Onconova Therapeutics, Inc.
Form 424B5
January 06, 2016
Table of Contents

Filed Pursuant to Rule 424(b)(5)

Registration No. 333-199219

PROSPECTUS SUPPLEMENT

(To the Prospectus Dated November 20, 2014)

1,936,842 Shares of Common Stock

ONCONOVA THERAPEUTICS, INC.

We are offering 1,936,842 shares of our common stock, $0.01 par value per share, to an institutional investor pursuant to this prospectus supplement and the accompanying prospectus and a securities purchase agreement with such investor. In a concurrent private placement, we are selling to such investor warrants to purchase one-half of the number of shares of our common stock purchased by such investor in this offering (the Warrants). The Warrants and the shares of our common stock issuable upon the exercise of the Warrants are not being registered under the Securities Act of 1933, as amended, (the Securities Act), are not being offered pursuant to this prospectus supplement and the accompanying prospectus and are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act and Rule 506(b) promulgated thereunder.

Our common stock is listed on the Nasdaq Global Select Market under the symbol ONTX . The Warrants being issued in the concurrent private placement are not listed on any securities exchange and we do not expect to list the Warrants. On January 5, 2016, the last reported sale price of our common stock on the Nasdaq Global Select Market was $0.95 per share. As of December 21, 2015, the aggregate market value of our outstanding common stock held by non-affiliates (the public float) was approximately $24.1 million, which was calculated based on 16,417,889 shares of outstanding common stock held by non-affiliates and on a price per share of $1.47, the closing price of our common stock on November 24, 2015. 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-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 $8.0 million

pursuant to General Instruction I.B.6 of Form S-3.

Investing in our securities involves a high degree of risk. See Risk Factors beginning on page S-9 to read about factors you should consider before investing in the securities.

We retained H.C. Wainwright & Co. as our exclusive placement agent to use their reasonable best efforts to solicit offers to purchase the securities in this offering. The placement agent has no obligation to buy any of the securities from us or to arrange for the purchase or sale of any specific number or dollar amount of the securities. We expect that delivery of the securities being offered pursuant to this prospectus supplement and the accompanying prospectus will be made on or about January 11, 2016.

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

Common Stock	Per Share	Maximum Offering
Public offering price	$ 0.95	$ 1,840,000
Placement agents fees(1)	$ 0.07125	$ 138,000
Proceeds to us, before expenses	$ 0.87875	$ 1,702,000

(1) We have also agreed to pay the placement agent a non-accountable expense reimbursement for all expenses incurred by them in connection with the offering, including the fees and disbursement of counsel, in the amount of $50,000. For additional information about the compensation paid to the placement agent, see Plan of Distribution.

Placement Agent

H.C. Wainwright & Co.

The date of this prospectus supplement is January 5, 2016.

Table of Contents

TABLE OF CONTENTS

Prospectus Supplement

Prospectus

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. Under this shelf registration process, we may sell, either separately or together, common stock, preferred stock, and warrants from time to time in one or more offerings up to an aggregate initial offering price of $100,000,000.

The accompanying prospectus provides you with a general description of the securities we may offer. In this prospectus supplement, we provide you with specific information about this offering of our common stock. Both this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, include important information about us, our common stock and other information you should know before investing. Any statement contained in this prospectus supplement, the accompanying prospectus or in a document incorporated by reference shall be deemed to be modified or superseded to the extent that a statement contained herein or in any subsequently filed document which is incorporated by reference modifies or supersedes such earlier statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement or the accompanying prospectus. You should read this prospectus supplement and the accompanying prospectus as well as the documents incorporated herein and therein before investing in our securities.

You should rely only on the information incorporated by reference or presented in this prospectus supplement and the accompanying prospectus. Neither we nor the placement agent has authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement, the accompanying prospectus or in any document incorporated herein or therein by reference is accurate as of any date other than the dates on the front of those documents, regardless of the time of delivery of this prospectus supplement or any sale of our securities.

In this prospectus supplement, unless the context indicates otherwise, as used in this prospectus, the terms Onconova, Onconova Therapeutics, Company, we, us and our refer to Onconova Therapeutics, Inc. and its consolidated subsidiaries. Our fiscal year ends on the last day of December.

Table of Contents

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements. We may, in some cases, use terms such as believes, estimates, anticipates, expects, plans, intends, may, might, will, should, approximately or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. These statements 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 herein, 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 report. 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 herein, they may not be predictive of results or developments in future periods.

