

PROSPECTUS



ZIOPHARM Oncology, Inc.

37,878,788 Shares

Common Stock

This prospectus relates to the disposition from time to time of up to 37,878,788 shares of our common stock, which includes 18,939,394 shares of our common stock issuable upon the exercise of outstanding warrants, which are held by the selling stockholders named in this prospectus. We are not selling any common stock under this prospectus and will not receive any of the proceeds from the sale of shares by the selling stockholders. We will, however, receive the net proceeds of any warrants exercised for cash.

The selling stockholders identified in this prospectus, or their permitted transferees or other successors-in-interest that may be identified in a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part, may offer the shares from time to time through public or private transactions at fixed prices, at prevailing market prices, at varying prices determined at the time of sale, or at privately negotiated prices. We provide more information about how the selling stockholders may sell their shares of common stock in the section titled “Plan of Distribution” beginning on page 11 of this prospectus. We have agreed to pay certain expenses incurred in connection with the registration of these shares, however, we will not be paying any underwriting discounts or commissions in connection with any offering of shares of common stock under this prospectus.

Our common stock is traded on the Nasdaq Capital Market under the symbol “ZIOP.” On February 21, 2019, the last reported sales price of our common stock was \$2.84 per share.

Investing in our common stock involves a high degree of risk. You should review carefully the risks and uncertainties we have described under the heading “[Risk Factors](#)” on page 3 of this prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus, including those filed after the date hereof.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is February 21, 2019.

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ABOUT THIS PROSPECTUS

This prospectus relates to a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under this shelf registration process, the selling stockholders may from time to time, in one or more offerings, sell the common stock described in this prospectus.

We have not authorized anyone to provide you with information other than the information contained in or incorporated by reference into this prospectus (as supplemented or amended). This document may only be used where it is legal to sell these securities. The information contained in this prospectus (and in any supplement or amendment to this prospectus) is accurate only as of the date on the front of the document, and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since those dates.

We urge you to read carefully this prospectus (as supplemented and amended), together with the information incorporated herein by reference as described under the heading “Incorporation of Certain Information by Reference” before deciding whether to invest in any of the common stock being offered.

This prospectus incorporates by reference market data, industry statistics and other data that have been obtained from, or compiled from, information made available by third parties. We have not independently verified their data. This prospectus and the information incorporated herein by reference includes trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus are the property of their respective owners.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus (as supplemented and amended), including the financial data and related notes, risk factors and other information incorporated by reference in this prospectus before making an investment decision.

Unless the context indicates otherwise, as used in this prospectus, the terms “Ziopharm,” “the Company,” “we,” “us” and “our” refer to Ziopharm Oncology, Inc., a Delaware corporation. This prospectus or information incorporated by reference in this prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to or incorporated by reference in this prospectus, including logos, artwork and other visual displays, may appear without the ® or TM symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies’ trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

About Ziopharm Oncology

We are a biopharmaceutical company focused on discovering, acquiring, developing and commercializing next generation immunotherapy platforms that leverage gene- and cell-based therapies to treat patients with cancer. We are developing two immuno-oncology platform technologies designed to utilize the patient’s immune system by employing novel, controlled gene expression and innovative cell engineering technologies to deliver safe, effective, and scalable cell- and viral-based therapies for the treatment of multiple cancer types. Our first platform is Controlled IL-12, which is designed to deliver interleukin 12 or IL-12, a master regulator of the immune system, in a controlled and safe manner to focus the patient’s immune system to cancer. Our second platform is referred to as *Sleeping Beauty* and is based on the genetic engineering of immune cells using the *Sleeping Beauty* system to rapidly reprogram T cells outside of the body for subsequent infusion. We believe these two platforms provide or will provide unique and powerful solutions intended to advance the field of immuno-oncology and address the issues associated with (1) treating heterogenous solid tumors and unknown antigens therein through control of IL-12 and (2) providing rapid and cost-effective manufacturing solutions for CAR and TCR-based cell therapies for hematologic malignancies and solid tumors against known antigens.

