

Onconova Therapeutics, Inc.
Form 424B5
April 20, 2017
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Filed Pursuant To Rule 424(b)(5)

Registration Statement No. 333-199219

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED APRIL 20, 2017

Prospectus Supplement

(to the Prospectus dated November 20, 2014)

Onconova Therapeutics, Inc.

Shares of Common Stock

We are offering _____ shares of our common stock. Our common stock is listed on the NASDAQ Capital Market under the symbol ONTX. On April 20, 2017, the last reported sale price of our common stock on the NASDAQ Capital Market was \$2.48 per share.

As of April 19, 2017, the aggregate market value of our outstanding common stock held by non-affiliates, which we may refer to as the public float, was approximately \$18,087,000, which was calculated based on 5,617,189 shares of outstanding common stock held by non-affiliates and on a price per share of \$3.22, the closing price of our common stock on April 4, 2017. In no event will we sell our common stock in a public primary offering with a value exceeding more than one-third of our public float in any 12 calendar month period so long as our public float remains below \$75.0 million. During the 12 calendar month period that ends on, and includes, the date of this prospectus supplement, and

including this offering, we have offered securities with an aggregate market value of approximately \$65,600 pursuant to General Instruction I.B.6 of Form S-3.

Investing in our common stock involves risks. See Risk Factors beginning on page S-9 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement.

| | Per Share | Total |
|---|-----------|-------|
| Public offering price | \$ | \$ |
| Underwriting discounts and commissions(1) | \$ | \$ |
| Proceeds, before expenses, to us | \$ | \$ |

(1) We have agreed to reimburse the underwriters for certain expenses. See Underwriting. The underwriting discount shall be \$ per share for shares delivered to certain investors previously identified to the underwriters, for up to a maximum (in aggregate) of 20% of the common stock sold in the offering, and then the underwriting discount shall be \$ for any additional shares delivered to these investors above the 20% threshold

We have granted the underwriters an option for a period of 45 days to purchase up to an additional shares of our common stock. If the underwriters exercise their option in full, the total underwriting discounts and commissions payable by us will be \$ and the total proceeds to us, before expenses, will be \$.

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The underwriters expect to deliver shares of common stock to purchasers on or about April , 2017

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

Laidlaw & Company (UK) Ltd.

The date of this prospectus supplement is April , 2017.

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ABOUT THIS PROSPECTUS SUPPLEMENT

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the underwriters have not, authorized anyone 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 the underwrites have not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted 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 supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized 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 supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized 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 supplement entitled *Where You Can Find More Information* and *Information Incorporated by Reference*.

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated November 20, 2014, including the documents incorporated by reference therein, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission (the *SEC*), before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. 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 the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

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 supplement, the accompanying 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 SUPPLEMENT SUMMARY

The following summary highlights certain information contained elsewhere in this prospectus supplement, the accompanying prospectus, any free writing prospectus that we have been authorized to use and the documents incorporated by reference herein and in the accompanying 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 prospectus, any free writing prospectus that we have been authorized to use and the documents incorporated by reference herein and in the accompanying prospectus. You should pay special attention to the Risk Factors section of this prospectus supplement and the accompanying prospectus and the financial statements and other information incorporated by reference in this prospectus supplement and the accompanying prospectus.

Our Business

Overview

We are a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule product candidates primarily to treat cancer. Using our proprietary chemistry platform, we have created an extensive library of targeted agents designed to work against cellular pathways important to cancer cells. We believe that the product candidates in our pipeline have the potential to be efficacious in a variety of cancers. We have one Phase 3 clinical-stage product candidate and two other clinical-stage product candidates (one of which is being developed for treatment of acute radiation syndromes) and several preclinical programs. Substantially all of our current effort is focused on our lead product candidate, rigosertib. Rigosertib is being tested in an intravenous formulation as a single agent, and an oral formulation in combination with azacitidine, in clinical trials for patients with higher-risk myelodysplastic syndromes (MDS).

In December 2015, we enrolled the first patient in a randomized controlled Phase 3 clinical trial of intravenous rigosertib (rigosertib IV) in a population of patients with higher-risk MDS after failure of hypomethylating agent (HMA) therapy. The trial, which we refer to as INSPIRE, is expected to enroll approximately 225 patients at more than 170 sites globally. The primary endpoint of INSPIRE is overall survival, and an interim analysis is anticipated in the second half of 2017. We anticipate reporting topline data from the INSPIRE trial in 2018.

Rigosertib

Rigosertib is a small molecule which we believe blocks cellular signaling by targeting RAS effector pathways. This is believed to be mediated by the binding of rigosertib to the RAS-binding domain (RBD), found in many RAS effector proteins, including the Raf and PI3K kinases. We believe this mechanism of action provides a new approach to block the interactions between RAS and its targets containing RBD sites. Rigosertib is currently being tested as a single agent and in combination with azacitidine, in clinical trials of patients with MDS. We have enrolled more than 1,200 patients in rigosertib clinical trials for MDS and other conditions. We were a party to a license and development agreement with Baxalta (as defined below), which granted Baxalta certain rights to commercialize rigosertib in Europe. The Baxalta agreement was terminated on August 30, 2016, at which time the European rights reverted to us at no cost. We are party to a collaboration agreement with SymBio, which grants SymBio certain rights to commercialize rigosertib in Japan and Korea. We have retained development and commercialization rights to rigosertib in the rest of the world, including in the United States and Europe, although we could consider licensing commercialization rights to other territories as we continue to seek additional funding.

