

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

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

ZIOPHARM Oncology, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or jurisdiction
of incorporation or organization)

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

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

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

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
Telephone: (612) 672-8200
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.

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

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. SEC File No. 333-161453

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

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

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

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

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

(Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title Of Each Class Of Securities To Be Registered	Amount To Be Registered ⁽¹⁾⁽²⁾⁽³⁾⁽⁴⁾	Proposed Maximum Aggregate Offering Price ⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾	Amount Of Registration Fee ⁽⁶⁾
Common stock, par value \$.001 per share			
Preferred Stock, par value \$0.001 per share			
Warrants			
Debt Securities			
Total	\$ 5,989,525	\$ 5,989,525	\$ 334.22

- (1) In accordance with Rule 462(b) promulgated under the Securities Act an additional amount of securities having a proposed maximum aggregate offering price of no more than 20% of the maximum aggregate offering price of the securities eligible to be sold under the Registration Statement on Form S-3 (File No. 333-161453), as amended, is hereby registered.
- (2) An indeterminate number of shares of common stock and preferred stock, an indeterminate number of warrants to purchase debt securities, common stock or preferred stock and an indeterminate amount of debt securities are being registered hereunder, but in no event will the aggregate initial offering price exceed \$75,000,000. If any debt securities are issued at an original issue discount, then the offering price of such debt securities shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed \$75,000,000, less the aggregate dollar amount of all securities previously issued hereunder. Any securities registered hereunder may be sold separately or as units with other securities registered hereunder. The securities registered also include such indeterminate amount and number of shares of common stock and preferred stock as may be issued upon conversion of or exchange for preferred stock and provide for conversion or exchange, upon exercise of warrants or pursuant to antidilution provisions of any such securities. In addition, pursuant to Rule 416 under the Securities Act, there are also being registered hereunder an indeterminate number of shares of common stock and preferred stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends or similar transactions.
- (3) Unspecified pursuant to General Instruction II.D to Form S-3 under the Securities Act.
- (4) Represents only the additional amount of securities being registered. Does not include the securities that the Registrant previously registered on the Registration Statement on Form S-3 (File No. 333-161453).
- (5) Estimated solely for the purpose of calculating the registration fee pursuant to Section 6(b) of the Securities Act and computed pursuant to Rule 457(o) under the Securities Act and based upon the average of the high and low sale prices for such stock on December 4, 2009, as reported by the NASDAQ Capital Market.
- (6) Represents the registration fee only for the additional number of shares being registered. A filing fee of \$4,185.00 was previously paid for the securities that the Registrant previously registered on the Registration Statement on Form S-3 (File No. 333-161453).

This registration statement shall become effective upon filing with the Securities and Exchange Commission in accordance with Rule 462(b) under the Securities Act of 1933, as amended.

**EXPLANATORY NOTE AND
INCORPORATION OF CERTAIN INFORMATION BY REFERENCE**

We are filing this registration statement with the Securities and Exchange Commission (the "Commission") pursuant to Rule 462(b) under the Securities Act of 1933, as amended. This registration statement relates to the public offering of securities contemplated by the registration statement on Form S-3 (File No. 333-161453), originally filed by us with the Commission on August 20, 2009, and subsequently amended, and includes the registration statement facing page, this page, the signature page, an exhibit index and exhibits. It is being filed for the sole purpose of registering an additional \$5,989,525 of securities pursuant to Rule 462(b), which amount does not represent more than 20% of the maximum aggregate offering price set forth for the securities in the "Calculation of Registration Fee" table in the registration statement on Form S-3 (File No. 333-161453), as amended.

The information in the registration statement on Form S-3 (File No. 333-161453), as amended by Pre-Effective Amendment No. 1 thereto filed with the Commission on September 14, 2009, is incorporated by reference into this registration statement. The required opinions and consents are listed on the exhibit index attached hereto and filed herewith.

EXHIBIT INDEX

Exhibit No.	Description of Document
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)

December 7, 2009

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

Re: Registration Statement on Form S-3 (the "Registration Statement")

Ladies and Gentlemen:

We have served as counsel for to ZIOPHARM Oncology, Inc., a Delaware corporation (the "**Company**"), in connection with the Registration Statement on Form S-3, Registration no. 333-161453 (the "**Registration Statement**"), filed with the Securities and Exchange Commission under the Securities Act of 1933, as amended (the "**Securities Act**"), and the additional Registration Statement on Form S-3 (the "**Abbreviated Registration Statement**") filed pursuant to Rule 462(b) under the Act. This opinion is being furnished in accordance with the requirements of Item 601(b)(5) of Regulation S-K under the Securities Act, and no opinion is expressed herein as to any matter pertaining to the contents of the Registration Statement, the Prospectus or any Prospectus Supplement (both as herein defined) other than as to (i) the enforceability of the Agreements, the Debt Securities and the Warrants (each as herein defined) and (ii) the validity of the shares of the Common Stock and the Preferred Stock (both as herein defined).

