



## Initiating Coverage Report

# Onconova Therapeutics Inc.

Back on track



Chief Research Analyst

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<b>Name:</b>	<b>Onconova Therapeutics</b>
<b>Country:</b>	<b>USA</b>
<b>Price:</b>	<b>USD 2.83</b>
<b>ISIN Code:</b>	<b>US68232V3069</b>
<b>Reuters Code:</b>	<b>ONTX</b>
<b>Market Cap (USD m):</b>	<b>19.1</b>
<b>EV (USD m):</b>	<b>-6.7</b>
<b>Cash &amp; cash eq. (USD m):</b>	<b>25.8</b>
<b>Shares outstanding (m):</b>	<b>6.76</b>
<b>Volume:</b>	<b>118,413</b>
<b>Free float:</b>	<b>79%</b>
<b>52-week Range:</b>	<b>2.11-8.17</b>

USD m	2014A	2015A	2016E
<b>Total Revenues</b>	0.800	11.456	6.500
<b>Net (Loss)/Profit</b>	(63.682)	(23.979)	(20.000)
<b>Net loss per share (pence)</b>	(29.41)	(10.54)	(2.96)
<b>R&amp;D costs</b>	49.425	25.895	20.000
<b>Cash increase/(decrease)</b>	(56.421)	(19.755)	1.201
<b>Cash and marketable sec.</b>	43.582	19.799	21.000



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## Executive Summary

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- Onconova Therapeutics (ONTX) is a late stage biopharmaceutical company with a focus on the development of innovative small molecule drugs to treat cancer. With its proprietary chemistry platform, the company has built a pipeline of targeted anti-cancer drugs based on specific cellular pathways while simultaneously causing minimal damage to normal cells. Its lead product is a small molecule called rigosertib that is currently in Phase III development as a second line treatment for higher risk myelodysplastic syndromes (HR-MDS). An oral version of rigosertib in combination with Celgene's Vidaza successfully concluded a Phase II trial and a pivotal Phase III trial for first-line MDS is expected to commence in 2017H2.
- Rigosertib acts as a RAS mimetic by directly binding to the RAS binding domain (RBD) found in a number of RAS proteins. Ras proteins function as binary molecular switches that control intracellular signalling networks. Mutations or overexpression of RAS genes can lead to the production of permanently activated RAS proteins which can contribute to the development of cancer. The three genes in humans (HRAS, KRAS and NRAS) are the most frequently mutated in 20-25% of all human tumors and up to 90% in certain types of cancer. That makes Onconova's platform applicable in multiple indications.
- Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. MDS is often referred to as a "bone marrow failure disorder". In addition, for roughly 30% of the patients diagnosed with MDS, this type of bone marrow failure syndrome will progress to acute myeloid leukemia (AML). To date, more than 1,000 MDS patients have been enrolled in clinical trials with rigosertib. Orphan designation has been granted for rigosertib for the treatment of MDS in the U.S., Europe and Japan.

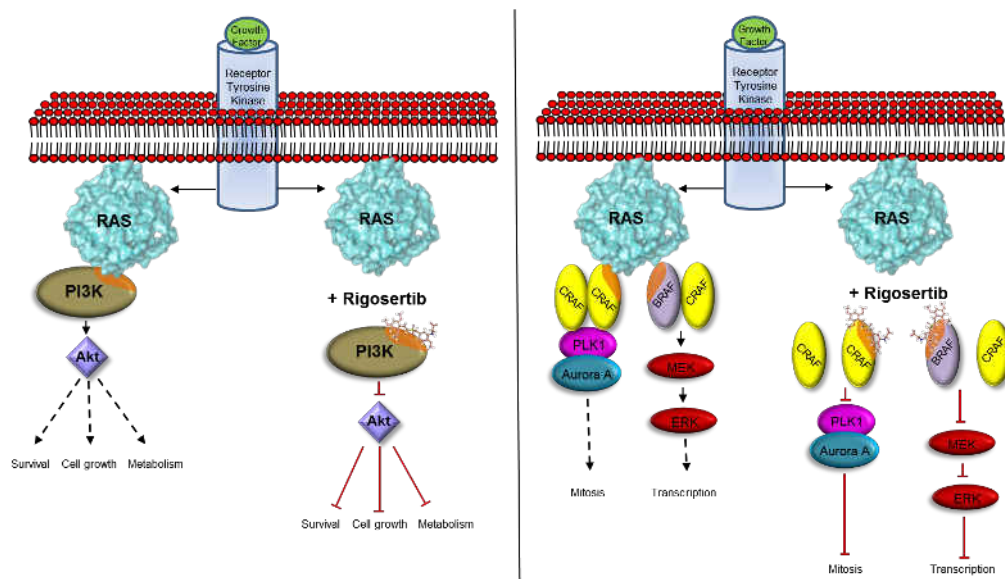


- Earlier last year, the company successfully raised USD 17.4 million from a rights offering. The Company's current cash position is USD 25.8 million. With a current market cap of USD 18 million, that adds up to an EV of –USD 6 million. With a current monthly cash burn of USD 1.5-1.7 million, we believe that this should be sufficient to continue further development of its pipeline in the coming 12 months. Furthermore, we expect the company is able to sign a lucrative partnering deal following interim data of the upcoming pivotal trials with rigosertib.
- There are a number of key milestones to focus on in the next 6-12 months which includes the commencement of the pivotal trial of the oral version of rigosertib in combination with Vidaza (Celgene) for first line HR-MDS, the interim analysis of the Phase III INSPIRE trial and the completion of the INSPIRE trial.
- **Based on NPV based valuation, we believe that Onconova Therapeutics is substantially undervalued at the current share price of USD 2.88. The current market value is even placed well below cash value. We have increased our valuation taking into account a higher LOA and potential partnerships with rigosertib. We feel that the company's current total value should be USD 103.2 million, or USD 15.27 per share. This represents a substantial upside from the current share price.**

## Company Profile & Technology

Onconova Therapeutics is an international biopharmaceutical company that is developing novel medicines for indications for which there are no existing or only inadequate therapies. With its proprietary chemistry platform, the company has built a late stage pipeline of targeted anti-cancer drugs based on specific cellular pathways while simultaneously causing minimal damage to normal cells.

The company's late stage clinical programs are focused on the higher-risk myelodysplastic syndrome (MDS). Its lead drug candidate, rigosertib (IV), is in Phase III trials for higher-risk MDS and an oral form of the drug has concluded Phase II for lower-risk MDS. Rigosertib is a small molecule that inhibits cellular signaling in cancer cells by acting as a Ras mimetic. Ras proteins function as binary molecular switches that control intracellular signalling networks (see graph below). Mutations or overexpression of RAS genes can lead to the production of activated RAS proteins which can lead to the development of cancer. The three genes in humans (HRAS, KRAS and NRAS) are the most commonly mutated in 20-25% of all human tumors and up to 90% in certain types of cancer. That makes Onconova's platform applicable in multiple indications.







Investigations to understand the critical biochemical and biological mechanisms of Ras function are at the forefront of cancer research. Studies have shown that Ras interacts with a large number of effector proteins by a highly conserved mechanism that involves the switch region of Ras and the Ras-binding domains (RBDs) of its effector proteins. Because these interactions play an essential role in oncogenic Ras function, inhibiting them constitutes an attractive and important therapeutic approach for myeloid neoplasias and other cancers. MDS is a complex disease involving deregulation of several regulatory pathways, including many involved in signal transduction. Indeed, mutations in more than two dozen genes have been found in MDS patients and most HR-MDS patient harbor multiple genetic changes involving many pathways. Thus, the novel mechanism of action of rigosertib may be well-suited to addressing the myriad aberrant signaling pathways driving MDS.

