

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

FORM S-8
REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

ZIOPHARM ONCOLOGY, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
Incorporation or organization)

1180 Avenue of the Americas, 19th Floor
New York, New York 10036
Telephone (212) 214-0700
(Address of principal executive offices)

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

2003 STOCK OPTION PLAN

(Full title of the Plan)

Dr. Jonathan Lewis
Chief Executive Officer
ZIOPHARM Oncology, Inc.
1180 Avenue of the Americas, 19th Floor
New York, New York 10036
Telephone (646) 214-0700
Facsimile: (646) 214-0711
(Name, address and telephone number, including area code, of agent for service)

Copy to:

Alan M. Gilbert, Esq.
Maslon Edelman Borman & Brand, LLP
3300 Wells Fargo Center
90 South 7th Street
Minneapolis, Minnesota 55402
Telephone: (612) 672-8200
Facsimile: (612) 642-8381

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 securities to be registered	Amount to be registered (1)	Proposed maximum offering price per share (2)	Proposed maximum aggregate offering price (2)	Amount of registration fee
Common Stock, par value \$.001 per share	3,000,000	\$3.625	\$10,875,000.00	\$775.39

- Pursuant to Rule 416(a), this Registration Statement also covers additional securities that may be offered as a result of stock splits, stock dividends, or similar transactions relating to the shares covered by this registration statement. In addition, pursuant to Rule 416(c) under the Securities Act of 1933, this registration statement also covers an indeterminate amount of interests to be offered or sold pursuant to the employee benefit plan(s) described herein.
- Estimated solely for the purpose of determining the registration fee pursuant to Rule 457(c) and (h) and based upon the average low and high sales prices of the registrant's Common Stock on June 28, 2010, as reported by the Nasdaq Capital Market.
- The registrant's 2003 Stock Option Plan (the "2003 Plan") authorizes the issuance of a maximum of 9,002,436 shares of the registrant's common stock, of which 6,002,436 shares were previously registered on Forms S-8, File Nos. 333-129884, 333-134280, 333-142701 and 333-160496, filed on November 22, 2005, May 19, 2006, May 5, 2007 and July 9, 2009, respectively. The contents of such prior registration statements are incorporated by reference herein. This registration statement registers an additional 3,000,000 shares under the 2003 Plan.



INCORPORATION OF CONTENTS OF REGISTRATION STATEMENT BY REFERENCE

Registration statements on Forms S-8 (File Nos. 333-129884, 333-134280, 333-142701 and 333-160496) were filed with the Securities and Exchange Commission on November 22, 2005, May 19, 2006, May 5, 2007 and July 9, 2009, respectively covering the registration of an aggregate of 6,002,436 shares previously authorized for issuance under the registrant's 2003 Stock Option Plan, as amended (the "2003 Plan"). Pursuant to Rule 429 and General Instruction E of Form S-8, this registration statement is being filed to register an additional 3,000,000 shares authorized under the 2003 Plan. This registration statement should also be considered a post-effective amendment to the prior registration statements. The contents of the aforementioned registration statements are incorporated herein by reference.

PART I INFORMATION REQUIRED IN THE SECTION 10(a) PROSPECTUS

Item 1. Plan Information.

Not required to be filed with this Registration Statement on Form S-8 (the "Registration Statement").

Item 2. Registrant Information and Employee Plan Annual Information.

Not required to be filed with this Registration Statement.

PART II INFORMATION REQUIRED IN THE REGISTRATION STATEMENT

Item 3. Incorporation of Documents by Reference.

The following documents filed by the registrant with the Securities and Exchange Commission are hereby incorporated herein by reference:

- (a) Annual Report on Form 10-K for the fiscal year ended December 31, 2009, filed on March 17, 2010, as amended by Amendment No. 1 to Annual Report on Form 10-K/A filed on April 30, 2010;
- (b) Quarterly Report on Form 10-Q for the quarter ended March 31, 2010, filed on April 30, 2010;
- (c) Current Reports on Form 8-K filed on January 27, 2010, April 6, 2010, May 21, 2010, June 2, 2010, June 7, 2010, June 21, 2010 and June 23, 2010; and
- (c) The description of the registrant's common stock set forth in the registration statement on Form 8-A registering the registrant's common stock under Section 12 of the Securities Exchange Act of 1934, which was filed with the Securities and Exchange Commission on September 20, 2006, including any amendments or reports filed for the purpose of updating such description.