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

- our need for additional financing and our ability to obtain sufficient funds on acceptable terms when needed, and our current plans and future needs to scale back operations if adequate financing is not obtained;

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

- the success and timing of our preclinical studies and clinical trials and regulatory approval of protocols for future 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, manufacture 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 regulation regarding the healthcare system;

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

Table of Contents

- our dependence on collaboration agreements with other pharmaceutical companies, such as Baxalta GmbH, or Baxalta, 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, or CROs and third-party manufacturers.

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

You should also read carefully the factors described in the Risk Factors section of this prospectus supplement and set forth in our most recent Annual Report on Form 10-K, as revised or supplemented by our Quarterly Reports on Form 10-Q filed with the SEC since the filing of our most recent Annual Report on Form 10-Kto 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 supplement.

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and information appearing elsewhere in this prospectus supplement, in the accompanying prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all of the information that you should consider before investing in our securities. To fully understand this offering and its consequences to you, you should read this entire prospectus supplement and the accompanying prospectus carefully, including the information referred to under the heading Risk Factors in this prospectus supplement beginning on page S-12, the financial statements and other information incorporated by reference in this prospectus supplement and the accompanying prospectus when making an investment decision. This is only a summary and may not contain all the information that is important to you. You should carefully read both this prospectus and any accompanying prospectus supplement and any other offering materials, together with the additional information described under the heading Where You Can Find More Information.

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 cellular pathways important to cancer cells. We believe that the drug candidates in our pipeline have the potential to be efficacious in a variety of cancers. We have three clinical-stage product candidates (one of which is being developed for treatment of acute radiation syndromes) and several preclinical programs, and the majority of our current effort is focused on our lead product candidate, rigosertib. Rigosertib is being tested in both intravenous and oral formulations as a single agent, and the oral formulation is also being tested in combination with azacitidine, in clinical trials for patients with myelodysplastic syndromes, or MDS, and related cancers.

After discussions with the U.S. Food and Drug Administration, or FDA, and European Medicines Agency, or EMA, we designed a randomized controlled Phase 3 trial of rigosertib IV in a population of patients with higher-risk MDS after failure of hypomethylating agent therapy. The pivotal trial, which we refer to as INSPIRE is open and enrolling higher-risk MDS, or HR-MDS, patients under 80 years of age who have progressed on, or failed to respond to, previous treatment with hypomethylating agents, or HMAs, within the first nine months of initiation of HMA treatment, and had their last dose of HMA therapy within six months prior to enrollment in the study. The primary endpoint of INSPIRE is overall survival, and an interim analysis is anticipated. This randomized trial of approximately 225 patients is expected to be conducted at about 100 sites globally. In August 2015, we submitted an updated investigational new drug application, or IND, to the FDA, and in September 2015 we submitted Clinical Trial Applications, or CTAs, to the United Kingdom, German and Austrian regulatory authorities for IV rigosertib as a treatment for HR-MDS after failure of HMA therapy. The first CTA has been cleared by the Medicines and Healthcare Products Regulatory Agency in the U.K. Our collaboration partner in Japan, SymBio Pharmaceuticals, Ltd., or SymBio, plans to enroll patients in Japan under the protocol. The first patient in the INSPIRE trial was enrolled at the MD Anderson Cancer Center in December 2015.

We have completed enrollment in the Phase 2 portion of a clinical trial of rigosertib oral in combination with azacitidine for patients with HR-MDS and acute myelogenous leukemia, or AML. Interim data from the ongoing Phase 2 clinical trial were presented in December 2015 at the American Society of Hematology (ASH) Annual Meeting.

We are assessing the utility of bone marrow genomic methylation patterns for selection of patients more likely to respond to treatment with rigosertib oral as a single agent in patients with lower-risk MDS, or LR-MDS.

At September 30, 2015, we had approximately $22.2 million in cash and cash equivalents. During 2015, we have taken significant actions to conserve cash, including personnel and expenditure reductions. While we will continue to take cash conservation actions where appropriate, our costs will increase in subsequent quarters as a result of initiation of the INSPIRE trial. We believe that our current cash balance, together with the proceeds of this offering and contractual cost-sharing payments from Baxalta for a portion of the costs of the INSPIRE trial, will be sufficient to fund our ongoing trials and current operations through the third quarter of 2016.

We are exploring various sources of funding for continued development of rigosertib in MDS and AML. If we are unable to successfully raise sufficient additional capital, through future financings or through strategic and collaborative ventures with third parties, we will not have sufficient cash to fund our planned business operations. In that event, we may be forced to limit many, if not all, of our programs and consider other means of creating value for our stockholders or we may be forced to curtail all of our activities and, ultimately, potentially cease operations. Additional financings may only be available on unattractive terms, and could result in significant dilution of stockholders interests.