Rigosertib IV for higher-risk MDS

In early 2014, we announced topline survival results from our ONTIME trial, a multi-center Phase 3 clinical trial of rigosertib IV as a single agent versus best supportive care including low dose Ara-C. The ONTIME trial did not meet its primary endpoint of an improvement in overall survival in the intent-to-treat population, although improvements in median overall survival were observed in various pre-specified and exploratory subgroups of higher-risk MDS patients. As a result, additional clinical work is required.

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During 2014 and 2015, we held meetings with the U.S. Food and Drug Administration (FDA) European Medicines Agency (EMA) and several European national regulatory authorities to discuss and seek guidance on a path for approval of rigosertib IV in higher-risk MDS patients whose disease had failed HMA therapy. After discussions with the FDA and EMA, we refined our patient eligibility criteria by defining what we believe to be a more homogenous patient population. After regulatory feedback, input from key opinion leaders in the U.S. and Europe and based on learnings from the ONTIME study, we designed a new randomized controlled Phase 3 trial, referred to as INSPIRE. The INSPIRE trial will enroll higher-risk MDS patients under 82 years of age who have progressed on, or failed to respond to, previous treatment with HMAs within nine months or nine cycles over the course of one year after initiation of HMA therapy, and had their last dose of HMA within six months prior to enrollment in the trial. The primary endpoint of this study is overall survival of all randomized patients in the intent-to-treat (ITT) population and the IPSS-R Very High Risk subgroup. An interim analysis is planned after fifty percent of the total death events have occurred. This randomized trial of approximately 225 patients is expected to be conducted at more than 170 sites globally. The first patient in the INSPIRE trial was enrolled at the MD Anderson Cancer Center in December 2015, the first patient in Europe was enrolled in March, 2016, and the first patient in Japan was enrolled in July, 2016.

Enrollment for the INSPIRE Phase 3 trial for second-line higher-risk MDS patients is highly selective and required us to search extensively to identify appropriate candidates meeting the stringent entry criteria. We are encouraged that the enrollment is on track, with trial sites across 17 countries on four continents. Our partner Symbio Pharmaceuticals has opened 33 sites in Japan collaborating on the INSPIRE protocol. The trial is expected to be active in 19 countries by the end of April following the activation of sites in Switzerland and the Netherlands. We intend to maintain this momentum. We continue to anticipate the pre-planned interim analysis in the second half of 2017 and full enrollment by the first quarter of 2018. The interim analysis will involve a review of the efficacy and safety data for the first half of the trial by our independent data monitoring committee (DMC). This interim analysis may result in the trial continuing as planned, randomization for the Very High Risk MDS subgroup continuing with the other subgroups closed to further accrual, or the trial being stopped for futility. This analysis may also result in an increase to the study's sample size. Our statistical analysis plan is currently under review by the FDA.

Safety and Tolerability of rigosertib in MDS and other hematologic malignancies

A comprehensive analysis of IV and oral rigosertib safety in patients with Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) was presented in December 2016 at the American Society of Hematology (ASH) Annual Meeting. The most commonly reported treatment-emergent adverse events (TEAEs) in $\geq 10\%$ of patients with MDS/AML receiving rigosertib intravenous (IV) monotherapy were fatigue (33%), nausea (33%), diarrhea (27%), constipation (25%), anaemia (24%) and pyrexia (24%). The most common \geq Grade 3 AEs were anaemia (21%), febrile neutropenia (13%), pneumonia (12%) and thrombocytopenia (11%). The most common serious AEs were febrile neutropenia (10%), pneumonia (9%), and sepsis (7%). The most common AEs leading to discontinuation of IV rigosertib were sepsis and pneumonia (3% each).

Rigosertib oral in combination with azacitidine for higher-risk MDS

In December 2016, at the American Society of Hematology (ASH) Annual Meeting, we presented Phase 2 data from an oral rigosertib and azacitidine combination trial in higher-risk MDS. 33 of 40 MDS patients enrolled were evaluable for response at the time of the analysis. The median age of patients was 66, with 73% being male. ECOG performance status was 0 or 1 in 95% of the patients. The ECOG Scale of Performance Status describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). ECOG Performance Status grades include: 0 or Fully active, able to carry on all pre-disease performance without restriction; 1 or Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 or Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; 3 or Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; 4 or Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; 5 or Dead. IPSS-R distribution was: 7.5% Low, 12.5% Intermediate, 37.5% High, 32.5%

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Very High and 10% unknown. 76% of patients responded per 2006 International Working Group criteria. Responses were as follows:

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Response per IWG 2006

| | Overall Evaluable (N=33) | No prior HMA (N=20) | Prior HMA (N=13) |
|-------------------------------------|---|------------------------------------|---------------------------------|
| Complete remission (CR) | 8 (24%) | 7 (35%) | 1 (8%) |
| Marrow CR + hematologic improvement | 10 (30%) | 6 (30%) | 4 (31%) |
| Marrow CR alone | 6 (18%) | 3 (15%) | 3 (23%) |
| Hematologic improvement alone | 1 (3%) | 1 (5%) | 0 |
| Stable disease | 8 (24%) | 3 (15%) | 5 (38%) |
| Overall IWG response | 25 (76%) | 17 (85%) | 8 (62%) |
| Clinical benefit response | 19 (58%) | 14 (70%) | 5 (38%) |

The median duration of response was 8 months for CR, 12.3 months for marrow CR.