#### *Business Strategy & Partnerships*

Initially, the company entered into two major product commercialization agreements on rigosertib. In 2011, Onconova entered into a license agreement with SymBio Pharmaceuticals Limited, which granted SymBio certain rights to commercialize rigosertib in Japan and Korea. Under the terms of the SymBio license agreement, the company received an upfront payment of USD 7.5 million. Onconova is eligible to receive milestone payments of up to an aggregate of USD 22 million from SymBio upon the achievement of specified development and regulatory milestones for specified indications. Further, SymBio will make royalty payments to Onconova at percentage rates ranging from the mid-teens to 20% based on net sales of rigosertib by SymBio.

In 2012, Onconova entered into a development and license agreement with Baxter Healthcare SA, the predecessor in interest to Baxalta GmbH, pursuant to which the Company granted an exclusive, royalty-bearing license for the research, development, commercialization and manufacture of rigosertib in all therapeutic indications in Europe. Baxter paid USD 100 million, including USD 50 million in an equity investment for this license. In March 2016, Baxalta, following the announcement of their acquisition by Shire, decided to terminate the agreement,



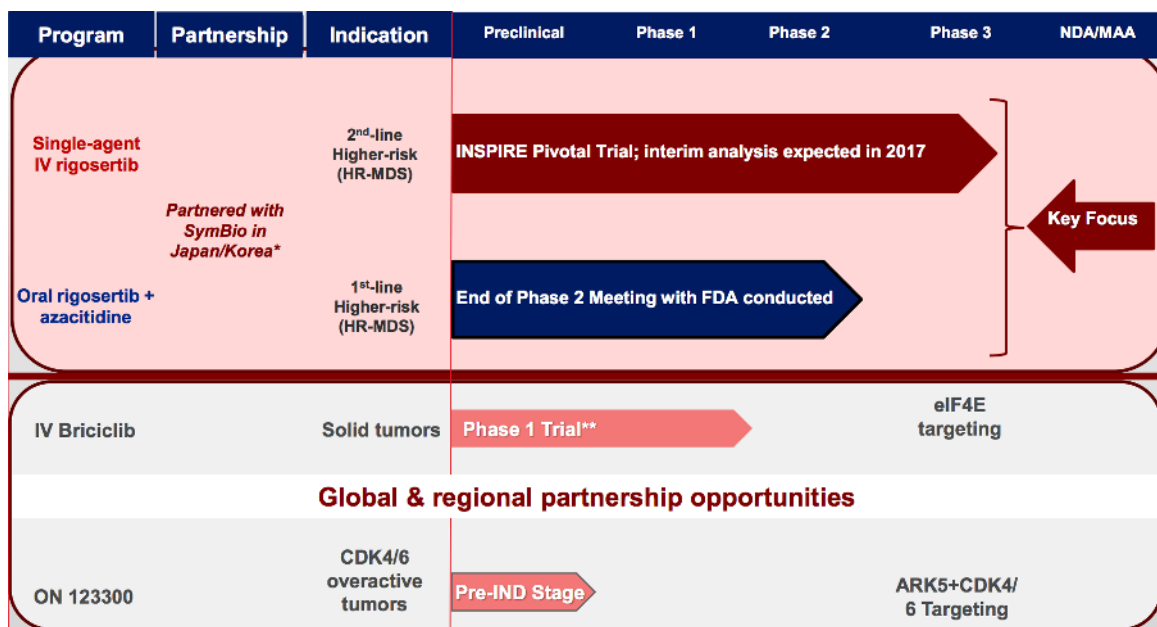
effective August 30, 2016, at which time the rights Onconova licensed to Baxalta reverted to Onconova at no cost. Onconova has retained development and commercialization rights to rigosertib in the rest of the world, including the United States.





## Pipeline: Focus on Rigosertib

Below is an overview of Onconova's pipeline. Onconova's lead product is a small molecule called rigosertib that is currently in Phase III development as a second line treatment for higher risk myelodysplastic syndromes (HR-MDS). A first line oral version of rigosertib in combination with azacitidine in HR-MDS recently showed positive Phase II data as well and is expected to be in a pivotal phase III trial in 2017. Preparations have already begun.



Source: Onconova Therapeutics

### Rigosertib in development as second line treatment for HR-MDS

Onconova's most advanced therapy in development is IV rigosertib as second line treatment for patients with HR-MDS after failing hypomethylating agent therapy (HMA). End of 2015 a Phase III pivotal trial was initiated. The **I**Nternational **S**tudy of Phase III **I**V **R**igos**E**rtib, or INSPIRE, is based on guidance received from the FDA and European Medicines Agency and derives from the findings of the previous ONTIME Phase III trial. INSPIRE is a multi-center, randomized controlled study to assess the efficacy and safety of IV rigosertib in HR-MDS patients under 82 years of age



who had progressed on, or failed to respond to, or relapse after previous treatment with HMAs within the first nine cycles of initiation of HMA treatment. The trial plans to enroll approximately 225 patients randomized at a 2:1 ratio into two treatment arms: IV rigosertib plus Best Supportive Care versus Physician's Choice of Therapy plus Best Supportive Care. The primary endpoint of the INSPIRE Trial is overall survival and an interim analysis is anticipated.

The INSPIRE trial is designed based on the previously completed ONTIME trial with IV rigosertib in HR-MDS patients who failed HMA treatment. In this trial overall survival of patients treated with rigosertib plus best supportive care (BSC) was compared with the survival of patients treated BSC and physicians choice (which included low-dose Ara C). This trial did not meet its primary endpoint of median overall survival, although a subsequent, pre-specified analysis showed that primary HMA failures were more likely to benefit from IV rigosertib. Primary HMA failures refer to patients who never respond to agents like azacitidine, which is typically apparent by 6 to 8 cycles of therapy. For this reason, Onconova has restricted patients in the INSPIRE trial to having received less than 9 cycles of HMA treatment prior to study enrollment.

Parameter	ONTIME Trial	INSPIRE Trial
Total patients	299( 270*)	225
Sites	79+	167
Geography	U.S. and EU (6 countries)	U.S., EU, Japan, Israel, Australia (19 countries)
Indication	Post-HMA HR-MDS	Post-HMA HR-MDS
<i>Key Eligibility Criteria</i>		
Age	No upper limit	< 82 years**
Duration of HMA therapy	No restriction	≤ 9 months and/or ≤ 9 cycles over 12 months**
Time after HMA therapy	≤ 24 months	≤ 6 months
<i>Efficacy Analysis</i>		
Primary endpoint	Overall Survival	Overall survival
Basis for approval	ITT analysis	ITT or IPSS-R VHR subgroup
Interim look	No	Yes

