



**Mark Guerin, CFO and Steven M. Fruchtman, M.D., President and CMO of Onconova discuss their efforts and the importance of their research drug Rigosertib that targets the RAS Effector Proteins, currently in a Phase 3 Clinical Trial studying Myelodysplastic Syndrome**



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**Interview conducted by: Bud Wayne, Editorial Executive CEOCFO Magazine**

**CEOCFO: Dr. Fruchtman, Mr. Guerin, we have had the pleasure of speaking with your CEO Dr. Kumar over the past few years, so would you introduce yourselves to our readers. How long have you been with Onconova, and what attracted you? Dr. Fruchtman, as President and CMO, what is your day-to-day role at Onconova? Are you heavily involved in running the business, as well as for example clinical trials and product development?**

**Dr. Fruchtman:** I have been with Onconova for approaching four years. There were two things that attracted me to Onconova. First was the space we are studying, which is known as Myelodysplastic Syndrome or MDS, and also referred to as pre-leukemia. I have always had an interest in bone marrow diseases. At one point in my career I ran the Bone Marrow Transplant Service at Mt. Sinai Hospital, a procedure that replaces bone marrow infiltrated with diseases such as leukemia or MDS with normal marrow stem cells, by replacing the diseased poorly function bone marrow with somebody else's bone marrow. Clearly a preferable route is to develop medications to improve bone marrow function rather than putting a patient through a very rigorous transplant therapy where stem cells come from a normal donor infused into the patient. At Onconova we are developing new drugs for Myelodysplastic Syndrome

**“Onconova has key milestones in the upcoming year, that can change the landscape of the treatment of MDS; which include full accrual to a pivotal phase 3 trial with intravenous rigosertib in patients who fail the standard of care, and also data in first line MDS of the combination of oral rigosertib with the standard of care in a study designed to optimize the response rate.”**

(MDS). The second thing that attracted me to Onconova was leadership. I was very impressed with the senior management; they had been in big pharma, small pharma, and clearly had a passion to get novel drugs approved for cancer. My day at Onconova is always very interesting and exciting. We are running a global trial with the goal of randomizing 360 patients with high-risk MDS. When you are running a global trial of such magnitude and importance there are always regulatory questions and clinical questions about the patients on your experimental drug or control arm. That is how I have managed most of my day as Chief Medical Officer. Since my promotion to president, I have also gotten more involved with the business aspects of running a small biotech company and that has been of great interest to me as well.

**CEOCFO: *Mr. Guerin, are you strictly a numbers guy as or do you play an extend role as well in your function as CFO?***

**Mr. Guerin:** I do more than just the numbers. Most of my time is spent on things involving numbers but not just preparing financial statements. I am responsible for the financial reporting and tax reporting. I also take care of all of our forecasting and projections, as well as critical financing transactions that we consider, as well as business development deals, looking at potential license partners, negotiating term sheets, drafting final agreements, and additional similar responsibilities. From an operations standpoint, I support our clinical team by helping review contracts and negotiating contracts involving consultants or manufacturers. I am also involved in and responsible for human resources, administrative and IT functions.

**CEOCFO: *Onconova has three product candidates in clinical trials and several active pre-clinical programs, with your lead compound, Rigosertib, are aimed at unmet medical needs of patients with myelodysplastic syndromes (MDS). Let us talk first about Rigosertib. How is it different from any other therapeutic approaches to MDS?***

