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Onconova Therapeutics, Inc.
Form S-3
October 08, 2014

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As filed with the Securities and Exchange Commission on October 8, 2014

Registration No. 333-

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

**Form S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

Onconova Therapeutics, Inc.

(Exact name of registrant as specified in charter)

Delaware

(State or other jurisdiction of incorporation or organization)

22-3627252

(I.R.S. Employer Identification No.)

**375 Pheasant Run
Newtown, PA 18940
(267) 759-3680**

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Ramesh Kumar, Ph.D.
President and Chief Executive Officer
Onconova Therapeutics, Inc.
375 Pheasant Run
Newtown, PA 18954
(267) 759-3680**

(Name, address, including zip code, and telephone number including area code, of agent for service)

Copy to:

**Jeffrey P. Libson
Donald R. Readlinger, Esq.
Pepper Hamilton LLP
Suite 400
301 Carnegie Center
Princeton, NJ 08543-5276
Tel: (609) 452-0808
Fax: (609) 452-1147**

Approximate date of commencement 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.

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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.

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 the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

| | | | |
|---|---|---|---|
| Large accelerated filer <input type="checkbox"/> | Accelerated filer <input type="checkbox"/> | Non-accelerated filer <input type="checkbox"/> | Smaller reporting company <input type="checkbox"/> |
| | | (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 | Proposed Maximum Offering Price Per Unit | Proposed Maximum Aggregate Offering Price | Amount of Registration Fee |
|---|----------------------------|--|---|-------------------------------|
| Primary Offering by Onconova Therapeutics, Inc.: | | | | |
| Common Stock, par value \$0.01 per share | (1) | (2) | (2) | |
| Preferred Stock, par value \$0.01 per share | (1) | (2) | (2) | |
| Debt Securities | (1) | (2) | (2) | |
| Warrants | (1) | (2) | (2) | |
| Units | (1) | (2) | (2) | |
| Total for Primary Offering | | | \$100,000,000.00 | \$11,620.00(3) |
| Secondary Offering by Selling Stockholders: | | | | |
| Common Stock, par value \$0.01 per share | 228,647(4) | \$4.26(4) | 974,036.22(4) | 113.18(4) |
| Total for Primary and Secondary Offering: | | | \$100,974,036.22 | \$11,733.18 |

- (1) With respect to the primary offering, there are being registered hereunder such indeterminate number of shares of common stock and preferred stock, such indeterminate principal amount of debt securities, such indeterminate number of warrants to purchase common stock, preferred stock or debt securities, and such indeterminate number of units as shall have an aggregate initial offering price not to exceed \$100,000,000, less the aggregate dollar amount of all securities previously issued hereunder in the primary offering. 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 offering price not to exceed \$100,000,000, less the aggregate dollar amount of all securities previously issued hereunder in the primary offering. Any such securities registered hereunder may be sold separately or as units with the other securities registered hereunder. The securities registered hereunder also include such indeterminate number of shares of common stock and preferred stock and amount of debt securities as may be issued upon conversion of or exchange for preferred stock or debt securities that provide for conversion or exchange, upon exercise of warrants or pursuant to the anti-dilution provisions of any of such securities. In addition, pursuant to Rule 416 under the Securities Act of 1933, as amended, or the Securities Act, the securities being registered hereunder include such indeterminate number of shares of common stock and preferred stock as may be issuable with respect to the securities being registered hereunder

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as a result of stock splits, stock dividends or similar transaction.

- (2) The proposed maximum offering price per unit of each class of security registered hereunder will be determined from time to time in connection with, and at the time of, the issuance of the securities and is not specified as to each class of security pursuant to General Instruction II.D. of Form S-3, as amended.
- (3) Calculated pursuant to Rule 457(o) under the Securities Act based on the proposed maximum aggregate offering price of all securities listed.
- (4) In addition, up to 228,647 shares of common stock may be sold from time to time pursuant to this registration statement by certain selling stockholders, including those named herein, in a secondary offering. With respect to shares of common stock to be offered by the selling stockholders in the secondary offering, the price has been estimated solely for the purpose of calculating the registration fee, pursuant to Rule 457(c) under the Securities Act, based on the average of the high and low prices reported for the shares of common stock as reported on the Nasdaq Global Market on October 2, 2014.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act or until the registration statement shall become effective on such date as the Securities and Exchange Commission, or SEC, acting pursuant to said Section 8(a), may determine.

EXPLANATORY NOTE

This registration statement contains two prospectuses:

A base prospectus which covers the offering, issuance and sale by the registrant from time to time of any combination of common stock, preferred stock, debt securities, warrants or units described in this prospectus in one or more offerings up to a maximum aggregate offering price of \$100,000,000, as well as the offering of up to 228,657 shares of common stock by certain selling stockholders, including those named in this prospectus; and

A supplemental prospectus covering the offering, issuance and sale by the registrant of up to a maximum aggregate offering price of \$20,000,000 of the registrant's common stock that may be issued and sold under a sales agreement with Cantor Fitzgerald & Co.

The base prospectus immediately follows this explanatory note. The supplemental prospectus immediately follows the base prospectus. The common stock that may be offered, issued and sold by the registrant under the supplemental prospectus is included in the \$100,000,000 of securities that may be offered, issued and sold by the registrant under the base prospectus.

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The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting offers to buy these securities in any state or other jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED OCTOBER 8, 2014

PROSPECTUS

Onconova Therapeutics, Inc.

\$100,000,000

**Common Stock, Preferred Stock,
Debt Securities, Warrants and Units
and
228,647 Shares of Common Stock**

This prospectus covers our offer and sale from time to time of any combination of common stock, preferred stock, debt securities, warrants or units described in this prospectus in one or more offerings. This prospectus provides a general description of the securities we may offer and sell. Each time we offer and sell securities we will provide specific terms of the securities offered in a supplement to this prospectus. The prospectus supplement will also describe the specific manner in which we will offer the securities and may also add, update or change information contained in this prospectus. The aggregate offering price of all securities sold by us under this prospectus may not exceed \$100,000,000.

This prospectus also covers the resale by selling stockholders, including those identified in the "Selling Stockholders" section of this prospectus, of up to an aggregate of 228,647 shares of our common stock. A prospectus supplement or amendment may also be required in connection with certain sales of common stock by the selling stockholders. The prospectus supplement may also add, update or change information contained in this prospectus. We will not receive proceeds from the sale of shares of our common stock by the selling stockholders.

You should read this prospectus and any supplement carefully before you purchase any of our securities. **This prospectus may not be used to offer and sell securities unless accompanied by a prospectus supplement.**

The securities may be offered and sold by us or selling stockholders from time to time at fixed prices, at market prices or at negotiated prices, and may be offered and sold to or through one or more underwriters, dealers or agents or directly to purchasers on a continuous or delayed basis. See "Plan of Distribution."

Our common stock is currently listed on the Nasdaq Global Market under the symbol "ONTX". On October 2, 2014, the last reported sale price of our common stock on the Nasdaq Global Market was \$4.29 per share.

As of August 29, 2014, the aggregate market value of our outstanding common stock held by non-affiliates, or the public float, was \$66,251,060, which was calculated based on shares of our outstanding common stock held by non-affiliates and on a price of \$5.22 per share, the last reported sale price for our common stock, on August 29, 2014. Other than the securities offered by this prospectus, we have not offered any securities pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus.

You should rely only on the information contained or incorporated by reference in this prospectus. We have not authorized any other person to provide you with different information.

Investing in these securities involves risks, including those set forth in the "Risk Factors" section of the applicable prospectus supplement and any related free writing prospectus and of our most recent Annual

Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-K, each of which is incorporated by reference into this prospectus.

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

This prospectus is dated _____, 2014.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the SEC. This prospectus covers the primary offering by us of up to an aggregate of \$100,000,000 of securities and the secondary offering by the selling stockholders identified herein of up to an aggregate of 228,647 shares of our common stock. We may offer and sell any combination of the securities described in this prospectus and the selling stockholders may offer and sell shares of common stock in one or more offerings. This prospectus provides you with a general description of the securities we may offer and sell. Each time we offer and sell securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus or in any documents that we have incorporated by reference into this prospectus. You should read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the heading "Where You Can Find More Information," before investing in any of the securities offered.

We have filed or incorporated by reference exhibits to the registration statement of which this prospectus forms a part. You should read the exhibits carefully for provisions that may be important to you.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

Neither we nor any selling stockholder has authorized any dealer, salesman or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and any accompanying supplement to this prospectus. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or any accompanying prospectus supplement. This prospectus and any accompanying supplement to this prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and any accompanying supplement to this prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any document we file with the SEC at the SEC's public reference room at 100 F Street NE, Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the SEC's public reference facilities by calling the SEC at 1-800-SEC-0330. You can request copies of these documents, upon payment of a duplicating fee, by writing to the SEC at its principal office at 100 F Street NE, Room 1580, Washington, D.C. 20549-1004. The SEC maintains an Internet website at <http://www.sec.gov> that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. Our SEC filings are accessible through the Internet at that website. Our reports on Forms 10-K, 10-Q and 8-K, and amendments to those reports, are also available for download, free of charge, as soon as reasonably practicable after these reports are filed with the SEC, at our website at www.onconova.com. The content contained in, or that can be accessed through, our website is not a part of this prospectus.

Unless the context indicates otherwise, as used in this prospectus, the terms "Onconova," "Onconova Therapeutics," "Company," "we," "us" and "our" refer to Onconova Therapeutics, Inc. and its consolidated subsidiaries.

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INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below:

Our Annual Report on Form 10-K for the fiscal year ended December 31, 2013 that we filed with the SEC on March 20, 2014, including the information required by Part III, Items 10 through 14, of Form 10-K, which is incorporated by reference to our definitive proxy statement for our 2014 annual meeting of stockholders filed on April 29, 2014;

Our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2014 and June 30, 2014, that we filed with the SEC on May 15, 2014 and August 14, 2014, respectively;

Our Current Reports on Form 8-K filed with the SEC on February 20, 2014, March 7, 2014, May 2, 2014 and May 23, 2014;

The description of our common stock contained in our registration statement on Form 8-A filed on July 23, 2013 (Registration no. 001-36020) with the SEC, including any amendment or report filed for the purpose of updating such description;

All documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, after the date of the initial filing of the registration statement of which this prospectus is a part and prior to the effectiveness of such registration statement; and

All documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act on or after the date of this prospectus and before we stop offering the securities under this prospectus.

We will provide without charge to each person, including any beneficial owner, to whom this prospectus is delivered, upon his or her written or oral request, a copy of any or all documents referred to above which have been or may be incorporated by reference into this prospectus but not delivered with this prospectus excluding exhibits to those documents unless they are specifically incorporated by reference into those documents. You can request those documents from us, at no cost, by writing or telephoning us at: Onconova Therapeutics, Inc., 375 Pheasant Run, Newtown, Pennsylvania, 18940, (267) 759-3036, Attention: Benjamin Hoffman.