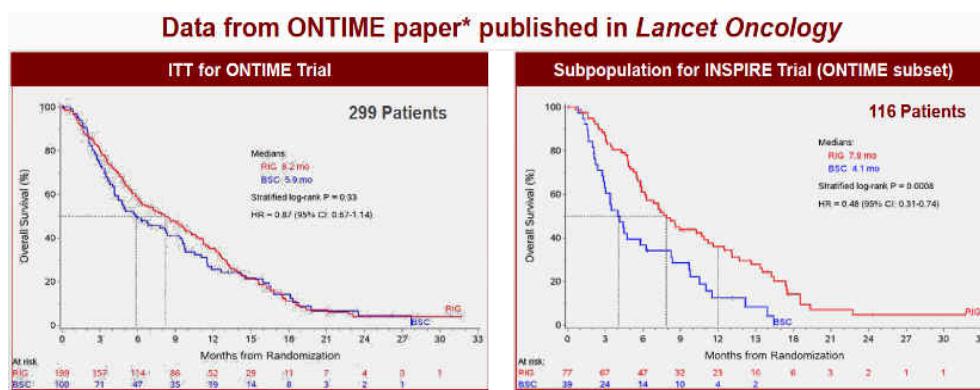
\* Original trial was for 270 patients; over-enrollment driven by site interest and patient need

\* Most productive site (MD Anderson) provided ~15% of total enrollment; enrolled first patient for INSPIRE

\*\* as per amendment 2 (age) or pending amendment 3 (9 cycles over 12 months rather than 9 months, but including 9 months)



When analyzing the patients in ONTIME that met the HMA treatment duration and age restriction, there was a 7.9-month median OS in the rigosertib arm compared to a 4.1 median OS in the best supportive care arm ( $p=0.0008$ ). See also the graphs below. If Onconova is able to repeat this result in the INSPIRE trial, it would demonstrate the drug's efficacy and provide a novel therapy for HR MDS patients. An interim analysis is planned for 2017H2.



### *Oral Rigosertib in combination with Azacitidine as first line therapy in HR-MDS*

Onconova is also developing an oral version of rigosertib as a first line treatment in HR-MDS patients in combination with azacitidine. In 2015, Azacitidine was approved in Europe as a single agent therapy for elderly AML patients, as many members of this population cannot endure commonly used intensive chemotherapy. This approval provides a clear regulatory path for combination studies in elderly AML. While the continuous infusion (CI) schedule is acceptable in the higher-risk MDS population, such a schedule would not be favoured in less advanced disease settings such as lower-risk MDS and most solid tumours. For this reason, Onconova has also developed an oral formulation of rigosertib. The oral formulation has also been tested, as a single agent, for Lower-risk MDS and encouraging Phase II trial data has been reported. Currently, Onconova is focusing on further development of oral rigosertib in combination with azacitidine for front-line HR MDS patients.

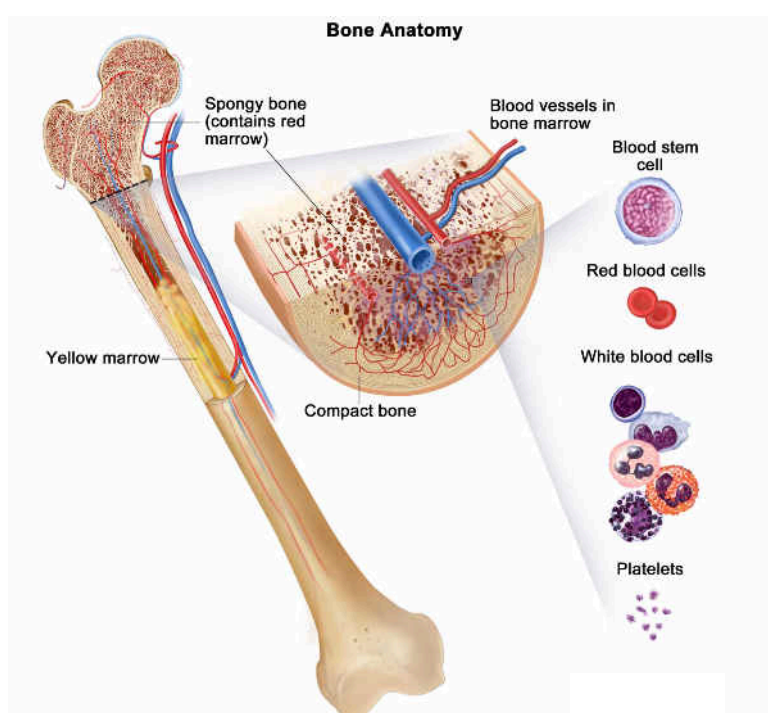


The current standard of care for higher-risk MDS patients is one of two approved hypomethylating agents (Azacitidine and Decitabine, approved by the FDA in 2004 and 2006). Although these drugs are currently the mainstays in HR-MDS therapy, their overall response rate and duration of benefit is limited to a subset of eligible patients and all responding patients. Therefore, there is an urgent need for developing therapeutic options for newly diagnosed MDS patients. The 09-08 trial tested oral rigosertib in combination with injectable azacitidine in a dose ranging study (Phase I), followed by an expansion cohort (Phase II) to evaluate the efficacy and safety of the combination. Both 1<sup>st</sup>-line and 2<sup>nd</sup>-line HR-MDS patients were included in the study. At the 2016 ASH meeting in San Diego, Onconova presented data from the Phase II trial of oral rigosertib in combination with azacitidine in HR-MDS. The phase II study enrolled 54 MDS patients, including those that had been previously treated with HMAs (but not Rigosertib). Patients were treated over three weeks in monthly cycles. Of the 33 evaluable patients, 25 (76%) experienced an overall response. Of these, eight patients had complete remission, 16 experienced a bone marrow CR with or without hematologic improvement, and eight had stable disease.

Earlier, in September the company announced positive End of Phase II meeting results from the FDA for the combination of oral rigosertib and azacitidine. Based on this outcome, the company decided to prepare for a Phase III trial comparing the combination of oral rigosertib and azacitidine to azacitidine and placebo in first line HR-MDS patients. The primary endpoint of this study will be the composite of CR plus PR per IWG (International Working Group) criteria. The use of a response-based endpoint is designed to reduce the time needed to complete the trial and allow for quicker data readouts.

## High Risk Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes are a group of cancers in which immature blood cells in the bone marrow do not mature or become healthy blood cells. In a healthy person, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time and released into the blood.



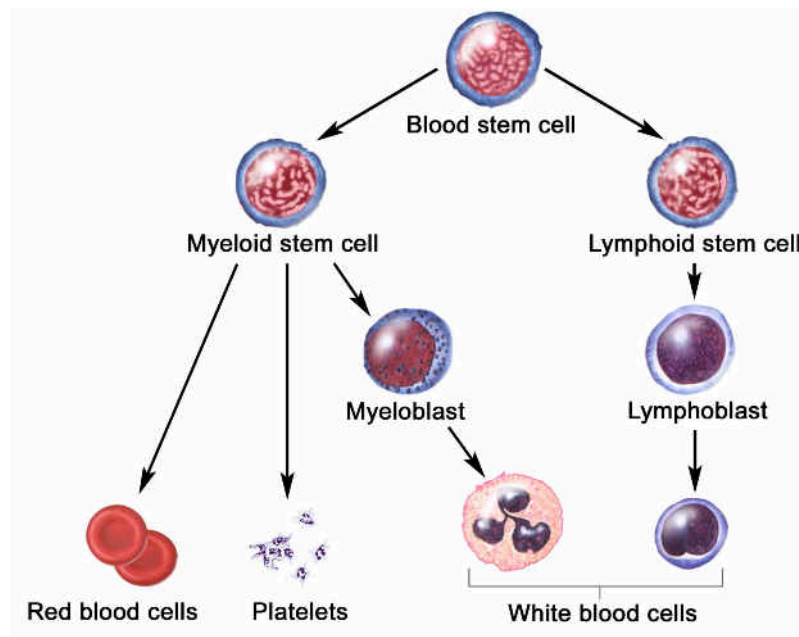
A blood stem cell may become a lymphoid stem cell or a myeloid stem cell. A myeloid stem cell becomes one of three types of mature blood cells:

- Red blood cells that carry oxygen and other substances to all tissues of the body.
- Platelets that form blood clots to stop bleeding.
- White blood cells that fight infection and disease.