Table of Contents

Rigosertib IV

Rigosertib is a small molecule that inhibits cellular signaling in cancer cells by acting as a Ras mimetic. This is believed to be mediated by the binding of rigosertib to the Ras-binding domain, or RBD, found in many Ras effector proteins, including the Raf and PI3K kinases. This mechanism of action provides a new approach to block the interactions between Ras and its targets containing RBD sites. Rigosertib is being tested as a single agent and in combination with azacitidine, in clinical trials of patients with MDS and related cancers. We have enrolled more than 1,100 patients in rigosertib clinical trials. We are a party to collaboration agreements with Baxalta GmbH, or Baxalta (successor in interest of Baxter Healthcare SA), which grant Baxalta certain rights to commercialize rigosertib in Europe, and with SymBio Pharmaceuticals Limited, or SymBio, which grant 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.

Rigosertib IV for higher-risk MDS

In early 2014, we announced topline survival results from our multi-center Phase 3 clinical trial of rigosertib IV as a single agent (the ONTIME trial). The ONTIME trial did not meet its primary endpoint in the intent-to-treat population, although improvements in median overall survival were observed in various pre-specified and exploratory subgroups of HR-MDS patients.

During 2014 and 2015, we held meetings with the FDA, 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 hypomethylating agent, or HMA, therapy. After discussions with the FDA and EMA, we have refined the patient eligibility criteria in the new trial by defining 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, with overall survival as a primary endpoint. The INSPIRE trial is open and enrolling higher-risk MDS, or HR-MDS, patients under 80 years of age who have progressed on, or failed to respond to, previous treatment with hypomethylating agents, or HMAs, within the first nine months of initiation of HMA treatment, and had their last dose of HMA therapy within six months prior to enrollment in the trial. The primary endpoint of this study is overall survival, and an interim analysis is anticipated. This randomized trial of approximately 225 patients is expected to be conducted at about 100 sites globally. In August 2015, we submitted an updated investigational new drug application, or IND, to the FDA, and in August 2015 we submitted Clinical Trial Applications, or CTAs, with the United Kingdom, German and Austrian regulatory authorities for IV rigosertib as a treatment for HR-MDS after failure of HMA therapy. The first CTA has been cleared by the Medicines and Healthcare Products Regulatory Agency in the U.K. Our collaboration partner in Japan, SymBio, plans to enroll patients in Japan under the INSPIRE protocol. The first patient in the INSPIRE trial was enrolled at the MD Anderson Cancer Center in December 2015.

Baxalta is providing a financial contribution of 50 percent of the clinical trial costs for the INSPIRE trial, with a cap of $15 million, pursuant to our collaboration agreement. For the second and third quarters of 2015, we recognized $1.5 million in revenue as a result of billing Baxalta under this arrangement. SymBio has confirmed its interest in enrolling patients in the INSPIRE trial at its expense.

Rigosertib Oral

Rigosertib Oral in combination with azacitidine in MDS and AML

We have completed enrollment in the Phase 2 portion of an open label Phase 1/2 clinical trial testing rigosertib oral in combination with the approved dose of injectable azacitidine for patients with HR-MDS and AML. This study is based on our published preclinical data demonstrating synergistic activity of this combination. We presented Phase 1 results from this trial at the ASH Annual Meeting in December 2014 and at the MDS Symposium in April 2015. These results showed encouraging activity in MDS and AML patients in terms of bone marrow and hematological responses. Patients in the Phase 1 portion were treated at the full standard dose of azacitidine, and the drug combination was well tolerated in repetitive cycles.

The Phase 2 portion of the trial was designed to assess whether treatment with rigosertib, in combination with the approved dose of injectable azacitidine, reduces the number of bone marrow blasts, improves peripheral blood counts and delays signs of disease progression in patients with MDS. Patient enrollment in the Phase 2 portion of this trial was completed in the fourth quarter of 2015 and interim data were summarized by way of an oral presentation at the ASH Annual Meeting in December 2015.

Table of Contents

The Phase 2 combination study included both de novo MDS patients (that is, patients not previously treated with hypomethylating agents, HMAs) and MDS patients whose disease had failed prior HMA treatment. The oral presentation at ASH presented results from a total of 37 MDS patients treated with the recommended Phase 2 dose of oral rigosertib (560 mg AM/280 mg PM) plus the full standard dose of injectable azacitidine. The combination of oral rigosertib and azacitidine was well tolerated, with a median duration of treatment of four months (range 1 to 27 months). Adverse events of Grade ≥3 experienced across all cycles with the combination included thrombocytopenia (27%), neutropenia (22%), hypokalaemia (5%), hematuria (5%) and diarrhoea (3%).