Safety/Tolerability of the Combination:

Oral rigosertib (560 mg qAM, 280 mg qPM) was administered on Day 1-21 of a 28-day cycle. Azacitidine 75 mg/m²/day SC or IV was administered for 7 days starting on Day 8. The combination of oral rigosertib and azacitidine was well tolerated. The most common TEAEs in ≥ 10% of patients were nausea (41%), fatigue (39%), diarrhea (37%), constipation (37%) and dysuria (28%). The most common serious AEs were pneumonia (11%) and febrile neutropenia (7%). The most common AEs leading to discontinuation were AML (4%) and pneumonia (4%).

Next steps for rigosertib oral in combination with azacitidine for higher-risk MDS

Following an end of Phase 2 meeting with the Food and Drug Administration (FDA) in September 2016, we began development of a Phase 3 protocol. We expect to submit this protocol for review by regulatory agencies in the US and Europe in the second or third quarter of 2017. The Phase 3 trial will be designed as a 1:1 randomized, placebo-controlled trial of oral rigosertib plus azacitidine compared to azacitidine plus placebo. We plan to use a full dose of azacitidine, as defined in the product insert. The patient population studied in this trial will be first-line (HMA naïve) higher-risk MDS patients. The primary endpoint for assessment of efficacy will be Response Rate of complete remission (CR) + partial remission (PR,) as per the IWG (International Working Group) 2006 Response criteria. Formal FDA review will be sought via the Special Protocol Assessment (SPA) mechanism. Further details, including sample size and other criteria will be available after completion of regulatory review, which is anticipated in the second half of 2017. We will not commence the Phase 3 trial without additional financing.

While the Phase 3 trial is being designed, we plan to expand the trial cohort by up to 40 subjects with the view of further studying the investigational therapy. Under a protocol amendment, we anticipate using the expanded cohorts to explore dose optimization by increasing the dose and varying the dose administration scheme of oral rigosertib to identify an optimal dose. We are currently in discussions with FDA concerning the trial expansion.

Rigosertib oral for lower-risk MDS

Higher-risk MDS patients suffer from a shortfall in normal circulating blood cells, or cytopenias, as well as elevated levels of cancer cells, or blasts in their bone marrow and peripheral blood, whereas lower-risk MDS patients suffer mainly from cytopenias, that is low levels of red blood cells, white blood cells or platelets. Thus, lower-risk MDS patients depend on transfusions and growth factors or other therapies to improve their low blood counts.

We have explored single agent rigosertib oral as a treatment for lower-risk MDS in two Phase 2 clinical trials, 09-05 and 09-07. In December 2013, we presented data at the Annual ASH Meeting from the 09-05 Phase 2 trial. To date, Phase 2 clinical data has indicated that further study of single agent oral rigosertib in transfusion-dependent, lower-risk MDS patients is warranted. Rigosertib has been generally well tolerated, except for urinary

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side effects at higher dose levels. Future clinical trials will be needed to evaluate dosing and schedule modifications and their impact on efficacy and toxicity of oral rigosertib in lower-risk MDS patients.

Data presented from the 09-05 trial also suggested the potential of a genomic methylation assessment of bone marrow cells to prospectively identify lower-risk MDS patients likely to respond to oral rigosertib. We therefore expanded the 09-05 trial by adding an additional cohort of 20 patients to advance the development of this genomic methylation test. To date, a biomarker which would predict response has not been identified. Further testing and development of oral rigosertib for lower-risk MDS will be required. We will not commence further development of oral rigosertib for lower-risk MDS without additional financing.

Safety and Tolerability of rigosertib oral in MDS and other hematologic malignancies

Oral rigosertib as a monotherapy has been evaluated in four Phase 1 and 2 studies in MDS and other hematologic malignancies. One study is completed and a clinical study report is available. The most common TEAEs in $\geq 10\%$ of patients were pollakiuria (increased urinary frequency) (35%), fatigue (32%), diarrhea (26%), dysuria (29%) and haematuria (24%). The most common \geq Grade 3 AEs were anaemia (17%), thrombocytopenia (5%), haematuria (4%) and urinary tract infection (4%). The most common serious AE was pneumonia (6%). The most common AEs leading to discontinuation of patients receiving oral rigosertib as monotherapy were dysuria (8%), urinary tract pain (7%), haematuria (5%) and urinary frequency (5%).

In addition to the above described clinical trials, we are continuing the preclinical and chemistry, manufacturing, and control work for IV and oral rigosertib.

Other Programs

The vast majority of the Company's efforts are now devoted to the advanced stage development of rigosertib for unmet medical needs of MDS patients. Other programs are either paused, inactive or require only minimal internal resources and efforts.

