyde have not been observed. Kidney toxicity seen with ifosfamide has occurred in the higher dose cohorts. One patient with advanced mesothelioma had stable disease for 18 cycles of therapy with ZIO-201 as a single agent. The Company recently initiated a phase I/II trial in advanced sarcoma at The University of Texas M. D. Anderson Cancer Center. The MDACC will be joined by additional centers in the U.S., Canada and Europe in the coming months. A phase II study in patients with advanced sarcoma utilizing a modified dosing regimen in the U.S. is expected to initiate in the first half of 2006 and plans for a phase I/II study in pediatric sarcoma are well advanced. The Company expects to pursue registration in the U.S. for the treatment of advanced sarcoma with a potentially pivotal trial to begin in 2007.

Currently, we are in U.S. phase I/II studies for both of these drug candidates. In January 2006, we initiated a phase I/II with ZIO-101 in advanced multiple myeloma and in February 2006 with ZIO-201 in advanced sarcoma. We intend to continue with clinical development of ZIO-101 for advanced myeloma and ZIO-201 for advanced sarcoma. However, the successful development of our product candidates is highly uncertain. Product development costs and timelines can vary significantly for each product candidate and are difficult to accurately predict. 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 these approvals, 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.

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.”

Plan of Operation

Our plan of operation for the next twelve months, is to continue implementing our business strategy, including the clinical development of our two lead product candidates, ZIO-101 and ZIO-201. We also intend to expand our drug candidate portfolio by seeking additional drug candidates through in-licensing arrangements. We expect our principal expenditures during those 12 months to include:

- Fees and milestone payments required under the license agreements relating to our existing product candidates and additional in-licensed candidates;
- Clinical trial expenses, including the costs incurred with respect to the conduct of clinical trials for ZIO-101 and ZIO-201 and preclinical costs associated with back-up candidates ZIO-102 and ZIO-202;
- Costs related to the scale-up and manufacture of ZIO-101 and ZIO-201;
- Rent for our facilities; and
- General corporate and working capital, including general and administrative expenses.

As part of our plan for additional employees, we anticipate hiring several additional full-time employees in medical, regulatory, clinical and financial. In addition, we intend to use senior advisors, consultants, clinical research organizations and third parties to perform certain aspects of product development, manufacturing, clinical and preclinical development, and regulatory and quality assurance functions.

At our current and desired pace of clinical development of our two product candidates, over the next 12 months we expect to spend approximately $5.9 million on clinical trials (including milestone payments that we expect to be triggered under the license agreements relating to our product candidates), approximately $3.2 million on manufacturing costs, approximately $400,000 on facilities, rent (including additional space not presently contracted) and other facilities related costs, and approximately $9.4 million on general corporate and working capital. We believe that we currently have sufficient capital to fund development and commercialization activities of ZIO-101 and ZIO-201 into the second quarter of 2008 with the proceeds from the offering received on May 3, 2006. (See “Note 7 - Subsequent Event” and “Liquidity and Capital Resources” below.)

Product Candidate Development and Clinical Trials

ZIO-101. ZIO-101, organic arsenic, is being developed presently to treat advanced myeloma. As a follow-on to the ongoing phase I trials, a phase I/II trial in advanced multiple myeloma was initiated in January 2006. With the completion of patient enrollment of this trial in 2006, we expect to initiate a registration trial in advanced multiple myeloma. We will continue to explore the use of ZIO-101 in solid tumors as well as other phase II trials. Preclinical development will continue with a back-up compound designated as ZIO-102. Additional compounds are being synthesized under our agreement with The University of Texas M.D. Anderson Cancer Center and the Texas A&M University System. Technology transfer and scale-up for the commercial manufacture of the active pharmaceutical ingredient, its lyophilization, and final product specification will continue through the period leading to the expected registration trial 2007. Preclinical development will continue with additional compounds and routes of administration.

ZIO-201. ZIO-201, stabilized isophosphoramide mustard, is being developed presently to treat advanced sarcoma. As follow-on to the ongoing phase I trial, a phase I/II trial in advanced sarcoma was initiated in February 2006 and other trials are in the advanced planning stage. With the completion of patient enrollment of this trial in 2006, we expect to initiate a registration trial in advanced sarcoma in 2007. Technology transfer and scale-up for the commercial manufacture of the active pharmaceutical ingredient, its lyophilization, and final product specification will continue through the period leading to the expected registration trial in 2007. Preclinical development will continue with back-up analogues.

Results of Operations

Revenues. We had no revenues for either of the three-month periods ended March 31, 2006 and 2005.