All documents subsequently filed by the registrant pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Securities Exchange Act of 1934, prior to the filing of a post-effective amendment which indicates that all securities offered have been sold or which deregisters all securities then remaining unsold, shall be deemed to be incorporated by reference in this Registration Statement and to be a part hereof from the date of filing of such documents.

Item 4. Description of Securities.

Not applicable.

Item 5. Interests of Named Experts and Counsel.

Not applicable.

Item 6. 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 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 of 1933, 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 and is therefore unenforceable.

Item 7. Exemption from Registration Claimed.

Not applicable.

Item 8. Exhibits.

<u>Exhibit</u>	<u>Description</u>
4.1	ZIOPHARM Oncology, Inc. 2003 Stock Option Plan (incorporated by reference to Exhibit 10.1 to the registrant's Registration Statement on Form SB-2, SEC File No. 333-129020, filed on October 14, 2005)
4.2	Amendment No. 1 to ZIOPHARM Oncology, Inc. 2003 Stock Option Plan (incorporated by reference to Exhibit 10.1 to the registrant's Current Report on Form 8-K filed on April 26, 2006)
4.3	Amendment No. 2 to ZIOPHARM Oncology, Inc. 2003 Stock Option Plan (incorporated by reference to Exhibit 10.1 to the registrant's Quarterly Report on Form 10-QSB filed on May 2, 2007)
4.4	Amendment No. 3 to ZIOPHARM Oncology, Inc. 2003 Stock Option Plan (incorporated by reference to Exhibit 4.4 to the registrant's Registration Statement on Form S-8 filed on July 9, 2009)
4.5	Amendment No. 4 to ZIOPHARM Oncology, Inc. 2003 Stock Option Plan (<i>filed herewith</i>)
5.1	Opinion of Maslon Edelman Borman & Brand, LLP as to the legality of the securities being registered (<i>filed herewith</i>)
23.1	Consent of Independent Registered Public Accounting Firm – Caturano and Company, P.C. (<i>filed herewith</i>)
23.3	Consent of Maslon Edelman Borman & Brand, LLP (included in Exhibit 5.1)
24.1	Power of Attorney (included on signature page hereof)

Item 9. 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 this 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 this 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 Securities and Exchange Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and prices represent no more than 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective Registration Statement;

(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 paragraphs (a)(1)(i) and (a)(1)(ii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed 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.

(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; and

(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.

(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 Section 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 into this 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.

(h) 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 of 1933 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 connected 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 of 1933 and will be governed by the final adjudication of such issue.

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-8 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Boston and the Commonwealth of Massachusetts, on the 1st day of July, 2010.

ZIOPHARM Oncology, Inc.

By: /s/ Richard E. Bagley

Richard E. Bagley
President, Chief Operating Officer, Chief Financial
Officer and Secretary

POWER OF ATTORNEY

Each person whose signature to this Registration Statement appears below hereby constitutes and appoints Richard E. Bagley as his true and lawful attorney-in-fact and agent, with full power of substitution, to sign on his or her behalf individually and in the capacity stated below and to perform any acts necessary to be done in order to file all amendments to this Registration Statement and any and all instruments or documents filed as part of or in connection with this Registration Statement or the amendments thereto and each of the undersigned does hereby ratify and confirm all that said attorney-in-fact and agent, or his substitutes, shall do or cause to be done by virtue hereof. The undersigned also grants to said attorney-in-fact, full power and authority to do and perform any and all acts necessary or incidental to the performance and execution of the powers herein expressly granted. This Power of Attorney shall remain in effect until revoked in writing by the undersigned.

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	Title	Date
<u>/s/ Jonathan Lewis</u> Jonathan Lewis	Director and Chief Executive Officer (Principal Executive Officer)	July 1, 2010
<u>/s/ Richard E. Bagley</u> Richard Bagley	Director, President, Chief Operating Officer, Chief Financial Officer and Secretary (Principal Accounting and Financial Officer)	July 1, 2010
<u>/s/ George B. Abercrombie</u> George B. Abercrombie	Director	July 1, 2010
<u>/s/ Murray Brennan</u> Murray Brennan	Director	July 1, 2010
<u>/s/ James Cannon</u> James Cannon	Director	July 1, 2010
<u>/s/ Timothy McNerney</u> Timothy McNerney	Director	July 1, 2010
<u>/s/ Wyche Fowler, Jr.</u> Wyche Fowler, Jr.	Director	July 1, 2010
<u>/s/ Michael Weiser</u> Michael Weiser	Director	July 1, 2010

INDEX TO EXHIBITS

<u>Exhibit</u>	<u>Description</u>
4.5	Amendment No. 4 to ZIOPHARM Oncology, Inc. 2003 Stock Option Plan
5.1	Opinion of Maslon Edelman Borman & Brand, LLP as to the legality of the securities being registered
23.1	Consent of Independent Registered Public Accounting Firm – Caturano and Company, P.C.