Briciclib

Briciclib, another of our product candidates, is a small molecule targeting an important intracellular regulatory protein, Cyclin D1, which is often found at elevated levels in cancer cells. Cyclin D1 expression is regulated through a process termed cap-dependent translation, which requires the function of eukaryotic initiation factor 4E protein. In vitro evidence indicates briciclib binds to eukaryotic initiation factor 4E protein, blocking cap-dependent translation of Cyclin D1 and other cancer proteins, such as c-MYC, leading to tumor cell death. We have been conducting a Phase 1 multi-site dose-escalation trial of briciclib in patients with advanced solid tumors refractory to current therapies. Safety and efficacy assessments are complete in six of the seven dose-escalation cohorts of patients in this trial. As of December 2015, the Investigational New Drug (IND) for briciclib is on full clinical hold following a drug product lot testing failure. We will be required to undertake appropriate remedial actions prior to re-initiating the clinical trial and completing the final dose-escalation cohort.

Recilisib

Recilisib is a product candidate being developed in collaboration with the U.S. Department of Defense for acute radiation syndromes. 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. We have also 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 conventional human efficacy studies are not feasible or ethical, by relying on evidence from studies in appropriate animal models to support efficacy in humans. Ongoing studies of recilisib, focusing on animal models and biomarker development to assess the efficacy of recilisib are being conducted by third parties with government funding. We anticipate that any future development of recilisib beyond these ongoing studies would be conducted solely with government funding or by collaboration. Use of government funds to finance the research and development in whole or in part means any future effort to

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commercialize recilisib will be subject to federal laws and regulations on U.S. government rights in intellectual property. Additionally, we are subject to laws and regulations governing any research contracts, grants, or cooperative agreements under which government funding was provided.

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 may explore additional collaborations to further the development of these product candidates as we focus internally on our more advanced programs.

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

| | |
|--|---|
| Common stock offered by us | Shares |
| Common stock to be outstanding after this offering | shares (or shares if the underwriters exercise in full their option to purchase additional shares) |
| Option to purchase additional shares | We have granted the underwriters an option to purchase up to an additional shares of our common stock. This option is exercisable, in whole or in part, for a period of 45 days from the date of this prospectus supplement. |
| Use of proceeds | We intend to use the net proceeds from this offering 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-15. |
| Risk factors | You should read the Risk Factors section of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement for a discussion of factors to consider before deciding to invest in our common stock. |
| NASDAQ Capital Market symbol | ONTX. |
| Underwriting Discount | The underwriting discount shall be \$ per share for shares delivered to certain investors previously identified to the underwriters, for up to a maximum (in aggregate) of 20% of the common stock sold in the offering, and then the underwriting discount shall be \$ for any additional shares delivered to these investors above the 20% threshold. |

The number of shares of our common stock outstanding after the offering is based on 6,759,895 shares outstanding as of December 31, 2016, and excludes as of such date:

- 746,353 shares of common stock issuable upon the exercise of stock options outstanding at December 31, 2016 with a weighted average exercise price of approximately \$53.50 per share;
- 3,525,771 shares of common stock issuable upon the exercise of outstanding warrants at December 31, 2016 with a weighted average exercise price of approximately \$4.77 per share;
- 6,275 shares of common stock reserved for future issuance under our 2013 Equity Compensation Plan at December 31, 2016; and

- any additional shares of common stock that we may issue to Lincoln Park Capital Fund, LLC (Lincoln Park), pursuant to a purchase agreement we entered into on October 8, 2015, which provides that, upon the terms and subject to the conditions and limitation set forth therein, Lincoln Park is committed to purchase up to an aggregate of an additional \$15 million of shares of our common stock over the term of the purchase agreement, should we elect to sell shares to Lincoln Park.

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Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase up to an additional shares of our common stock.

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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 filed with the SEC, which is incorporated by reference into this prospectus supplement, as well as any amendment or update to our risk factors reflected in subsequent filings with the SEC, and you should also carefully consider any other information we include or incorporate by reference in this prospectus supplement.

Any of the risks we describe below or in the information incorporated herein by reference in this prospectus supplement 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.

Risks Associated with this Offering

Our management will have broad discretion over the use of any net proceeds from this offering, you may not agree with how we use the proceeds, and the proceeds may not be invested successfully.

Our management will have broad discretion as to the use of any net proceeds from this offering and could use them for purposes other than those contemplated at the time of this offering. Accordingly, you will be relying on the judgment of our management with regard to the use of any proceeds from the sale of shares of common stock in this offering, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that the proceeds will be invested in a way that does not yield a favorable, or any, return for you.

You will experience immediate dilution.

Since the price per share of our common stock being offered is higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on the public offering price of \$ _____ per share, and after deducting the underwriting discount and estimated offering expenses payable by us, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$ _____ per share in the net tangible book value of the common stock as of December 31, 2016. See the section entitled Dilution in this prospectus supplement for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering. To the extent outstanding stock options or warrants are exercised, there will be further dilution to new investors.

Our shareholders may experience significant dilution as a result of future equity offerings or issuances and exercise of outstanding options and warrants.

