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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-224315

PROSPECTUS SUPPLEMENT
(To Prospectus dated December 28, 2017)

2,198,938 Shares of Common Stock

ONCONOVA THERAPEUTICS, INC.

We are offering 2,198,938 shares of our common stock to institutional and accredited investors at a negotiated price of $1.60 per share.

Our common stock is listed on the Nasdaq Capital Market under the symbol "ONTX." On September 20, 2019, the closing price of our common stock on the Nasdaq Capital Market was $1.60 per share.

The aggregate market value of our outstanding common stock held by non-affiliates, or our public float, is approximately $15,329,730, based on 5,998,524 shares of common stock outstanding, of which 5,720,051 shares are held by non-affiliates, and a per share value of $2.68, based on the closing price of our common stock on the Nasdaq Capital Market on September 10, 2019. During the 12 calendar month period that ends on, and includes, the date of this prospectus supplement (excluding this offering), we have not offered and sold any shares of our common stock pursuant to General Instruction I.B.6. of Form S-3. Pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell securities registered on the registration statement, of which this prospectus supplement is a part, 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.

Investing in our shares involves a high degree of risk. Please read "Risk Factors" beginning on page S-6 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement.

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

	PER SHARE OF COMMON STOCK	TOTAL
Offering price	$ 1.60	$ 3,518,300.80
Proceeds to us before expenses(1)	$ 1.60	$ 3,518,300.80

(1) We have agreed to issue to the placement agent certain warrants to purchase our common stock and pay the placement agent for certain expenses as described in the "Plan of Distribution" section of this prospectus supplement.

We have engaged H.C. Wainwright & Co., LLC ("Wainwright" or the "Placement Agent") to act as our exclusive placement agent in connection with this offering. Wainwright is not purchasing or selling the shares offered by us, and is not required to sell any specific number or dollar amount of shares, but will use its reasonable best efforts to arrange for the sale of the shares offered. We have agreed to pay Wainwright $56,000 for non-accountable expenses, and $10,000 for clearing expenses. Because there is no minimum offering amount required as a condition to closing in this offering, the actual offering amount, the proceeds to us, if any, are not presently determinable and may be substantially less than the total maximum offering amounts set forth above. This offering is expected to close on or about September 25, 2019, subject to customary closing conditions, without further notice to you. We have not arranged to place the funds from investors in an escrow, trust or similar account.

H.C. Wainwright & Co.

Prospectus Supplement dated September 23, 2019

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PROSPECTUS SUPPLEMENT

PROSPECTUS

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is part of the registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process and consists of two parts. The first part is this prospectus supplement, including the documents incorporated by reference, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference, gives more general information, some of which may not apply to this offering. Generally, when we refer only to the "prospectus," we are referring to both parts of this document combined. This prospectus supplement may add to, update or change information in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement or the accompanying prospectus.

If information in this prospectus supplement is inconsistent with the accompanying prospectus or with any document incorporated by reference that was filed with the SEC before the date of this prospectus supplement, you should rely on this prospectus supplement. This prospectus supplement, the accompanying prospectus and the documents incorporated into each by reference include important information about us, the shares being offered and other information you should know before investing in our shares. You should also read and consider information in the documents we have referred you to in the sections of this prospectus supplement and the accompanying prospectus entitled "Where You Can Find More Information."

You should rely only on this prospectus supplement, the accompanying prospectus and any free writing prospectus we may provide to you in connection with this offering and the information incorporated or deemed to be incorporated by reference therein. We have not authorized anyone to provide you with information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. If anyone provides you with different or inconsistent information, you should not rely on it. We are not offering to sell these shares in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than as of the date of this prospectus supplement or the accompanying prospectus, as the case may be, or in the case of the documents incorporated by reference, the date of such documents regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of our shares. Our business, financial condition, liquidity, results of operations and prospects may have changed since those dates.

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.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus and in documents incorporated by reference 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 prospectus.

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

- our need for additional financing for our INSPIRE trial and other operations, and our ability to obtain sufficient funds on acceptable terms when needed, and our plans and future needs to scale back operations if adequate financing is not obtained;
- our ability to continue as a going concern;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- the success and timing of our preclinical studies and clinical trials, including site initiation and patient enrollment, and regulatory approval of protocols for future clinical trials;
- our ability to enter into, maintain and perform collaboration agreements with other pharmaceutical companies, for funding and commercialization of our clinical product candidates or preclinical compounds, and our ability to achieve certain milestones under those agreements;
- the difficulties in obtaining and maintaining regulatory approval of our product candidates, and the labeling under any approval we may obtain;
- our plans and ability to develop, manufacture and commercialize our product candidates;
- our failure to recruit or retain key scientific or management personnel or to retain our executive officers;
- 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;
- our ability to maintain the listing of our securities on a national securities exchange;
- the potential for third party disputes and litigation;

- the performance of third parties, including contract research organizations ("CROs") and third-party manufacturers; and
- our expectations regarding CRO transition.

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

INDUSTRY DATA

Unless otherwise indicated, information contained or incorporated by reference in this prospectus supplement concerning our industry, including our general expectations and market opportunity, is based on information from our own management estimates and research, as well as from industry and general publications and research, surveys and studies conducted by third parties. Management estimates are derived from publicly available information, our knowledge of our industry and assumptions based on such information and knowledge, which we believe to be reasonable. In addition, assumptions and estimates of our and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those referred to under "Risk Factors" on page S-6 of this prospectus supplement. These and other factors could cause our future performance to differ materially from our assumptions and estimates.