The most recent information that we file with the SEC automatically updates and supersedes older information. The information contained in any such filing will be deemed to be a part of this prospectus, commencing on the date on which the filing is made.

Information furnished under Items 2.02 or 7.01 (or corresponding information furnished under Item 9.01 or included as an exhibit) in any past or future Current Report on Form 8-K that we file with the SEC, unless otherwise specified in such report, is not incorporated by reference in this prospectus.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference in this prospectus contain, and any prospectus supplement may contain, forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements, other than statements of historical facts, included or incorporated in this prospectus or any prospectus supplement regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and

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objectives of management are forward-looking statements. We may, in some cases, use terms such as "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements appear in a number of places throughout this prospectus and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned non-clinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, protection of our intellectual property portfolio, the degree of clinical utility of our product candidates, particularly in specific patient populations, our ability to develop commercial functions, expectations regarding clinical trial data, our results of operations, cash needs, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this prospectus. In addition, even if our results of operations, financial condition and liquidity, and events in the industry in which we operate are consistent with the forward-looking statements contained in this prospectus, they may not be predictive of results or developments in future periods.

Actual results could differ materially from our forward-looking statements due to a number of factors, including risks related to:

our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;

the success and timing of our nonclinical studies and clinical trials;

the difficulties in obtaining and maintaining regulatory approval of our product candidates, and the labeling under any approval we may obtain;

our plans and ability to develop and commercialize our product candidates;

our failure to recruit or retain key scientific or management personnel or to retain our executive officers;

the size and growth of the potential markets for our product candidates and our ability to serve those markets;

regulatory developments in the United States and foreign countries;

the rate and degree of market acceptance of any of our product candidates;

obtaining and maintaining intellectual property protection for our product candidates and our proprietary technology;

the successful development of our commercialization capabilities, including sales and marketing capabilities;

recently enacted and future legislation and regulations regarding the healthcare system;

the success of competing therapies and products that are or become available;

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our dependence on collaboration agreements with other pharmaceutical companies, such as Baxter Healthcare SA, or Baxter, and SymBio Pharmaceuticals Limited, or SymBio, for commercialization of our products and our ability to achieve certain milestones under those agreements; and

the performance of third parties, including contract research organizations and third-party manufacturers.

Any forward-looking statements that we make in this prospectus speak only as of the date of such statements, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events. Comparisons of results for current and any prior periods are not intended to express any future trends or indications of future performance, unless expressed as such, and should only be viewed as historical data.

You should also read carefully the factors described in the "Risk Factors" section of this prospectus and set forth in our most recent Annual Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-K, to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

We obtained the industry, market and competitive position data in this prospectus and the documents incorporated into this prospectus from our own internal estimates and research as well as from industry and general publications and research surveys and studies conducted by third parties. Industry publications and surveys generally state that the information contained therein has been obtained from sources believed to be reliable. We believe this data is accurate in all material respects as of the date of this prospectus.

RISK FACTORS

Our business is influenced by many factors that are difficult to predict, and that involve uncertainties that may materially affect actual operating results, cash flows and financial condition. Before making an investment decision, you should carefully consider these risks, including those set forth in the "Risk Factors" section of our most recent Annual Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-K, each of which is incorporated by reference into this prospectus, and you should also carefully consider any other information we include or incorporate by reference in this prospectus or include in any applicable prospectus supplement. Each of the risks described in these sections and documents could materially and adversely affect our business, financial condition, results of operations and prospects, and could result in a partial or complete loss of your investment.

ONCONOVA THERAPEUTICS, INC.

Overview

We are a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule drug candidates to treat cancer. Using our proprietary chemistry platform, we have created an extensive library of targeted anti-cancer agents designed to work against specific cellular pathways important to cancer cells. We believe that the drug candidates in our pipeline have the

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potential to be efficacious in a wide variety of cancers without causing harm to normal cells. We have three clinical-stage product candidates and several preclinical programs.

Rigosertib

Rigosertib, our most advanced product candidate, is being tested as a single agent and in combination with azacitidine and with chemoradiation therapy, in clinical trials of patients with myelodysplastic syndromes, or MDS, and other cancers. To date, we have enrolled more than 1,000 patients in rigosertib clinical trials. We have collaboration agreements with Baxter Healthcare SA, or Baxter, and Symbio Pharmaceuticals Limited, or Symbio, which grant Baxter certain rights to commercialize rigosertib in Europe and Symbio in Japan and Korea. We have retained development and commercialization rights to rigosertib in the rest of the world, including in the United States. Rigosertib is believed to act in cancer cells as an inhibitor of two important cellular signaling pathways, PI3K and PLK, both of which are frequently over-active in cancer cells. By inhibiting the PI3K pathway, rigosertib promotes tumor cell apoptosis. By modulating PLK pathway activity in cancer cells, rigosertib inhibits cellular division, leading to chromosome disorganization and death in these cells.

Rigosertib IV for higher risk MDS

In February 2014, we announced top-line results of a Phase 3 trial of an intravenous formulation of rigosertib, or rigosertib IV, in higher-risk MDS patients who had progressed on, failed to respond to, or relapsed after prior therapy with hypomethylating agents, or HMAs. Although the results of this study showed numerical improvement in median overall survival in the rigosertib treated patients, the observed improvement in survival of 2.4 months was not sufficient to establish the required level of statistical significance and, therefore did not achieve the primary endpoint of the trial.

During the second quarter of this year, we met with the FDA to discuss the future development of rigosertib IV for higher-risk MDS patients. Based on that meeting, we believe that we may be able to seek approval of rigosertib IV specifically for patients who had progressed on or failed to respond to previous treatment with HMAs. These type of patients are also known collectively as Primary HMA Failures. In addition, together with Baxter, our commercialization partner in Europe, we have met with several European national regulatory agencies to discuss the unmet medical need and appropriate regulatory pathways in Primary HMA Failure patients within Europe. We anticipate a further update of our development plan for rigosertib IV in higher-risk MDS patients during the fourth quarter of 2014.

Oral Rigosertib for lower-risk MDS

In December 2013, we presented data at the Annual ASH Meeting from our Phase 2 trial of an oral formulation of rigosertib in lower-risk MDS patients. Unlike higher-risk MDS patients who suffer from a shortfall in normal blood cells, or cytopenias, and elevated levels of cancer, or blast, cells in their bone marrow, lower-risk MDS patients suffer from cytopenias only, typically low levels of red blood cells, white blood cells and/or platelets. Thus, all MDS patients need interventions to improve their low blood counts, either by therapeutic approaches or by transfusions. Phase 2 clinical data revealed the activity of single agent oral rigosertib in transfusion-dependent, lower-risk MDS patients and the potential of a DNA-based test performed on bone marrow cells of patients before they receive oral rigosertib to identify lower-risk MDS patients who are more likely to respond to oral rigosertib. We are currently enrolling an additional 20 lower-risk MDS patients in this Phase 2 trial to expand our data on the utility of this genomic DNA test for the identification of patients likely to respond to rigosertib. If we and Baxter mutually agree to progress the development of oral rigosertib in lower-risk MDS patients, we would be entitled to a milestone payment of \$25 million under our development and license agreement with Baxter, and we would be required to use our commercially reasonable efforts to progress the development of rigosertib for this indication to a drug approval application in Europe.

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In addition, recruitment is continuing in a second Phase 2 trial of oral rigosertib in lower-risk MDS patients to explore oral rigosertib dose and schedule optimization. We are comparing continuous dosing with interrupted (two out of three weeks) dosing in a three-week treatment cycle in both of the ongoing Phase 2 trials. Based on the anticipated timing of the DNA-based test and dosing optimization data, which we expect to receive in the fourth quarter of 2014, we believe that a pivotal study of oral rigosertib in lower-risk MDS patients will not commence before the first half of 2015. Any such pivotal study will depend on the results of the ongoing Phase 2 trials and would be subject to regulatory discussions and guidance.

Oral rigosertib in combination with azacitidine in MDS and AML

We have completed the Phase 1 portion of a Phase 1/2 clinical trial of oral rigosertib in combination with azacitidine, and we are now enrolling patients in the Phase 2 portion at multiple sites in the U.S. and Europe. In the Phase 1 portion of the trial, the combination therapy was well tolerated in the study population. The combination dosing schedule of oral rigosertib in the final cohort (two doses per day; 560mg in the morning and 280 mg in the afternoon) given during weeks one, two and three of a four-week treatment cycle) with the indicated dose of azacitidine (75 mg/m² administered every day either subcutaneously or intravenously, given during week two of a four-week treatment cycle) has been selected for the Phase 2 portion of the trial. The Phase 2 portion of the trial has been designed to assess whether treatment with rigosertib, in combination with azacitidine, has a beneficial effect on bone marrow and peripheral blood blast cell counts and symptoms of disease progression in patients with MDS and AML. We expect to present results of the Phase 1 portion of this combination trial in the fourth quarter of 2014.

Oral rigosertib in head and neck and other carcinomas

We recently announced results from a single-agent Phase 2 study of oral rigosertib in patients with second- and third-line head and neck cancers and other refractory cancers. In this trial, oral rigosertib was well tolerated in advanced cancer patients. Stable disease, lasting up to nine months, was the best response observed in the head and neck cancer patients. One patient with lung cancer and one patient with anal cancer also achieved stable disease. Based on these findings, we have concluded that there is not sufficient justification for further development of oral rigosertib as a single agent in these indications.

A Phase 1 study of oral rigosertib in combination with chemoradiotherapy (platinum plus radiation) has been initiated in head and neck and other carcinoma patients. We expect to have evaluable data from this study in 2015.

Briciclib

Our second clinical-stage product candidate is briciclib, a small molecule targeting an important intracellular regulatory protein, cyclin D1, which is often found at elevated levels in cancer cells. We have initiated a multi-center Phase 1 clinical trial testing IV briciclib in adult patients with advanced cancer and solid tumors. Upon completion of this ongoing Phase 1 trial, we will assess potential further development for briciclib.

Recilisib

Our third clinical-stage product candidate, recilisib, is being developed in collaboration with the U.S. Department of Defense for acute radiation syndromes. We have conducted animal studies and clinical trials of recilisib under the FDA's Animal Efficacy Rule, which permits marketing approval for new medical countermeasures for which human efficacy studies are not feasible or ethical, by relying on evidence from animal studies in appropriate animal models to support efficacy in humans. We have

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completed four Phase 1 trials to evaluate the safety and pharmacokinetics of recilisib in healthy human adult subjects using both subcutaneous and oral formulations. Ongoing studies of recilisib are being conducted with government funding, and we anticipate that any future development of recilisib beyond our ongoing studies would be conducted solely with government funding.