**Dr. Fruchtman:** The most commonly mutated gene in cancer is the RAS gene, which is mutated in a variety of cancers including Myelodysplastic Syndrome. In the mutated condition the gene protein is turned on and it gives the cell an advantage over the normal cell, so it proliferates abnormally because of this mutated gene. Even though it proliferates abnormally, the cell with the mutated protein does not produce a normal number of circulating blood cells, so many of these patients require blood transfusions. With Rigosertib and its mechanism of action, it has the ability to interact through what is called effector proteins that bind with the RAS protein, and in the presence of Rigosertib the mutated abnormal pathway shuts down and hopefully gives the normal cellular pathway, that also may be present in the marrow, the ability to return in a more productive manner, improving the production of peripheral circulating blood cells, and hopefully if that happens, prolong life as well. What is unique about Rigosertib is we believe this is the only agent or new medical entity in development that targets the protein product of the Ras mutated gene through effector proteins that bind to the Ras protein. This is the mechanism of action of rigosertib, and hopefully to be proven in a randomized trial in Myelodysplastic Syndrome that it can prolong the survival of these patients.

**CEOCFO: *Would you explain MDS? Is it a precursor to leukemia; are they linked as disease states? Is it a disease to affects mainly the ageing population?***

**Dr. Fruchtman:** MDS was previously referred to as pre-leukemia and that perhaps was a better term and easier to understand. But since many patients do not develop acute leukemia the *nomenclature has evolved*. Most people have a concept of what leukemia is; most people do not have a concept of what MDS is. In both conditions; perhaps due to viruses or environmental toxins, or just associated with the aging process, the bone marrow cells begin to accumulate genetic abnormalities and these genetic abnormalities go on to create replicating leukemia cells in the bone marrow. This occurs in both Myelodysplastic Syndrome, and in acute leukemia, in both the bone marrow and the peripheral blood. So there is a transition between MDS and acute leukemia based solely on how many of these leukemia cells are in the bone marrow. Myelodysplastic Syndrome has fewer leukemia cells in the marrow, and when the leukemia cells increase in the marrow, then the disease is called acute leukemia. Obviously acute leukemia has a poor prognosis but there are patients with MDS that also have a very poor prognosis. That is the differentiation between MDS and acute leukemia; it is determined by how many leukemia cells are in the bone marrow of the patient.

The other key question you asked is one that is posed regularly, which is whether MDS is a disease of the elderly. The answer is yes. The mean age is about 65, but unfortunately there are also children who develop an MDS type syndrome which is somewhat different in these children. We anticipate that Rigosertib, at some point in 2019, in association with the National Cancer Institute in Bethesda, Maryland, and their Pediatric Oncology Branch, we will be giving Rigosertib to children that have leukemia that is RAS mutated, or other cancers that these children develop that are also caused by the mutated RAS gene. So we anticipate studying Rigosertib in these children at some point in 2019. The clinical trial that we have ongoing with Rigosertib, the INSPIRE trial, is a Pivotal Phase 3 trial. That means that on the basis of this trial, in negotiation with United States FDA and the European EMA, if the overall survival endpoint is prolonged in a significant fashion, i.e. the life expectancy of patients with MDS when randomized to Rigosertib is improved, we will have a pathway for regulatory approval and opportunity to commercialize Rigosertib. That is why it is called a Pivotal Trial and we are currently conducting an international Pivotal Trial for patients with Myelodysplastic Syndrome who failed the standard of care, which is a hypomethylating agent. Once a patient fails a hypomethylating agent with high-risk Myelodysplastic Syndrome, there is no FDA or EMA approved drug in the world, so that is where we hope Rigosertib will be able to help these patients. We anticipate the completion of this Pivotal Trial in approximately another year. That is for the adult patients with MDS.

**CEOCFO:** *Would you tell us about your Rigosertib and azacitidine combination trial and where you are today?*

**Dr. Fruchtman:** The reason the combination trial is being conducted is that the FDA and EMA approved drug Azacitidine, although approved by the health authorities, the clinicians who care for these patients, understand that single agent Azacitidine in MDS patients has only marginal benefit for patients. Therefore, we would like to improve the benefit of single agent Azacitidine by adding oral Rigosertib to Azacitidine. The reason it was studied is because in preclinical models of leukemia stem cells, if one combines Rigosertib and Azacitidine in a study of leukemia cell lines, you have synergistic killing of the leukemia

cells. Synergy means when you combine the drug, you do not just get an additive effect of the two drugs, but they work together in a manner that increases significantly the leukemia cell death. Therefore we took this preclinical model and put it into the clinic for patients who had both MDS and acute leukemia, and we recently completed enrollment in a Phase 2 trial of the combination in patients with high-risk MDS. We anticipate presenting this new data at an upcoming medical meeting sometime in 2018.