In order to raise additional capital or pursue strategic transactions, we may in the future offer, issue or sell additional shares of common stock or other securities convertible into or exchangeable for shares of our common stock. We cannot assure you that we will be able to sell shares or other securities in any other transaction at a price per share or that have an exercise price or conversion price per shares that is equal to or greater than the price for the securities purchased by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing shareholders. The price per share at which we sell or issue additional shares of common stock or other securities convertible into or exchangeable for our common stock future transactions may be higher or lower than such price.

Sales of a significant number of shares of our common stock in the public markets, or the perception that such sales could occur, could depress the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public markets could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity

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securities. We cannot predict the effect that future sales of our common stock would have on the market price of our common stock.

We do not intend to pay any cash dividends on our common stock in the foreseeable future and, therefore, any return on your investment in our common stock must come from increases in the fair market value and trading price of our common stock.

We do not intend to pay any cash dividends on our common stock in the foreseeable future and, therefore, any return on your investment in our common stock must come from increases in the fair market value and trading price of our common stock.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein 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, contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein 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, 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 supplement, the accompanying prospectus and the documents incorporated by reference herein and therein, and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical 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 products, particularly in specific patient populations, our ability to develop commercial and manufacturing 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 supplement, the accompanying prospectus and in documents incorporated by reference herein and therein, 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.

Actual results could differ materially and adversely from our forward-looking statements due to a number of factors, including, without limitation, risks related to:

- our need for additional financing for our INSPIRE trial and other operations, and our ability to obtain sufficient funds on acceptable terms when needed, and our plans and future needs to scale back operations if adequate financing is not obtained;
- our ability to continue as a going concern;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- the success and timing of our preclinical studies and clinical trials, including site initiation and patient enrollment, and regulatory approval of protocols for future clinical trials;

- our ability to enter into, maintain and perform collaboration agreements with other pharmaceutical companies, for funding and commercialization of our clinical drug candidates or preclinical compounds, and our ability to achieve certain milestones under those agreements;
- 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, manufacture and commercialize our product candidates
- our failure to recruit or retain key scientific or management personnel or to retain our executive officers;

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- 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 regulation regarding the healthcare system;
- the success of competing therapies and products that are or may become available;
- our ability to maintain the listing of our common stock on a national securities exchange;
- the potential for third party disputes and litigation; and
- the performance of third parties, including contract research organizations and third-party manufacturers.

Any forward-looking statements that we make in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein speak only as of the date of such statement, and we undertake no obligation to update such statements whether as a result of any new information, future events, changed circumstances or otherwise. 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.

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You should also read carefully the factors described in the Risk Factors section of this prospectus supplement, the accompanying prospectus and in documents incorporated by reference herein, 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 supplement, the accompanying prospectus and in documents incorporated by reference herein 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 supplement, the accompanying prospectus and in documents incorporated by reference herein 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 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 with respect to the common stock offered by this prospectus supplement. This prospectus supplement does not contain all the information set forth in the registration statement and its exhibits and schedules, portions of which have been omitted as permitted by the rules and regulations of the SEC. For further information about us, as well as our common stock, we refer you to the registration statement and to its exhibits and schedules.

In addition, we file annual, quarterly and current reports, proxy and information statements and other information with the SEC. Our SEC filings, including the registration statement, are available to the public from the SEC's website at www.sec.gov. To receive copies of public records not posted to the SEC's website at prescribed rates, you may complete an online form at www.sec.gov, send a fax to (202) 772-9337 or submit a written request to the SEC, Office of FOIA/PA Operations, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information.

We also make available free of charge on our website, www.onconova.com, all materials that we file electronically with the SEC, including our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, Section 16 reports and amendments to those reports as soon as reasonably practicable after such materials are electronically filed with, or furnished to, the SEC. Information contained on our website or any other website is not incorporated by reference into this prospectus supplement and does not constitute a part of this prospectus supplement.

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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, 2016 that we filed with the SEC on March 29, 2017, 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 2017 annual meeting of stockholders filed on April 12, 2017;
- Our Current Report on Form 8-K filed with the SEC on April 20, 2017;
- 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 supplement and the accompanying 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 supplement but not delivered with this prospectus supplement and the accompanying 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: Mark Guerin.

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.

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USE OF PROCEEDS

We estimate that we will receive net proceeds of approximately \$ _____ million from the sale of the shares of common stock offered by us in this offering, or approximately \$ _____ million if the underwriters exercise in full their option to purchase _____ additional shares of common stock, after deducting the underwriting discounts and commissions and estimated offering costs payable by us.

We intend to use the net proceeds from this offering 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.

Table of Contents**DILUTION**

If you invest in our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering. As of December 31, 2016, our historical net tangible book value was \$5,127,000, or \$0.76 per share, based on 6,759,895 shares of our common stock outstanding as of December 31, 2016. Our historical net tangible book value per share represents the amount of our total tangible assets reduced by the amount of our total liabilities, divided by the total number of shares of our common stock outstanding as of December 31, 2016. After giving effect to our sale in this offering of _____ shares of common stock at the public offering price of \$ _____ per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of December 31, 2016 would have been \$ _____ million, or \$ _____ per share. This represents an immediate increase of net tangible book value of \$ _____ per share to our existing stockholders and an immediate dilution of \$ _____ per share to investors purchasing shares in this offering. The following table illustrates this per share dilution.

| | | |
|--|----|------|
| Public offering price per share | | \$ |
| Historical Net tangible book value per share at December 31, 2016 | \$ | 0.76 |
| Increase in net tangible book value per share attributable to investors purchasing our common stock in this offering | | |
| As adjusted net tangible book value per share as of December 31, 2016 after giving effect to this offering | | |
| Dilution per share to investors purchasing our common stock in this offering | | \$ |

If the underwriters exercise in full its option to purchase up to an additional _____ shares of our common stock at the public offering price of \$ _____ per share, the pro forma net tangible book value after this offering would be \$ _____ per share, representing an increase in net tangible book value of \$ _____ per share to our existing stockholders and immediate dilution in net tangible book value of \$ _____ per share to investors purchasing shares in this offering.