Thirty MDS patients were evaluable for efficacy assessment per 2006 International Working Group, or IWG, criteria. Twenty-three of 30 patients (77%) responded to the combination therapy, including six patients who had complete remissions. Hematologic improvement was observed in 13 of 26 patients that were evaluable for this part of the analysis. Notably, 16 of 19 (84%) HMA-naïve patients had a response to the combination therapy and 7 of 11 (64%) patients whose disease had previously failed HMAs responded. As of December 2015, the median duration of these responses had not yet been reached. Additional data collection continues for the patients remaining on study and may impact the final results of the trial.

Rigosertib Oral for LR-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 LR-MDS patients suffer mainly from cytopenias, that is low levels of red blood cells, white blood cells or platelets. Thus, LR-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 LR-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 have shown encouraging signs of efficacy of single agent oral rigosertib in transfusion-dependent, LR-MDS patients. Rigosertib has been generally well tolerated, except for urinary side effects previously reported at higher dose levels. Future clinical studies will be needed to evaluate dosing and schedule modifications and their impact on efficacy and toxicity of oral rigosertib in LR-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 LR-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. Enrollment in this expansion cohort has been completed. We are collaborating with a methylation genomics company and an academic collaborator to refine this genomic methylation test.

Briciclib

Our second clinical-stage product candidate is briciclib, a small molecule targeting an important intracellular regulatory protein, cyclin D1, which is often found at elevated levels in cancer cells. Cyclin D1 expression is regulated through a process termed cap-dependent translation, which requires the function of eukaryotic initiation factor 4E protein, or eIF4E. In vitro evidence indicates briciclib binds to eIF4E, 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 multisite 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. On December 3, 2015 we received notification from the FDA that a full clinical hold has been placed on the briciclib IND following a drug product lot testing failure due to visible particulates. We will be required to undertake appropriate remedial actions prior to re-initiating the clinical trial and completing the final dose-escalation cohort.

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 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

Table of Contents

funding. We anticipate that any future development of recilisib beyond these ongoing studies would be conducted solely with government funding or by collaboration.

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. Our most advanced preclinical stage compound is ON 123300, a targeted inhibitor of CDK4/6 and ARK5 kinases.

Table of Contents

THE OFFERING

Common Stock	
Common Stock offered by us	1,936,842 shares of common stock
Public offering price	$0.95 per share
Common stock to be outstanding immediately after the offering (1)	27,401,035 shares
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 our working capital needs. See Use of Proceeds.
Market and Trading Symbol	Our common stock is listed on the Nasdaq Global Select Market under the symbol ONTX.
Risk factors	Investing in our securities involves a high degree of risk. See Risk Factors beginning on page S-9 of this prospectus supplement and page 4 of the accompanying prospectus.
Concurrent Offering	In a concurrent private placement, we are selling to the purchaser of shares of our common stock in this offering warrants to purchase one-half the number of shares of our common stock purchased by such investor in this offering, or up to 968,421 warrants. We will receive gross proceeds from the concurrent private placement transaction solely to the extent such warrants are exercised for cash. The warrants will be exercisable on the six month anniversary of the issuance date at an exercise price of $1.15 per share and will expire five years from the date on which first exercisable. The warrants and the shares of our common stock issuable upon the exercise of the warrants are not being offered pursuant to this prospectus supplement and the accompanying prospectus and are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act and Rule 506(b) promulgated thereunder. See Private Placement of Warrants.

(1) The number of shares of common stock to be outstanding immediately after this offering as shown above is based on 25,464,193 shares of common stock outstanding as of January 5, 2016, and does not include as of that date:

- 5,157,602 shares of common stock issuable upon the exercise of stock options outstanding under our 2013 Equity Compensation Plan at a weighted average exercise price of $8.54 per share;

- 1,354,133 additional shares of common stock reserved for future issuance under our 2013 Equity Compensation Plan; and

- 968,421 shares of common stock issuable upon exercise of warrants to be issued in a private placement, as described below under Private Placement of Warrants.

Table of Contents

RISK FACTORS

An investment in our securities involves a high degree of risk and uncertainty. Before making an investment decision, you should carefully consider the risks described below, together with all of the other information included in this prospectus supplement, accompanying prospectus, and the documents incorporated by reference. If any of the following risks actually occurs, our business, financial condition or results of operations could suffer. In that case, the trading price of our shares of common stock could decline, and you may lose all or part of your investment. You should read the section entitled Cautionary Note Regarding Forward-Looking Statements for a discussion of what types of statements are forward-looking statements, as well as the significance of such statements in the context of this prospectus supplement.