Research and development expenses. For the three-month period ended March 31, 2006, research and development expenses increased by $169,679, or 11%, to $1,768,250 from $1,598,571 in the three-month period ended March 31, 2005. The increase is attributable to an increase of approximately $28,000 in stock compensation expense related to stock options and approximately $160,000 in employee related costs. We had an increase of approximately $314,000 spent on clinical trials offset by decrease of approximately $382,000 in manufacturing related costs. For the remainder of the year, we expect research and development spending related to our existing product candidates to approximate the same level as seen in the first quarter of 2006, as we continue with clinical trials and our manufacturing activities.

General and administrative expenses. For the three month period ended March 31, 2006, general and administrative expenses increased by $838,771, or 126%, to $1,504,628 from $665,857 in the three-month period ended March 31, 2005. The increase is attributable to approximately $166,000 in stock compensation expense related to stock options, approximately $106,000 as compensation expense for common stock issued to an investor relations consultant, approximately $80,000 for investors relations services, approximately $60,000 in legal and accounting costs resulting in part from our becoming a public reporting company, and approximately $153,000 in employee related costs as we have built infrastructure to support the research and development efforts. For the remainder of the year, we expect general and administrative spending to approximate the same level as seen in the first quarter of 2006.

Other income (expense). Other income increased by $49,965 to $53,838 in the three-month period ended March 31, 2006 from $3,873 recorded in the three-month period ended March 31, 2005. Other income during the three month periods ended March 31, 2006 and 2005, respectively, was comprised of interest income. The increase in is due to higher cash balances available for investing purposes.

Net income (loss). For the reasons described above, the net loss increased by $958,485, or 42%, to $3,219,040 in the three month period ended March 31, 2006 from $2,260,555.

Liquidity and Capital Resources

As of March 31, 2006, we had approximately $5.6 million in cash, cash equivalents and short-term investments. With the proceeds from the offering completed on May 3, 2006 (See Note 7 - Subsequent Event), we believe we currently have sufficient capital to fund development and commercialization activities of ZIO-101 and ZIO-201 into the second quarter of 2008. Because our business does not generate any cash flow, however, we will need to raise additional capital to continue development of the product candidates beyond that time. We anticipate raising such additional capital by either borrowing money or by selling shares of our capital stock. To the extent additional capital is not available when we need it, we may be forced to abandon our development and commercialization efforts, which would have a material adverse effect on the prospects of our business. Further, our assumptions relating the expected costs of development and commercialization and timeframe for completion are dependent on numerous factors other than available financing, including significant unforeseen delays in the clinical trial and regulatory approval process, which could be extremely costly. In addition, our estimates assume that we will be able to enroll a sufficient number of patients in each clinical trial.

The Company anticipates that losses will continue for the foreseeable future. At March 31, 2006, the Company's accumulated deficit was approximately $18.6 million. The Company has incurred significant losses from operations and has an accumulated deficit that raises substantial doubt about the Company's ability to continue as a going concern. The Company's ability to continue operations after its current cash resources are exhausted depends on its ability to obtain additional financing and achieve profitable operations, as to which no assurances can be given.

Our actual cash requirements may vary materially from those now planned because of a number of factors including:

- changes in the focus and direction of our research and development programs, including the acquisition and pursuit of development of new product candidates
- competitive and technical advances;
- costs of commercializing any of product candidates;
- costs of filing, prosecuting, defending and enforcing any patent claims and any other intellectual property rights;
- or other developments.

We will need to raise additional capital to continue to fund our research and development and operations after we exhaust our current cash resources in order to continue our long-term plans for clinical trials and new product development. We expect to finance our cash needs through the sale of equity securities and possibly strategic collaborations or debt financings or through other sources that may be dilutive to existing stockholders. There can be no assurance that any such financing can be realized by the Company, or if realized, what the terms thereof may be, or that any amount that Company is able to raise will be adequate to support the Company's working capital requirements until it achieves profitable operations. If we are unable to raise additional funds when needed, we may not be able to market our products as planned or continue development and regulatory approval of our products, or we could be required to delay, scale back or eliminate some or all our research and development programs.

On May 3, 2006, the Company completed the sale of an aggregate of 7,991,256 shares (the "Shares") of the Company's common stock at a price of $4.63 per Share in a private placement (the "Offering") for total gross proceeds of approximately $37 million before deducting selling commissions and expenses. In addition to the Shares, the Company also issued to each investor a five-year warrant (each a "Warrant") to purchase, at an exercise price of $5.56 per share, an additional number of shares of common stock equal to 30 percent of the Shares purchased by such investor in the Offering. In the aggregate, these Warrants entitle investors to purchase an additional 2,397,392 shares of common stock.The Company engaged Paramount BioCapital, Inc. and Griffin Securities, Inc. (the "Placement Agents") as co-placement agents in connection with the Offering. In consideration for their services, the Company paid the Placement Agents and certain selected dealers engaged by the Placement Agents aggregate cash commissions of $2,589,966 and issued 7-year warrants to the Placement Agents and their designees to purchase an aggregate of 799,125 shares at an exercise price of $5.09 per share. The Company also agreed to reimburse the Placement Agents for their accountable expenses incurred in connection with the Offering. Following the completion of Offering, the Company has 15,264,248 shares of common stock outstanding.