Preclinical Product Candidates

In addition to our three clinical-stage product candidates, we have several product candidates that target kinases, cellular metabolism or cell division in preclinical development. We intend to explore additional collaborations to further the development of these product candidates as we focus internally on our more advanced programs.

Our operations to date have included our organization and staffing, business planning, raising capital, in-licensing technology from research institutions, identifying potential product candidates, developing product candidates and building strategic alliances, as well as undertaking non-clinical studies and clinical trials of our product candidates.

Since commencing operations, we have dedicated a significant portion of our resources to our development efforts for our clinical-stage product candidates, particularly rigosertib. We anticipate that a significant portion of our operating expenses will continue to be related to research and development as we continue to advance rigosertib and our other clinical-stage product candidates and, to a lesser extent, our preclinical programs. In July 2013, we completed our initial public offering, or IPO, of common stock, from which we received net proceeds of \$79.8 million. Prior to the consummation of the IPO, we funded our operations primarily through the sale of preferred stock amounting to \$144.7 million, including \$50.0 million that Baxter invested in our Series J Preferred Stock in 2012, as well as proceeds from the issuance of convertible debt and a stockholder loan amounting to \$26.8 million in the aggregate, all of which was later converted into shares of our preferred stock, which shares converted to common stock upon the IPO. We have also received upfront payments of \$7.5 million from Symbio and \$50.0 million from Baxter in connection with our collaboration agreements with those parties. We have also received an aggregate of \$8.0 million from The Leukemia and Lymphoma Society, or LLS, under a funding agreement.

We expect to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, and seek regulatory approval for, our product candidates, even if milestones under our license and collaboration agreements are met. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses. We do not currently have an organization for the sales, marketing and distribution of pharmaceutical products. We may rely on licensing and co-promotion agreements with strategic or collaborative partners for the commercialization of our products in the United States and other territories. If we choose to build a commercial infrastructure to support marketing in the United States for any of our product candidates that achieve regulatory approval, such commercial infrastructure could be expected to include a targeted, oncology sales force supported by sales management, internal sales support, an internal marketing group and distribution support. To develop the appropriate commercial infrastructure internally, we would have to invest financial and management resources, some of which would have to be deployed prior to having any certainty about marketing approval.

Furthermore, we have incurred, and expect to continue to incur, additional costs associated with operating as a public company. Accordingly, we will seek to fund our operations primarily through business development transactions, public equity or debt financings or other sources. Other additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed or on less favorable terms could have a material adverse effect on our financial condition and our ability to pursue our business strategy.

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You can get more information regarding our business and industry by reading our most recent Annual Report on Form 10-K and the other reports we file with the SEC. See "Where You Can Find More Information" and "Incorporation of Information by Reference."

CORPORATE INFORMATION

We were incorporated in Delaware in December 1998 and commenced operations in January 1999. Our principal executive offices are located at 375 Pheasant Run, Newtown, Pennsylvania 18940, and our telephone number is (267) 759-3680. Our website address is www.onconova.com. The information on, or that can be accessed through, our website is not part of this prospectus.

USE OF PROCEEDS

Unless otherwise indicated in a prospectus supplement, we anticipate that the net proceeds from our sale of any securities will be used to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding our working capital needs. We expect from time to time to evaluate the acquisition of businesses, products and technologies for which a portion of the net proceeds may be used, although we currently are not planning or negotiating any such transactions. Pending such uses, we may invest the net proceeds in investment grade interest-bearing securities.

The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering and progress with our clinical development programs. Expenditures will also depend upon the establishment of collaborative arrangements with other companies, the availability of additional financing and other factors. Investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of securities.

In the case of sales by selling stockholders, we will not receive any of the proceeds from such sales.

RATIO OF EARNINGS TO FIXED CHARGES AND COMBINED FIXED CHARGES AND PREFERRED STOCK DIVIDENDS

Earnings were insufficient to cover fixed charges by \$35.5 million for the six months ended June 30, 2014 and \$62.1 million, \$29.9 million and \$26.3 million for the fiscal years ended December 31, 2013, 2012 and 2011, respectively. "Earnings" consists of net loss from continuing operations before income tax expense and fixed charges. "Fixed charges" consist of interest expense, capitalized interest and the portion of rents that we believe to be representative of the interest factor. Currently, we have no shares of preferred stock outstanding and have not paid any dividends on preferred stock in the periods presented.

DESCRIPTION OF SECURITIES

We may offer shares of our common stock and preferred stock, various series of debt securities, warrants or units to purchase any of such securities, with a total value of up to \$100,000,000, from time to time in one or more offerings under this prospectus at prices and on terms to be determined by market conditions at the time of the offering. This prospectus provides you with a general description of the securities that we may offer. In connection with each offering, we will provide a prospectus supplement that will describe the specific amounts, prices and terms of the securities being offered, including, to the extent applicable:

designation or classification;

aggregate offering price;

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rates and times of payment of dividends;

redemption, conversion or exchange terms;

conversion or exchange prices or rates and any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;

restrictive covenants;

voting or other rights; and

important federal income tax considerations.

The prospectus supplement also may add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus supplement will offer a security that is not included in the Registration Statement at the time of its effectiveness or offer a security of a type that is not described in this prospectus.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 75,000,000 shares of common stock, par value \$0.01 per share, and 5,000,000 shares of preferred stock, par value \$0.01 per share. As of September 30, 2014, 21,692,240 shares of our common stock, and no shares of our preferred stock, were outstanding.

Common Stock

Subject to the preferences that may be applicable to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that may be declared by our board of directors out of funds legally available for that purpose. Holders of our common stock are entitled to one vote for each share on all matters voted on by stockholders, including the election of directors. Holders of our common stock do not have any conversion, redemption, sinking fund or preemptive rights. In the event of our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in any assets remaining after the satisfaction in full of the prior rights of creditors and the aggregate liquidation preference of any preferred stock then outstanding. The rights, preferences and privileges of the holders of our common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. All outstanding shares of our common stock are, and any shares of common stock that we may issue in the future will be, fully paid and non-assessable.

Preferred Stock

We may issue any class of preferred stock in any series. Our board of directors has the authority, subject to limitations prescribed under Delaware law, to issue preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of its qualifications, limitations and restrictions. Our board of directors can also increase or decrease the number of shares of any series, but not below the number of shares of that series then outstanding. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of the common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in

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control of our company and may adversely affect the market price of our common stock and the voting and other rights of the holders of common stock.

Delaware Anti-Takeover Law and Provisions in Our Certificate of Incorporation and Bylaws

Delaware Anti-Takeover Law

We are subject to Section 203 of the Delaware General Corporation Law. Section 203 generally prohibits a public Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a period of three years after the date of the transaction in which the person became an interested stockholder, unless:

prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding specified shares; or

at or subsequent to the date of the transaction, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66²/₃% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a "business combination" to include:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, lease, exchange, mortgage, pledge, transfer or other disposition of 10% or more of the assets of the corporation to or with the interested stockholder;

subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an "interested stockholder" as any person that is:

the owner of 15% or more of the outstanding voting stock of the corporation;

an affiliate or associate of the corporation who was the owner of 15% or more of the outstanding voting stock of the corporation at any time within three years immediately prior to the relevant date; or

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the affiliates and associates of the above.

Under specific circumstances, Section 203 makes it more difficult for an "interested stockholder" to effect various business combinations with a corporation for a three-year period, although the stockholders may, by adopting an amendment to the corporation's certificate of incorporation or bylaws, elect not to be governed by this section, effective 12 months after adoption.

Our certificate of incorporation and bylaws do not exclude us from the restrictions of Section 203. We anticipate that the provisions of Section 203 might encourage companies interested in acquiring us

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to negotiate in advance with our board of directors since the stockholder approval requirement would be avoided if a majority of the directors then in office approve either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder.

Certificate of Incorporation and Bylaws

Provisions of our certificate of incorporation and bylaws may delay or discourage transactions involving an actual or potential change of control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our common stock. Among other things, our certificate of incorporation and bylaws will:

permit our board of directors to issue up to 5,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate;

provide that all vacancies on our board of directors, including as a result of newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;

require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;

provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;

not provide for cumulative voting rights, thereby allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election; and

provide that special meetings of our stockholders may be called only by the board of directors or by such person or persons requested by a majority of the board of directors to call such meetings.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Wells Fargo Shareowner Services.

Listing

Our common stock is listed on the Nasdaq Global Market under the symbol "ONTX."

DESCRIPTION OF DEBT SECURITIES

This prospectus describes certain general terms and provisions of our debt securities. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. The following description of debt securities will apply to the debt securities offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of debt securities may specify different or additional terms.

We may offer under this prospectus up to \$100,000,000 aggregate principal amount of secured or unsecured debt securities, or if debt securities are issued at a discount, or in a foreign currency or composite currency, such principal amount as may be sold for an initial public offering price of up to

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\$100,000,000. The debt securities may be either senior debt securities, senior subordinated debt securities or subordinated debt securities. The debt securities offered hereby will be issued under an indenture between us and a trustee. A form of indenture, which will be qualified under, subject to, and governed by, the Trust Indenture Act of 1939, as amended, is filed as an exhibit to the registration statement.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and detailed or determined in the manner provided in a board of directors' resolution, an officers' certificate or by an indenture. The particular terms of each series of debt securities will be described in a prospectus supplement relating to the series, including any pricing supplement.

We can issue debt securities that may be in one or more series with the same or various maturities, at par, at a premium or at a discount. We will set forth in a prospectus supplement, including any pricing supplement, relating to any series of debt securities being offered, the initial offering price, the aggregate principal amount and the following terms of the debt securities:

the title of the debt securities;

the price or prices (expressed as a percentage of the aggregate principal amount) at which we will sell the debt securities;

any limit on the aggregate principal amount of the debt securities;

the date or dates on which we will pay the principal on the debt securities;

the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;

the place or places where the principal of, and premium and interest on, the debt securities will be payable;

the terms and conditions upon which we may redeem the debt securities;

any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities;

the dates on which and the price or prices at which we will repurchase the debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;

the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;

whether the debt securities will be issued in the form of certificated debt securities or global debt securities;

the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;

the currency of denomination of the debt securities;

the designation of the currency, currencies or currency units in which payment of principal of, and premium and interest on, the debt securities will be made;

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if payments of principal of, and premium or interest on, the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;

the manner in which the amounts of payment of principal of, and premium or interest on, the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies other than that in which the debt securities are denominated or designated to be payable or by reference to a commodity, commodity index, stock exchange index or financial index;

any provisions relating to any security provided for the debt securities;

any addition to or change in the events of default described in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;

any addition to or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;

any other terms of the debt securities, which may modify or delete any provision of the indenture as it applies to that series; and

any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities.