SUMMARY OF PROSPECTUS SUPPLEMENT

This summary highlights information contained elsewhere, or incorporated by reference, in this prospectus supplement, in the accompanying prospectus and in the documents incorporated by reference herein and therein. As a result, it does not contain all the information that may be important to you. Before making an investment decision, to fully understand this offering, you should read this entire prospectus supplement and the accompanying prospectus carefully, including the risk factors under the section entitled "Risk Factors," any free writing prospectus that we have authorized for use in connection with this offering, the financial statements and related notes, and the other information incorporated by reference herein and therein.

Company Overview

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

In December 2015, we enrolled the first patient into our INSPIRE trial, a randomized controlled Phase 3 clinical trial of intravenous rigosertib ("rigosertib IV") in a population of patients with higher-risk MDS after failure of hypomethylating agent ("HMA") therapy. The primary endpoint of INSPIRE is improvement in overall survival. An interim analysis of the trial was performed in January 2018. During March 2019, we exceeded 75 percent completion of INSPIRE enrollment. Our goal is to complete enrollment by the end of 2019 and we anticipate reporting survival top-line data in the first half of 2020 following full enrollment and 288 death events. We are planning to open new trial sites in Brazil in November 2019 and China thereafter. We believe the addition of sites in Brazil, China, and other additional new sites could contribute significantly to achieving our timelines for completing enrollment and for reporting survival top-line data.

Our net losses were $11.2 million and $9.4 million for the six months ended June 30, 2019 and 2018, respectively. As of June 30, 2019, we had an accumulated deficit of $393.1 million. 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 may be met. As of June 30, 2019, we had $5.9 million in cash and cash equivalents.

Concurrent Warrant Amendment

The investors in this offering are holders of our warrants to purchase shares of our convertible preferred stock issued in February 2018 (which we refer to as the "February 2018 warrants") and May 2018 (which we refer to as the "May 2018 warrants"). Concurrent with this offering, we also have entered into a warrant amendment with each investor pursuant to which, for each share of common stock purchased by the investor in this offering, we will amend one outstanding February 2018 warrant held by the investor and/or one outstanding May 2018 warrant held by the investor, as applicable, to reduce the exercise price of the February 2018 warrants and/or May 2018 warrants to $1.60 per share (on an as-converted basis per share of common stock) and to extend the term of the February 2018 warrants and/or May 2018 warrants to December 31, 2022. The price for amending one outstanding February 2018 warrant and/or one outstanding May 2018 warrant was $0.125 per share (on an as-converted basis per share of common stock). The warrant amendment (i) for the February 2018 warrants is pursuant to our registration statement on Form S-1 (Registration No. 333-222374), and (ii) for the May 2018 warrants is pursuant to our registration statement on Form S-1 (Registration No. 333-224315).

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.

THE OFFERING

Common stock offered by us	2,198,938 shares.
Common stock to be outstanding after this offering	8,197,462 shares.
Insider Participation	One of our directors intends to purchase approximately 7,260 shares of common stock sold in this offering at the offering price and on the same terms as the other purchasers in this offering.
Use of proceeds	We intend to use the net proceeds from this offering to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding working capital needs. Please see "Use of Proceeds" below.
Risk factors	See "Risk Factors" beginning on page S-6 of this prospectus supplement for a discussion of factors you should read and consider carefully before investing in our shares.
Common stock Nasdaq Capital Market symbol	ONTX

Except as otherwise indicated, all information in this prospectus supplement is based on 5,998,524 shares outstanding on September 12, 2019, and excludes, as of that date,

- 404,957 shares of common stock issuable upon the exercise of stock options outstanding at September 12, 2019 with a weighted average exercise price of approximately $66.65 per share;
- 5,504,722 shares of common stock issuable upon the exercise of outstanding or issuable warrants at September 12, 2019 with a weighted average exercise price of approximately $9.113 per share (includes common stock issuable for warrants which are exercisable for our Series A or Series B Convertible Preferred Stock, each of which is convertible to common stock); and
- 649,227 shares of common stock reserved for future issuance under our 2018 Equity Compensation Plan, as amended.

RISK FACTORS

An investment in our securities involves a high degree of risk. We urge you to consider carefully the risks described below, together with all of the other information contained in this prospectus supplement and the accompanying prospectus and incorporated by reference herein and therein, before making an investment decision, including those risks described under "Item 1A. Risk Factors" in our Annual Report on Form 10-K, as filed with the SEC on April 1, 2019, and our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2019 and June 30, 2019, as filed with the SEC on May 15, 2019 and August 14, 2019, respectively, each of which is incorporated by reference in this prospectus supplement and which may be amended, supplemented or superseded from time to time by other reports that we subsequently file with the SEC. Our business, financial condition, results of operations or cash flow could be materially and adversely affected by these risks. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. In addition, our past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results in the future. Please read carefully the section below entitled "Special Note Regarding Forward-Looking Information."

Risks Associated With Our Common Stock

We are not in compliance with the Nasdaq continued listing requirements. If we are unable to comply with the continued listing requirements of the Nasdaq Capital Market, our common stock could be delisted, which could affect our common stock's market price and liquidity and reduce our ability to raise capital.

We are required to meet certain qualitative and financial tests to maintain the listing of our securities on The Nasdaq Capital Market. As previously reported in a Current Report on Form 8-K filed with the SEC on May 24, 2019, the Company was notified on May 21, 2019 by Nasdaq that the Company was not in compliance with the minimum stockholders' equity requirement under Nasdaq Listing Rule 5550(b) for continued listing on The Nasdaq Capital Market because the Company's stockholders' deficit of approximately $1.5 million, as reported in the Company's Quarterly Report on Form 10-Q for the period ended March 31, 2019, is below the required minimum stockholders' equity of $2.5 million, and as of the date of the notification, the Company did not meet the alternatives of market value of listed securities or net income from continuing operations. In accordance with Nasdaq Listing Rules, the Company had 45 calendar days, or until July 5, 2019, to submit a plan to regain compliance.