You have provided us with the Registration Statement and a draft of the Abbreviated Registration Statement in the form in which it will be filed, which include or incorporate by reference the prospectus (the "**Prospectus**"). The Prospectus provides that it will be supplemented in the future by one or more supplements to the Prospectus (each, a "**Prospectus Supplement**"). The Prospectus, as supplemented by various Prospectus Supplements, will provide for the registration by the Company of (i) one or more series of debt securities (the "**Debt Securities**"), (ii) shares of preferred stock, par value \$0.001 per share (the "**Preferred Stock**"), (iii) shares of common stock, par value \$0.001 per share (the "**Common Stock**") and (iv) warrants to purchase Common Stock, Preferred Stock or Debt Securities (the "**Warrants**"), or any combination of the foregoing (collectively, the "**Securities**"), for an aggregate initial offering price of up to \$80,989,525.00, which includes securities having a maximum aggregate offering price of up to \$75,000,000 covered by the Registration Statement and securities having a maximum aggregate offering price of up to \$5,989,525 covered by the Abbreviated Registration Statement. Any Debt Securities may be exchangeable for and/or convertible into shares of Common Stock or Preferred Stock or into other securities. The Preferred Stock may also be convertible into shares of Common Stock or another series of Preferred Stock or into other securities. The Debt Securities may be issued pursuant to an indenture by and between the Company and a financial institution to be identified therein as trustee (the "**Trustee**") in the form filed as Exhibit 4.8 to the Registration Statement, as such indenture may be supplemented from time to time (the "**Indenture**"). The Warrants may be issued under one or more warrants and warrant agreements in the forms to be incorporated by reference as Exhibits 4.9 and 4.10 to the Registration Statement (each, a "**Warrant Agreement**") between the Company and a bank or trust company to be identified therein as warrant agent (each, a "**Warrant Agent**"). The Indenture and the Warrant Agreements are herein collectively called the "**Agreements**."

For the purposes of this opinion, we have assumed that such proceedings to be taken in the future will be timely completed in the manner presently proposed and that the terms of each issuance will otherwise be in compliance with law. As such counsel, we have examined such matters of fact and questions of law as we have considered appropriate for purposes of this letter. With your consent, we have relied upon the foregoing and upon certificates and other assurances of officers of the Company and others as to factual matters without having independently verified such factual matters.

We are opining herein as to the effect on the subject transaction only of the General Corporation Law of the State of Delaware and we express no opinion with respect to the applicability thereto, or the effect thereon, of the laws of any other jurisdiction or, in the case of Delaware, any other laws, or as to any matters of municipal law or the laws of any local agencies within any state. With respect to our opinion in Paragraph 1 relating to the enforceability of the Indenture, which the form of which is by its terms governed by the laws of the State of New York, we have assumed without investigation or review that the internal law of the State of New York is identical to the internal law of the State of Delaware.

Subject to the foregoing and the other matters set forth herein, it is our opinion that as of the date hereof:

1. When (i) the Indenture has been duly authorized, executed and delivered by the Company and the Trustee, (ii) the Debt Securities have been duly authorized and duly established in accordance with the Indenture and applicable law (including, without limitation, by the adoption by the Board of Directors of the Company of a resolution duly authorizing the issuance and delivery of the Debt Securities) (the “**Debt Securities Authorization**”), duly authenticated by the Trustee and duly executed and delivered on behalf of the Company against payment therefor in accordance with the terms and provisions of the Indenture and as contemplated by the Registration Statement, the Prospectus and the related Prospectus Supplement(s), and the Debt Securities Authorization, and assuming that (a) the terms of the Debt Securities as executed and delivered are as described in the Registration Statement, the Prospectus and the related Prospectus Supplement(s), and the Debt Securities Authorization, (b) the Debt Securities as executed and delivered do not violate any law applicable to the Company or result in a default under or breach of any agreement or instrument binding upon the Company, (c) the Debt Securities as executed and delivered comply with all requirements and restrictions, if any, applicable to the Company, whether imposed by any court or governmental or regulatory body having jurisdiction over the Company or otherwise, and (d) the Debt Securities are then issued and sold as contemplated in the Registration Statement, the Prospectus and the related Prospectus Supplement(s), and the Debt Securities Authorization, the Debt Securities (including any Debt Securities duly issued (i) upon the exchange or conversion of any Debt Securities that are exchangeable or convertible into another series of Debt Securities or (ii) upon the exercise of any Warrants pursuant to the terms thereof that are exercisable for the purchase of Debt Securities) will constitute legally valid and binding obligations of the Company, enforceable against the Company in accordance with their terms.