We are developing a gene therapy that delivers Controlled IL-12 to treat patients with solid tumors including brain cancer. Based on technology licensed from MD Anderson Cancer Center, we are developing CAR T-cell or CAR+ T targeting CD19, and T-cell receptor T-cell, or TCR+ T, therapies. These programs are being advanced in collaboration with MD Anderson and the National Cancer Institute, or NCI.

Corporate Information

We 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 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 affect 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, or the SEC, and the historical financial statements of Ziopharm, Inc. became our historical financial statements.

Our principal executive offices are located at One First Avenue, Parris Building 34, Navy Yard Plaza, Boston, Massachusetts 02129, and our telephone number is (617) 259-1970.

The Offering

The selling stockholders named in this prospectus may offer and sell up to 37,878,788 shares of our common stock, which includes 18,939,394 shares of our common stock issuable upon the exercise of outstanding warrants. The shares issuable upon exercise of the warrants will become eligible for sale by the selling stockholders under this prospectus only as the warrants are exercised. Our common stock is currently listed on the Nasdaq Capital Market under the symbol “ZIOP.” Shares of common stock that may be offered under this prospectus, when issued and paid for in the case of shares issuable upon exercise of the outstanding warrants, will be fully paid and non-assessable. We will not receive any of the proceeds of sales by the selling stockholders of any of the common stock covered by this prospectus. Throughout this prospectus, when we refer to the shares of our common stock being registered on behalf of the selling stockholders, we are referring to the shares and the shares underlying the warrants issued to the selling stockholders pursuant to the securities purchase agreement we entered into with the selling stockholders on November 11, 2018, and when we refer to the selling stockholders in this prospectus, we are referring to the purchasers under the securities purchase agreement and, as applicable, their permitted transferees or other successors-in-interest that may be identified in a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully review the risks and uncertainties described under the heading “Risk Factors” contained in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 filed with the SEC on November 9, 2018, as updated by our subsequent annual, quarterly and other reports and documents that are incorporated by reference into this prospectus, before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations. Please also read carefully the section below titled “Special Note Regarding Forward-Looking Statements.”

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements are based on our management's beliefs and assumptions and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the sections titled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent annual report on Form 10-K and in our most recent quarterly report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC. All statements, other than statements of historical facts, are forward-looking statements for purposes of these provisions, including, without limitation, any statements relating to:

- our ability to raise substantial additional capital to fund our planned operations in the near term and to continue as a going concern;
- our estimates regarding expenses, use of cash, timing of future cash needs and capital requirements;
- the development of our product candidates, including statements regarding the timing of initiation, completion and the outcome of clinical studies or trials and related preparatory work and the period during which the results of the trials will become available;
- our ability to advance our product candidates through various stages of development, especially through pivotal safety and efficacy trials;
- the risk that final trial data may not support interim analysis of the viability of our product candidates;
- our expectation regarding the safety and efficacy of our product candidates, the progress and timing of our research and development programs;
- the timing, scope or likelihood of regulatory filings and approvals from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies for our product candidates and for which indications;
- our ability to license additional intellectual property relating to our product candidates from third parties and to comply with our existing license agreements;
- our ability to achieve the results contemplated by our collaboration agreements and the benefits to be derived from relationships with collaborators;
- developments and projections relating to competition from other pharmaceutical and biotechnology companies or our industry;
- our estimates regarding the potential market opportunity for our product candidates;
- the anticipated rate and degree of market acceptance of our product candidates for any indication if approved;
- the anticipated amount, timing and accounting of contract liability (formerly deferred revenue), milestones and other payments under licensing, collaboration or acquisition agreements, research and development costs and other expenses;
- our intellectual property position, including the strength and enforceability of our intellectual property rights;
- our ability to attract and retain qualified employees and key personnel; and
- the impact of government laws and regulations in the United States and foreign countries.

