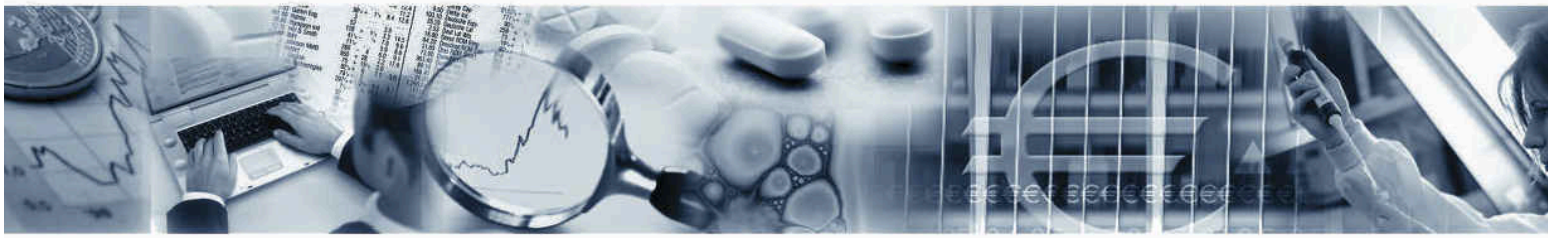

Research Note

Onconova Therapeutics Inc.

Back on track

Chief Research Analyst

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Date: 19 December 2016

Name:	**Onconova Therapeutics**
Country:	**USA**
Price:	**USD 2.41**
ISIN Code:	**US68232V3069**
Reuters Code:	**ONTX**
Market Cap (USD m):	**16.29**
EV (USD m):	**-9.49**
Cash & cash eq. (USD m):	**25.78**
Shares outstanding (m):	**6.76**
Volume:	**83,528**
Free float:	**79%**
52-week Range:	**2.11-11.60**

USD m	2014A	2015A	2016E
Total Revenues	0.800	11.456	5.500
Net (Loss)/Profit	(63.682)	(23.979)	(20.000)
Net loss per share (pence)	(29.41)	(10.54)	(2.96)
R&D costs	49.425	25.895	20.000
Cash increase/(decrease)	(56.421)	(19.755)	1.201
Cash and marketable sec.	43.582	19.799	21.000

Executive Summary

- 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 so-called RAS mimetic by directly binding to the RAS binding domain (RBS) 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 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 in MDS in the U.S., Europe and Japan.

- Earlier this 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 17 million, that adds up to a EV of –USD 10 million. With a current monthly cash burn of USD 1.5-1.7 million, we believe that this should be sufficient to carry out the 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.

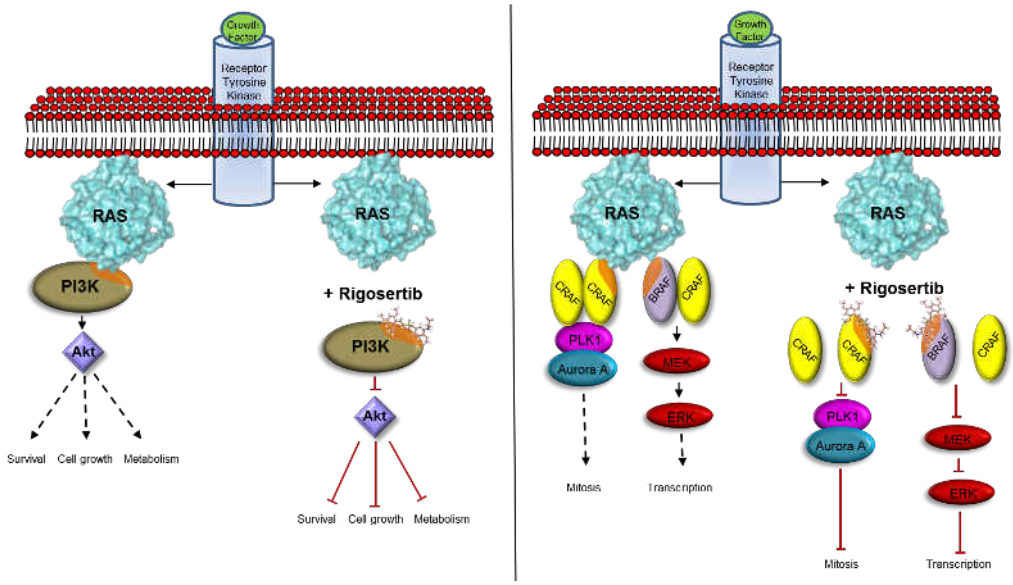
- There are a number of key milestones to focus on in the next 6-12 months which includes the commencement of the pivotal trial of the oral version of rigosertib in combination with Vidaza (Celgene) for first line HR-MDS, the interim analysis of the Phase III INSPIRE trial and the completion of the enrolment of the INSPIRE trial.