The above discussion and table are based on 6,759,895 shares of our common stock outstanding as of December 31, 2016 and exclude:

- 746,353 shares of common stock issuable upon the exercise of stock options outstanding at December 31, 2016 with a weighted average exercise price of approximately \$53.50 per share;
- 3,525,771 shares of common stock issuable upon the exercise of outstanding warrants at December 31, 2016 with a weighted average exercise price of approximately \$4.77 per share;
- 6,275 shares of common stock reserved for future issuance under our 2013 Equity Compensation Plan at December 31, 2016; and

- any additional shares of common stock that we may issue to Lincoln Park, pursuant to a purchase agreement we entered into on October 8, 2015, which provides that, upon the terms and subject to the conditions and limitation set forth therein, Lincoln Park is committed to purchase up to an aggregate of an additional \$15 million of shares of our common stock over the term of the purchase agreement, should we elect to sell shares to Lincoln Park.

To the extent that outstanding options or warrants 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

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raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

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UNDERWRITING

Laidlaw & Company (UK) Ltd. is acting as the representative (the Representative) of the underwriters named below. Subject to the terms and conditions set forth in an underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

| Underwriters | Number of Shares |
|-----------------------------|---------------------|
| Laidlaw & Company (UK) Ltd. | |
| Total | |

Over-Allotment Option

We have granted the underwriters an option, exercisable for 45 days from the date of this prospectus, to purchase up to an aggregate of additional shares of common stock to cover over-allotments, if any, at the public offering price set forth on the cover page of this prospectus, less the underwriting discount. The underwriters may exercise this option solely for the purpose of covering overallotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus. If the underwriters exercise this option, the underwriters will be obligated subject to certain conditions, to purchase the additional shares for which the option has been exercised.

Discount, Commissions and Expenses

The underwriters have advised us that they proposes to offer the shares of common stock to the public at the public offering price set forth on the cover page of this prospectus supplement and to certain dealers at that price less a concession not in excess of \$ per share. After this offering, the public offering price, concession and reallowance to dealers may be changed by the underwriters. No such change shall change the amount proceeds to be received by us as set forth on the cover page of this prospectus supplement. The shares of common stock are offered by the underwriters stated herein, subject to receipt and acceptance by them and subject to their right to reject any order in whole or in part. The underwriters have informed us that it does not intend to confirm sales to any accounts over which it exercises discretionary authority.

The following table shows the underwriting discount payable to the underwriters by us in connection with this offering. Such amounts are show assuming both no exercise and full exercise of the underwriters over-allotment option to purchase additional shares.

| | Per Share | Total Without Exercise of Over Allotment Option | Total With Exercise of Over Allotment Option |
|----------------------------------|-----------|---|--|
| Public Offering Price | | | |
| Underwriting discount (1) | | | |
| Proceeds, before expenses, to us | | | |

(1) The underwriting discount shall be \$ per share for shares delivered to certain investors previously identified to the underwriters, for up to a maximum (in aggregate) of 20% of the common stock sold in the offering, and then the underwriting discount shall be \$ for any additional shares delivered to these investors above the 20% threshold.

The expenses of the offering, not including the underwriting discount, payable by us are estimated to be \$, which includes up to \$60,000 that we have agreed to reimburse the underwriters for their out-of-pocket expenses, including reasonable fees and disbursements of underwriters counsel, incurred in connection with this offering. The Company will pay the Representative a non-refundable retainer of \$25,000.

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Indemnification

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933, as amended (the Securities Act), and liabilities arising from breaches of representations and warranties contained in the underwriting agreement, or to contribute to payments that the underwriters may be required to make in respect of those liabilities.

Lock-up Agreements

The Company has agreed, subject to certain exceptions, for a period of 90 days after the date of the underwriting agreement, not to offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise dispose of, directly or indirectly any shares of common stock or any securities convertible into or exchangeable for our common stock either owned as of the date of the underwriting agreement or thereafter acquired without the prior written consent of the Representative.

The Company's officers, directors and certain shareholders have agreed, subject to limited exceptions, for a period of 90 days after the date of the underwriting agreement, not to offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise dispose of, directly or indirectly any shares of common stock or any securities convertible into or exchangeable for our common stock either owned as of the date of the underwriting agreement or thereafter acquired, subject to certain exceptions, without the prior written consent of the Representative. Two shareholders, who in the aggregate own approximately 18.1% of the Company's common stock, are not subject to lockup agreements.