In order to maintain its listing, the Company submitted a plan of compliance addressing how it intended to regain compliance with Nasdaq Listing Rule 5550(b) within 180 days of notification, or November 18, 2019, which was accepted by Nasdaq on July 26, 2019. We do not expect the proceeds from this offering to be sufficient for the Company to satisfy Nasdaq's continued listing requirements. If the Company does not regain compliance by November 18, 2019, or if the Company fails to satisfy another Nasdaq requirement for continued listing, Nasdaq staff could provide notice that the Company's shares of common stock will become subject to delisting. In such event, Nasdaq rules permit the Company to appeal any delisting determination to a Nasdaq Hearings Panel. There can be no guarantee that the Company will be able to maintain its Nasdaq listing.

Risks Associated With This Offering

Our management will have broad discretion as to the use of the proceeds of this offering.

We have not designated the amount of net proceeds from this offering to be used for any particular purpose. Accordingly, our management will have broad discretion as to the application of the net proceeds and could use them for purposes other than those contemplated at the time of this offering. Our stockholders may not benefit from the manner in which our management chooses to allocate and spend the net proceeds.

You will experience immediate and substantial dilution in the net tangible book value per share of the stock you purchase.

You will suffer substantial dilution. See "Dilution" in this prospectus supplement for more information of the dilution you will incur in this offering.

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

To raise additional capital, we may in the future offer additional shares of our common stock, preferred stock or other shares convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other shares in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering. The price per share at which we sell additional shares of our common stock or other shares convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share in this offering.

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

Sales of a substantial number of shares of common stock or securities convertible or exchangeable into common stock in the public markets could depress the market price of common stock and impair our ability to raise capital through the sale of additional equity securities. We cannot predict the effect that future sales of common stock would have on the market price of common stock.

Upon completion of this offering, based on our shares outstanding as of September 12, 2019, we will have 8,197,462 shares of common stock outstanding based on the issuance and sale of 2,198,938 shares of common stock in this offering. These shares can be sold, subject to any applicable volume limitations under federal securities laws. The balance of our outstanding shares of common stock purchased in this offering may be resold into the public market immediately without restriction, unless owned or purchased by our affiliates. Moreover, some of the holders of common stock have the right, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders.

As of September 12, 2019, there were approximately 1,054,184 shares subject to outstanding options or that are otherwise issuable under our 2018 Equity Compensation Plan, as amended, all of which shares we have registered under the Securities Act of 1933, as amended, or the Securities Act, on a registration statement on Form S-8. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described above, to the extent applicable.

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

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

USE OF PROCEEDS

We estimate that the net proceeds of this offering, after deducting the placement agent expenses and the other estimated offering expenses payable by us, will be approximately $3.3 million. We intend to use the net proceeds from this offering to fund the development of our clinical and preclinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding working capital needs.

We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds from this offering. Pending application of the net proceeds as described above, we expect to invest the net proceeds in short-term, interest-bearing, investment-grade shares pursuant to our investment policy. As of the date of this prospectus supplement, we cannot specify with certainty the particular uses of the proceeds from this offering.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future.

CAPITALIZATION

The following table sets forth our cash and cash equivalents and capitalization as of June 30, 2019:

- on an actual basis; and
- on an as adjusted basis to give effect to the issuance of 2,198,9381 shares of our common stock at the offering price of $1.60 per share, after deducting placement agent expenses and the other estimated offering expenses payable by us.

The information set forth in the following table should be read in conjunction with and is qualified in its entirety by our "Management's Discussion and Analysis of Financial Condition and Results of Operations" and consolidated financial statements and notes thereto incorporated by reference in this prospectus supplement and the accompanying prospectus. See "Summary—The Offering" in this prospectus supplement for information relating to the expected number of shares of our common stock to be outstanding after this offering.

	AS OF JUNE 30, 2019	
(unaudited) (in thousands, except share data)	**ACTUAL**	**AS ADJUSTED**
Cash and cash equivalents	$ 5,882,000	$ 9,217,000
Total assets	$ 8,580,000	11,915,000
Long-term liabilities	$ 4,380,000	4,380,000
Total liabilities	$ 13,126,000	13,126,000
Stockholders' (deficit) equity:		
Preferred stock, $0.01 par value, 5,000,000 authorized, none issued and outstanding, actual and as adjusted	$ —	—
Common stock, $0.01 par value, 250,000,000 authorized, 5,998,524 shares issued and outstanding, actual; 8,197,462 shares issued and outstanding, as adjusted	$ 60,000	82,000
Additional paid-in capital	$ 388,465,000	391,778,000
Accumulated other comprehensive loss	$ (14,000)	(14,000)
Accumulated deficit	$ (393,057,000)	(393,057,000)
Total stockholders' (deficit) equity	$ (4,546,000)	(1,211,000)
Total liabilities and stockholders' (deficit) equity	$ 8,580,000	$ 11,915,000

DILUTION

Purchasers of shares in this offering will suffer immediate and substantial dilution in the net tangible book value per share of common stock. Our net tangible book value as of June 30, 2019 was approximately $(4,546,000), or $(0.76) per share of our common stock. Net tangible book value per share represents the amount of total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding as of June 30, 2019.

Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers in this offering and the net tangible book value per share of our common stock immediately after this offering. After giving effect to the sale of 2,198,938 shares of common stock at an offering price of $1.60 per share, and after deducting the placement agent expenses and the estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2019 would have been approximately $(0.15) per share of our common stock. This represents an immediate increase in net tangible book value of $0.61 per share of our common stock to our existing stockholders and an immediate dilution in net tangible book value of $1.75 per share of our common stock to investors participating in this offering. The following table illustrates this per share dilution:

Offering price per share		$ 1.60
Net tangible book value per share as of June 30, 2019	$ (0.76)	
Increase per share attributable to this offering	$ 0.61	
As adjusted net tangible book value per share as of June 30, 2019 after this offering		$ (0.15)
Dilution per share to new investors participating in this offering		$ 1.75

The above table is based on 5,998,524 shares of common stock outstanding as of June 30, 2019 and excludes, as of that date:

- 404,957 shares of common stock issuable upon the exercise of stock options outstanding at June 30, 2019 with a weighted average exercise price of approximately $66.65 per share;
- 5,504,722 shares of common stock issuable upon the exercise of outstanding or issuable warrants at June 30, 2019 with a weighted average exercise price of approximately $9.133 per share (includes common stock issuable for warrants which are exercisable for our Series A or Series B Convertible Preferred Stock, each of which is convertible to common stock); and
- 649,227 shares of common stock reserved for future issuance under our 2018 Equity Compensation Plan, as amended, at June 30, 2019.

To the extent that any options or warrants are exercised, new options or other equity awards are issued under our equity incentive plan, or we otherwise issue additional shares of common stock or convertible debt securities in the future, there will be further dilution to new investors.

PLAN OF DISTRIBUTION

Pursuant to an engagement agreement dated September 21, 2019, we have engaged H.C. Wainwright & Co., LLC, or Wainwright or the placement agent, to act as our exclusive placement agent in connection with the offering of shares pursuant to this prospectus supplement and accompanying prospectus. Under the terms of the engagement agreement, the placement agent has agreed to be our exclusive placement agent, on a reasonable best efforts basis, in connection with this offering. The terms of this offering were subject to market conditions and negotiations between us, the placement agent and prospective investors. We entered into securities purchase agreements directly with investors in connection with this offering and we only sell the shares of common stock to investors who have entered into the securities purchase agreement. The engagement agreement provides that the obligations of the placement agent are subject to certain conditions precedent, including the absence of any material adverse change in our business and the receipt of certain certificates, opinions and letters from us and our counsel. The engagement agreement does not give rise to any commitment by the placement agent to purchase any of our shares of common stock and warrants, and the placement agent will have no authority to bind us by virtue of the engagement agreement. We expect to deliver the shares being offered pursuant to this prospectus supplement and the accompanying prospectus to the investors on or about September 25, 2019, subject to customary closing conditions.

We have agreed to pay Wainwright $56,000 for non-accountable expenses and $10,000 for clearing expenses.

We have agreed to indemnify the placement agent and specified other persons against certain civil liabilities, including liabilities under the Securities Act, and the Securities Exchange Act of 1934, as amended, or the Exchange Act, and to contribute to payments that the placement agent may be required to make in respect of such liabilities.

We estimate the total expenses payable by us for this offering, excluding the placement agent expenses, to be approximately $117,000.

We have agreed to issue to the underwriter warrants to purchase up to 109,585 shares of common stock, which represents a number of shares of common stock equal to 5% of the aggregate number of shares of common stock sold in this offering but excluding the number of shares sold to one of insiders who participated in this offering. The placement agent warrants has an exercise price of $2.00 per share of common stock, which equals to 125% of the offering price for the shares sold in this offering. The placement agent warrants will be immediately exercisable and will expire on September 23, 2023. Pursuant to FINRA Rule 5110(g), the placement agent warrants and any shares issued upon exercise of the placement agent warrants shall not be sold, transferred, assigned, pledged, or hypothecated, or be the subject of any hedging, short sale, derivative, put or call transaction that would result in the effective economic disposition of the securities by any person for a period of 180 days immediately following the date of effectiveness or commencement of sales of this offering, except the transfer of any security: (i) by operation of law or by reason of our reorganization; (ii) to any FINRA member firm participating in the offering and the officers or partners thereof, if all securities so transferred remain subject to the lock-up restriction set forth above for the remainder of the time period; (iii) if the aggregate amount of our securities held by the placement agent or related persons do not exceed 1% of the securities being offered; (iv) that is beneficially owned on a pro rata basis by all equity owners of an investment fund, provided that no participating member manages or otherwise directs investments by the fund and the participating members in the aggregate do not own more than 10% of the equity in the fund; or (v) the exercise or conversion of any security, if all securities remain subject to the lock-up restriction set forth above for the remainder of the time period.

Additionally, we have granted to Wainwright, subject to certain conditions, a six-month right of first refusal with respect to additional raises of funds by us. In addition, if any investor introduced to us by Wainwright participates in a capital raising transaction during the eight months following termination or expiration of our engagement of Wainwright, we have agreed to pay to Wainwright the cash compensation described herein in connection with capital provided by such investor.

The engagement agreement provides that we will indemnify the placement agent against specified liabilities, including liabilities under the Securities Act of 1933, as amended. 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 resale of the shares sold by it while acting as principal might be deemed to be underwriting discounts or commissions under the Securities Act. As an underwriter, the placement agent would be required to

comply with the Securities Act and 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 shares of common stock, overallotment purchase rights and warrants by the placement agent acting as principal. Under these rules and regulations, the placement agent:

- may not engage in any stabilization activity in connection with our securities; and
- may not 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 it has completed its participation in the distribution.

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

Insider Participation

One of our directors intends to purchase less than 1% of the shares of common stock to be sold in this offering at the offering price and on the same terms as the other purchasers in this offering.

LEGAL MATTERS

The validity of the shares offered hereby will be passed upon for us by Morgan, Lewis & Bockius LLP, Philadelphia, Pennsylvania.