We may require additional financing to sustain our operations and without it we may not be able to continue operations.

At September 30, 2015 we had an accumulated deficit of $321.7 million. Since our inception, we have incurred net losses and generally negative cash flows from our operations. We incurred net losses of $63.8 million, $62.6 million, and $29.9 million for the years ended December 31, 2014, 2013 and 2012, respectively. We do not currently have sufficient financial resources to fund our operations or those of our subsidiaries. Therefore, we need additional funds to continue these operations.

The net proceeds to us of this offering will be approximately $1,702,000 before expenses. We will still need additional capital to fully implement our business, operating and development plans. Should the financing we require to sustain our working capital needs be unavailable or prohibitively expensive when we require it, the consequences could be a material adverse effect on our business, operating results, financial condition and prospects.

We will require additional funds to complete the INSPIRE trial.

In December 2015, we commenced enrollment in our INSPIRE trial. The trial is designed to enroll approximately 225 patients and the earliest we anticipate reporting topline data is the second half of 2018. In accordance with our agreement with Baxlata, we have elected to have Baxalta fund fifty percent of the costs of the INSPIRE trial, up to $15.0 million. We estimate that our cash and cash equivalents at September 30, 2015 of $22.2 million, together with the proceeds of this offering and cost-sharing payments from Baxalta, will be sufficient to fund operations through the third quarter of 2016. If we are not successful in raising substantial additional funds or if Baxter terminates our agreement, our ability to complete the INSPIRE trial, our financial condition and results of operations would be adversely effected.

Raising additional funds may require us to relinquish rights to our technologies or product candidates.

If we raise additional funds through strategic collaborations and alliances or licensing arrangements with third parties, which may including existing collaboration partners, we may have to relinquish valuable rights to our technologies or product candidates, including rigosertib, or grant licenses on terms that are not favorable to us. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant rights to develop and market product candidates or formulations that we would otherwise prefer to develop and market ourselves.

We are in regular communication with Baxalta and SymBio regarding the development of rigosertib and, as we have neared completion of our combination trial and commenced enrollment in the INSPIRE trial, we have had informal discussions with Baxalta about potential modifications of our collaboration. Because these discussions have been informal and preliminary, we cannot say whether any modifications will be made or, if made, what their nature would be. Potential modifications could be made to any of the rights and obligations of the parties, including with respect to licensed indications or territories, and could include certain or all rights reverting to us.

If we are unable to regain compliance with the requirements to maintain a continued listing on the NASDAQ Global Select Market, our common stock may be delisted and the price of our common stock and our ability to access the capital markets could be negatively impacted.

Our common stock is currently listed for trading on the NASDAQ Global Select Market. We must satisfy NASDAQ s continued listing requirements or risk delisting, which would have a material adverse effect on our business. On September 29, 2015, we received written notice from NASDAQ notifying us that for the preceding 30 consecutive business days, our Market Value of Listed Securities, or MLVS, had closed below the minimum $50 million requirement for continued listing on the NASDAQ Global Select Market and granting us a 180-day grace period to regain compliance. Compliance can be achieved automatically and without further action if our MVLS closes at $50 million or more for at least

Table of Contents

10 consecutive business days at any time during the 180-day compliance period. If we do not regain compliance by March 28, 2016, NASDAQ will notify us that our common stock will be subject to delisting. We are currently considering available options to resolve the listing deficiency and to regain compliance. The issuance of shares of our common stock pursuant to this offering will not be sufficient to resolve the listing deficiency. There can be no assurance that we will be able to regain compliance with the NASDAQ Global Select Market listing requirements, and, if we do regain compliance, there can be no assurance that we will remain in compliance with NASDAQ Global Select Market listing requirements. A delisting of our common stock from the NASDAQ Global Market could materially reduce the liquidity of our common stock, including the shares of common stock purchased in this offering, and result in a corresponding material reduction in the price of our common stock. In addition, delisting could harm our ability to raise capital through alternative financing sources on terms acceptable to us, or at all, and may result in the potential loss of confidence by investors, suppliers, customers and employees and fewer business development opportunities.

Since we have broad discretion in how we use the proceeds from this offering, we may use the proceeds in ways with which you disagree.

We have not allocated specific amounts of the net proceeds from this offering for any specific purpose. Accordingly, our management will have significant flexibility in applying the net proceeds of this offering. You will be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used in ways with which you would agree. It is possible that the net proceeds will be invested in a way that does not yield a favorable, or any, return for us. The failure of our management to use such funds effectively could have a material adverse effect on our business, financial condition, operating results and cash flow.