In a patient with a myelodysplastic syndrome, the bone marrow stem cells (immature cells) are ineffective in becoming more mature red blood cells, white blood cells, or platelets in the bone



marrow and eventually released into the blood. These immature blood cells, called blasts, do not mature in the way they should. These blasts are assumed to interfere with the bone marrow's ability to produce healthy white blood cells, red blood cells, and platelets to form in the bone marrow. When there are fewer healthy blood cells, infection, anemia, or easier bleeding may occur.



With a few exceptions, the exact causes of MDS are unknown. Some evidence suggests that certain people are born with a tendency to develop MDS. This tendency can be thought of as a switch that is triggered by an external factor. If the external factor cannot be identified, then the disease is referred to as "primary MDS". Radiation and chemotherapy for cancer are among the known triggers for the development of MDS. Patients who take chemotherapy drugs or who receive radiation therapy for potentially curable cancers, such as breast or testicular cancers, Hodgkin's disease and non-Hodgkin's lymphoma, are at risk of developing MDS for up to 10 years following treatment. MDS that develops after use of cancer chemotherapy or radiation is



called “secondary MDS” and is usually associated with multiple chromosome abnormalities in cells in the bone marrow. This type of MDS often develops rapidly into AML. The most common symptom is anaemia, which if severe would require blood transfusion. Other symptoms are also related to inadequate haematopoiesis, including neutropenia (low neutrophil count), thrombocytopenia (low platelet count) and the consequential symptoms of infection or bleeding.

Myelodysplastic syndrome (MDS) is difficult to treat. Although the only curative treatment option is allogeneic bone marrow transplant, most patients with MDS are older and not appropriate candidates for this approach. Therefore, novel strategies are needed. The prognosis and treatment for MDS vary depending on the patient's International Prognostic Scoring System (IPSS) score. Patients with a low/intermediate-1 risk score (IPSS 0-1), who may live with their disease for a number of years, have been the focus of many of the new biological, targeted therapies. Patients with higher scores (intermediate-2 and high risk; IPSS  $\geq 1.5$ ) are at higher risk of transformation to acute myelogenous leukemia (AML) and have been the focus of more intensive therapies and novel chemotherapeutic agents. Most patients with high-risk disease who fail hypomethylating agents die from their disease within 1 year of diagnosis.

Hypomethylating agents (HMAs) have been a major focus of clinical research over the last few years and have been evaluated in patients with advanced HR-MDS. The two best-studied hypomethylating agents are the structurally similar nucleoside analogs decitabine and azacitidine. However, with increasing cumulative clinical experience, it has become apparent that these agents are not curative and have their own shortcomings. The majority of patients do not respond to frontline therapy, and a large, growing cohort of patients loses response or progress while on hypomethylating agent-based therapy. Therefore it has become obvious that there is a clear market opportunity for rigosertib in MDS.





# SWOT Analysis

## Strengths

Strong management with extensive relevant technical, commercial and financial expertise

Late stage pipeline in a disease with a relatively high prevalence as well as having an ODS

Direct product cost savings and work place cost efficiencies

Orphan indication with no approved second line products in MDS

## Weaknesses

Operating losses cumulating year-on-year

Relatively low market value makes its more challenging to be on investor's radar.

Competition with established players

## Opportunities

Ageing population offers predictable and ongoing strong growth in number of patients with MDS

Large growing markets

Potential indications beyond MDS

## Threats

Delay in trials due to discontinuation with European commercialization partner (Baxalta)

Increasing competition from larger companies

Failure to sign partnerships in key markets



## Patent Position

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Onconova's intellectual property is derived through its internal research, licensing agreements with Temple University and licensing research agreements with the Mount Sinai School of Medicine.

As of 2016, Onconova owned or exclusively licensed 77 issued patents and 13 pending patent applications covering composition-of-matter, process, formulation and various indications for method-of-use for rigosertib filed worldwide, including seven patents and two patent applications in the United States. The U.S. composition-of-matter patent for rigosertib, which the company in-licensed pursuant to the license agreement with Temple, currently expires in 2026. The U.S. method of treatment patent for rigosertib, which it also in-licensed from Temple, expires in 2025. A patent covering the use of rigosertib in combination with anticancer agents including azacitidine is issued and will expire in 2028. Patent term extensions may be available, depending on various provisions in the law. Additional issued and filed patents covering formulations and other characteristics could become useful in extending the life and coverage of the intellectual property protection.



## Financials

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For the 9 months ended 30 September 2016, total revenues amounted to USD 5.4 million compared to USD 1.9 in the same period in the previous year. Revenues primarily increased as a result of contractual cost-sharing revenue from Baxalta for a portion of the costs of the INSPIRE trial in the 2016 period. The Baxalta agreement terminated as of August 30, 2016, at which time, the rights licensed to Baxalta reverted to Onconova at no cost. Additionally, any rights Onconova had to funding, pre-commercial milestone payments and royalties from Baxalta terminated in accordance with the agreement. Already in 2011, the company entered into a license agreement with Japanese pharma company SymBio, granting SymBio an exclusive, royalty-bearing license for the development and commercialization of rigosertib in Japan and Korea. Under the terms of the SymBio license agreement, Onconova received an upfront payment of USD 7.5 million and is eligible to receive mile stone payments of up to USD 22 million. Of these mile stones:

- USD 5 million is due upon receipt of the marketing approval of rigosertib IV in the US in HR-MDS
- USD 3 million for approval of rigosertib IV in Japan in HR-MDS,
- USD 5 million for approval of rigosertib oral in the US in HR-MDS
- USD 5 million for approval of rigosertib oral in Japan in HR-MDS

In addition to these pre-commercial milestones, Onconova is eligible to receive tiered milestone payments based upon annual net sales of rigosertib by SymBio of up to an aggregate of USD 30 million. Furthermore, SymBio will make royalty payments to Onconova ranging from the mid-teens to 20% based on net sales of rigosertib by SymBio.

Expenses for the period totaled to USD 22.6 million (2015: USD 29.0 million) including R&D expenses of USD 15.4 million. Net loss for this period increased by USD 0.9 million to USD 4.4 million R&D expenses decreased by USD 5.9 million, or 28%, due to a USD 2.5 million decrease in pre-clinical and clinical development costs and a USD 0.9 million decrease in institutional



research in the 2016 period, as the Company's development efforts were focused on the INSPIRE trial and the Company worked to reduce expenses related to other programs and legacy studies. The decrease in research and development expenses in 2016 was also caused by a reduction of USD 1.7 million in API manufacturing costs and a reduction of USD 0.3 million in consulting expenses related to analyzing clinical trial results and preparing for meetings with regulatory authorities in the 2015 period.

At September 30, 2016, the company had cash and cash equivalents of USD 25.8 million, an increase of USD 6 million compared to beginning of 2016. In August 2016, the company closed on a rights offering of units of common stock and warrants. Net proceeds were approximately USD 15.8 million.