EXPERTS

The consolidated financial statements of Onconova Therapeutics, Inc. at December 31, 2018 and 2017, and for the years then ended, appearing in our Annual Report (Form 10-K) for the year ended December 31, 2018 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon (which contains an explanatory paragraph describing conditions that raise substantial doubt about the Company's ability to continue as a going concern as described in Note 1 to the consolidated financial statements) included therein and incorporated herein 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 are a public company and file annual, quarterly and current reports, proxy statements and other information with the SEC. The SEC maintains an internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC, at www.sec.gov. Our SEC filings are also available to the public on our website at www.onconova.com. The information contained on, or accessible through, our website is not part of this prospectus supplement or the accompanying prospectus.

This prospectus supplement and the accompanying prospectus are only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act, and therefore omit certain information contained or incorporated by reference in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus supplement and the accompanying prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document. You may obtain a copy from the SEC's website or our website.

We have not incorporated by reference into this prospectus supplement the information on our website, and you should not consider it to be a part of this prospectus supplement.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" the information we have filed with it, which means that we can disclose important information to you by referring you to another document that we have filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus supplement and the accompanying prospectus. Any statement in a document we incorporate by reference into this prospectus supplement or the accompanying prospectus will be considered to be modified or superseded to the extent a statement contained in this prospectus supplement or any other subsequently filed document that is incorporated by reference into this prospectus supplement modifies or supersedes that statement. The modified or superseded statement will not be considered to be a part of this prospectus supplement or the accompanying prospectus, as applicable, except as modified or superseded.

We incorporate by reference the following information or documents that we have filed with the SEC (excluding those portions of any Form 8-K that are not deemed "filed" pursuant to the General Instructions of Form 8-K):

- Our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, which we filed with the SEC on April 1, 2019;
- Our Definitive Proxy Statement on Schedule 14A for our 2019 Annual Meeting of Stockholders held June 17, 2019, which we filed with the SEC on April 29, 2019;
- Our Quarterly Reports on Form 10-Q for the fiscal periods ended March 31, 2019 and June 30, 2019, which we filed with the SEC on May 15, 2019 and August 14, 2019, respectively;
- Our current reports on Form 8-K filed with the SEC on January 15, 2019, May 16, 2019, May 17, 2019, May 24, 2019, June 19, 2019, July 29, 2019 and September 13, 2019; 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;

We also incorporate by reference all documents filed pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and prior to the termination of this offering (excluding those portions of any Form 8-K that are not deemed "filed" pursuant to the General Instructions of Form 8-K).

Statements made in this prospectus supplement or the accompanying prospectus or in any document incorporated by reference in this prospectus supplement or the accompanying prospectus as to the contents of any contract or other document referred to herein or therein are not necessarily complete, and in each instance reference is made to the copy of such contract or other document filed as an exhibit to the documents incorporated by reference, each such statement being qualified in all material respects by such reference.

We will provide without charge upon written or oral request to each person, including any beneficial owner, to whom a prospectus supplement is delivered, a copy of any or all of the documents which are incorporated by reference into this prospectus supplement but not delivered with the prospectus (other than exhibits to those documents unless such exhibits are specifically incorporated by reference as an exhibit in this prospectus supplement). Requests should be directed to:

Onconova Therapeutics, Inc.
375 Pheasant Run
Newtown, Pennsylvania 18940
Attention: Suzanne Hutchinson
(267) 759-3680

PROSPECTUS

Onconova Therapeutics, Inc.

$84,546,394
Common Stock, Preferred Stock,
Debt Securities, Warrants and Units
and
1,671 Shares of Common Stock Offered by Selling Stockholders

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 $84,546,394.

In addition, the selling stockholders to be named in the applicable prospectus supplement may offer and sell up to an aggregate of 1,671 shares of our common stock from time to time, in amounts, at prices and on terms that will be determined at the time the shares of our common stock are offered. 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 the 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 Capital Market under the symbol “ONTX.” On December 20, 2017, the last reported sale price of our common stock on the Nasdaq Capital Market was $1.50 per share.

As of December 20, 2017, the aggregate market value of our outstanding common stock held by non-affiliates, or the public float, was $21,659,846 which was calculated based on shares of our outstanding common stock held by non-affiliates and on a price of $2.35 per share, the last reported sale price for our common stock, on October 24, 2017. During the 12 calendar month period that ends on, we have offered securities with an aggregate market value of approximately $7,409,115 pursuant to General Instruction I.B.6 of Form S-3.

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.

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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 December 28, 2017.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the SEC. This prospectus covers the primary offering by us of up to an aggregate offering price of $84,546,394 of securities. In addition, under this prospectus, the selling stockholders, to be named in a prospectus supplement to this prospectus, may, from time to time, offer and sell up to an aggregate 1,671 shares of our common stock in one or more offerings. We may offer and sell any combination of the securities described in this prospectus and the selling stockholders may offer and sell shares of common stock in one or more offerings. This prospectus provides you with a general description of the securities we may offer and sell. Each time we offer and sell securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus or in any documents that we have incorporated by reference into this prospectus. You should read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the heading “Where You Can Find More Information,” before investing in any of the securities offered.

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

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

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

WHERE YOU CAN FIND MORE INFORMATION

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

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

INCORPORATION OF INFORMATION BY REFERENCE

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

- Our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 that we filed with the SEC on March 29, 2017, including the information required by Part III, Items 10 through 14, of Form 10-K, which is incorporated by reference to our definitive proxy statement for our 2017 annual meeting of stockholders filed on April 12, 2017;

- Our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2017, June 30, 2017 and September 30, 2017 that we filed with the SEC on May 15, 2017, August 14, 2017 and November 9, 2017, respectively;

- Our Current Reports on Form 8-K filed with the SEC on April 20, 2017, April 24, 2017, May 18, 2017, May 25, 2017, August 18, 2017, November 13, 2017 and November 17, 2017;

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

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

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

We will provide without charge to each person, including any beneficial owner, to whom this prospectus 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) 759-3680, Attention: Suzanne Hutchison.