The investor in this offering will pay a substantially higher price than the book value of the shares of our common stock.

If you purchase shares of our common stock in this offering, you will incur an immediate and substantial dilution in net tangible book value. Our net tangible book value was $0.177 per share as of September 30, 2015. Upon the sale by us of all 1,936,842 shares of common stock offered hereby at a price of $0.95 per share, and after deducting the placement agent fees and expenses payable by us, our adjusted net tangible book value as of September 30, 2015 would have been approximately $0.226 per share of common stock.

A substantial number of shares of our common stock may be sold in this offering, which could cause the price of our common stock to decline.

In this offering we will sell 1,936,842 shares of common stock, which represent approximately 7.1% of our outstanding common stock as of January 5, 2016 after giving effect to the sale of the shares of common stock. In addition, the investor in this offering will receive an unregistered warrant to purchase one-half of the number of shares such investor purchased in this offering. This sale and any future sales of a substantial number of shares of our common stock in the public market, or the perception that such sales may occur, could adversely affect the price of our common stock on the NASDAQ Global Select Market. We cannot predict the effect, if any, that market sales of those shares of common stock or the availability of those shares of common stock for sale will have on the market price of our common stock.

Table of Contents

MARKET PRICE OF COMMON STOCK

Our common stock began trading on the NASDAQ Global Select Market on July 25, 2013 under the symbol ONTX. Prior to that time, there was no public market for our common stock. Shares sold in our initial public offering on July 24, 2013 were priced at $15.00 per share. The following table sets forth for the periods indicated the high and low intra-day sale prices per share of our common stock as reported on the NASDAQ Global Market:

	Price of Common Stock	
	Low ($)	High ($)
2016		
First Quarter (through January 5, 2016)	$ 0.91	$ 1.03
2015		
Fourth Quarter	$ 0.92	$ 1.89
Third Quarter	$ 1.35	$ 2.85
Second Quarter	$ 2.26	$ 2.84
First Quarter	$ 2.07	$ 4.37
2014		
Fourth Quarter	$ 4.20	$ 4.38
Third Quarter	$ 4.24	$ 5.78
Second Quarter	$ 4.10	$ 6.49
First Quarter	$ 6.05	$ 16.22

On January 5, 2016, the last reported sale price of our common stock on the NASDAQ Global Select Market was $0.95 per share. As of January 5, 2016, we had 169 holders of record of our common stock. The actual number of holders of common stock is greater than these numbers of record holders and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and nominees. The number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering, after deducting placement agent fees but before paying offering expenses, will be approximately $1,702,000 assuming all offered shares are sold.

We intend to use the net proceeds from this offering primarily to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding 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.

Our management will have broad discretion in the application of the net proceeds from this offering, and investors will be relying on the judgment of our management with regard to the use of these net proceeds. Pending the use of the net proceeds from this offering as described above, we intend to invest the net proceeds in short-term, investment-grade, interest-bearing instruments.

Table of Contents

PRIVATE PLACEMENT OF WARRANTS

Concurrently with the closing of the sale of shares of common stock in this offering, we also expect to issue and sell to the investor warrants to purchase an aggregate of 968,421 shares of our common stock, at an initial exercise price equal to $1.15 per share (the Warrants).

Each Warrant shall be exercisable on the six month anniversary of the issuance date and have a term of exercise equal to five (5) years from the date on which first exercisable. Subject to limited exceptions, a holder of Warrants will not have the right to exercise any portion of its warrants if the holder, together with its affiliates, would beneficially own in excess of 9.99% of the number of shares of our common stock outstanding immediately after giving effect to such exercise.

Such securities will be issued and sold without registration under the Securities Act, or state securities laws, in reliance on the exemptions provided by Section 4(a)(2) of the Act and/or Regulation D promulgated thereunder and in reliance on similar exemptions under applicable state laws. Accordingly, the investor may exercise those warrants and sell the underlying shares only pursuant to an effective registration statement under the Securities Act covering the resale of those shares, an exemption under Rule 144 under the Securities Act, or another applicable exemption under the Securities Act.

Table of Contents

DILUTION AND COMPARATIVE SHARE DATA

The net tangible book value of our common stock on September 30, 2015 was approximately $4,198,000 or approximately $0.177 per share, based on 23,683,976 shares of our common stock outstanding as of September 30, 2015. Net tangible book value per share represents the amount of our total tangible assets, less our total liabilities, divided by the total number of shares of our common stock outstanding. Dilution in net tangible book value per share to the new investor represents the difference between the amount per share paid by purchasers of shares of our common stock in this offering and the net tangible book value per share of our common stock immediately afterwards.