The Representative may, in its sole discretion and at any time or from time to time before the termination of the lock-up period, without notice, release all or any portion of the securities subject to lock-up agreements.

Stabilization, Short Positions and Penalty Bids

In connection with the offering, the underwriters may engage in stabilizing transactions, short sales and purchases to cover positions created by short sales, and penalty bids or purchases for the purpose of pegging, fixing or maintaining the price of the common stock, in accordance with Regulation M under the Exchange Act:

- Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum.
- A short position involves a sale by the underwriters of shares in excess of the number of shares the underwriters are obligated to purchase in the offering, which creates the syndicate short position. This short position

may be either a covered short position or a naked short position. In a covered short position, the number of shares involved in the sales made by the underwriters in excess of the number of shares they are obligated to purchase is not greater than the number of shares that they may purchase by exercising its option to purchase additional shares. In a naked short position, the number of shares involved is greater than the number of shares in its option to purchase additional shares. The underwriters may close out any short position by either exercising its option to purchase additional shares and/or purchasing shares in the open market. In determining the source of shares to close out the short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through its option to purchase additional shares. A naked short position is more likely to be created if the underwriters are concerned that there could be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchase in the offering.

- Syndicate covering transactions involve purchases of the common stock in the open market after the distribution has been completed in order to cover syndicate short positions.
- Penalty bids permit the underwriters to reclaim a selling concession from a syndicate member when the common stock originally sold by the syndicate member is purchased in a stabilizing or syndicate covering transaction to cover syndicate short positions.

These stabilizing transactions, syndicate covering transactions and penalty bids may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price

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of the common stock. As a result, the price of the common stock may be higher than the price that might otherwise exist in the open market. These transactions may be effected on the NASDAQ Capital Market or otherwise and, if commenced, may be discontinued at any time.

Neither we nor the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor the underwriters make any representation that the underwriters will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Electronic Distribution

A prospectus in electronic format may be made available on the websites maintained by the underwriters or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares of common stock to itself and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the underwriters and selling group members that may make Internet distributions on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters' websites and any information contained in any other website maintained by the underwriters are not part of this prospectus or the registration statement of which this prospectus forms a part.

Right of First Refusal

If within the ninety-day period following the earlier of the consummation of the offering or the termination of the engagement letter between us and the Representative, the Company will require additional financing or other capital raising transaction (Subsequent Transactions) involving a placement agent or financial advisor, the Representative will have the right to act as our financial advisor and investment banker on such Subsequent Transactions (the Right of First Refusal) as the book runner, lead manager, or lead placement agent. The Representative may exercise the Right of First Refusal within thirty days of the receipt of notice by us (as well as any reasonable requested due diligence of its decision to pursue a Subsequent Transaction). If the Representative determines to exercise its Right of First Refusal, we agree to retain it under separate cover to advise us in respect to such Subsequent Transaction, subject to the execution of a mutually acceptable separate agreement which shall include terms customary for the type of Subsequent Transaction being sought and compensation to be decided by us and the Representative at the time of the Subsequent Transaction.

Other Relationships

From time to time, the underwriters and their affiliates have provided, and may provide in the future, various advisory, investment and commercial banking and other services to us in the ordinary course of business, for which they have received and may continue to receive customary fees and commissions. However, except as disclosed in this prospectus, we have no present arrangements with the underwriters for any further services.

Offer Restrictions Outside the United States

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

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European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive, or the Relevant Member States, with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, or the Relevant Implementation Date, our securities will not be offered to the public in that Relevant Member State prior to the publication of a prospectus in relation to the securities that has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the competent authority in that Relevant Member State, all in accordance with the Prospectus Directive, except that, with effect from and including the Relevant Implementation Date, an offer of securities may be made to the public in that Relevant Member State at any time:

- to any legal entity that is a qualified investor as defined in the Prospectus Directive;
- to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the manager for any such offer; or
- in any other circumstances which do not require the publication by the issuer of a prospectus pursuant to Article 3(2) of the Prospectus Directive.

For the purposes of this provision, the expression an offer of common shares to the public in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the common shares to be offered so as to enable an investor to decide to purchase or subscribe the common shares, as the same may be varied in that Relevant Member State by any measure implementing the Prospectus Directive in that Relevant Member State. The expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in each Relevant Member State and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

We have not authorized, and do not authorize the making of, any offer of shares through any financial intermediary on our behalf, other than offers made by the underwriters with a view to the final placement of the shares as contemplated by this prospectus. Accordingly, no purchaser of the securities, other than the underwriters, is authorized to make any further offer of the shares on our or the underwriters' behalf.

United Kingdom

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Our securities may not be offered or sold and will not be offered or sold to any persons in the United Kingdom other than persons whose ordinary activities involve acquiring, holding, managing or disposing of investments (as principal or as agent) for the purposes of their businesses and in compliance with all applicable provisions of the Financial Services and Markets Act 2000, or FSMA, with respect to anything done in relation to our securities in, from or otherwise involving the United Kingdom.