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 herein contain, and any prospectus supplement may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. 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,” “should,” “approximately” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements appear in a number of places throughout this prospectus and the documents incorporated by reference herein, and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, protection of our intellectual property portfolio, the degree of clinical utility of our products, particularly in specific patient populations, our ability to develop commercial and manufacturing functions, expectations regarding clinical trial data, our results of operations, cash needs, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus and in documents incorporated by reference 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 prospectus.

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

- our need for additional financing for our INSPIRE trial and other operations, and our ability to obtain sufficient funds on acceptable terms when needed, and our plans and future needs to scale back operations if adequate financing is not obtained;
- our ability to continue as a going concern;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- the success and timing of our preclinical studies and clinical trials, including site initiation and patient enrollment, and regulatory approval of protocols for future clinical trials;
- our ability to enter into, maintain and perform collaboration agreements with other pharmaceutical companies, for funding and commercialization of our clinical product candidates or preclinical compounds, and our ability to achieve certain milestones under those agreements;
- the difficulties in obtaining and maintaining regulatory approval of our product candidates, and the labeling under any approval we may obtain;
- our plans and ability to develop, manufacture and commercialize our product candidates;
- our failure to recruit or retain key scientific or management personnel or to retain our executive officers;
- 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;
- our ability to maintain the listing of our Common Stock on a national securities exchange;
- the potential for third party disputes and litigation;
- the performance of third parties, including contract research organizations ("CROs") and third-party manufacturers; and
- our expectations regarding CRO transition.

Any forward-looking statements that we make in this prospectus and the documents incorporated by reference herein speak only as of the date of such statement, and we undertake no obligation to update such statements whether as a result of any new information, future events, changed circumstances or otherwise. Comparisons of results for current and any prior periods are not intended to express any future trends or indications of future performance, unless expressed as such, and should only be viewed as historical data.

You should also read carefully the factors described in the "Risk Factors" section of this prospectus and in documents incorporated by reference herein, to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus and in documents incorporated by reference herein will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

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

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 set forth in the "Risk Factors" section of our Annual Report on Form 10-K, as filed with the SEC on March 29, 2017, and our Quarterly Reports on Form 10-Q for the quarter ended September 30, 2017, as filed with the SEC on November 9, 2017, which are incorporated by reference into this prospectus, as well as any amendment or update to our risk factors reflected in subsequent filings with the SEC and any applicable prospectus supplement or any free writing prospectus. You should also carefully consider any other information we include or incorporate by reference in this prospectus. Any such risk could cause our business, financial condition or operating results to suffer. The market price of our common stock could decline if one or more of these risks and uncertainties develop into actual events. You could lose all or part of your investment.

ONCONOVA THERAPEUTICS, INC.

Overview

We are a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule product candidates primarily to treat cancer. Using our proprietary chemistry platform, we have created a library of targeted agents designed to work against cellular pathways important to cancer cells. We believe that the product candidates in our pipeline have the potential to be efficacious in a variety of cancers. We have one Phase 3 clinical-stage product candidate and two other clinical-stage product candidates (one of which is being developed for treatment of acute radiation syndromes) and several preclinical programs. Substantially all of our current effort is focused on our lead product candidate, rigosertib. Rigosertib is being tested in an intravenous formulation as a single agent, and an oral formulation in combination with azacitidine, in clinical trials for patients with higher-risk myelodysplastic syndromes ("MDS"). The Company has and may continue to delay, scale-back, or eliminate certain of its research and development activities and other aspects of its operations until such time as the Company is successful in securing additional funding.

In December 2015, we enrolled the first patient in a randomized controlled Phase 3 clinical trial of intravenous rigosertib "rigosertib IV" in a population of patients with higher-risk MDS after failure of hypomethylating agent ("HMA") therapy. The trial, which we refer to as INSPIRE, is expected to enroll approximately 225 patients at more than 170 sites globally. The primary endpoint of INSPIRE is overall survival.

Our net losses were $17.9 million and $14.2 million for the nine months ended September 30, 2017 and 2016, respectively. As of September 30, 2017, we had an accumulated deficit of $356.1 million.

Rigosertib

Rigosertib is a small molecule which we believe blocks cellular signaling by targeting RAS effector pathways. This is believed to be mediated by the interaction of rigosertib to the RAS-binding domain ("RBD"), found in many RAS effector proteins, including the Raf and PI3K kinases. We believe this mechanism of action provides a new approach to block the interactions between RAS and its targets containing RBD sites. Rigosertib is currently being tested in clinical trials as a single agent, and in combination with azacitidine, in patients with MDS. We have enrolled more than 1,300 patients in rigosertib clinical trials for MDS and other conditions. We were a party to a license and development agreement with Baxalta (as defined below), which granted Baxalta certain rights to commercialize rigosertib in Europe. The Baxalta agreement was terminated on August 30, 2016, at which time the European rights reverted to us at no cost. We are party to a collaboration agreement with SymBio, which grants SymBio certain rights to commercialize rigosertib in Japan and Korea. We have retained development and commercialization rights to rigosertib in the rest of the world, including in the United States and Europe, although we could consider licensing commercialization rights to other territories as we continue to seek additional funding.

Rigosertib IV for higher-risk MDS

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

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

The first patient in the INSPIRE trial was enrolled at the MD Anderson Cancer Center in December 2015, the first patient in Europe was enrolled in March, 2016, and the first patient in Japan was enrolled in July, 2016.