In some cases, you can identify forward-looking statements by terms such as "anticipate," "believe," "estimate," "expect," "forecast," "intend," "may," "plan," "project," "target," "will" and other words and terms

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of similar meaning. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance, time frames or achievements to be materially different from the information expressed or implied by these forward-looking statements. While we believe that we have a reasonable basis for each forward-looking statement, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. We discuss many of these risks, uncertainties and other factors in greater detail under the heading “Risk Factors” contained in our quarterly report on Form 10-Q for the quarter ended September 30, 2018 filed with the SEC on November 9, 2018 and incorporated by reference in this prospectus, as the same may be amended, supplemented or superseded by the risks and uncertainties described under similar headings in the other documents that are filed after the date hereof and incorporated by reference into this prospectus. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements. Also, these forward-looking statements represent our estimates and assumptions only as of the date such forward-looking statements are made. You should carefully read this prospectus, together with the information incorporated herein by reference as described under the heading “Incorporation of Certain Information by Reference,” completely and with the understanding that our actual future results may be materially different from what we expect. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our business, results of operations and financial condition. We hereby qualify all of our forward-looking statements by these cautionary statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

USE OF PROCEEDS

The selling stockholders will receive all of the net proceeds from sales of the common stock pursuant to this prospectus. However, in the case of warrants issued to the selling stockholders pursuant to the securities purchase agreement dated November 11, 2018, upon any exercise of these warrants for cash, the selling stockholders would pay us an exercise price of \$3.01 per share of common stock, subject to any adjustment pursuant to the terms of the warrants. We expect to use any such warrant exercise proceeds primarily for working capital and general corporate purposes. These warrants are also exercisable on a cashless basis by net exercise under certain conditions contained therein. If any of these warrants are exercised on a cashless basis, we would not receive any cash payment from the applicable selling stockholder upon any such cashless exercise of a warrant.

SELLING STOCKHOLDERS

On November 11, 2018, we entered into a securities purchase agreement with the selling stockholders pursuant to which we issued and sold in a private placement an aggregate of 18,939,394 immediately separable units, comprised of an aggregate of 18,939,394 shares of our common stock and warrants to purchase up to 18,939,394 additional shares of common stock, which warrants we refer to in this prospectus as the 2018 Warrants, for an aggregate purchase price of approximately \$50.0 million. Pursuant to the securities purchase agreement, we agreed to file the registration statement of which this prospectus is a part to cover the resale of the shares of our common stock and the shares underlying the 2018 Warrants, and to keep such registration statement effective with respect to each selling stockholder until the earlier to occur of (i) November 13, 2020 or (ii) the date on which all of the shares of our common stock registered for resale under the registration statement have been disposed of in accordance with such registration statement, disposed of pursuant to Rule 144 under the Securities Act or can be resold pursuant to Rule 144 without restriction or limitation (including without the requirement to be in compliance with Rule 144(c)(1)) or another similar exemption under the Securities Act. The 2018 Warrants, which have a five-year term expiring on November 13, 2023, have a per share exercise price of \$3.01. The exercise price and number of shares of common stock issuable upon exercise of the 2018 Warrants may be adjusted in certain circumstances, including stock splits, stock dividends, reclassifications and the like. The shares issuable upon exercise of the 2018 Warrants will become eligible for sale by the selling stockholders under this prospectus only as the 2018 Warrants are exercised. We cannot predict when or whether any of the selling stockholders will exercise their 2018 Warrants.

We are registering the resale of the above-referenced shares to permit each of the selling stockholders identified below, or their permitted transferees or other successors-in-interest that may be identified in a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part, to resell or otherwise dispose of the shares in the manner contemplated under “Plan of Distribution” in this prospectus (as may be supplemented and amended). This prospectus covers the sale or other disposition by the selling stockholders of up to the total number of shares of common stock issued to the selling stockholders pursuant to the securities purchase agreement, plus the total number of shares of common stock issuable upon exercise of the 2018 Warrants issued to the selling stockholders. Throughout this prospectus, when we refer to the shares of our common stock being registered on behalf of the selling stockholders, we are referring to the shares of our common stock and the shares underlying the 2018 Warrants issued to the selling stockholders pursuant to the securities purchase agreement, and when we refer to the selling stockholders in this prospectus, we are referring to the purchasers under the securities purchase agreement and, as applicable, their permitted transferees or other successors-in-interest that may be identified in a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part.