Since inception, our primary source of funding for our operations has been the private sale of our securities. During the twelve months ended December 31, 2005, we received $4,815 proceeds from the exercise of stock options and gross proceeds of approximately $18.1 million ($16.8 net of issuance costs) as a result of the sale by ZIOPHARM, Inc. of Series A Convertible Preferred Stock in a private placement transaction. During the twelve months ended December 31, 2004, we received proceeds of approximately $4.5 million as a result of the sale by ZIOPHARM, Inc. of common stock in a private placement transaction.

At March 31, 2006, working capital was approximately $3.9 million, compared to working capital of approximately $6.8 million at December 31, 2005. The decrease in working capital reflects the use of funds for operations.

Capital expenditures were approximately $70,000 for the three months ended March 31, 2006. We anticipate additional capital expenditures of approximately $30,000 for the fiscal year ended December 31, 2006.

The Company's significant lease obligation payable is as follows:

	Payments due by Period				
	Total	Less than 1 Year	1 - 3 Years	4 - 5 Years	After 5 Years
Operating lease	$ 796,241	$ 190,457	$ 399,400	$ 206,384	$ –

Critical Accounting Policies

The preparation of financial statements requires the Company to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue and expenses, and related disclosure of contingent assets and liabilities. On an on-going basis, the Company evaluates its estimates, including those related to accounting for stock-based compensation and research and development activities. The Company bases its estimates on historical experience and on various other assumptions that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under difference assumptions or conditions.

Research and development expenses consist primarily of salaries and related personnel costs, fees paid to consultants and outside service providers for development, legal expenses resulting from intellectual property prosecution and organizational affairs and other expenses relating to the design, development, testing, and enhancement of our product candidates. We expense our research and development costs as they are incurred. General and administrative expenses consist primarily of salaries and related expenses for executive, finance and other administrative personnel, recruitment expenses, professional fees and other corporate expenses, including business development and general legal activities.

Our results include non-cash compensation expense as a result of the issuance of stock option and warrants grants. On January 1, 2006, the Company adopted Statement of Financial Accounting Standards No. 123(R) ("SFAS 123R") Share-Based Payment, using the modified prospective method, which results in the provision of SFAS 123R only being applied to the consolidated financial statements on a going-forward basis (that is, the prior period results have not been restated). Under the fair value recognition provisions of SFAS 123R, stock-based compensation cost is measured at the grant date based on the value of the award using the Black Scholes Model and is recognized as expense over the service period. Previously, the Company had followed Accounting Principles Board (APB) Opinion No. 25, *Accounting for Stock Issued to Employees*, and related interpretations which resulted in account for employee share options at their intrinsic value in the financial statements. The Company's most critical estimates consist of accounting for stock-based compensation.

Off-Balance Sheet Arrangements

We do not have any "off-balance sheet agreements," as that term is defined by SEC regulation.

Unaudited Interim Financial Statements:

ZIOPHARM Oncology, Inc.
(A Development Stage Enterprise)
Balance Sheets

	March 31, 2006 (Unaudited)	December 31, 2005
ASSETS		
Current assets:		
Cash and cash equivalents	**$ 1,079,203**	$ 8,880,717
Short-term investments	**4,500,000**	-
Prepaid expenses and other current assets	**296,132**	211,837
Total current assets	**5,875,335**	**9,092,554**
Property and equipment, net	**301,770**	269,702
Deposits	**5,700**	5,700
Other non current assets	**125,200**	124,343
Total assets	**$ 6,308,005**	**$ 9,492,299**
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	**$ 544,907**	$ 835,997
Accrued expenses	**1,443,077**	1,418,819
Total current liabilities	**1,987,984**	**2,254,816**
Deferred rent	**36,436**	**35,557**
Commitments and contingencies		
Stockholders' equity:		
Common stock, $.001 par value; 280,000,000 shares authorized;		
7,272,992 and 7,247,992 shares issued and outstanding		
at March 31, 2006 and December 31, 2005, respectively	**7,273**	7,248
Additional paid-in capital	**22,859,708**	22,559,034
Deficit accumulated during the development stage	**(18,583,396)**	(15,364,356)
Total stockholders' equity	**4,283,585**	