We may issue debt securities that are exchangeable and/or convertible into shares of our common stock or any class or series of preferred stock. The terms, if any, on which the debt securities may be exchanged and/or converted will be set forth in the applicable prospectus supplement. Such terms may include provisions for conversion, either mandatory, at the option of the holder or at our option, in which case the number of shares of common stock, preferred stock or other securities to be received by the holders of debt securities would be calculated as of a time and in the manner stated in the prospectus supplement.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of and any premium and interest on any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Payment of Interest and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, as Depository, or a nominee of the Depository (we will refer to any debt security represented by a global debt security as a book-entry debt security), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a certificated debt security), as described in the applicable prospectus supplement.

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Certificated Debt Securities

You may transfer or exchange certificated debt securities at the trustee's office or paying agencies in accordance with the terms of the indenture. No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange.

You may transfer certificated debt securities and the right to receive the principal of, and premium and interest on, certificated debt securities only by surrendering the old certificate representing those certificated debt securities and either we or the trustee will reissue the old certificate to the new holder or we or the trustee will issue a new certificate to the new holder.

Book-Entry Debt Securities

We may issue the debt securities of a series in the form of one or more book-entry debt securities that would be deposited with a depository or its nominee identified in the prospectus supplement. We may issue book-entry debt securities in either temporary or permanent form. We will describe in the prospectus supplement the terms of any depository arrangement and the rights and limitations of owners of beneficial interests in any book-entry debt security.

DESCRIPTION OF WARRANTS

We may issue warrants to purchase debt securities, common stock, preferred stock or other securities or any combination of the foregoing. We may issue warrants independently or together with other securities. Warrants sold with other securities may be attached to or separate from the other securities. We will issue warrants under one or more warrant agreements between us and a warrant agent that we will name in the prospectus supplement.

The prospectus supplement relating to any warrants that we may offer will include specific terms relating to the offering. We will file the form of any warrant agreement with the SEC, and you should read the warrant agreement for provisions that may be important to you. The prospectus supplement will include some or all of the following terms:

the title of the warrants;

the aggregate number of warrants offered;

the designation, number and terms of the debt securities, common stock, preferred stock or other securities purchasable upon exercise of the warrants, and procedures by which those numbers may be adjusted;

the exercise price of the warrants;

the dates or periods during which the warrants are exercisable;

the designation and terms of any securities with which the warrants are issued;

if the warrants are issued as a unit with another security, the date, if any, on and after which the warrants and the other security will be separately transferable;

if the exercise price is not payable in U.S. dollars, the foreign currency, currency unit or composite currency in which the exercise price is denominated;

any minimum or maximum amount of warrants that may be exercised at any one time;

any terms, procedures and limitations relating to the transferability, exchange, exercise, amendment or termination of the warrants; and

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any adjustments to the terms of the warrants resulting from the occurrence of certain events or from the entry into or consummation by us of certain transactions.

We currently have outstanding warrants to purchase 4,597 shares of common stock, issued in connection with a credit facility obtained in 2007. The warrants are immediately exercisable and expire in July 2016. The exercise price per share is \$13.05.

DESCRIPTION OF UNITS

As specified in any applicable prospectus supplement, we may issue units consisting of one or more warrants, debt securities, shares of preferred stock, shares of common stock or any combination of such securities.

SELLING STOCKHOLDERS

Selling Stockholders for the Secondary Offering of up to 228,647 Shares of Common Stock

This prospectus also relates to the possible resale by certain of our stockholders of up to an aggregate of 228,647 shares of our common stock which were previously acquired by such stockholders through several private placements of our preferred stock completed by us prior to our IPO, which were all converted to shares of our common stock in connection with our IPO. In connection with such private placements, these persons have registration rights with respect to their shares as described further below under the heading "Certain Relationships and Related Party Transactions." The term "selling stockholders" includes the stockholders listed below and their transferees, pledgees, donees, assignees or other successors. Additional information about selling stockholders, including the number of shares of common stock owned by them before and after the offering, will be set forth in a post-effective amendment. In addition to selling their shares pursuant to this registration statement, the selling stockholders may sell or transfer all or a portion of their shares of our common stock pursuant to any available exemption from the registration requirements of the Securities Act, including Rule 144, if available.

Unless otherwise indicated, the selling stockholders have sole voting and investment power with respect to their shares of common stock. All of the information contained in the table below is based solely upon information provided to us by the selling stockholders or otherwise known by us. In addition to the shares offered hereby, the selling stockholders may otherwise beneficially own our shares of common stock as a result of, among others, open market purchases, which information is not obtainable by us without undue effort and expense. The selling stockholders may have sold, transferred or otherwise disposed of, or may sell, transfer or otherwise dispose of, at any time or from time to time since the date on which the information regarding the shares beneficially owned was last known by us, all or a portion of the shares beneficially owned in transactions exempt from the registration requirements of the Securities Act.

The number of shares outstanding and the percentages of beneficial ownership are based on 21,692,240 shares of our common stock outstanding as of September 30, 2014.

For the purposes of the following table, the number of shares of our common stock beneficially owned has been determined in accordance with Rule 13d-3 under the Exchange Act, and such information is not necessarily indicative of beneficial ownership for any other purpose. Under Rule 13d-3, beneficial ownership includes any shares as to which a selling stockholder has sole or

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shared voting power or investment power and also any shares which that selling stockholder has the right to acquire within 60 days of the date of this prospectus through the exercise of any stock option.

| Name of Selling Stockholder | Number of Shares Beneficially Owned Prior to the Offering | Number of Shares Offered | Number of Shares Beneficially Owned After the Offering | % of Common Stock Beneficially Owned After the Offering |
|---------------------------------|--|--------------------------------|---|--|
| DKG Leasing-2000 LLC | 1,185 | 1,185 | 0 | 0% |
| ICMC Strategic Asset Fund, Ltd. | 1,425 | 1,425 | 0 | 0 |
| Kathryn Jane McDonald | 187 | 187 | 0 | 0 |
| Utkarsh Palnitkar | 15,325 | 15,325 | 0 | 0 |
| Radha Gurram Reddy | 5,746 | 5,746 | 0 | 0 |

Certain Relationships and Related Party Transactions

We entered into an Eighth Amended and Restated Stockholders' Agreement on July 27, 2012, with certain holders of our common and preferred stock. Under the stockholders' agreement, holders of shares of our preferred stock have been granted registration rights with respect to the shares of common stock issued upon conversion as further described below.

Demand Registration Rights

At any time, the holders of 25% or more of the shares having demand registration rights may request that we register all or a portion of their shares of common stock. We will effect the registration as requested, unless, in the good faith judgment of our board of directors, such registration would be materially detrimental to us and our stockholders and should be delayed. We have the right to defer the filing of such registration statement once for up to 120 days during any 12-month period. We are not obligated to file a registration statement pursuant to this provision on more than two occasions. In addition, when we are eligible for the use of Form S-3, or any successor form, holders of a majority of the shares having demand registration rights may make unlimited requests that we register all or a portion of their common stock for sale under the Securities Act on Form S-3, or any successor form, so long as the aggregate price to the public in connection with any such offering is at least \$500,000. However, we are not obligated to file a Form S-3 pursuant to this provision on more than two occasions in any 12-month period.

Piggyback Registration Rights

In addition, if at any time we register any shares of our stock, the holders of all shares having registration rights are entitled to notice of the filing of the applicable registration statement and to include all or a portion of their common stock in the registration.

The secondary offering of up to 228,647 shares of our common stock is being made pursuant to the exercise of these piggyback registration rights.

Other Provisions

In the event that any registration in which the holders of registrable shares participate pursuant to the stockholders' agreement is an underwritten public offering, the number of registrable shares to be included may, in specified circumstances, be limited due to market conditions. The number of registrable shares to be excluded from registration pursuant to the above shall not be reduced below 20% of the shares to be offered.

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We will pay all registration expenses, other than underwriting discounts and selling commissions, and the reasonable fees and expenses, other than underwriting discounts and selling commissions, and the reasonable fees and expenses of a single special counsel for the selling stockholders, related to any demand or piggyback registration.

PLAN OF DISTRIBUTION

We and/or the selling stockholders, if applicable, may sell the securities in one or more of the following ways (or in any combination) from time to time:

to or through one or more underwriters or dealers in a public offering and sale by them;

directly to a limited number of purchasers or to a single purchaser;

through agents;

through block trades in which the broker or dealer engaged to handle the block trade will attempt to sell the securities as agent, but may position and resell a portion of the block as principal to facilitate the transaction; or

in any manner, as provided in the applicable prospectus supplement.

Each time we offer and sell securities under this prospectus, we will file a prospectus supplement. The prospectus supplement will state the terms of the offering of the securities, including:

the name or names of any underwriters, dealers or agents;

the purchase price of such securities and the proceeds to be received by us, if any;

any underwriting discounts or agency fees and other items constituting underwriters' or agents' compensation;

any public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any securities exchanges on which the securities may be listed.

Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time.

If we and/or the selling stockholders, if applicable, use underwriters in the sale, the securities will be acquired by the underwriters for their own account and may be resold from time to time in one or more transactions, including:

negotiated transactions;

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at a fixed public offering price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to prevailing market prices; or

at negotiated prices.

Unless otherwise stated in a prospectus supplement, the obligations of the underwriters to purchase any securities will be conditioned on customary closing conditions and the underwriters will be obligated to purchase all of such series of securities, if any are purchased.

We and/or the selling stockholders, if applicable, may sell the securities through agents from time to time. The prospectus supplement will name any agent involved in the offer or sale of the securities

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and any commissions we pay to them. Generally, any agent will be acting on a best efforts basis for the period of its appointment.

We and/or the selling stockholders, if applicable, may authorize underwriters, dealers or agents to solicit offers by certain purchasers to purchase the securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. The contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

In offering the shares covered by this prospectus, the selling stockholders, and any broker-dealers and any other participating broker-dealers who may execute sales for the selling stockholders, may be deemed to be "underwriters" within the meaning of the Securities Act in connection with these sales. Any profits received by the selling stockholders and the compensation of such broker-dealers may be deemed to be underwriting discounts and commissions.

Underwriters and agents may be entitled under agreements entered into with us and/or the selling stockholders, if applicable, to indemnification by us and/or the selling stockholders, if applicable, against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments which the underwriters or agents may be required to make. Underwriters and agents may be customers of, engage in transactions with, or perform services for us and our affiliates in the ordinary course of business.

Each series of securities will be a new issue of securities and will have no established trading market other than the common stock which is listed on the Nasdaq Global Market. Any underwriters to whom securities are sold for public offering and sale may make a market in the securities, but such underwriters will not be obligated to do so and may discontinue any market making at any time without notice. The securities, other than the common stock, may or may not be listed on a national securities exchange.