ZIOPHARM Oncology, Inc.**Amendment No. 4 to
2003 Stock Option Plan**

This Amendment No. 4 to 2003 Stock Option Plan (the “**Amendment**”) dated as of June 23, 2010, amends the 2003 Stock Option Plan (the “**2003 Plan**”) of ZIOPHARM Oncology, Inc. (the “**Company**”). Except as otherwise explicitly set forth herein, all provisions of the 2003 Plan shall remain in full force and effect. Capitalized terms used in this Amendment without definition shall have the meanings set forth in the 2003 Plan.

WHEREAS, the 2003 Plan provides that the number of shares of Common Stock which may be issued under the Plan shall not exceed 6,002,436 shares; and

WHEREAS, an amendment to the 2003 Plan increasing the number of shares of Common Stock which may be issued under the Plan to 9,002,436 was adopted by the Company pursuant to resolutions of the Board of Directors on March 31, 2010 and approved by the Company’s stockholders at a meeting of the stockholders held on June 23, 2010.

NOW, THEREFORE, the 2003 Plan is hereby amended as follows:

1. Increase in Number of Shares Subject to the Plan. Section 5.1 of the 2003 Plan is hereby amended in its entirety to read as follows:

“5.1. Number of Shares. Subject to adjustment as provided in Section 10.6, the number of shares of Common Stock which may be issued under the Plan shall not exceed 9,002,436 shares of Common Stock. Shares of Common Stock that are issued under the Plan or are subject to outstanding Incentives will be applied to reduce the maximum number of shares of Common Stock remaining available for issuance under the Plan.”

2. Effective Date. This Amendment shall be effective upon the date first written above.

IN WITNESS WHEREOF, the Company has caused this Amendment to be executed by the undersigned officer, thereunto duly authorized pursuant to the resolutions of the Board of Directors.

ZIOPHARM Oncology, Inc.:

By: /s/ Richard E. Bagley

Richard E. Bagley,
*President, Chief Operating Officer, Chief Financial
Officer and Secretary*

July 1, 2010

ZIOPHARM Oncology, Inc.
1180 Avenue of the Americas, 19th Floor
New York, New York 10036

Re: Registration Statement on Form S-8

Ladies and Gentlemen:

We have acted on behalf of ZIOPHARM Oncology, Inc. (the "Company") in connection with a Registration Statement on Form S-8 (the "Registration Statement") filed by the Company with the Securities and Exchange Commission relating to registration of 3,000,000 shares of Common Stock, \$.001 par value, issued or to be issued by the Company (the "Shares"), pursuant to the terms of the Company's 2003 Stock Option Plan, as amended (the "Plan"). Upon examination of such corporate documents and records as we have deemed necessary or advisable for the purposes hereof, it is our opinion that:

1. The Company is a validly existing corporation in good standing under the laws of the State of Delaware.
2. The Shares, when issued and paid for as contemplated by the Plan, and when delivered against payment thereof in the manner contemplated by the Plan, will be validly issued, fully paid and non-assessable.

We hereby consent to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

/s/ Maslon Edelman Borman & Brand, LLP

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

As independent registered public accountants, we hereby consent to the use of the report of Caturano and Company, P.C dated March 17, 2010 relating to the financial statements of ZIOPHARM Oncology, Inc. as of December 31, 2009 and 2008, and for each of the three years in the three-year period ended December 31, 2009 and from September 9, 2003 (date of inception) through December 31, 2009 (which report expresses an unqualified opinion and includes an explanatory paragraph relating to the change in the manner in which the Company accounts for certain warrants), and to all references to our Firm included in or made part of this Registration Statement on Form S-8.

/s/ Caturano and Company P.C.
Boston, Massachusetts
July 1, 2010