The investor participating in this offering will incur immediate and significant dilution. After giving effect to the issuance and sale of shares of our common stock in this offering at a public offering price of $0.95 per share of our common stock, after deducting the placement agent fees and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2015 would have been approximately $5,800,000, or approximately $0.226 per share of our common stock.

This represents an immediate increase in net tangible book value of $0.049 per share to existing stockholders and immediate dilution in net tangible book value of $0.724 per share to the new investor purchasing our common stock in this offering at the public offering price.

The following table illustrates this per share dilution:

Public offering price per share of common stock	$	0.950
Net tangible book value per share as of September 30, 2015	$	0.177
Increase in net tangible book value per share attributable to this offering	$	0.049
Pro forma net tangible book value per share as of September 30, 2015 after giving effect to this offering	$	0.226
Dilution per share to the new investor in this offering	$	0.724

The table above excludes the following:

- 5,157,602 shares of common stock issuable upon the exercise of stock options outstanding under our 2013 Equity Compensation Plan at a weighted average exercise price of $8.54 per share;

- 1,354,133 additional shares of common stock reserved for future issuance under our 2013 Equity Compensation Plan; and

- 968,421 shares of common stock issuable upon exercise of warrants to be issued in a private placement, as described below under Private Placement of Warrants.

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

Table of Contents

PLAN OF DISTRIBUTION

We engaged H.C. Wainwright & Co., LLC, or H.C. Wainwright or the Placement Agent, to act as our exclusive placement agent to solicit offers to purchase the securities offered by this prospectus supplement from institutional investors. H.C. Wainwright is not purchasing or selling any shares, nor are they required to arrange for the purchase and sale of any specific number or dollar amount of shares, other than to use their reasonable best efforts to arrange for the sale of shares by us. Therefore, we may not sell the entire amount of shares being offered. We will enter into a securities purchase agreement directly with accredited institutional investors who purchase our common stock in this offering.

Upon the closing of this offering, we will pay the Placement Agent a cash transaction fee equal to 7.5% of the gross proceeds to us from the sale of the shares of our common stock in the offering. We will reimburse H.C. Wainwright for its expenses incurred in connection with this offering in an amount equal to $50,000.

The following table shows the per share and total placement agent fees we will pay in connection with the sale of the securities in this offering, assuming the purchase of all of the securities we are offering.

Per share placement agent cash fees	$	0.07125
Total	$	138,000.00

We estimate the total expenses of this offering, which will be payable by us, excluding the placement agent fees in the table above, will be approximately $100,000. After deducting the fees due to the placement agent and our estimated offering expenses, we expect the net proceeds from this offering to be approximately $1.60 million.

The Placement Agent may be deemed to be an underwriter within the meaning of Section 2(a)(11) of the Securities Act and any commissions received by it and any profit realized on the sale of the securities by it while acting as principal might be deemed to be underwriting discounts or commissions under the Securities Act. The placement agent will be required to comply with the requirements of the Securities Act and the Exchange Act of 1934, as amended, or the Exchange Act, including, without limitation, Rule 10b-5 and Regulation M under the Exchange Act. These rules and regulations may limit the timing of purchases and sales of our securities by the Placement Agent. Under these rules and regulations, the Placement Agent may not (i) engage in any stabilization activity in connection with our securities; and (ii) bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities, other than as permitted under the Exchange Act, until they have completed their participation in the distribution.

Indemnification

We have agreed to indemnify the placement agent against certain liabilities, including liabilities under the Securities Act of 1933, as amended, and liabilities arising from breaches of representations and warranties contained in the engagement letter. We have also agreed to contribute to payments the placement agent may be required to make in respect of such liabilities.

In addition, we will indemnify the purchaser against liabilities arising out of or relating to (a) any breach of any of the representations, warranties, covenants or agreements made by us in the stock purchase agreement or related documents or (b) any action instituted against a purchaser by a third party (other than a third party who is affiliated with such purchaser) with respect to the offering, subject to certain exceptions.

Trading Market

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

Table of Contents

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon for us by Pepper Hamilton, LLP of Princeton, New Jersey. The placement agent has been represented in connection with this offering by Ellenoff Grossman & Schole LLP.

EXPERTS

The consolidated financial statements of Onconova Therapeutics, Inc. appearing in Onconova Therapeutics, Inc. s Annual Report (Form 10-K) for the year ended December 31, 2014 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated in the prospectus by reference. Such financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the Securities and Exchange Commission, or SEC. You may read and copy any documents we file with the SEC at the SEC s Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. In addition, our filings with the SEC are available to the public through the SEC s Internet site at http://www.sec.gov. Information about us is also available on our website at http://www.onconova.com. This URL and the SEC s URL above are intended to be inactive textual references only. The information on the SEC s website and our website is not part of, and is not incorporated into, this prospectus.