EXPERTS

The consolidated financial statements of Onconova Therapeutics, Inc. at December 31, 2013 and December 31, 2012, and for the years then ended, included in our Annual Report on Form 10-K for the year ended December 31, 2013 and incorporated by reference herein have been audited by Ernst & Young LLP, independent registered public accounting firm, and for the year ended December 31, 2011, by EisnerAmper LLP, independent registered public accounting firm, as set forth in their respective reports thereon incorporated by reference herein, and are included in reliance upon such reports given on the authority of such firms as experts in accounting and auditing.

LEGAL MATTERS

Pepper Hamilton LLP will provide us with an opinion as to certain legal matters in connection with the securities being offered hereby.

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The information in this prospectus supplement is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus supplement is not an offer to sell these securities and it is not soliciting offers to buy these securities in any state or other jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED OCTOBER 8, 2014

PROSPECTUS SUPPLEMENT

Onconova Therapeutics, Inc.

Up to \$20,000,000 of Shares of Common Stock

Onconova Therapeutics, Inc. has entered into a Controlled Equity OfferingSM Sales agreement with Cantor Fitzgerald & Co., or the sales agreement, relating to shares of our common stock, par value US\$0.01 per share, offered by this prospectus supplement. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$20,000,000 from time to time through Cantor Fitzgerald & Co., acting as sales agent. Sales of the shares of common stock, if any, may be made on the Nasdaq Global Market at market prices and such other sales as agreed upon by Onconova Therapeutics, Inc. and Cantor Fitzgerald & Co.

Our common stock is currently listed on the Nasdaq Global Market under the symbol "ONTX". On October 2, 2014, the last reported sale price of our common stock on the Nasdaq Global Market was \$4.29 per share.

Sales of our common stock, if any, under this prospectus supplement may be made in sales deemed to be "at-the-market" equity offerings as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act, including sales made directly on or through the Nasdaq Global Market, the existing trading market for our common stock, sales made to or through a market maker other than on an exchange or otherwise, in negotiated transactions at market prices prevailing at the time of sale or at prices related to such prevailing market prices, and/or any other method permitted by law, including in privately negotiated transactions. Cantor Fitzgerald & Co. will act as sales agent on a best efforts basis and use commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us, consistent with its normal trading and sales practices, on mutually agreed terms between Cantor Fitzgerald & Co. and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Cantor Fitzgerald & Co. will be entitled to compensation at a fixed commission rate of up to 3.0% of the gross sales price per share sold. In connection with the sale of our common stock on our behalf, Cantor Fitzgerald & Co. will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Cantor Fitzgerald & Co. will be deemed to be underwriting commissions or discounts.

As of August 29, 2014, the aggregate market value of our outstanding common stock held by non-affiliates, or the public float, was \$66,251,060, which was calculated based on shares of our outstanding common stock held by non-affiliates and on a price of \$5.22 per share, the last reported sale price for our common stock, on August 29, 2014. Other than the securities offered by this prospectus supplement, we have not offered any securities pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus supplement.

Investing in these securities involves risks, including those set forth in the "Risk Factors" section beginning on page S-10 of this prospectus supplement and in our most recent Annual Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-K, each of which is incorporated by reference into this prospectus supplement.

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

This prospectus supplement is dated _____, 2014.

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ABOUT THIS PROSPECTUS

This prospectus supplement is part of a registration statement that we have filed with the Securities and Exchange Commission, or SEC, utilizing a "shelf" registration process. Under the shelf registration process, we may offer shares of our common stock having an aggregate offering price of up to \$20,000,000 from time to time under this prospectus supplement at prices and on terms to be determined by market conditions at the time of offering.

We provide information to you about this offering of shares of our common stock in two separate documents that are bound together: (1) this at-the-market sales agreement prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying base prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this "prospectus," we are referring to both documents combined. If information in this at-the-market prospectus supplement is inconsistent with the accompanying base prospectus, you should rely on this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in this prospectus the statement in the document having the later date modifies or supersedes the earlier statement as our business, financial condition, results of operations and prospects may have changed since the earlier dates.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and in any free writing prospectus that we may authorize for use in connection with this offering. We have not, and Cantor Fitzgerald & Co., or Cantor, has not, authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and Cantor is not, making an offer to sell or soliciting an offer to buy our securities in any jurisdiction in which an offer or solicitation is not authorized or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus, the documents incorporated by reference into this prospectus, and in any free writing prospectus that we may authorize for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus, the documents incorporated by reference into this prospectus, and any free writing prospectus that we may authorize for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus entitled "Where You Can Find More Information" and "Incorporation of Information By Reference."

We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus outside the United States. This prospectus does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

For purposes of this prospectus, references to "Onconova," "Onconova Therapeutics," "Company," "we," "us" and "our" refer to Onconova Therapeutics, Inc. and its consolidated subsidiaries.

We have filed or incorporated by reference exhibits to the registration statement of which this prospectus forms a part. You should read the exhibits carefully for provisions that may be important to you.

This prospectus and the information incorporated by reference herein and therein include 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.

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PROSPECTUS SUMMARY

The following summary highlights certain information contained elsewhere in this prospectus supplement, the accompanying base prospectus, any free writing prospectus that we have been authorized to use and the documents incorporated by reference herein and in the accompanying base prospectus. This summary does not contain all the information you will need in making your investment decision. You should carefully read this entire prospectus supplement, the accompanying base prospectus, any free writing prospectus that we have been authorized to use and the documents incorporated by reference herein and in the accompanying base prospectus. You should pay special attention to the "Risk Factors" section of this prospectus and the financial statements and other information incorporated by reference in this prospectus.

Our Business

Overview

We are a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule drug candidates to treat cancer. Using our proprietary chemistry platform, we have created an extensive library of targeted anti-cancer agents designed to work against specific cellular pathways important to cancer cells. We believe that the drug candidates in our pipeline have the potential to be efficacious in a wide variety of cancers without causing harm to normal cells. We have three clinical-stage product candidates and several preclinical programs.

Rigosertib

Rigosertib, our most advanced product candidate, is being tested as a single agent and in combination with azacitidine and with chemoradiation therapy, in clinical trials of patients with myelodysplastic syndromes, or MDS, and other cancers. To date, we have enrolled more than 1,000 patients in rigosertib clinical trials. We have collaboration agreements with Baxter Healthcare SA, or Baxter and SymBio Pharmaceuticals Limited, or SymBio, which grant Baxter certain rights to commercialize rigosertib in Europe and SymBio in Japan and Korea. We have retained development and commercialization rights to rigosertib in the rest of the world, including in the United States. Rigosertib is believed to act in cancer cells as an inhibitor of two important cellular signaling pathways, PI3K and PLK, both of which are frequently over-active in cancer cells. By inhibiting the PI3K pathway, rigosertib promotes tumor cell apoptosis. By modulating PLK pathway activity in cancer cells, rigosertib inhibits cellular division, leading to chromosome disorganization and death in these cells.

Rigosertib IV for higher risk MDS

In February 2014, we announced top-line results of a Phase 3 trial of an intravenous formulation of rigosertib, or rigosertib IV, in higher-risk MDS patients who had progressed on, failed to respond to, or relapsed after prior therapy with hypomethylating agents, or HMAs. Although the results of this study showed numerical improvement in median overall survival in the rigosertib treated patients, the observed improvement in survival of 2.4 months was not sufficient to establish the required level of statistical significance and, therefore did not achieve the primary endpoint of the trial.

During the second quarter of this year, we met with the FDA to discuss the future development of rigosertib IV for higher-risk MDS patients. Based on that meeting, we believe that we may be able to seek approval of rigosertib IV specifically for patients who had progressed on or failed to respond to previous treatment with HMAs. These type of patients are also known collectively as Primary HMA Failures. In addition, together with Baxter, our commercialization partner in Europe, we have met with several European national regulatory agencies to discuss the unmet medical need and appropriate regulatory pathways in Primary HMA Failure patients within Europe. We anticipate a further update of our development plan for rigosertib IV in higher-risk MDS patients during the fourth quarter of 2014.

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Oral Rigosertib for lower-risk MDS

In December 2013, we presented data at the Annual ASH Meeting from our Phase 2 trial of an oral formulation of rigosertib in lower-risk MDS patients. Unlike higher-risk MDS patients who suffer from a shortfall in normal blood cells, or cytopenias, and elevated levels of cancer, or blast, cells in their bone marrow, lower-risk MDS patients suffer from cytopenias only, typically low levels of red blood cells, white blood cells and/or platelets. Thus, all MDS patients need interventions to improve their low blood counts, either by therapeutic approaches or by transfusions. Phase 2 clinical data revealed the activity of single agent oral rigosertib in transfusion-dependent, lower-risk MDS patients and the potential of a DNA-based test performed on bone marrow cells of patients before they receive oral rigosertib to identify lower-risk MDS patients who are more likely to respond to oral rigosertib. We are currently enrolling an additional 20 lower-risk MDS patients in this Phase 2 trial to expand our data on the utility of this genomic DNA test for the identification of patients likely to respond to rigosertib. If we and Baxter mutually agree to progress the development of oral rigosertib in lower-risk MDS patients, we would be entitled to a milestone payment of \$25 million under our development and license agreement with Baxter, and we would be required to use our commercially reasonable efforts to progress the development of rigosertib for this indication to a drug approval application in Europe.

In addition, recruitment is continuing in a second Phase 2 trial of oral rigosertib in lower-risk MDS patients to explore oral rigosertib dose and schedule optimization. We are comparing continuous dosing with interrupted (two out of three weeks) dosing in a three-week treatment cycle in both of the ongoing Phase 2 trials. Based on the anticipated timing of the DNA-based test and dosing optimization data, which we expect to receive in the fourth quarter of 2014, we believe that a pivotal study of oral rigosertib in lower-risk MDS patients will not commence before the first half of 2015. Any such pivotal study will depend on the results of the ongoing Phase 2 trials and would be subject to regulatory discussions and guidance.

Oral rigosertib in combination with azacitidine in MDS and AML

We have completed the Phase 1 portion of a Phase 1/2 clinical trial of oral rigosertib in combination with azacitidine, and we are now enrolling patients in the Phase 2 portion at multiple sites in the U.S. and Europe. In the Phase 1 portion of the trial, the combination therapy was well tolerated in the study population. The combination dosing schedule of oral rigosertib in the final cohort (two doses per day; 560mg in the morning and 280 mg in the afternoon) given during weeks one, two and three of a four-week treatment cycle) with the indicated dose of azacitidine (75 mg/m² administered every day either subcutaneously or intravenously, given during week two of a four-week treatment cycle) has been selected for the Phase 2 portion of the trial. The Phase 2 portion of the trial has been designed to assess whether treatment with rigosertib, in combination with azacitidine, has a beneficial effect on bone marrow and peripheral blood blast cell counts and symptoms of disease progression in patients with MDS and AML. We expect to present results of the Phase 1 portion of this combination trial in the fourth quarter of 2014.

