

ZIOPHARM ONCOLOGY INC  
Form 424B3  
April 27, 2011

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Prospectus Supplement No. 2  
(To Prospectus dated May 31, 2006 and  
Prospectus Supplement No. 1 dated March 4, 2011)

Filed Pursuant to Rule 424(b)(3)  
File No. 333-134279

ZIOPHARM Oncology, Inc.

11,187,774 Shares

Common Stock

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This prospectus supplement (this “Supplement”) supplements and amends the prospectus dated May 31, 2006 and included in our registration statement on Form S-3 (File No. 333-134279) filed on May 19, 2006 and declared effective by the U.S. Securities and Exchange Commission on May 30, 2006, as supplemented by Prospectus No. 1 dated March 4, 2011 (the “Prospectus”). The Prospectus relates to the sale of up to 11,187,774 shares of our common stock by the selling shareholders named in the Prospectus or their donees, pledgees, transferees or other successors in interest, including 7,991,256 shares issued in a private placement transaction that we completed on May 3, 2006 (the “May 2006 Private Placement”) and 3,196,518 additional shares issuable upon the exercise of warrants that were issued in the May 2006 Private Placement. This Supplement does not relate to our issuance of additional shares of common stock beyond the 11,187,774 originally covered by the Prospectus.

This Supplement should be read in conjunction with, and may not be delivered or utilized without, the Prospectus, which is to be delivered with this Supplement. This Supplement is qualified by reference to the Prospectus, except to the extent that the information in this Supplement updates and supersedes the information contained in the Prospectus.

Our common stock trades on the NASDAQ Capital Market under the symbol “ZIOP.”

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

The date of this prospectus supplement is April 27, 2011.

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## SELLING STOCKHOLDERS

The information in the table appearing under the caption “Selling Stockholders” commencing on page S-1 of Prospectus No. 1 is hereby supplemented and amended by adding the information below with respect to selling stockholders not previously listed in the Prospectus, and by superseding the information with respect to the selling stockholders identified below that were previously listed in the Prospectus. This information has been updated only to reflect the assignment to Ionic Capital Master Fund Ltd. of a warrant to purchase 323,974 shares of our common stock previously held by ProQuest Investments III, L.P.; and the assignment to Visium Balanced Master Fund, LTD of four warrants to purchase an aggregate of 211,879 shares of our common stock previously held by Visium Balanced Fund, LP, Visium Balanced Offshore Fund, LTD, Visium Long Bias Fund, LP and Visium Long Bias Offshore Fund, LTD.

The information set forth in the table below is current as of April 27, 2011. Since the date on which we were provided with the information regarding their security ownership in ZIOPHARM Oncology, Inc., selling stockholders may have acquired, sold, transferred or otherwise disposed of all or a portion of their securities. Accordingly, the information provided herein for any particular selling stockholder may understate or overstate, as the case may be, such stockholder’s current ownership.

Selling Stockholder	Shares Beneficially Owned Before Offering (1)	Number of Shares Outstanding Offered by Selling Stockholder	Number of Shares Offering by Selling Stockholder Upon Exercise of Certain Warrants	Percentage Beneficial Ownership After Offering (2)
Ionic Capital Master Fund Ltd. (a)	323,974	0	323,974	*
ProQuest Investments III, L.P. (b)	1,413,430	755,940	0	*
Visium Balanced Master Fund, LTD (c)	211,879	0	211,879	*
Visium Balanced Fund, LP (c)	185,699	185,699	0	*
Visium Balanced Offshore Fund, LTD (c)	277,532	277,532	0	*
Visium Long Bias Fund, LP (c)	55,841	55,841	0	*
Visium Long Bias Offshore Fund, LTD (c)	187,191	187,191	0	*

(1)Beneficial ownership is determined in accordance with SEC rules, beneficial ownership includes any shares as to which the security or stockholder has sole or shared voting power or investment power, and also any shares which the security or stockholder has the right to acquire within 60 days of the date hereof, whether through the exercise or conversion of any stock option, convertible security, warrant or other right. The indication herein that shares are beneficially owned is not an admission on the part of the security or stockholder that he, she or it is a direct or indirect beneficial owner of those shares.

(2)Assumes sales of all shares by the selling stockholders.

(a)Based upon its most recent SEC filing, Ionic Capital Partners LP is the Investment Advisor for Ionic Capital Master Fund Ltd. and has voting and investment control over these shares. Ionic Capital Management LLC is the

General Partner of Ionic Capital Partners LP. John C. Richardson is the General Counsel for Ionic Capital Management LLC.

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(b) Jay Moorin and Alain Schreiber share voting and investment control over the shares held by the selling stockholder.

(c) According to its most recent SEC filings, Visium Asset Management, LP is the investment manager for the Selling stockholder. JG Asset, LLC is the General Partner of Visium Asset Management, LP and Jacob Gottlieb, as Managing Member of JG Asset, LLC, has voting and investment control over the shares held by the selling stockholder.

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