#### *Profit & Loss Statement*

USD million	2014A	2015A	2016E
Revenues	0.800	11.456	6.500
R&D Costs	49.425	25.895	20.000
SG&A	15.119	9.533	10.000
Operating Profit/(Loss)	(63.744)	(23.972)	(20.000)
Income Taxes	0	0	0
Net Profit/(Loss)	(63.795)	(24.023)	(20.000)

#### *Consolidated statement of cash flows*

USD million	Dec 31* 2015A (12 months)	Dec 31* 2016E (12 months)
Cash flow from operating activities	(31.238)	(16.000)
Cash flow from investing activities	-	-
Cash flow from financing activities	7.464	17.500
Cash and cash equivalents at beginning of the period	43.582	19,800
Net change in cash and cash equivalents	(23.783)	2.000



## Valuation

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We have increased our valuation on Onconova to USD 103.2 million or USD 15.27 per share from USD 80 million or USD 11.50 per share due to the fact that we have increase our LOA and market potential for Onconova's lead product rigosertib. We also have altered our valuation model to incorporate both Europe and Japan as potential markets for rigosertib. At this moment we do not address value to other programs in Onconova's pipeline. This is a potential upside for the company.

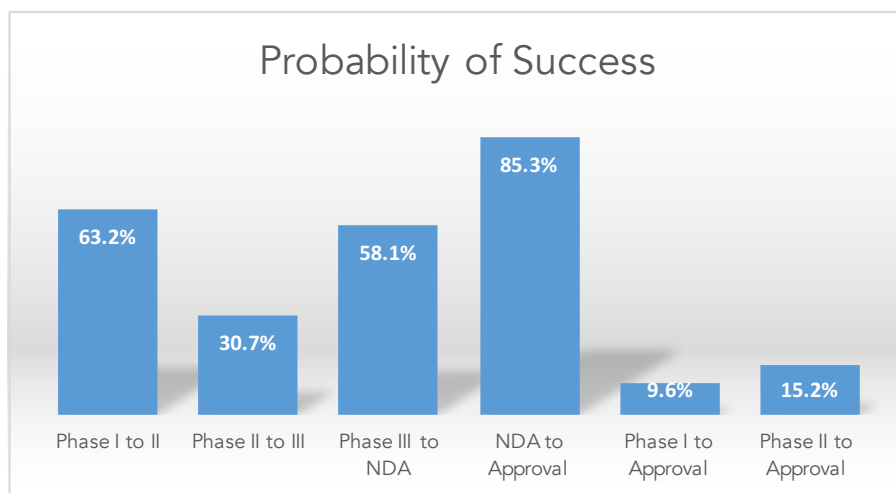
### *Phase Success and Likelihood of Approval (LOA)*

In estimating a value for the clinical programs with rigosertib, we made use of several studies that were done on the clinical development success rates for investigational drugs to measure success rates for investigational drugs. We analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development. These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications. Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis.

The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage

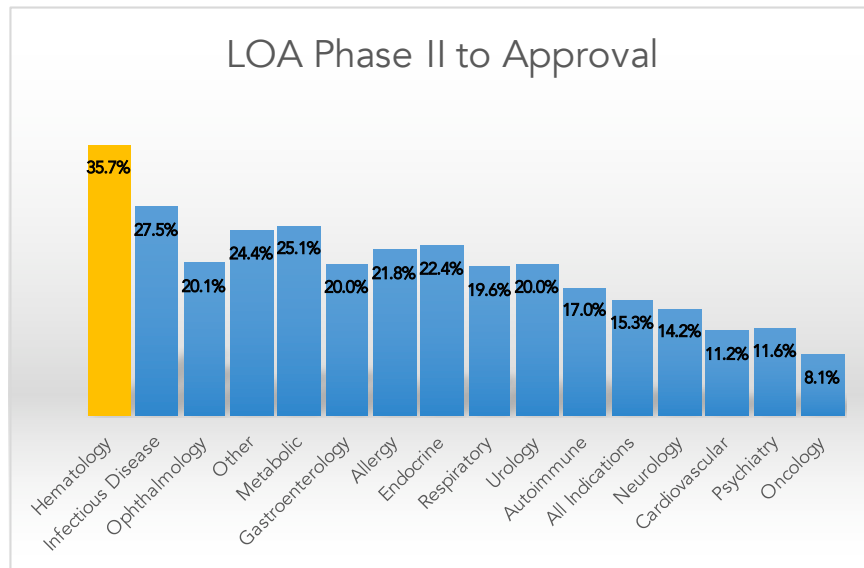


where proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct. The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (see graph below)



Source: BIO Industry Analysis

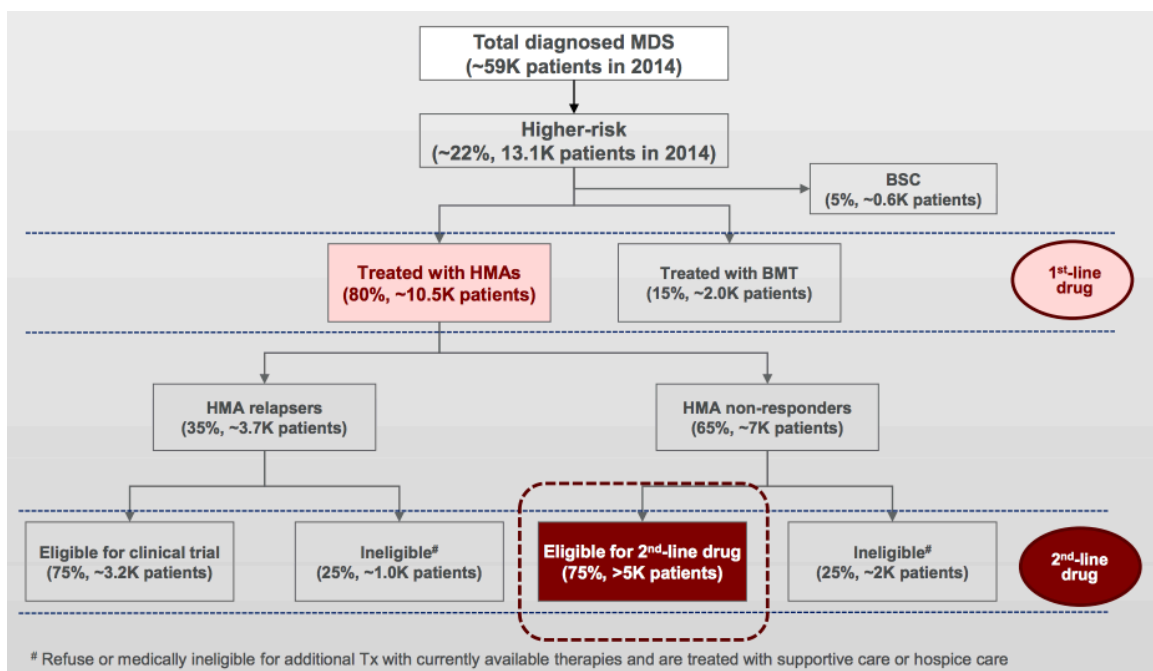
Major disease areas were segmented according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. As can be seen in the graphs below, there is a wide range of Likelihood of Approval (LOA) from Phase I, II and III.