Oral rigosertib in head and neck and other carcinomas

We recently announced results from a single-agent Phase 2 study of oral rigosertib in patients with second- and third-line head and neck cancers and other refractory cancers. In this trial, oral rigosertib was well tolerated in advanced cancer patients. Stable disease, lasting up to nine months, was the best response observed in the head and neck cancer patients. One patient with lung cancer and one patient with anal cancer also achieved stable disease. Based on these findings, we have concluded that there is not sufficient justification for further development of oral rigosertib as a single agent in these indications.

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A Phase 1 study of oral rigosertib in combination with chemoradiotherapy (platinum plus radiation) has been initiated in head and neck and other carcinoma patients. We expect to have evaluable data from this study in 2015.

Briciclib

Our second clinical-stage product candidate is briciclib, a small molecule targeting an important intracellular regulatory protein, cyclin D1, which is often found at elevated levels in cancer cells. We have initiated a multi-center Phase 1 clinical trial testing IV briciclib in adult patients with advanced cancer and solid tumors. Upon completion of this ongoing Phase 1 trial, we will assess potential further development for briciclib.

Recilisib

Our third clinical-stage product candidate, recilisib, is being developed in collaboration with the U.S. Department of Defense for acute radiation syndromes. We have conducted animal studies and clinical trials of recilisib under the FDA's Animal Efficacy Rule, which permits marketing approval for new medical countermeasures for which human efficacy studies are not feasible or ethical, by relying on evidence from animal studies in appropriate animal models to support efficacy in humans. We have completed four Phase 1 trials to evaluate the safety and pharmacokinetics of recilisib in healthy human adult subjects using both subcutaneous and oral formulations. Ongoing studies of recilisib are being conducted with government funding, and we anticipate that any future development of recilisib beyond our ongoing studies would be conducted solely with government funding.

Preclinical Product Candidates

In addition to our three clinical-stage product candidates, we have several product candidates that target kinases, cellular metabolism or cell division in preclinical development. We intend to explore additional collaborations to further the development of these product candidates as we focus internally on our more advanced programs.

Our operations to date have included our organization and staffing, business planning, raising capital, in-licensing technology from research institutions, identifying potential product candidates, developing product candidates and building strategic alliances, as well as undertaking non-clinical studies and clinical trials of our product candidates.

Since commencing operations, we have dedicated a significant portion of our resources to our development efforts for our clinical-stage product candidates, particularly rigosertib. We anticipate that a significant portion of our operating expenses will continue to be related to research and development as we continue to advance rigosertib and our other clinical-stage product candidates and, to a lesser extent, our preclinical programs. In July 2013, we completed our initial public offering, or IPO, of common stock, from which we received net proceeds of \$79.8 million. Prior to the consummation of the IPO, we funded our operations primarily through the sale of preferred stock amounting to \$144.7 million, including \$50.0 million that Baxter invested in our Series J Preferred Stock in 2012, as well as proceeds from the issuance of convertible debt and a stockholder loan amounting to \$26.8 million in the aggregate, all of which was later converted into shares of our preferred stock, which shares converted to common stock upon the IPO. We have also received upfront payments of \$7.5 million from SymBio and \$50.0 million from Baxter in connection with our collaboration agreements with those parties. We have also received an aggregate of \$8.0 million from The Leukemia and Lymphoma Society, or LLS, under a funding agreement.

We expect to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, and seek regulatory approval for, our product candidates, even if milestones under our license and collaboration agreements are met. If we obtain

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regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses. We do not currently have an organization for the sales, marketing and distribution of pharmaceutical products. We may rely on licensing and co-promotion agreements with strategic or collaborative partners for the commercialization of our products in the United States and other territories. If we choose to build a commercial infrastructure to support marketing in the United States for any of our product candidates that achieve regulatory approval, such commercial infrastructure could be expected to include a targeted, oncology sales force supported by sales management, internal sales support, an internal marketing group and distribution support. To develop the appropriate commercial infrastructure internally, we would have to invest financial and management resources, some of which would have to be deployed prior to having any certainty about marketing approval.

Furthermore, we have incurred, and expect to continue to incur, additional costs associated with operating as a public company. Accordingly, we will seek to fund our operations primarily through business development transactions, public equity or debt financings or other sources. Other additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed or on less favorable terms could have a material adverse effect on our financial condition and our ability to pursue our business strategy.

You can get more information regarding our business and industry by reading our most recent Annual Report on Form 10-K and the other reports we file with the SEC. See "Where You Can Find More Information" and "Incorporation of Information by Reference."

CORPORATE INFORMATION

We were incorporated in Delaware in December 1998 and commenced operations in January 1999. Our principal executive offices are located at 375 Pheasant Run, Newtown, Pennsylvania 18940, and our telephone number is (267) 759-3680. Our website address is www.onconova.com. The information on, or that can be accessed through, our website is not part of this prospectus.

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THE OFFERING

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| Common stock to be offered by us | Shares of our common stock having an aggregate offering price of up to \$20,000,000. |
| Manner of offering | "At-the-market" offering that may be made from time to time through our sales agent, Cantor Fitzgerald & Co. See "Plan of Distribution" on page S-13 of this prospectus supplement. |
| Use of proceeds | We currently expect to use the net proceeds primarily to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding working capital needs. See "Use of Proceeds" on page S-11 of this prospectus supplement. |
| Nasdaq Global Market symbol | "ONTX." |
| Risk Factors | Before investing in our common stock, you should carefully read and consider the "Risk Factors" beginning on page S-10 of this prospectus supplement. |

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WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-3 under the Securities Act, of which this prospectus forms a part. The rules and regulations of the SEC allow us to omit from this prospectus certain information included in the registration statement. For further information about us and the securities we are offering under this prospectus, you should refer to the registration statement and the exhibits and schedules filed with the registration statement. With respect to the statements contained in this prospectus regarding the contents of any agreement or any other document, in each instance, the statement is qualified in all respects by the complete text of the agreement or document, a copy of which has been filed as an exhibit to the registration statement.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any document we file with the SEC at the SEC's public reference room at 100 F Street NE, Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the SEC's public reference facilities by calling the SEC at 1-800-SEC-0330. You can request copies of these documents, upon payment of a duplicating fee, by writing to the SEC at its principal office at 100 F Street NE, Room 1580, Washington, D.C. 20549-1004. The SEC maintains an Internet website at <http://www.sec.gov> that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. Our SEC filings are accessible through the Internet at that website. Our reports on Forms 10-K, 10-Q and 8-K, and amendments to those reports, are also available for download, free of charge, as soon as reasonably practicable after these reports are filed with the SEC, at our website at www.onconova.com. Webcasts of presentations we make at certain conferences may also be available on our website from time to time. We have not incorporated by reference into this prospectus the information on our website, and you should not consider any of the information posted on or hyperlinked to our website to be a part of this prospectus.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below:

Our Annual Report on Form 10-K for the fiscal year ended December 31, 2013 that we filed with the SEC on March 20, 2014, including the information required by Part III, Items 10 through 14, of Form 10-K, which is incorporated by reference to our definitive proxy statement for our 2014 annual meeting of stockholders filed on April 29, 2014;

Our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2014 and June 30, 2014, that we filed with the SEC on May 15, 2014 and August 14, 2014, respectively;

Our Current Reports on Form 8-K filed with the SEC on February 20, 2014, March 7, 2014, May 2, 2014 and May 23, 2014;

The description of our common stock contained in our registration statement on Form 8-A filed on July 23, 2013 (Registration no. 001-36020) with the SEC, including any amendment or report filed for the purpose of updating such description;

All documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, after the date of the initial filing of the registration statement of which this prospectus is a part and prior to the effectiveness of such registration statement; and

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All documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act on or after the date of this prospectus and before we stop offering the securities under this prospectus.

We will provide without charge to each person, including any beneficial owner, to whom this prospectus is delivered, upon his or her written or oral request, a copy of any or all documents referred to above which have been or may be incorporated by reference into this prospectus but not delivered with this prospectus excluding exhibits to those documents unless they are specifically incorporated by reference into those documents. You can request those documents from us, at no cost, by writing or telephoning us at: Onconova Therapeutics, Inc., 375 Pheasant Run, Newtown, Pennsylvania, 18940, (267) 759-3036, Attention: Benjamin Hoffman.

The most recent information that we file with the SEC automatically updates and supersedes older information. The information contained in any such filing will be deemed to be a part of this prospectus, commencing on the date on which the filing is made.

Information furnished under Items 2.02 or 7.01 (or corresponding information furnished under Item 9.01 or included as an exhibit) in any past or future Current Report on Form 8-K that we file with the SEC, unless otherwise specified in such report, is not incorporated by reference in this prospectus.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents we incorporate by reference in this prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, included or incorporated in this prospectus regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. We may, in some cases, use terms such as "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements appear in a number of places throughout this prospectus and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned non-clinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, protection of our intellectual property portfolio, the degree of clinical utility of our product candidates, particularly in specific patient populations, our ability to develop commercial functions, expectations regarding clinical trial data, our results of operations, cash needs, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this prospectus. In addition, even if our results of operations, financial condition and liquidity, and events in the industry in which we operate are consistent with the forward-looking statements contained in this prospectus, they may not be predictive of results or developments in future periods.

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Actual results could differ materially from our forward-looking statements due to a number of factors, including risks related to:

our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;

the success and timing of our nonclinical studies and clinical trials;

the difficulties in obtaining and maintaining regulatory approval of our product candidates, and the labeling under any approval we may obtain;

our plans and ability to develop and commercialize our product candidates;

our failure to recruit or retain key scientific or management personnel or to retain our executive officers;

the size and growth of the potential markets for our product candidates and our ability to serve those markets;

regulatory developments in the United States and foreign countries;

the rate and degree of market acceptance of any of our product candidates;

obtaining and maintaining intellectual property protection for our product candidates and our proprietary technology;

the successful development of our commercialization capabilities, including sales and marketing capabilities;

recently enacted and future legislation and regulations regarding the healthcare system;

the success of competing therapies and products that are or become available;

our dependence on collaboration agreements with other pharmaceutical companies, such as Baxter and SymBio, for commercialization of our products and our ability to achieve certain milestones under those agreements; and

the performance of third parties, including contract research organizations and third-party manufacturers.

Any forward-looking statements that we make in this prospectus speak only as of the date of such statements, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events. Comparisons of results for current and any prior periods are not intended to express any future trends or indications of future performance, unless expressed as such, and should only be viewed as historical data.