2. When (i) a form of certificate representing the shares of Preferred Stock has been duly adopted by resolution of the Board of Directors and certificates in such form have been executed, countersigned, registered and delivered, (ii) a series of Preferred Stock has been duly established in accordance with the terms of the Company’s certificate of incorporation (the “**Certificate of Incorporation**”), and applicable law, and upon adoption by the Board of Directors of the Company of a resolution in form and content as required by applicable law authorizing the issuance of such shares and upon issuance and delivery of and payment of legal consideration not less than the par value thereof, and assuming that (a) the terms of such shares as issued and delivered are as described in the Registration Statement, the Prospectus and the related Prospectus Supplement(s), and such resolution, (b) at the time of issuance of such shares, the Company has a sufficient number of authorized but unissued shares under the Certificate of Incorporation, (c) such shares as issued and delivered comply with all requirements and restrictions, if any, applicable to the Company, whether imposed by any court or governmental or regulatory body having jurisdiction over the Company or otherwise and (d) such shares are then issued and sold as contemplated in the Registration Statement, the Prospectus and the related Prospectus Supplement(s), and such resolution, such shares of such series of Preferred Stock (including any Preferred Stock duly issued (i) upon the exchange or conversion of any shares of Preferred Stock that are exchangeable or convertible into another series of Preferred Stock, (ii) upon the exercise of any Warrants pursuant to the terms thereof that are exercisable for the purchase of Preferred Stock or (iii) upon the exchange or conversion of Debt Securities that are exchangeable or convertible into Preferred Stock) will be validly issued, fully-paid and nonassessable.

3. Upon adoption by the Board of Directors of the Company of a resolution in form and content as required by applicable law authorizing the issuance of shares of Common Stock and upon issuance and delivery of and payment of legal consideration not less than the par value thereof for certificates representing the shares of Common Stock in the form of the specimen certificate incorporated by reference as Exhibit 4.5 to the Registration Statement being duly executed, countersigned, registered and delivered, and assuming that (i) at the time of issuance of such shares, the Company has a sufficient number of authorized but unissued shares under the Certificate of Incorporation, (ii) such shares as issued and delivered comply with all requirements and restrictions, if any, applicable to the Company, whether imposed by any court or governmental or regulatory body having jurisdiction over the Company or otherwise and (iii) such shares are then issued and sold as contemplated in the Registration Statement, the Prospectus, the related Prospectus Supplement(s) and such resolution, such shares of Common Stock (including any Common Stock duly issued (a) upon the exchange or conversion of any shares of Preferred Stock that are exchangeable or convertible into Common Stock, (b) upon the exercise of any Warrants pursuant to the terms thereof that are exercisable for the purchase of Common Stock or (c) upon the exchange or conversion of Debt Securities that are exchangeable or convertible into Common Stock) will be validly issued, fully paid and nonassessable.

4. When (i) the applicable Warrant Agreement has been duly authorized, executed and delivered by the Company and the Warrant Agent, (ii) the Warrants have been duly authorized and duly established in accordance with the terms of the Warrant Agreement and applicable law (including, without limitation, by the adoption by the Board of Directors of the Company of a resolution duly authorizing the issuance and delivery of the Warrants) (the “**Warrant Authorization**”) and (iii) the Warrants have been duly executed, authenticated and/or countersigned in accordance with the Warrant Agreement relating to such Warrants and delivered on behalf of the Company against payment therefor (which, in the case of Warrants for Common Stock or Preferred Stock, shall consist of legal consideration not less than the par value of such shares) as contemplated by the Registration Statement, the Prospectus, the related Prospectus Supplement(s) and the Warrant Authorization, and assuming that (a) the terms of the Warrants as executed and delivered are as described in the Registration Statement, the Prospectus, the related Prospectus Supplement(s) and the Warrant Authorization, (b) the Warrants as executed and delivered do not violate any law applicable to the Company or result in a default under or breach of any agreement or instrument binding upon the Company, (c) the Warrants as executed and delivered comply with all requirements and restrictions, if any, applicable to the Company, whether imposed by any court or governmental or regulatory body having jurisdiction over the Company or otherwise and (d) the Warrants are then issued and sold as contemplated by the Registration Statement, the Prospectus, the related Prospectus Supplement(s) and the Warrant Authorization, the Warrant Agreement and the Warrants will constitute legally valid and binding obligations of the Company, enforceable against the Company in accordance with their terms.