#### *Valuation rigosertib in HR-MDS (IV) and LR-MDS (oral)*

In estimating a value for rigosertib in MDS, we took into account potential markets in the US, Europe and Japan with a total number of patients of 60,000 in the US, 105,000 in Europe and 10,000 in Japan, with a market launch in the US in 2019, 2020 in Europe and 2021 in Japan. For the second line therapy (HR-MDS IV) we calculate the number of eligible patients to be 9%. ( $23\% \times 80\% \times 65\% \times 75\%$ , see graph below), whereas for first line oral therapy in HR-MDS we calculate the number of eligible patients to be 18%. We calculate a Risk adjusted Discount Rate of 15%. Annual pricing per treatment is set at USD 60,000 which is comparable with pricing of competitive drugs like Vidaza. In Europe we calculate lower price of USD 30,000 due to lower reimbursement. For the first line oral therapy we have worked annual pricing of USD 40,000 and USD 20,000 as this is part of a combination therapy. Although we believe that Onconova will potentially partner its program in in MDS with a large pharmaceutical, in our model we have calculated its value by marketing the drug independently. In Japan with go with a royalty of 20% based on its partnership with SymBio. We estimate that a peak market share of 15-20% is possible. In line with the report of BioMedTracker (see hematological disorders, we used a LOA of 35%. This leads to a total valuation of USD 103.2 million or USD 15.27 per share.





Source: Onconova

#### Valuation rigosertib HR-MDS IV US Market

Year	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
No of patients US (yoy growth 3.5% as of 2015)	73,755	76,337	79,009	81,774	84,636	87,598	90,664	93,837	97,122	100,521
No of patients eligible (9%)	5,974	6,183	6,400	6,624	6,856	7,095	7,344	7,601	7,867	8,142
Penetration	1.5%	3.0%	5.3%	6.8%	8.3%	10.1%	11.7%	12.9%	14.3%	15.0%
Total Revenues (USD m)	5.5	11.6	21.2	28.5	36.4	46.3	56.4	65.0	75.0	82.6
Margin 50%	2.8	5.8	10.6	14.2	18.2	23.2	28.2	32.5	37.5	41.3
WACC 15%	0.66	0.57	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19
NPV (million)	1.8	3.3	5.3	6.2	6.8	7.6	8.0	8.0	8.1	7.7
<b>Total NPV (million)</b>	<b>69.5</b>									
<b>LOA 35%</b>	<b>24.3</b>									



### Valuation rigosertib HR-MDS IV EU Market

Year	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
No of patients EU (yoy growth 3.5% as of 2015)	133,589	138,265	143,104	148,113	153,297	158,662	164,215	169,963	175,912	182,069
No of patients eligible (9%)	10,821	11,199	11,591	11,997	12,417	12,852	13,301	13,767	14,249	14,748
Penetration	1.5%	3.0%	5.3%	6.8%	8.3%	10.1%	11.7%	12.9%	14.3%	15.0%
Total Revenues (USD m)	6.1	12.7	23.3	31.3	39.9	50.9	61.9	71.3	82.4	90.6
Margin 50%	3.0	6.4	11.6	15.6	20.0	25.4	30.9	35.7	41.2	45.3
WACC 15%	0.57	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16
NPV (million)	1.7	3.2	5.0	5.9	6.5	7.2	7.6	7.7	7.7	7.4
<b>Total NPV (million)</b>										<b>59.9</b>
<b>LOA 35%</b>										<b>21.0</b>

### Valuation rigosertib HR-MDS IV Japanese Market

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
No of patients US (yoy growth 3.5% as of 2015)	13,140	13,600	14,076	14,568	15,078	15,606	16,152	16,717	17,303	17,908
No of patients eligible (9%)	1,064	1,102	1,140	1,180	1,221	1,264	1,308	1,354	1,402	1,451
Penetration	1.1%	3.6%	6.3%	8.1%	9.9%	12.1%	14.0%	15.5%	17.1%	18.0%
Total Revenues (USD m)	1.2	2.6	4.7	6.3	8.1	10.3	12.5	14.5	16.7	18.4
Royalty Symbio 20%	0.2	0.5	0.9	1.3	1.6	2.1	2.5	2.9	3.3	3.7
Milestone payment SymBio	8.0	5.0								
WACC 15%	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16	0.14
NPV (million)	4.1	2.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5
<b>Total NPV (million)</b>										<b>10.4</b>



### Valuation rigosertib HR-MDS first line oral US Market

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
No of patients US (yoy growth 3.5% as of 2015)	13,140	13,600	14,076	14,568	15,078	15,606	16,152	16,717	17,303	17,908
No of patients eligible (18%)	14,222	14,719	15,234	15,768	16,320	16,891	17,482	18,094	18,727	19,382
Penetration	1.0%	3.6%	6.3%	8.1%	9.9%	12.1%	14.0%	15.5%	17.1%	18.0%
Total Revenues (USD m)	10.8	22.5	41.2	55.3	70.7	90.0	109.5	126.2	145.8	160.4
Margin 50%	5.4	11.2	20.6	27.7	35.3	45.0	54.8	63.1	72.9	80.2
WACC 15%	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16	0.14
NPV (million)	2.7	4.9	7.7	9.0	10.0	11.1	11.8	11.8	11.8	11.3
<b>Total NPV (million)</b>	<b>92.2</b>									
<b>LOA 30%</b>	<b>27.7</b>									

### Valuation rigosertib HR-MDS first line oral EU Market

Year	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
No of patients EU (yoy growth 3.5% as of 2015)	143,104	148,113	153,297	158,662	164,215	169,963	175,912	182,069	188,441	195,036
No of patients eligible (18%)	25,759	26,660	27,593	28,559	29,559	30,593	31,664	32,772	33,919	35,107
Penetration	1.0%	3.6%	6.3%	8.1%	9.9%	12.1%	14.0%	15.5%	17.1%	18.0%
Total Revenues (USD m)	9.8	20.6	37.6	50.6	64.6	82.3	100.2	115.5	133.3	146.7
Margin 50%	4.9	10.3	18.8	25.3	32.3	41.2	50.1	57.7	66.7	73.4
WACC 15%	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16	0.14	0.12
NPV (million)	2.1	3.9	6.2	7.2	8.0	8.8	9.4	9.4	9.4	9.0
<b>Total NPV (million)</b>	<b>73.4</b>									
<b>LOA 30%</b>	<b>22.0</b>									



## Management Capabilities

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Onconova is being built by seasoned biotechnology innovators. The company is led by an experienced Board and management team, which has been responsible for the development of the business and has a long term track record of developing, protecting and commercializing innovative scientific products and processes. In the past several years, the company has been investing in developing a team of experts that have a focus on patient outcomes and can deliver results. Its board and senior management team are highly experienced in the early and late stage development and commercialization of therapeutics in hematology.

### Management Team

#### Ramesh Kumar PhD, Chief Executive Officer

Dr. Kumar co-founded Onconova in 1998. He received his Ph.D. in Molecular Biology from the University of Illinois, Chicago, and trained at the National Cancer Institute. He has held positions in R&D or management at Princeton University, Bristol-Myers Squibb, DNX (later Nextran, a subsidiary of Baxter) and Kimeragen (later Valigen), where he was President of the Genomics and Transgenics Division. Dr. Kumar has more than 50 publications spanning molecular oncology, transgenic animals, gene therapy and recombination. He is an inventor in eight U.S. patents and many patent applications. He co-edited the 1993 book "Molecular Basis of Human Cancer."