- **Based on NPV based valuation, we believe that Onconova Therapeutics is substantially undervalued at the current share price of USD 2.41. The current market value is even placed well below cash value. Using our valuation model and taking into account potential partnerships with rigosertib, the company's current total value should be USD 80 million, or USD 11.50 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 high 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 permanently activated RAS proteins which can lead to 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.

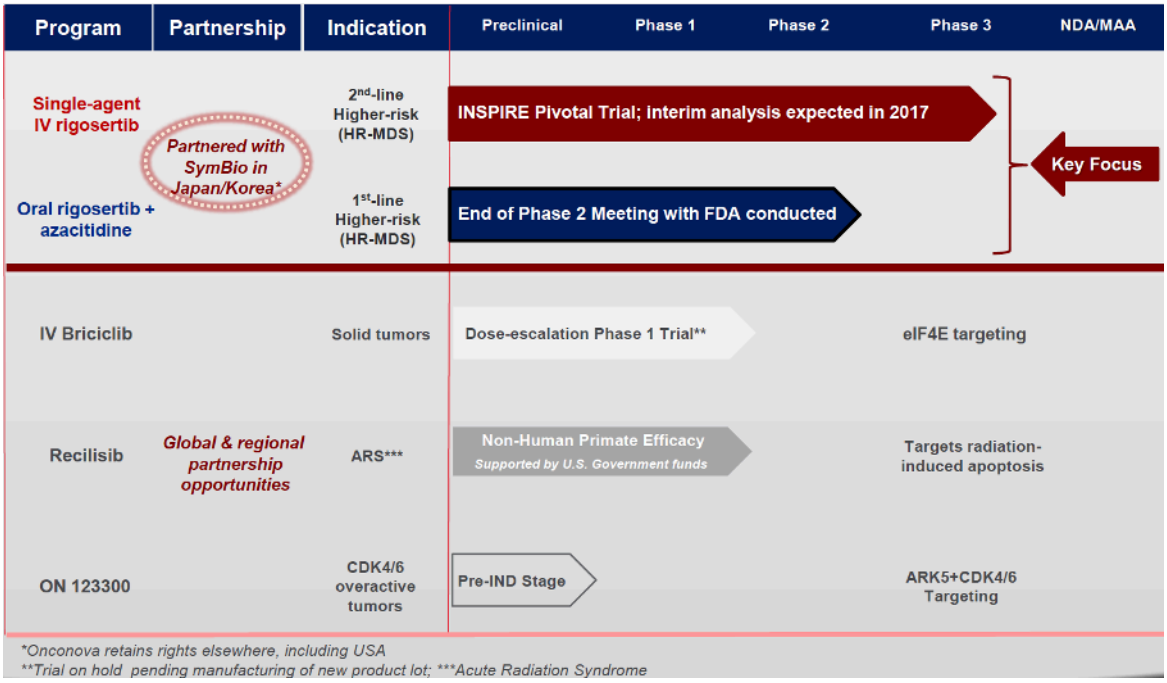
Business Strategy & Partnerships

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. In March 2016, Baxalta 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 Oncogene'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 **IN**ternational **S**tudy of **P**hase III IV **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

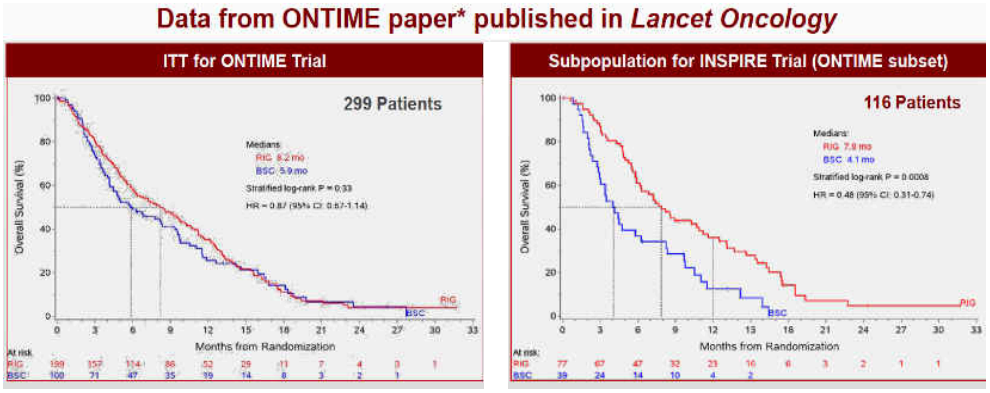
study to assess the efficacy and safety of IV rigosertib in HR-MDS patients under 82 years of age who had progressed on, or failed to respond to, or relapse after previous treatment with HMAs within the first nine cycles of initiation of HMA treatment. The trial currently enrolls approximately 225 patients randomized at a 2:1 ratio into two treatment arms: IV rigosertib plus Best Supportive Care versus Physician's Choice plus Best Supportive Care. The primary endpoint of INSPIRE 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. 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 months of therapy. For this reason, Onconova has restricted patients in the INSPIRE trial to having received less than 9 months 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
Key Eligibility Criteria		
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
Efficacy Analysis		
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.