**CEOCFO: *What is the purpose of the Phase 2 trials? What are you looking to see?***

**Dr. Fruchtman:** The idea of doing a Phase 2 is to see the response of the combination and help to determine the optimal dose. Once a response appears to be impressive, and the optimal dose of the combination is determined, then we plan to take that information into a new Pivotal Phase 3 trial, which would be the combination of Azacitidine plus oral Rigosertib versus the control arm, which would be the FDA approved single agent of Azacitidine plus oral placebo. We anticipate based on our need for additional funding, to open up a new Pivotal Phase 3 trial of this novel doublet at some point in 2019.

**CEOCFO: *Are there any other trials with regard to Rigosertib or what you are working on that we should be aware of?***

**Dr. Fruchtman:** Based on the mechanism of action of Rigosertib involving the RAS pathway and on preclinical models, we are exploring studying Rigosertib in K-RAS mutated lung cancer. For patients with this disease, one of the new therapies available are immuno-oncology drugs, also referred to as Checkpoint inhibitors. The next step will be to initiate a new Phase 1 trial looking at Rigosertib in K-RAS mutated lung cancer, perhaps in association with an immuno-oncology agent. Also in 2019, as I mentioned, we anticipate studying children who have RAS driven cancers, in collaboration with the National Cancer Institute. In addition to Rigosertib, our scientists have an agent early in development referred to as ON 123300. This is a molecule that targets a pathway referred to as a Cyclin-dependent kinase (CDK) 4/6 pathway, along with the ARK 5 pathway. Drugs that target Cyclin 4/6, are commonly used for women with metastatic breast cancer, and they are approved for that indication, in combination with an Aromatase inhibitor. We have begun pre-IND studies, toxicology studies in a number of animal models to determine efficacy and safety in these models. We anticipate in early 2019 to file an IND with the US FDA, and to initiate the first in human trial with ON 123300. Briciclib and Recilisib are two additional agents we have in our portfolio; both of them have very interesting mechanisms of action but will require additional funding for programs studying these drugs.

**CEOCFO: *Onconova has patients enrolled in clinical trials in the United States, Europe, Japan and Australia? Was this accomplished through partnering? What does it take to accomplish an operation that is so massive and then run it?***

**Dr. Fruchtman:** We have a global trial. In Japan we have a corporate partner who helps us conduct the INSPIRE trial with intravenous Rigosertib. Our corporate partner in Japan is a pharma company called SymBio Pharmaceuticals. They have been very helpful to us in conducting our trial in Japan. In addition, we recently started a new corporate partnership in South America with Pint Pharmaceuticals who will help us initiate the INSPIRE trial in Latin America. We also work with contract research organizations that are expert in the conduct of Pivotal Phase 3 trials, and they help us conduct our trials in the US and the rest

of the world. They are very important to us and we have a very productive and collegial arrangements with them to be sure that the INSPIRE trial is expertly conducted throughout the world. We have experts internally at Onconova who manage these trials as well.