In addition, each underwriter:

- has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of section 21 of FSMA) to persons who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act of 2000 (Financial Promotion) Order 2005 or in circumstances in which section 21 of FSMA does not apply to us; and
- has complied with, and will comply with all applicable provisions of FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

Australia

No prospectus or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia, or the Corporations Act) in relation to the securities has been or will be lodged with the Australian Securities &

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Investments Commission, or the ASIC. This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

- (1) you confirm and warrant that you are either:
 - (a) a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;
 - (b) a sophisticated investor under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;
 - (c) a person associated with us under section 708(12) of the Corporations Act; or
 - (d) a professional investor within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act, any offer made to you under this document is void and incapable of acceptance; and
- (2) you warrant and agree that you will not offer any of the securities for resale in Australia within 12 months of those securities being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Hong Kong

The securities may not be offered or sold in Hong Kong by means of any document other than (1) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), (2) to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (3) in other circumstances which do not result in the document being a prospectus within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Japan

The securities offered in this prospectus have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The securities have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (i) pursuant to an exemption from the registration requirements of the Financial Instruments and Exchange Law and (ii) in compliance with any other applicable requirements of Japanese law.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the securities may not be circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (1) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (2) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA, or (3) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

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Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

- a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than \$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions specified in Section 275 of the SFA;

- where no consideration is or will be given for the transfer; or

- where the transfer is by operation of law.

Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or the SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the securities or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

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Neither this document nor any other offering or marketing material relating to the offering, us, or the securities have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of the shares.

Canada

Resale Restrictions

The distribution of our securities in Canada is being made only in the provinces of Ontario, Quebec, Alberta, British Columbia and Manitoba on a private placement basis exempt from the requirement that we prepare and file a prospectus with the securities regulatory authorities in each province where trades of common stock are made. Any resale of the common stock in Canada must be made under applicable securities laws which may vary depending on the relevant jurisdiction, and which may require resales to be made under available statutory exemptions or under a discretionary exemption granted by the applicable Canadian securities regulatory authority. Purchasers are advised to seek legal advice prior to any resale of the common stock.

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Representations of Purchasers

By purchasing securities in Canada and accepting delivery of a purchase confirmation, a purchaser is representing to us and the dealer from whom the purchase confirmation is received that:

the purchaser is entitled under applicable provincial securities laws to purchase the securities without the benefit of a prospectus qualified under those securities laws as it is an accredited investor as defined under National Instrument 45-106 Prospectus and Registration Exemptions;

- the purchaser is a Canadian permitted client as defined in National Instrument 31-103 Registration Requirements and Exemptions, or as otherwise interpreted and applied by the Canadian Securities Administrators;
- where required by law, the purchaser is purchasing as principal and not as agent;
- the purchaser has reviewed the text above under Resale Restrictions ; and
- the purchaser acknowledges and consents to the provision of specified information concerning the purchase of the securities to the regulatory authority that by law is entitled to collect the information, including certain personal information. For purchasers in Ontario, questions about such indirect collection of personal information should be directed to Administrative Support Clerk, Ontario Securities Commission, Suite 1903, Box 55, 20 Queen Street West, Toronto, Ontario M5H 3S8 or on (416) 593-3684.

Rights of Action Ontario Purchasers

Under Ontario securities legislation, certain purchasers who purchase any securities offered by this prospectus during the period of distribution will have a statutory right of action for damages, or while still the owner of the securities, for rescission against us in the event that this prospectus contain a misrepresentation without regard to whether the purchaser relied on the misrepresentation. The right of action for damages is exercisable not later than the earlier of 180 days from the date the purchaser first had knowledge of the facts giving rise to the cause of action and three years from the date on which payment is made for the securities. The right of action for rescission is exercisable not later than 180 days from the date on which payment is made for the securities. If a purchaser elects to exercise the right of action for rescission, the purchaser will have no right of action for damages against us. In no case will the amount recoverable in any action exceed the price at which the securities were offered to the purchaser and if the purchaser is shown to have purchased the securities with knowledge of the misrepresentation, we will have no liability. In the case of an action for damages, we will not be liable for all or any portion of the damages that are proven to not represent the depreciation in value of the common stock as a result of the misrepresentation relied upon. These rights are in addition to, and without derogation from, any other rights or remedies available at law to an Ontario purchaser. The foregoing is a summary of the rights available to an Ontario purchaser. Ontario purchasers should refer to the complete text of the relevant statutory provisions.

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EXPERTS

The consolidated financial statements of Onconova Therapeutics, Inc. at December 31, 2016 and December 31, 2015, and for the years then ended, included in our Annual Report on Form 10-K for the year ended December 31, 2016 and incorporated by reference herein have been audited by Ernst & Young LLP, independent registered public accounting firm, 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 Morgan, Lewis & Bockius LLP, Philadelphia, Pennsylvania. The underwriters are being represented in connection with this offering by Sichenzia Ross Ference Kesner LLP, New York, New York.

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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 November 20, 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.

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

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;

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- 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

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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 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, or 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 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.

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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 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 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

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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.

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

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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.

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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;
- 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;

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- 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

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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 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;

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- 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 66 $\frac{2}{3}$ % 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
- 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 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;

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- 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

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of up to \$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;

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- 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 depositories, 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.

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.

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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
- 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.

Table of Contents**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 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

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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.

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.

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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;

- 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 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.

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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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Shares of Common Stock

PROSPECTUS SUPPLEMENT

April , 2017

Laidlaw & Company (UK) Ltd.