Enrollment for the INSPIRE Phase 3 trial for second-line higher-risk MDS patients is highly selective and required us to search extensively to identify appropriate candidates meeting the stringent entry criteria. Accordingly, this trial has been opened at more than 175 sites on four continents. Our partner, SymBio Pharmaceuticals, has opened more than 30 sites in Japan for the INSPIRE protocol. As of October 31, 2017, the trial is active at approximately 170 sites in 22 countries. The selection of countries and trial sites is carefully undertaken to ensure availability of appropriate patients meeting eligibility criteria. Since these criteria are purposely designed to be narrow and selective, extensive screening and trial site education is integral to our plan. INSPIRE trial outcome is measured by overall survival and includes a pre-planned interim analysis which is triggered by 88 events (deaths). The timing of interim analysis is difficult to precisely define. Based on our statistical analysis plan, the enrollment rate, and the expected survival in a comparable patient subgroup from the ONTIME trial, we expect the interim analysis to occur late in the fourth quarter of 2017. The interim analysis involves an initial analysis of efficacy by an independent statistical consultant. These results will be submitted to the independent data monitoring committee (DMC). The interim analysis may result in the trial stopping due to futility, trial continuation as planned without any changes, or continuation with changes according to the preset criteria for trial expansion or continued randomization only for the Very High Risk subgroup. The adaptive design element has been reviewed by regulatory agencies in the US and Europe. The actual timing of the interim analysis and its outcome will permit better estimates for complete enrollment and top-line analysis. Since the date of the interim analysis is tied to the unpredictability of reaching a pre-identified number of death events, the precise time of completing the interim analysis, which will be roughly a couple of weeks after reaching the number of events, cannot be forecast precisely, and could occur early next year.

In an attempt to optimize enrollment, we have taken proactive measures to increase enrollment including the addition of trial sites in three new countries, replacement of the principal CRO and addition of another CRO to our trial management group. Due to these changes full enrollment may take longer than initially expected. Since the interim analysis could potentially change the required number of patients to be randomized for the trial, a better estimate of these timelines can be provided after this analysis is completed. Should enrollment not return to desired levels, full enrollment may be delayed even if the adaptive design is not required as per the statistical analysis plan.

As called for in the INSPIRE Charter, the DMC has previously conducted two periodic safety reviews, and after each review, the trial continued per plan.

Safety and Tolerability of rigosertib in MDS and other hematologic malignancies

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

Rigosertib oral in combination with azacitidine for higher-risk MDS

In December 2016, at the American Society of Hematology (ASH) Annual Meeting, we presented Phase 1/2 data from an oral rigosertib and azacitidine combination trial in higher-risk MDS. 33 of 40 MDS patients enrolled were evaluable for response at the time of the analysis. The median age of patients was 66, with 73% being male. The IPSS-R distribution was: 7.5% Low, 12.5% Intermediate, 37.5% High, 32.5% Very High and 10% unknown. 76% of patients responded per 2006 International Working Group (IWG) criteria. Responses were as follows:

Response per IWG 2006

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

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

Safety/Tolerability of the Combination:

Oral rigosertib (560 mg qAM, 280 mg qPM) was administered on Day 1-21 of a 28-day cycle. Azacitidine 75 mg/m 2 /day SC or IV was administered for 7 days starting on Day 8. The combination of oral rigosertib and azacitidine was well tolerated. The most common TEAEs in $\geq$ 10% of patients were nausea (41%), fatigue (39%), diarrhea (37%), constipation (37%) and dysuria (28%). The most common serious AEs were pneumonia (11%) and febrile neutropenia (7%). The most common AEs leading to discontinuation were AML (4%) and pneumonia (4%).

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

Following an end of Phase 2 meeting with the Food and Drug Administration (FDA) in September 2016, we began development of a Phase 3 protocol. The Phase 3 trial will be designed as a global 1:1 randomized, placebo-controlled trial of oral rigosertib plus azacitidine compared to azacitidine plus placebo. Based on the results of the Phase 1/2 Study, we plan to use the full dose of azacitidine, as defined in the product insert. The patient population studied in this trial will be first-line (HMA naïve) higher-risk MDS patients. The primary endpoint for assessment of efficacy will be the composite Response Rate of complete remission (CR) + partial remission (PR,) as per the IWG 2006 Response Criteria. Formal FDA review will be sought via the Special Protocol Assessment (SPA) mechanism. We will not commence the Phase 3 trial without additional financing.

While the Phase 3 trial is being designed, we have expanded the Phase 1/2 trial cohort by up to 40 subjects. Under a protocol expansion, we plan to use the expanded cohorts to explore dose optimization by increasing the dose of rigosertib and varying the dose administration scheme of rigosertib oral to identify an optimal dose and schedule. After amendments were filed with the regulatory agencies, we started the expansion phase of this trial in the U.S. sites that participated in the initial trial. The first patient was enrolled in April and since then, more than half of the planned patients have been enrolled in the expansion trial. We plan to add more sites in the U.S. to complete enrollment of the expanded trial.

In June 2017, at the Congress of the European Hematology Association Meeting, we updated the data from the Phase 1/2 trial and highlighted results in AML patients included in this study. Response data was presented on eight evaluable patients with AML who were tested with the rigosertib and azacitidine combination. For the eight evaluable patients with AML, the combination was well tolerated and the safety profile was similar to single-agent azacitidine, based on safety information in the azacitidine FDA approved label. Based on the presented results of the combination studies, the authors

concluded that continued study in AML was warranted. We will not commence further development of rigosertib oral in combination with azacitidine for AML without additional financing.

Rigosertib oral for lower-risk MDS

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

We have explored single agent rigosertib oral as a treatment for lower-risk MDS in two Phase 2 clinical trials, 09-05 and 09-07. In December 2013, we presented data at the Annual ASH Meeting from the 09-05 Phase 2 trial. To date, Phase 2 clinical data has indicated that further study of single agent oral rigosertib in transfusion-dependent, lower-risk MDS patients is warranted. Rigosertib has been generally well tolerated, except for urinary side effects at higher dose levels. Future clinical trials will be needed to evaluate dosing and schedule modifications and their impact on efficacy and safety results of oral rigosertib in lower-risk MDS patients.