The selling stockholders may sell some, all or none of their shares. We do not know how long the selling stockholders will hold the shares before selling them, and we currently have no agreements, arrangements or understandings with the selling stockholders regarding the sale or other disposition of any of the shares. The shares of our common stock covered hereby may be offered from time to time by the selling stockholders.

The following table sets forth the name of each selling stockholder, the number and percentage of our common stock beneficially owned by the selling stockholders as of December 31, 2018, the number of shares of our common stock that may be offered under this prospectus, and the number and percentage of our common stock beneficially owned by the selling stockholders assuming all of the shares of our common stock registered hereunder are sold. Beneficial ownership is determined in accordance with the rules of the SEC and includes voting or investment power with respect to our common stock. Generally, a person “beneficially owns” shares of our common stock if the person has or shares with others the right to vote those shares or to dispose of them, or if the person has the right to acquire voting or disposition rights within 60 days. The number of shares of our common stock in the column “Number of Shares Offered” represents all of the shares of our common stock that a selling stockholder may offer and sell from time to time under this prospectus.

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All information contained in the table below and the footnotes thereto is based upon information provided to us by the selling stockholders. The information in the table below and the footnotes thereto regarding shares of common stock to be beneficially owned after the offering assumes that all of the selling stockholders have exercised the 2018 Warrants in full pursuant to cash exercises and further assumes the sale of all shares being offered by the selling stockholders under this prospectus. The percentage of shares owned prior to and after the offering is based on 161,137,689 shares of common stock outstanding as of December 31, 2018 and, with respect to the percentage of shares owned after the offering, on the assumption that all of the selling stockholders have exercised the 2018 Warrants in full pursuant to cash exercises and therefore that all shares of common stock issuable upon exercise of the 2018 Warrants were outstanding as of that date. Unless otherwise indicated in the footnotes to this table, we believe that each of the selling stockholders named in this table has sole voting and investment power with respect to the shares of common stock indicated as beneficially owned. Except as otherwise indicated below, based on the information provided to us by the selling stockholders, none of the selling stockholders is a broker-dealer or an affiliate of a broker-dealer.

Name and Address	Prior to Offering		Number of Shares Offered(2)	After Offering	
	Number of Shares Beneficially Owned(1)	Percentage of Shares Beneficially Owned(1)		Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
MSD Credit Opportunity Master Fund, L.P. 645 Fifth Avenue, 21st Floor New York, New York 10022	16,664,957(3)	9.9	15,151,516	3,410,500	1.9
White Rock Capital Partners, L.P. 3131 Turtle Creek Blvd., Suite 800 Dallas, Texas 75219	12,375,758(4)	7.5	7,575,758	4,800,000	2.7
Miller Opportunity Trust, a series of Trust for Advised Portfolios One South Street, Suite 2550 Baltimore, Maryland 21202	11,380,658(5)	6.9	7,575,758	3,804,900	2.1
Level One Partners, LLC 210 Ridge McIntire Rd., Suite 350 Charlottesville, Virginia 22903	5,795,061(6)	3.6	3,787,880	2,007,181	1.1
Robert W. Postma Roth IRA 141 Mecox Road P.O. Box 207 Water Mill, New York 11976	1,896,352(7)	1.2	1,893,940	2,412	*
WJD Investment Partners LLC 2305 SW 18th Avenue Ft. Lauderdale, Florida 33315	1,515,150(8)	*	1,515,150	—	*
Steven Denstman 5235 Hidden Harbor Road Sarasota, Florida 34242	588,786(9)	*	378,786	210,000	*

* Less than one percent.

- (1) Under the terms of the 2018 Warrants, the number of shares of our common stock that may be acquired by a selling stockholder upon any exercise of a 2018 Warrant is generally limited to the extent necessary to ensure that, following such exercise, such selling stockholder would not, together with its affiliates and any other persons or entities whose beneficial ownership of our common stock would be aggregated with such selling stockholder for purposes of Section 13(d) of the Exchange Act, beneficially own in excess of 9.99% of the total number of shares of our common stock then issued and outstanding and/or the then combined voting power of all of our voting securities, which we refer to in this prospectus as the Exercise Limitation. The Exercise Limitation (i) may be increased, decreased or terminated, in each selling stockholder's sole discretion, upon at least 61 days' prior notice to us and (ii) terminates automatically on the date that is 15

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days prior to the expiration of the 2018 Warrant. If the operation of the Exercise Limitation currently limits the beneficial ownership of a selling stockholder, such limitation is noted in the footnotes that follow. In addition, as noted in footnote (2), the number of shares shown under the column titled "Number of Shares Offered" is shown without regard to the Exercise Limitation.