5. When the Indenture has been duly authorized, executed and delivered by the Company and the Trustee, and assuming that (i) the Indenture does not violate any law applicable to the Company or result in a default under or breach of any agreement or instrument binding upon the Company, and (ii) the Indenture complies with all requirements and restrictions, if any, applicable to the Company, whether imposed by any court or governmental or regulatory body having jurisdiction over the Company or otherwise, the Indenture will constitute the legally valid and binding obligation of the Company, enforceable against the Company in accordance with its terms.

Our opinions are subject to:

(i) the effect of bankruptcy, insolvency, reorganization, preference, fraudulent transfer, moratorium or other similar laws relating to or affecting the rights and remedies of creditors; (ii) the effects of general principles of equity, whether enforcement is considered in a proceeding in equity or at law (including the possible unavailability of specific performance or injunctive relief), concepts of materiality, reasonableness, good faith and fair dealing, and the discretion of the court before which a proceeding is brought; (iii) the invalidity under certain circumstances under law or court decisions of provisions for the indemnification of or contribution to a party with respect to a liability where such indemnification or contribution is contrary to public policy; and (iv) we express no opinion with respect to (a) consents to, or restrictions upon, governing law, jurisdiction, venue, arbitration, remedies or judicial relief; (b) advance waivers of claims, defenses, rights granted by law, or notice, opportunity for hearing, evidentiary requirements, statutes of limitation, trial by jury or at law, or other procedural rights; (c) waivers of broadly or vaguely stated rights; (d) covenants not to compete; (e) provisions for exclusivity, election or cumulation of rights or remedies; (f) provisions authorizing or validating conclusive or discretionary determinations; (g) grants of setoff rights; (h) provisions to the effect that a guarantor is liable as a primary obligor, and not as a surety; (i) provisions for the payment of attorneys’ fees where such payment is contrary to law or public policy; (j) proxies, powers and trusts; (k) provisions prohibiting, restricting, or requiring consent to assignment or transfer of any right or property; (l) provisions for liquidated damages, default interest, late charges, monetary penalties, make-whole premiums or other economic remedies to the extent such provisions are deemed to constitute a penalty; and (m) the severability, if invalid, of provisions to the foregoing effect.

In addition, we express no opinion with respect to (i) whether acceleration of the Debt Securities may affect the collectibility of that portion of the stated principal amount thereof that might be determined to constitute unearned interest thereon, (ii) compliance with laws relating to permissible rates of interest, (iii) the creation, validity, perfection or priority of any security interest, mortgage, or lien, or (iv) any provision to the extent it requires any party to indemnify any other person against loss in obtaining the currency due following a court judgment in another currency.

We have not been requested to express and, with your consent, do not render any opinion as to the applicability to the obligations of the Company under the Indenture or the Debt Securities of Sections 547 and 548 of the United States Bankruptcy Code or applicable state law relating to preferences and fraudulent transfers and obligations.

With your consent, we have assumed for purposes of this opinion that (i) each of the parties to the Agreements, the Debt Securities and the Warrants other than the Company (a) is duly organized, validly existing and in good standing under the laws of its jurisdiction of organization; (b) has the requisite power and authority to execute and deliver and to perform its obligations under each of the Agreements, the Debt Securities and the Warrants to which it is a party; and (c) has duly authorized, executed and delivered each such Agreement, Debt Security and Warrant; (ii) that the Agreements, the Debt Securities and the Warrants will have been duly authorized, executed and delivered by, and constitute legally valid and binding obligations of, the parties thereto and will be, other than as to the Company, enforceable against it in accordance with their respective terms; and (iii) that the status of the Agreements, the Debt Securities and the Warrants as legally valid and binding obligations of the respective parties thereto will not be affected by any (a) breaches of, or defaults under, agreements or instruments, (b) violations of statutes, rules, regulations or court or governmental orders, or (c) failures to obtain required consents, approvals or authorizations from, or make required registrations, declarations or filings with, governmental authorities.

We hereby consent to the filing of this opinion as an exhibit to the Abbreviated Registration Statement and to the use of our name in the Prospectus forming a part of the Registration Statement and the Abbreviated Registration Statement under the caption "Legal Matters." In giving this consent, we do not admit that we are within the category of persons whose consent is required under Section 7 of the Securities Act and the rules and regulations thereunder.

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 Vitale, Caturano & Company, P.C. (whose name has been changed to Caturano and Company, P.C. effective May 1, 2009) dated March 16, 2009 relating to the financial statements of ZIOPHARM Oncology, Inc. as of December 31, 2008 and 2007, and for each of the three years in the three-year period ended December 31, 2008 and from September 9, 2003 (date of inception) through December 31, 2008 (which report expresses an unqualified opinion), and to all references to our Firm included in or made a part of this Registration Statement on Form S-3.

Caturano and Company, P.C.
December 6, 2009