**CEOCFO:** *Running such an operation with worldwide clinical trials takes a great deal of resources. You closed a \$28.75 Million upsized underwritten public offering recently, would you tell us about that and other fund raising efforts, as well as where you are today with your financing? Are you continually looking for partners and investors?*

**Mr. Guerin:** We closed a nearly \$29 million offering in early May of 2018. As you mentioned that was an underwritten and upsized public offering. Prior to that in mid-February we raised about \$10 million in another public offering. Therefore, in the first four months of the year we raised approximately \$40 million. We are excited about those financings not just because they brought us the capital that they did, but because they also brought in some key investors who are biotech focused investors and not only hedge fund type investors. That is good because when people like that invest in a biotech offering, they generally do a fair amount of diligence and they are generally long. We were excited to upgrade our investor base with these offerings. The other thing about it is that without raising any additional money, and if our cash burn stays the same, our cash will last us to the 4<sup>th</sup> Quarter of 2019. The reason that is important is because we have a number of milestones between now and then and most notably top line data in our INSPIRE study; which we expect in the second half of 2019. Because of our cash position, we are not currently planning on a financing, although we have been actively pursuing business development deals over the past year or so. Some of that you saw come to fruition in December of 2017, when we signed a deal with a company called HanX Biopharma for our CDK4/6 compound, our ON 123300 agent. Then in January of 2018 we signed our collaborative research and development arrangement with the National Cancer Institute, and in March of 2018 we signed a deal with Pint for Latin America for Rigosertib. We remain active in pursuing partners and we do expect that we will be able to get some more regional partnerships over the coming months.

**CEOCFO:** *You are presenting at the 2018 BIO Investor Forum. Would you tell us about that and any other conferences we should be aware of?*

**Mr. Guerin:** Between Steve, our CEO and myself, we present at conferences and meetings together. Sometimes it is two of us and sometimes it is just one of us. We are able to cover a lot of different conferences and meetings with this approach. Right now our CEO, Dr. Ramesh Kumar, PhD is at the BIO Investor Forum in San Francisco. That is happening as we speak. One of the most important upcoming conferences and meetings for us will be the American Society of Hematology in December this year. Steve will tell you about that conference.

**Dr. Fruchtman:** That is the most important Malignant and Benign Hematology Conference in the world. It happens once a year, typically the first week in December. This year it is in San Diego. One of the featured presentations always are abstracts on Myelodysplastic Syndrome, acute leukemia and new drug development, so we will have a robust team at ASH to participate in their MDS conference as well.

**CEOCFO: *Onconova announced a reverse stock split? What was that meant to accomplish and how will it help you going forward?***

**Mr. Guerin:** We announced that in September 25<sup>th</sup>. The reason we did the reverse split is because as you and many of your readers probably know, to maintain our listing on the Nasdaq capital markets exchange, we need to have closing bid price that is over a dollar. Earlier in 2018 our stock price went below a dollar and we got a notice of that fact from Nasdaq that we had 180 days to remedy that. The most common way that biotech companies fix that problem is with a reverse split. In our annual shareholder meeting in June of this year, our shareholders approved of us doing a reverse split at the discretion of the board. We executed that reverse split in September and the result is that we just filed an 8-K on Monday of this week announcing that we had received a letter from Nasdaq acknowledging that we were back in compliance with their continued listing requirements. We were successful in addressing that non-compliance, and we remain listed on Nasdaq.

**CEOCFO: *What can we expect over the next year, and why do you think Onconova is a special company?***

**Dr. Fruchtman:** We have some very important and influential milestones coming up in the next year. One is we anticipate full accrual in the second half of 2019 to our INSPIRE trial in high-risk MDS, studying intravenous Rigosertib. We anticipate our data from the combination trial of oral Rigosertib to be presented at a major medical meeting towards the end of 2018. We anticipate in early mid-2019 to have a first pediatric patient with a RAS driven cancer to be put on a study with Rigosertib as well. In addition in 2019, we anticipate a first in human trial with our research drug ON 123300. Therefore, we have some very important milestones towards the end of 2018 and 2019 as well.

**Mr. Guerin:** The other thing that I would add is at any point or at many points between now and the end of 2019, we should expect to close business development deals for certain geographies. I mentioned before that we have been pursuing that for a while, and as we achieved the milestone Steve just mentioned, we will also be making progress on business development deals. I expect to see some of them coming in, as well.