#### Mark Guerin, Chief Financial Officer

Mr. Guerin joined Onconova Therapeutics in September 2013 to augment the financial reporting, forecasting, and internal controls capabilities of the company following the IPO in July 2013. Prior to joining Onconova, Mr. Guerin worked as an interim senior finance & accounting executive facilitating the post-acquisition integration activities of newly-acquired private equity portfolio companies. Previously, Mr. Guerin was the VP Finance & CFO of



Cardiokine, Inc. through that company's filing of a New Drug Application and the sale of the company. Prior to joining Cardiokine, Mr. Guerin was Director, Financial Reporting & Internal Controls at Barrier Therapeutics, Inc. during Barrier's IPO and follow-on offering. Mr. Guerin started his career at Coopers & Lybrand in Philadelphia. He received his bachelor's degree in Accounting from DeSales University and has earned the CPA, CMA, and CFM professional certifications.

### **Steven Fruchtman, Chief Medical Officer and Senior Vice President R&D**

Dr. Fruchtman joined Onconova in January, 2015. He has extensive experience in large and small biopharmaceutical companies and has led successful clinical development programs while serving in senior positions at Ortho Biotech Products, Novartis, Allos Therapeutics, Spectrum Pharmaceuticals and Syndax Pharmaceuticals. Earlier, Dr. Fruchtman was on the faculty of the Mount Sinai School of Medicine and the Director of the Stem Cell Transplantation and Myeloproliferative Disorder Programs at Mount Sinai Hospital in New York City. He is an author of more than 170 lectures, presentations, books, chapters, and abstracts and serves as an external reviewer for multiple medical journals. Dr. Fruchtman received his medical degree from New York Medical College with the distinction of membership in the Alpha Omega Alpha honorary medical fraternity.

### **Manoj Maniar, Senior Vice President Product Development**

Dr. Maniar received his B.S. in Pharmacy from Bombay College of Pharmacy and his Ph.D. in Pharmaceutics from the University of Connecticut. He has led the development and commercialization of several pharmaceutical products and medical devices during his career. Prior to joining Onconova, Dr. Maniar was with SRI International, where he served as Senior Director, Formulations and Drug Delivery. He has authored more than 100 patents, publications, and presentations in the field of pharmaceutical sciences.



## Near Term Milestones

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In the past year, Onconova has already reached a number of important mile stones that brought the company back on track towards commercialization of its lead candidate:

- Dec. 2015: 1<sup>st</sup> patient enrolled in US for Phase III INSPIRE trial of rigosertib for MDS
- March 2016: Publication of ONTIME (first Phase III trial of rigosertib in MDS) results in *Lancet Oncology*
- March 2016: 1<sup>st</sup> patient enrolled in Europe for INSPIRE trial
- April 2016: Publication of rigosertib mechanism of action in *Cell*
- June 2016: ASCO presentation of INSPIRE trial design
- July 2016: 1<sup>st</sup> patient enrolled in Japan for INSPIRE trial
- July 2016: Successful rights issue close; proceeds of USD 17.4 million
- Sept 2016: Successful End of Phase II meeting for oral rigosertib + azacitidine, pivotal trial ahead
- Oct 2016: KOL meeting featuring novel ras targeted moa of rigosertib
- Dec 2016: 3 ASH presentations including Phase II data for rigosertib + Azacitidine in MDS/AML

In the coming 12 months we expect a number of important mile stones that can drive the stock price upwards. These are:

- Initiation of Phase III oral rigosertib + azacitidine in first line HR-MDS
- Interim analysis Phase III INSPIRE trial
- Completion of enrollment Phase III INSPIRE trial



## Competitive Landscape

During examination of comparable companies, we looked at companies that have a focus on hematological diseases, particularly MDS. The table below provides an overview of the companies and their specific target. Compared to the competitive landscape, Onconova is clearly at the forefront in MDS.

### *Overview Drugs in Clinical Development and Approved in MDS*

Company	Product	Activity/Target	Stage
Celgene	Vidaza	DNA Methyltransferase (DNMT)	Approved
Otsuka	Dacogen	DNA Methyltransferase (DNMT)	Approved
Celgene	Revlimid	Immune system; Angiogenesis; E3 ubiquitin ligase	Approved
Acceleron Pharma	Luspatercept	Transforming Growth Factor-beta (TGF-beta) Receptor	Phase III
CTI BioPharma	Tosedostat	Aminopeptidase	Phase II/III
Geron	Imetelstat	Telomerase	Phase II/III
Eli Lilly	Galunisertib	Transforming Growth Factor-beta (TGF-beta) Receptor	Phase II/III
Syros Pharma	Tamibarotene	Retinoic acid receptor (RARs)	Phase II
Cyclacel	Sapacitabine	DNA Synthesis	Phase II
Helsinn Healthcare/ MEI Pharma	Pracinostat	Histone Deacetylase (HDAC)	Phase II
Incyte	INCB54828	Fibroblast Growth Factor Receptor (FGFR)	Phase II
Cornerstone Pharma	CPI-613	Redox Homeostasis^ Tricarboxylic Acid (TCA) Cycle/Citric Acid Cycle (CAC)	Phase II

### *Celgene*

Celgene Corporation is a biopharmaceutical company focused on the discovery, development, and commercialization of therapies for the treatment of cancer and immune-inflammatory related diseases. The company has two approved products for MDS, Vidaza (Azacitidine) and Revlimid (lenalidomide). Vidaza is used mainly in the treatment of MDS for which it received approval by the FDA in May, 2004. In two randomized controlled trials comparing azacitidine to





supportive treatment, 16% of subjects with MDS who were randomized to receive azacitidine had a complete or partial normalization of blood cell counts and bone marrow morphology, compared to none who received supportive care, and about two-thirds of patients who required blood transfusions no longer needed them after receiving azacitidine. Revlimid was approved in 2004 for multiple myeloma. Revlimid has also shown efficacy in MDS. It was approved by the FDA on December 27, 2005 for patients with low or intermediate-1 risk MDS with 5q- with or without additional cytogenetic abnormalities. A completed Phase II, multi-centre, single-arm, open-label study evaluated the efficacy and safety of Revlimid monotherapy treatment for achieving haematopoietic improvement in red blood cell (RBC) transfusion dependent subjects with low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality. 63.8% of subjects had achieved RBC-transfusion independence accompanied by a median increase of 5.8 g/dL in blood Hgb concentration from baseline to the maximum value during the response period. Major cytogenetic responses were observed in 44.2% and minor cytogenetic responses were observed in 24.2% of the evaluable subjects. Improvements in bone marrow morphology were also observed. The results of this study demonstrate the efficacy of Revlimid for the treatment of subjects with Low- or Intermediate-1-risk MDS and an associated Del 5 cytogenetic abnormality. Lenalidomide was approved on June 17, 2013 by the EMA for use in low- or intermediate-1-risk MDS patients who have the deletion 5q cytogenetic abnormality and no other cytogenetic abnormalities, are dependent on red blood cell transfusions, and for whom other treatment options have been found to be insufficient or inadequate.