You should also read carefully the factors described in the "Risk Factors" section of this prospectus supplement and set forth in our most recent Annual Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-K to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant

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uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

We obtained the industry, market and competitive position data in this prospectus and the documents incorporated into this prospectus from our own internal estimates and research as well as from industry and general publications and research surveys and studies conducted by third parties. Industry publications and surveys generally state that the information contained therein has been obtained from sources believed to be reliable. We believe this data is accurate in all material respects as of the date of this prospectus.

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RISK FACTORS

Our business is influenced by many factors that are difficult to predict, and that involve uncertainties that may materially affect actual operating results, cash flows and financial condition. Before making an investment decision, you should carefully consider these risks, including those set forth below and those described in the "Risk Factors" section of our most recent Annual Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-K, each of which is incorporated by reference into this prospectus, and you should also carefully consider any other information we include or incorporate by reference in this prospectus.

Any of the risks we describe below or in the information incorporated herein by reference in this prospectus could cause our business, financial condition or operating results to suffer. The market price of our common stock could decline if one or more of these risks and uncertainties develop into actual events. You could lose all or part of your investment.

A substantial number of shares may be sold in the market following this offering, which may depress the market price for our common stock.

Sales of a substantial number of shares of our common stock in the public market following this offering could cause the market price of our common stock to decline. Although there can be no assurance that all \$20,000,000 worth of shares being offered under this prospectus will be sold or the price at which any such shares might be sold, assuming that an aggregate of 4,662,005 shares of our common stock are sold during the term of the sales agreement with Cantor, in each case, for example, at a price of \$4.29 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on October 2, 2014, upon completion of this offering, based on our shares outstanding as of September 30, 2014, we will have outstanding an aggregate of 26,354,245 shares of common stock, assuming no exercise of outstanding stock options. A substantial majority of the outstanding shares of our common stock are, and all of the shares sold in this offering upon issuance will be, freely tradable without restriction or further registration under the Securities Act of 1933, as amended, or the Securities Act, unless these shares are owned or purchased by "affiliates" as that term is defined in Rule 144 under the Securities Act. In addition, we have also registered all of the shares of common stock that we may issue under our 2013 Equity Compensation Plan, and as of September 30, 2014, 4,112,326 shares of common stock were issuable upon the exercise of stock options outstanding under our 2013 Equity Compensation Plan at a weighted average exercise price of \$11.14 per share and 1,542,216 additional shares of common stock were reserved for issuance under our 2013 Equity Compensation Plan. As a result, these shares can be freely sold in the public market upon issuance, subject to restrictions under the securities laws.

We may use the net proceeds of this offering in ways with which you may disagree.

We currently expect to use the net proceeds of this offering to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, including working capital, acquisitions, retirement of debt and other business opportunities. Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Accordingly, you will be relying on the judgment of our management with regard to the use of net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the price of our common stock to decline.

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You may experience future dilution as a result of future equity offerings or other equity issuances.

In order to raise additional capital, we may in the future offer and issue additional shares of our common stock or other securities convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share in this offering. As of September 30, 2014, an aggregate of 1,542,216 shares of common stock were reserved and available for future grant under our 2013 Equity Compensation Plan. Also as of such date, options to purchase 4,112,326 shares of our common stock were outstanding. You will incur dilution upon the grant of any shares pursuant to such plan, upon vesting of any stock awards under any such plan, or upon exercise of any such outstanding options.

USE OF PROCEEDS

The amount of proceeds from this offering will depend upon the number of shares of our common stock sold and the market price at which they are sold. There can be no assurance that we will be able to sell any shares under or fully utilize the sales agreement with Cantor as a source of financing. We currently expect to use the net proceeds from the sale of the shares of common stock under this prospectus to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding our working capital needs. We expect from time to time to evaluate the acquisition of businesses, products and technologies for which a portion of the net proceeds may be used, although we currently are not planning or negotiating any such transactions.

The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering and progress with the clinical development of our product candidates. Expenditures will also depend upon the establishment of collaborative arrangements with other companies, the availability of additional financing and other factors. Investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of shares of our common stock.

As of the date of this prospectus, we cannot specify with certainty all of the particular uses of the proceeds from this offering. Accordingly, we will retain broad discretion over the use of such proceeds. Pending the use of the net proceeds from this offering as described above, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

DILUTION

If you invest in our common stock, your interest will be diluted immediately to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of common stock after this offering.

The net tangible book value of our common stock as of June 30, 2014, was approximately \$48.9 million, or approximately \$2.26 per share. Net tangible book value per share represents the amount of our total tangible assets less total liabilities divided by the total number of shares of our common stock outstanding.

Dilution per share to new investors represents the difference between the amount per share paid by purchasers for our common stock in this offering and the net tangible book value per share of our common stock immediately following the completion of this offering.

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After giving effect to the sale of shares of common stock offered by this prospectus at an assumed public offering price of \$4.29 per share (the last reported sale price of our common stock on the Nasdaq Global Market on October 2, 2014), and after deducting commissions and estimated aggregate offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2014 would have been approximately \$67.9 million, or approximately \$2.58 per share. This represents an immediate increase in net tangible book value of approximately \$0.32 per share to our existing stockholders and an immediate dilution in as adjusted net tangible book value of approximately \$1.71 per share to purchasers of our common stock in this offering, as illustrated by the following table:

| | | |
|--|----|------|
| Assumed public offering price per share | \$ | 4.29 |
| Net tangible book value per share at June 30, 2014 | \$ | 2.26 |
| Increase in net tangible book value per share attributable to investors purchasing our common stock in this offering | | 0.32 |
| | | |
| As adjusted net tangible book value per share as of June 30, 2014 after giving effect to this offering | | 2.58 |
| | | |
| Dilution per share to investors purchasing our common stock in this offering | \$ | 1.71 |

The table above assumes for illustrative purposes that an aggregate of 4,662,005 shares of our common stock are sold at a price of \$4.29 per share, the last reported sale price of our common stock on the Nasdaq Global Market on October 2, 2014, for aggregate gross proceeds of approximately \$20,000,000. The shares sold in this offering, if any, will be sold from time to time at various prices. An increase of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$4.29 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$20,000,000 is sold at that price, would increase our as adjusted net tangible book value per share after the offering to \$2.67 per share and would increase the dilution in net tangible book value per share to new investors to \$2.62 per share, after deducting commissions and estimated aggregate offering expenses payable by us. A decrease of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$4.29 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$20,000,000 is sold at that price, would decrease our as adjusted net tangible book value per share after the offering to \$2.45 per share and would decrease the dilution in net tangible book value per share to new investors to \$0.84 per share, after deducting commissions and estimated aggregate offering expenses payable by us.

The information discussed above is illustrative only and will adjust based on the actual public offering price and other terms of this offering determined at pricing.

The above table is based on 21,673,486 shares outstanding as of June 30, 2014, and excludes as of such date:

4,236,439 shares of common stock issuable upon the exercise of stock options outstanding under our 2013 Equity Compensation Plan at a weighted average exercise price of \$11.15 per share; and

1,436,857 additional shares of common stock reserved for future issuance under our 2013 Equity Compensation Plan.

To the extent that outstanding options are exercised, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

Table of Contents**PRICE RANGE OF COMMON STOCK**

Our common stock began trading on the Nasdaq Global Market on July 25, 2013 under the symbol "ONTX." Prior to that time, there was no public market for our common stock. Shares sold in our initial public offering on July 24, 2013 were priced at \$15.00 per share.

The following table sets forth the high and low sales prices per share of our common stock as reported on the NASDAQ Global Market for the period indicated.

| | Common Stock Price | |
|--|--------------------|----------|
| | Low | High |
| Year ended December 31, 2013 | | |
| Third Quarter (beginning July 25, 2013) | \$ 19.42 | \$ 30.00 |
| Fourth Quarter | 11.31 | 31.13 |
| Year ending December 31, 2014 | | |
| First Quarter | \$ 6.05 | \$ 16.22 |
| Second Quarter | 4.10 | 6.49 |
| Third Quarter | 4.24 | 5.78 |
| Fourth Quarter (through October 2, 2014) | 4.20 | 4.38 |

The closing sale price of our common stock as reported on the Nasdaq Global Market on October 2, 2014 was \$4.29 per share. As of that date there were approximately 178 holders of record of the common stock. This does not include the number of persons whose stock is in nominee or "street name" accounts through brokers.

PLAN OF DISTRIBUTION

We have entered into a Controlled Equity OfferingSM Sales Agreement, dated October 8, 2014 with Cantor, or the sales agreement, under which we may issue and sell shares of our common stock having an aggregate gross sales price of up to \$20,000,000 from time to time through Cantor acting as agent. Sales of the shares of common stock, if any, may be made on the Nasdaq Global Market at market prices and such other sales as agreed upon by us and Cantor. The sales agreement has been filed as an exhibit to our registration statement on Form S-3 of which this prospectus forms a part.

Upon delivery of a placement notice and subject to the terms and conditions of the sales agreement, Cantor may sell our common stock by any method permitted by law deemed to be an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act, including sales made directly on the Nasdaq Global Market, on any other existing trading market for our common stock or to or through a market maker. Cantor may also sell our common stock by any other method permitted by law, including in privately negotiated transactions. We may instruct Cantor not to sell common stock if the sales cannot be effected at or above the price designated by us from time to time. We or Cantor may suspend the offering of common stock upon notice and subject to other conditions.

We will pay Cantor commissions, in cash, for its services in acting as agent in the sale of our common stock. Cantor will be entitled to compensation at a commission rate of up to 3.0% of the aggregate gross proceeds from each sale of our common stock. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. If so requested by Cantor, and unless otherwise agreed, we will reimburse Cantor for certain specified expenses, including the fees and disbursements of its legal counsel. We estimate that the total expenses for the offering, excluding compensation and reimbursements payable to Cantor under the terms of the sales agreement, will be approximately \$150,000.

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Settlement for sales of common stock will occur on the third business day following the date on which any sales are made, or on some other date that is agreed upon by us and Cantor in connection with a particular transaction, in return for payment of the net proceeds to us. Sales of our common stock as contemplated in this prospectus will be settled through the facilities of The Depository Trust Company or by such other means as we and Cantor may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

Cantor will use its commercially reasonable efforts, consistent with its normal sales and trading practices and applicable state and federal laws, rules and regulations and the rules of the NASDAQ Global Market, to solicit offers to purchase the common stock shares under the terms and subject to the conditions set forth in the sales agreement. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Cantor will be deemed to be underwriting commissions or discounts. We or Cantor may suspend the offering of shares of common stock by notifying the other. We have agreed to provide indemnification and contribution to Cantor against certain civil liabilities, including liabilities under the Securities Act.

The offering of our common stock pursuant to the sales agreement will terminate upon the earlier of (i) the sale of all shares of our common stock subject to the sales agreement, or (ii) termination of the sales agreement as permitted therein. We and Cantor may each terminate the sales agreement at any time upon 10 days' prior notice.