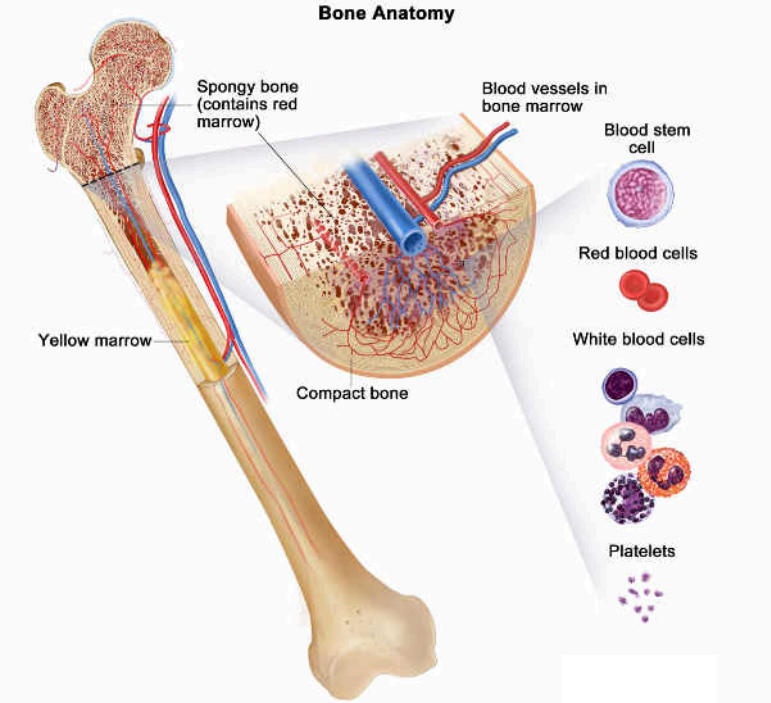
The current standard of care for higher-risk MDS patients is one of two approved hypomethylating agents (Azacitidine and Decitabine, approved by the FDA in 2004 and 2006). Although these drugs are currently the mainstays in HR-MDS therapy, their overall response rate

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 1st-line and 2nd-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 HS-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. 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.

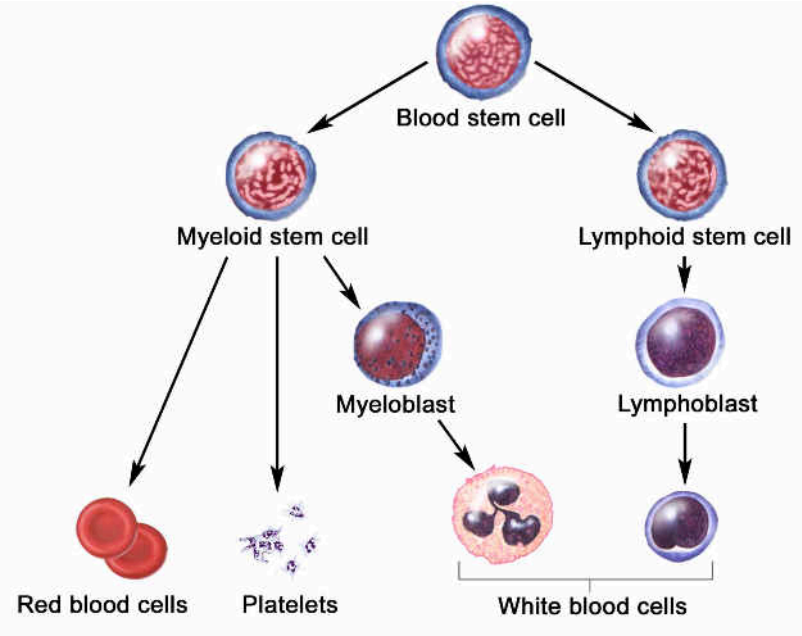


A blood stem cell may become a lymphoid stem cell or a myeloid stem cell. A myeloid stem cell becomes one of three types of mature blood cells:

- 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 blood 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 haematopoiesis related, 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 ≥ 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 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 who do not respond to frontline therapy and a large, growing cohort of patients that lose response or progress while on hypomethylating agent-based therapy. So therefore it has become obvious that there is a clear market opportunity for rigosertib in MDS.

Near Term Milestones

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: 1st 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: 1st 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: 1st patient enrolled in Japan for INSPIRE trial
- July 2016: Successful rights issue close; proceeds of USD 17.4 million
- Sept 2016: Succesful 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 enrollment Phase III INSPIRE trial

Analyst: Marcel Wijma MSc
Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck 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.