### *Otsuka*

Otsuka Pharmaceutical Co is a Japanese company and engaged in the manufacturing, distributing, exporting, and importing of pharmaceuticals, clinical testing equipment, medical equipment, food products, cosmetics and other related products. In 2014, Otsuka acquired the rights to Dacogen (Decitabine from Eisai. Dacogen was developed by SuperGen (now Astex Pharmaceuticals, Inc.) as a therapeutic agent for MDS and acute myeloid leukemia (AML) possessing cell differentiation-inducing activity through the inhibition of DNA methylation. U.S.-



based MGI Pharma., (acquired by Eisai Inc. in 2008) acquired worldwide rights to develop and market Dacogen from SuperGen, Inc. and sublicensed worldwide rights (except for the U.S., Canada and Mexico) to Janssen Pharmaceutical. Dacogen was approved for sale in the U.S. and is currently indicated for treatment for MDS including previously treated and untreated de novo and secondary MDS of all hematological subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and for intermediate-1, intermediate-2, and high-risk MDS. Janssen is responsible for R&D and commercialization of Dacogen in the EU (where it is approved for acute myeloid leukemia (AML)) and in other specified countries (where it is approved for AML and/or MDS).

### *Acceleron Pharma*

Acceleron is a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of innovative therapeutics to treat serious and rare diseases. lead therapeutic candidate, luspatercept, is being evaluated in Phase III studies for the treatment of the hematologic diseases, MDS) and beta-thalassemia under a global partnership with Celgene. Luspatercept is a modified activin receptor type IIB fusion protein that acts as a ligand trap for members in the Transforming Growth Factor-Beta (TGF-beta) superfamily involved in the late stages of erythropoiesis (red blood cell production). Luspatercept regulates late-stage erythrocyte (red blood cell) precursor cell differentiation and maturation. This mechanism of action is distinct from that of erythropoietin (EPO), which stimulates the proliferation of early-stage erythrocyte precursor cells. Acceleron and Celgene are jointly developing luspatercept as part of a global collaboration. Acceleron and Celgene are enrolling Phase III clinical trials that are designed to evaluate the safety and efficacy of luspatercept in patients with MDS (the "MEDALIST" study) and in patients with beta-thalassemia (the "BELIEVE" study).



### *Geron*

Geron is a clinical stage biopharmaceutical company focused on the collaborative development of a first-in-class telomerase inhibitor, imetelstat, in hematologic myeloid malignancies. Imetelstat is a specific inhibitor of telomerase that is administered by intravenous infusion. This first-in-class compound, discovered by Geron, is a specially designed and modified short oligonucleotide, which targets and binds directly with high affinity to the active site of telomerase. On November 13, 2014, Geron entered into an exclusive worldwide license and collaboration agreement with Janssen Biotech, to develop and commercialize imetelstat for oncology, including hematologic myeloid malignancies, and all other human therapeutics uses. Under the terms of the agreement, Geron received an upfront payment of USD 35 million and is eligible to receive additional payments up to a potential total of USD 900 million for the achievement of development, regulatory and commercial milestones, as well as royalties on worldwide net sales. Imetelstat is currently in a clinical development program called IMerge. IMerge is a Phase II/III clinical trial evaluating imetelstat in transfusion dependent patients with Low or Intermediate-1 risk MDS who have relapsed after or are refractory to prior treatment with an erythropoiesis stimulating agent (ESA). The clinical trial is in two parts: Part 1 is a Phase II, open-label, single-arm design in approximately 30 patients and Part 2 is a Phase III, randomized, double-blind, placebo-controlled design in approximately 170 patients. The primary efficacy endpoint is the rate of red blood cell transfusion-independence lasting at least 8 weeks. Part 1 of the trial is fully enrolled.

### *Cyclacel*

Cyclacel is a biopharmaceutical company developing oral therapies that target the various phases of cell cycle control for the treatment of cancer and other serious diseases. Sapacitabine, Cyclacel's most advanced product candidate, is the subject of SEAMLESS, a Phase III trial, which has completed enrollment and is being conducted under an SPA with the U.S. FDA as front-line treatment for acute myeloid leukemia (AML) in the elderly, and other indications, including MDS. Sapacitabine is currently being evaluated in Phase II trials in elderly patients with MDS. Sapacitabine is an oral nucleoside analogue prodrug that acts through a novel mechanism. The



compound interferes with DNA synthesis by introducing single-strand DNA breaks leading to arrest of the cell division cycle at G2 phase and development of double-strand DNA breaks.

### *Syros Pharmaceuticals*

Syros is focused on discovering and developing treatments for cancer and immune-mediated diseases. It is building a pipeline of gene control medicines, including two lead programs SY-1425, a potent and selective RARa agonist that is initially developing for genomically defined subsets of patients with relapsed or refractory acute myeloid leukemia (AML) and relapsed high-risk MDS, and SY-1365, a selective CDK7 inhibitor, which are initially developing in acute leukemia. SY-1425 is currently in a Phase II trial. This ongoing Phase II clinical trial of SY-1425 is a biomarker-directed multi-center, open-label trial exploring safety and efficacy in relapsed or refractory AML and high-risk MDS patients, newly diagnosed AML patients 60 years of age or older who are not suitable candidates for standard chemotherapy and low-risk transfusion-dependent MDS patients with high levels of *RARA* gene expression. The primary endpoint is overall response rate for AML and high-risk MDS patients and red blood cell transfusion-independence rate for low-risk MDS patients. Other endpoints include assessment of pharmacodynamic markers, duration of response, safety and tolerability, and overall and progression-free survival.

### *Helsinn Pharma/Mei Pharma*

Helsinn is a privately owned cancer supportive care pharmaceutical group with an extensive portfolio of marketed products and a broad development pipeline. MEI Pharma, Inc. (Nasdaq: MEIP) is a San Diego-based oncology company focused on the clinical development of novel therapies for cancer. The Company's lead drug candidate is Pracinostat, a potential best-in-class, oral HDAC inhibitor that has been granted Breakthrough Therapy Designation from the FDA in combination with azacitidine for the treatment of patients with newly diagnosed AML who are  $\geq 75$  years of age or unfit for intensive chemotherapy. In May 2016 both companies entered into a partnership for pracinostat. The deal provides the complementary resources from both



organizations to rapidly advance Pracinostat into Phase III clinical development and expand into additional indications, including high-risk MDS. Under the terms of the agreement, Helsinn got exclusive worldwide rights, including manufacturing and commercialization rights, and will be responsible for funding the global development of Pracinostat. As compensation for such grant of rights, MEI Pharma received near-term payments of USD 20 million, comprised of a USD 15 million upfront payment and a USD 5 million payment upon dosing of the first patient in the upcoming Phase III study of Pracinostat in newly diagnosed AML patients unfit to receive induction therapy. In addition, MEI Pharma will be eligible to receive up to USD 444 million in potential development, regulatory and sales-based milestone payments, along with additional tiered royalty payments in selected territories. As part of the development and commercialization agreement, Helsinn and MEI Pharma will also collaborate to explore an optimal dosing regimen of Pracinostat in combination with azacitidine for the treatment of high-risk MDS. This clinical study is expected to commence in the first half of 2017. In a related transaction, Helsinn made a USD 5 million equity investment in MEI Pharma.

### *Cornerstone Pharmaceuticals*

Cornerstone Pharmaceuticals, Inc. is a privately held, clinical-stage, oncology-focused pharmaceutical company committed to the development and commercialization of therapies that exploit the metabolic differences between normal cells and cancer cells. Cornerstone's first-in-class clinical lead compound, CPI-613 is being evaluated in multiple Phase I, I/II, and II clinical studies. The U.S. FDA has designated CPI-613 an orphan drug for the treatment of acute myeloid leukemia (AML), pancreatic cancer and myelodysplastic syndromes (MDS). No recent news flow was found on the MDS trial which is currently in Phase II (according to the company's website).



*Analyst: Marcel Wijma MSc*

*Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoek Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.*

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