Cantor and its affiliates may in the future provide various investment banking, commercial banking and other financial services for us and our affiliates, for which services they may in the future receive customary fees. To the extent required by Regulation M, Cantor will not engage in any market making activities involving our common stock while the offering is ongoing under this prospectus.

This prospectus in electronic format may be made available on a website maintained by Cantor and Cantor may distribute this prospectus electronically.

EXPERTS

The consolidated financial statements of Onconova Therapeutics, Inc. at December 31, 2013 and December 31, 2012, and for the years then ended, included in our Annual Report on Form 10-K for the year ended December 31, 2013 and incorporated by reference herein have been audited by Ernst & Young LLP, independent registered public accounting firm, and for the year ended December 31, 2011, by EisnerAmper LLP, independent registered public accounting firm, as set forth in their respective reports thereon incorporated by reference herein, and are included in reliance upon such reports given on the authority of such firms as experts in accounting and auditing.

LEGAL MATTERS

The validity of the securities being offered by this prospectus will be passed upon by Pepper Hamilton LLP of Princeton, New Jersey. Cantor is being represented in connection with this offering by Cooley LLP, New York, New York.

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Up to \$20,000,000 of Shares

Common Stock

PROSPECTUS SUPPLEMENT

, 2014

Table of Contents**PART II****Information Not Required in Prospectus****Item 14. Other Expenses of Issuance and Distribution**

The following table sets forth the expenses (other than underwriting discounts and commissions) to be incurred by us in connection with the registration, issuance and distribution of the securities described in this registration statement being registered hereby.

| | |
|---|---------------------|
| Securities and Exchange Commission registration fee | \$ 11,733.18 |
| FINRA fee (if applicable) | 15,500.00 |
| Printing expenses | 25,000.00** |
| Legal fees and expenses | 25,000.00** |
| Accounting fees and expenses | 40,000.00** |
| Transfer agent and trustee fees and expenses | 5,000.00** |
| Miscellaneous | 27,766.82** |
| Total | \$ 150,000.00** |

**

Amounts are estimated pursuant to Item 511 of Regulation S-K.

Item 15. Indemnification of Directors and Officers

We are incorporated under the laws of the State of Delaware. Section 145 of the Delaware General Corporation Law provides that a Delaware corporation may indemnify any persons who are, or are threatened to be made, parties to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of such corporation), by reason of the fact that such person was an officer, director, employee or agent of such corporation, or is or was serving at the request of such person as an officer, director, employee or agent of another corporation or enterprise. The indemnity may include expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such action, suit or proceeding, provided that such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the corporation's best interests and, with respect to any criminal action or proceeding, had no reasonable cause to believe that his or her conduct was illegal. A Delaware corporation may indemnify any persons who are, or are threatened to be made, a party to any threatened, pending or completed action or suit by or in the right of the corporation by reason of the fact that such person was a director, officer, employee or agent of such corporation, or is or was serving at the request of such corporation as a director, officer, employee or agent of another corporation or enterprise. The indemnity may include expenses (including attorneys' fees) actually and reasonably incurred by such person in connection with the defense or settlement of such action or suit provided that such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the corporation's best interests except that no indemnification is permitted without judicial approval if the officer or director is adjudged to be liable to the corporation. Where an officer or director is successful on the merits or otherwise in the defense of any action referred to above, the corporation must indemnify him or her against the expenses which such officer or director has actually and reasonably incurred. Our certificate of incorporation and bylaws provide for the indemnification of our directors and officers to the fullest extent permitted under the Delaware General Corporation Law.

Section 102(b)(7) of the Delaware General Corporation Law permits a corporation to provide in its certificate of incorporation that a director of the corporation shall not be personally liable to the

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corporation or its stockholders for monetary damages for breach of fiduciary duties as a director, except for liability for any:

transaction from which the director derives an improper personal benefit;

act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;

unlawful payment of dividends or redemption of shares; or

breach of a director's duty of loyalty to the corporation or its stockholders.

Our certificate of incorporation includes such a provision. Expenses incurred by any officer or director in defending any such action, suit or proceeding in advance of its final disposition shall be paid by us upon delivery to us of an undertaking, by or on behalf of such director or officer, to repay all amounts so advanced if it shall ultimately be determined that such director or officer is not entitled to be indemnified by us.

As permitted by the Delaware General Corporation Law, we have entered into indemnification agreements with our directors and executive officers. These agreements, among other things, require us to indemnify each director and officer to the fullest extent permitted by law and advance expenses to each indemnitee in connection with any proceeding in which indemnification is available.

At present, there is no pending litigation or proceeding involving any of our directors or executive officers as to which indemnification is required or permitted, and we are not aware of any threatened litigation or proceeding that may result in a claim for indemnification.

We have an insurance policy covering our officers and directors with respect to certain liabilities, including liabilities arising under the Securities Act.

Item 16. Exhibits

A list of exhibits filed herewith is contained in the exhibit index that immediately precedes such exhibits and is incorporated herein by reference.

Item 17. Undertakings

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 the 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 the 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 SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

(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;

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provided, however, that paragraphs (i), (ii) and (iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the registrant pursuant to Section 13 or Section 15(d) of the Exchange Act that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of 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.

(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.

(4) That, for the purpose of determining liability under the Securities Act to any purchaser:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5) or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii) or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which the prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. *Provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date; or

(5) That, for the purpose of determining liability of the registrant under the Securities Act to any purchaser in the initial distribution of the securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

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(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

(6) That, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in the 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.

(7) 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 Act 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 in connection 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 Act and will be governed by the final adjudication of such issue.

(8) To file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Act.

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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-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in Newtown, Pennsylvania on October 8, 2014.

Onconova Therapeutics, Inc.

By: /s/ RAMESH KUMAR, PH.D

Name: Ramesh Kumar, Ph.D
Title: *President and Chief Executive Officer*

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that the undersigned officers and directors of Onconova Therapeutics, Inc., a Delaware corporation (the "Corporation"), hereby constitute and appoint each of Ramesh Kumar, Ph.D and Ajay Bansal the true and lawful agents and attorneys-in-fact of the undersigned with full power and authority in said agents and attorneys-in-fact, and in any one or more of them, to sign for the undersigned and in their respective names as an officer/director of the Corporation, any and all amendments (including post-effective amendments) to this registration statement on Form S-3 (or any other registration statement for the same offering that is to be effective upon filing pursuant to Rule 462(b) under the Securities Act) and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, and with full power of substitution, hereby ratifying and confirming all that each of said attorneys-in-fact, or his substitute or substitutes, may do or cause to be done by virtue hereof.

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Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed by the following persons in the capacities indicated on October 8, 2014.

| Name | Title |
|---|--|
| <hr/> <i>/s/ RAMESH KUMAR, PH.D.</i> Ramesh Kumar, Ph.D. | Director, President and Chief Executive Officer (Principal Executive Officer) |
| <hr/> <i>/s/ AJAY BANSAL</i> Ajay Bansal | Chief Financial Officer (Principal Financial Officer) |
| <hr/> <i>/s/ MARK GUERIN</i> Mark Guerin | Vice President, Financial Planning and Accounting (Principal Accounting Officer) |
| <hr/> <i>/s/ HENRY S. BIENEN, PH.D.</i> Henry S. Bienen, Ph.D. | Director |
| <hr/> <i>/s/ JEROME E. GROOPMAN, M.D.</i> Jerome E. Groopman, M.D. | Director |
| <hr/> <i>/s/ MICHAEL B. HOFFMAN</i> Michael B. Hoffman | Chairman, Board of Directors |
| <hr/> <i>/s/ VIREN MEHTA, PHARM.D</i> Viren Mehta, Pharm.D | Director |
| <hr/> <i>/s/ E. PREMKUMAR REDDY, PH.D</i> E. Premkumar Reddy, Ph.D | Director |
| <hr/> <i>/s/ ANNE M. VANLENT</i> Anne M. VanLent | Director |

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EXHIBIT INDEX

| Exhibit No. | Description of Exhibit |
|--------------------|--|
| 1.1 | Sales Agreement, dated October 8, 2014, by and between the Company and Cantor Fitzgerald & Co. |
| 1.2* | Form of Underwriting Agreement |
| 3.1 | Tenth Amended and Restated Certificate of Incorporation of Onconova Therapeutics, Inc. (Incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K filed on July 25, 2013) |
| 3.2 | Amended and Restated Bylaws of Onconova Therapeutics, Inc. (Incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K filed on July 25, 2013) |
| 4.1 | Form of Certificate of Common Stock (Incorporated by reference to Exhibit 4.1 to Pre-Effective Amendment No. 1 the Company's Registration Statement on Form S-1 filed on July 11, 2013) |
| 4.2 | Eighth Amended and Restated Stockholders' Agreement, effective as of July 27, 2012, by and among Onconova Therapeutics, Inc. and certain stockholders named therein (Incorporated by reference to Exhibit 4.2 to Pre-Effective Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on July 11, 2013) |
| 4.3 | Amendment No. 1 to Eighth Amended and Restated Stockholders' Agreement, effective as of July 9, 2013 (Incorporated by reference to Exhibit 4.2 to Pre-Effective Amendment No. 1 the Company's Registration Statement on Form S-1 filed on July 11, 2013) |
| 4.4* | Form of Preferred Stock Certificate |
| 4.5* | Form of any Certificate of Designation setting forth the preferences and rights with respect to any preferred stock issued hereunder |
| 4.6 | Form of Indenture |
| 4.5* | Form of Debt Securities |
| 4.6* | Form of Warrant |
| 4.7* | Form of Warrant Agreement for Common Stock, including Warrant Certificate for Common Stock |
| 4.8* | Form of Warrant Agreement for Preferred Stock, including Warrant Certificate for Preferred Stock |
| 4.9* | Form of Warrant Agreement for Debt Securities, including Warrant Certificate for Debt Securities |
| 4.10* | Form of Unit Agreement |
| 5.1 | Opinion of Pepper Hamilton LLP |
| 12.1 | Statement regarding computation of Ratio of Earnings to Combined Fixed Charges and Preferred Stock Dividends |
| 23.1 | Consent of Ernst & Young LLP |
| 23.2 | Consent of EisnerAmper LLP |
| 23.3 | Consent of Pepper Hamilton LLP (included in the opinion filed as Exhibit 5.1) |
| 24.1 | Power of attorney (included on the signature page of this registration statement) |

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| Exhibit No. | Description of Exhibit |
|--------------------|---|
| 25.1** | Form T-1 Statement of Eligibility and Qualification under the Trust Indenture Act of 1939 of Trustee for Form of Indenture. |

*
To be filed by amendment or as an exhibit to a report pursuant to Section 13(a), 13(c) or 15(d) of the Exchange Act.

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To be filed in accordance with the requirements of Section 305(b)(2) of the Trust Indenture Act of 1939 and Rule 5b-3 thereunder.