We have filed a registration statement covering our shares of common stock subject to this offering, of which this prospectus forms a part. This prospectus, however, does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information concerning us and the securities we may offer and sell, you should read the entire registration statement and the exhibits to the registration statement. The registration statement has been filed electronically and may be obtained in any manner listed above. Any statements contained in this prospectus concerning the provisions of any document are not necessarily complete, and, in each instance, reference is made to the copy of such document filed as an exhibit to the registration statement or otherwise filed with the SEC. Each such statement is qualified in its entirety by such reference

Table of Contents

INFORMATION INCORPORATED BY REFERENCE

The SEC and applicable law permits us to incorporate by reference into this prospectus supplement information that we have filed or may in the future file with the SEC. This means that we can disclose important information by referring you to those documents. You should read carefully the information incorporated herein by reference because it is an important part of this prospectus supplement. We hereby incorporate by reference the following documents into this prospectus supplement (other than any portion of such filings that are furnished rather than filed pursuant to Items 2.02 and 7.01 of a Current Report on Form 8-K):

- Our Annual Report on Form 10-K for the fiscal year ended December 31, 2014, which we filed with the SEC on March 30, 2015, 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 2015 annual meeting of shareholders filed on April 29, 2015;

- Our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2015, June 30, 2015, and September 30, 2015, which we filed with the SEC on May 15, 2015, August 13, 2015 and November 12, 2015 respectively;

- Our Current Reports on Form 8-K filed with the SEC on June 17, 2015, July 8, 2105, October 5, 2015, October 8, 2015, December 4, 2015 and December 8, 2015 (except for Information furnished under Items 2.02 or 7.01 (or corresponding information furnished under Item 9.01 or included as an exhibit) which is not incorporated by reference into this prospectus); and

- 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.

Additionally, all documents filed by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than any portions of filings that are furnished rather than filed pursuant to Items 2.02 and 7.01 of a Current Report on Form 8-K), after the date of this prospectus supplement and before the termination or completion of this offering shall be deemed to be incorporated by reference into this prospectus supplement from the respective dates of filing of such documents. Any information that we subsequently file with the SEC that is incorporated by reference as described above will automatically update and supersede any previous information that is part of this prospectus supplement.

In accordance with Rule 402 of Regulation S-T, the XBRL related information in Exhibit 101 to our Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q will not be deemed to be incorporated by reference into any registration statement or other document filed under the Securities Act, except as will be expressly set forth by specific reference in such filing.

You may obtain any of the documents incorporated by reference through the SEC or the SEC s website as described above. You may request copies of the documents incorporated by reference in this prospectus, at no cost, by writing or telephoning us at Onconova Therapeutics, Inc., 375 Pheasant Run, Newtown, Pennsylvania, 18940, (267) 759-3036, Attention: Benjamin Hoffman.

Table of Contents

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.

Table of Contents

TABLE OF CONTENTS

Table of Contents

ABOUT THIS PROSPECTUS

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

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

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

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

WHERE YOU CAN FIND MORE INFORMATION

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

Unless the context indicates otherwise, as used in this prospectus, the terms Onconova, Onconova Therapeutics, Company, we, us and our 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;

Table of Contents

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

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

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

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

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

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

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

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

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

Table of Contents

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.

Table of Contents

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

Table of Contents

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 benefical effect on bone marrow and peripheral blood blast cell counts and symptoms of disease progression in patients with MDS and AML. We expect to present results of the Phase 1 portion of this combination trial in the fourth quarter of 2014.

Oral rigosertib in head and neck and other carcinomas

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

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

Briciclib

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

Recilisib

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

Table of Contents

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.

Table of Contents

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;

Table of Contents

- restrictive covenants;
- voting or other rights; and
- important federal income tax considerations.

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

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

DESCRIPTION OF CAPITAL STOCK

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

Common Stock

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

Preferred Stock

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

Table of Contents

- 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 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;

Table of Contents

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

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

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

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

Transfer Agent and Registrar

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

Listing

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

DESCRIPTION OF DEBT SECURITIES

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

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

of up to $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;

Table of Contents

- 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;

11

Table of Contents

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

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

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

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

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

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

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

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

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

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

Payment of Interest and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, as Depositary, or a nominee of the Depositary (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.

Table of Contents

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 depositary 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 depositary 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

Table of Contents

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 reallowed 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 reallowed or paid to dealers may be changed from time to time.

Table of Contents

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.

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.