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

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

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

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

Other Programs

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

Briciclib

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

Recilisib

Recilisib is a product candidate being developed in collaboration with the U.S. Department of Defense for acute radiation syndromes. We have completed four Phase 1 trials to evaluate the safety and pharmacokinetics of recilisib in healthy

human adult subjects using both subcutaneous and oral formulations. We have also conducted animal studies and clinical trials of recilisib under the FDA's Animal 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 adequate and well-controlled studies in appropriate animal models to support efficacy in humans when the results of those studies establish that the drug is reasonably likely to produce a human clinical benefit. Human safety data, however, is still required. Ongoing studies of recilisib, focusing on animal models and biomarker development to assess the efficacy of recilisib are being conducted by third parties with government funding. We anticipate that any future development of recilisib beyond these ongoing studies would be conducted solely with government funding or by collaboration. Use of government funds to finance the research and development in whole or in part means any future effort to commercialize recilisib will be subject to federal laws and regulations on U.S. government rights in intellectual property. Additionally, we are subject to laws and regulations governing any research contracts, grants, or cooperative agreements under which government funding was provided.

Preclinical Product Candidates

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

Positive preclinical data was announced at the American Association for Cancer Research (AACR) annual meeting, which took place April 1-5 in Washington, DC, for ON 123300, a first-in-class dual inhibitor of CDK4/6 + ARK5, and for ON 150030, a novel Type 1 inhibitor of FLT3 and Src pathways. We believe our CDK inhibitor is differentiated from other agents in the market (Palbociclib, Ribociclib and Abemaciclig) or in development (such as the compounds being developed by G1 Therapeutics) by its dual inhibition of CDK4/6 + ARK5. We continue to carry out research to enhance the pre-clinical data package for this compound in an attempt to seek partners for co-development of this novel compound.

In a preclinical Rb+ve xenograft model for breast cancer, ON 123300 activity was shown to be similar to Palbociclib (Pfizer's Ibrance®). Moreover, based on the same preclinical model, the new molecule may have the potential advantage of reduced neutropenia when compared to Palbociclib. Whereas both compounds resulted in decreased RBC and platelet counts in this preclinical model system, Palbociclib was found to have a more prominent and statistically significant ($P < 0.05$) inhibitory effect on neutrophil counts when compared to ON 123300.

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 of such sales.

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 $84,546,394, 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;
- 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 December 20, 2017, 10,771,163 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;
- 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 Tenth Amended and Restated Certificate of Incorporation, as amended, or our "certificate of incorporation," and our Amended and Restated Bylaws, or our "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;
- 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 Capital 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 $84,546,394 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 $84,546,394. The debt securities may be either senior debt securities, senior

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

General

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

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

- the title of the debt securities;
- the price or prices (expressed as a percentage of the aggregate principal amount) at which we will sell the debt securities;
- any limit on the aggregate principal amount of the debt securities;
- the date or dates on which we will pay the principal on the debt securities;
- the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;
- the place or places where the principal of, and premium and interest on, the debt securities will be payable;
- the terms and conditions upon which we may redeem the debt securities;
- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities;
- the dates on which and the price or prices at which we will repurchase the debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;
- the denominations in which the debt securities will be issued, if other than denominations of $1,000 and any integral multiple thereof;
- whether the debt securities will be issued in the form of certificated debt securities or global debt securities;
- the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;
- the currency of denomination of the debt securities;
- the designation of the currency, currencies or currency units in which payment of principal of, and premium and interest on, the debt securities will be made;
- 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.

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.

As of November 17, 2017, we had (i) non-tradable warrants with an expiration date of July 2021 to purchase 96,842 shares of common stock at an exercise price of $11.50 per share, (ii) tradable warrants with an expiration date of July 2021 to purchase 3,192,022 shares of common stock at an exercise price of $4.92 per share and (iii) non-tradable pre-funded warrants with an expiration date of July 2023 to purchase 5,907 shares of common stock at an exercise price of $0.01 per share. Our tradable warrants are traded on the Nasdaq Capital Market under the symbol “ONTXW.”

DESCRIPTION OF UNITS

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

SELLING STOCKHOLDERS

Selling Stockholders for the Secondary Offering of up to 1,671 Shares of Common Stock

This prospectus also relates to the possible resale by certain of our stockholders of up to an aggregate of 1,671 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 initial public offering, which were all converted to shares of our common stock in connection with our initial public offering. 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.”

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 10,771,163 shares of our common stock outstanding as of December 20, 2017.

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.

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	119	119	0	0
Kathryn Jane McDonald	19	19	0	0
Utkarsh Palnitkar	1,533	1,533	0	0

Certain Relationships and Related Party Transactions

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

Demand Registration Rights

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

S-3, or any successor form, so long as the aggregate price to the public in connection with any such offering is at least $500,000. However, we are not obligated to file a Form S-3 pursuant to this provision on more than two occasions in any 12-month period.

Piggyback Registration Rights

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

The secondary offering of up to 1,671 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.

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 Capital 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, 2016 and 2015, and for the years then ended, appearing in our Annual Report (Form 10-K) for the year ended December 31, 2016 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon (which contains an explanatory paragraph describing conditions that raise substantial doubt about the Company’s ability to continue as a going concern as described in Note 1 to the consolidated financial statements) included therein and incorporated herein 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.

LEGAL MATTERS

The validity of the securities being offered by this prospectus will be passed upon by Morgan, Lewis & Bockius LLP, Philadelphia, Pennsylvania.

2,198,938 Shares of Common Stock

ONCONOVA THERAPEUTICS, INC.

PROSPECTUS SUPPLEMENT

H.C. Wainwright & Co.

September 23, 2019