- (2) The number of shares offered hereby, for each selling stockholder, consists solely of the shares issued to such selling stockholder pursuant to the securities purchase agreement and the shares issuable upon exercise of the 2018 Warrants issued to such selling stockholder. The shares issuable upon exercise of the 2018 Warrants will become eligible for sale by the selling stockholders under this prospectus only as the 2018 Warrants are exercised. In addition, the number of shares offered hereby shown under the column titled "Number of Shares Offered" includes the maximum number of shares issuable upon the exercise of the 2018 Warrants without regard to Exercise Limitation described in footnote (1) above.
- (3) Represents (i) 10,986,258 outstanding shares of common stock and (ii) 5,678,699 shares of common stock issuable upon exercise of 2018 Warrants. The beneficial ownership of 2018 Warrants held by the selling stockholder is currently limited by the Exercise Limitation. MSD Partners, L.P. is the investment manager of, and may be deemed to beneficially own the securities held by, MSD Credit Opportunity Master Fund, L.P. MSD Partners (GP), LLC is the general partner of, and may be deemed to beneficially own the securities beneficially owned by, MSD Partners, L.P. Each of Glenn R. Fuhrman, John C. Phelan and Marc R. Lisker is a manager of, and may be deemed to beneficially own the securities beneficially owned by, MSD Partners (GP), LLC.
- (4) Represents (i) 8,587,879 outstanding shares of common stock and (ii) 3,787,879 shares of common stock issuable upon exercise of 2018 Warrants. White Rock Management, L.P. is the general partner of, and may be deemed to beneficially own the securities held by, White Rock Capital Partners, L.P. White Rock Capital (TX), Inc. is the general partner of, and may be deemed to beneficially own the securities beneficially owned by, White Rock Management, L.P. Thomas U. Barton and Joseph U. Barton are the shareholders of, and may be deemed to beneficially own the securities beneficially owned by, White Rock Capital (TX), Inc.
- (5) Represents (i) 7,592,779 outstanding shares of common stock and (ii) 3,787,879 shares of common stock issuable upon exercise of 2018 Warrants. Miller Value Partners, LLC is the investment manager of, and may be deemed to beneficially own the securities held by, Miller Opportunity Trust, a series of Trust for Advised Portfolios. William H. Miller III is the managing member of, and may be deemed to beneficially own the securities beneficially owned by, Miller Value Partners, LLC.
- (6) Represents (i) 3,901,121 outstanding shares of common stock and (ii) 1,893,940 shares of common stock issuable upon exercise of 2018 Warrants. Robert D. Hardie has voting and investment control over, and may be deemed to beneficially own, the securities held by Level One Partners, LLC.
- (7) Represents (i) 949,382 outstanding shares of common stock and (ii) 946,970 shares of common stock issuable upon exercise of 2018 Warrants. Robert W. Postma has voting and investment control over, and may be deemed to beneficially own, the securities held by Robert W. Postma Roth IRA.
- (8) Represents (i) 757,575 outstanding shares of common stock and (ii) 757,575 shares of common stock issuable upon exercise of 2018 Warrants. Donald Kleckner is the manager of, and may be deemed to beneficially own the securities held by, WJD Investment Partners LLC.
- (9) Represents (i) 399,393 outstanding shares of common stock and (ii) 189,393 shares of common stock issuable upon exercise of 2018 Warrants.

Relationships with the Selling Stockholders

Neither the selling stockholders nor any of the persons that control them has had any material relationships with us or our affiliates within the past three years.

PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes donees, pledgees, transferees or other successors-in-interest selling shares of common stock previously issued and the shares of common stock issuable upon exercise of the warrants or interests in shares of common stock received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of common stock or interests in shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. The selling stockholders may sell their shares of our common stock pursuant to this prospectus at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling stockholders may use any one or more of the following methods when disposing of shares or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;
- a combination of any such methods of sale; and
- any other method permitted pursuant to applicable law.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of common stock or warrants owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock, from time to time, under this prospectus, or under an amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus. The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

In connection with the sale of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the common stock in the course of hedging the positions they assume. The selling stockholders may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge the common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

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The aggregate proceeds to the selling stockholders from the sale of the common stock offered by them will be the purchase price of the common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the common stock or interests therein may be “underwriters” within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. Selling stockholders who are “underwriters” within the meaning of Section 2(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act.

To the extent required, the shares of our common stock to be sold, the names of the selling stockholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

In order to comply with the securities laws of some states, if applicable, the common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the common stock may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus (as it may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

We have agreed to indemnify the selling stockholders against liabilities, including liabilities under the Securities Act and state securities laws, relating to the registration of the shares offered by this prospectus.

We have agreed with the selling stockholders to keep the registration statement of which this prospectus constitutes a part effective until such time as the shares offered by the selling stockholders have been effectively registered under the Securities Act and disposed of in accordance with such registration statement, the shares offered by the selling stockholders have been disposed of pursuant to Rule 144 under the Securities Act or the shares offered by the selling stockholders may be resold pursuant to Rule 144 without restriction or limitation (including without the requirement to be in compliance with Rule 144(c)(1)) or another similar exemption under the Securities Act.

LEGAL MATTERS

The validity of the common stock being offered hereby has been passed upon for us by Cooley LLP, Boston, Massachusetts.

EXPERTS

The financial statements of Ziopharm Oncology, Inc. as of December 31, 2017 and 2016 and for each of the years in the three-year period ended December 31, 2017 and the effectiveness of internal control over financial reporting as of December 31, 2017, incorporated in this prospectus by reference from the Ziopharm Oncology, Inc. Annual Report on Form 10-K for the year ended December 31, 2017, have been audited by RSM US LLP, an independent registered public accounting firm, as stated in their report thereon (which report expresses an unqualified opinion and includes an explanatory paragraph related to the Company's ability to continue as a going concern) incorporated herein by reference, and have been incorporated in this prospectus and registration Statement in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-3 under the Securities Act with respect to the resale of the common stock the selling stockholders are offering under this prospectus. This prospectus does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the common stock we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. Neither we nor any agent, underwriter or dealer has authorized any person to provide you with different information. We are not making an offer of common stock in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front page of this prospectus, regardless of the time of delivery of this prospectus or any sale of common stock offered by this prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy statements and other information regarding issuers that file electronically with the SEC, including us. The address of the SEC website is www.sec.gov.

We maintain a website at www.ziopharm.com. Information contained in, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2017 and filed with the SEC on March 1, 2018, as amended on April 30, 2018;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 filed with the SEC on May 10, 2018, our Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 filed with the SEC on August 8, 2018 and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 filed with the SEC on November 9, 2018;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2017 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed) filed with the SEC on August 8, 2018;
- our Current Reports on Form 8-K (other than information furnished rather than filed) filed with the SEC on January 9, 2018, February 5, 2018, February 6, 2018, February 22, 2018, March 13, 2018, June 18, 2018, July 27, 2018, September 24, 2018, October 9, 2018, October 11, 2018, October 16, 2018, November 13, 2018, December 14, 2018, January 10, 2019 and February 4, 2019; and
- the description of our common stock which is registered under Section 12 of the Exchange Act, in our registration statement on Form 8-A, filed with the SEC on September 20, 2006, including any amendments or reports filed for the purpose of updating such description.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including those made after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of such registration statement, until we file a post-effective amendment that indicates the termination of the offering of the common stock made by this prospectus and will become a part of this prospectus from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

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

Ziopharm Oncology, Inc.
One First Avenue, Parris Building 34, Navy Yard Plaza
Boston, Massachusetts 02129
Attention: General Counsel
(617) 259-1970