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Company Report

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Onconova Therapeutics (ONTX - $1.74)

Healthcare/Biotechnology

KOL Call Pointed Out Serious Unmet Medical Need in 2nd-Line Risky MDS Patients

Ticker:	**ONTX**
Rating:	**Buy**
Price Target:	**$10.00**

We recently hosted a KOL call with Azra Raza, MD, an expert in MDS therapeutic development after ONTX announced the continuation of the rigosertib in 2nd-line MDS Phase III (INSPIRE) trial following their interim analysis. Dr. Raza is a world-renowned researcher and a physician regarding MDS, and currently the Chan Soon-Chiong Professor of Medicine and Director of the MDS Center at Columbia University. We are providing the excerpt from the transcript in this note, and highlights from the discussion include:

- **Highlights.** 1) The treatment goal in lower-risk MDS is to improve the blood counts, while in higher-risk disease, the focus is on improving survival; 2) current therapy landscape indicated that in lower-risk MDS, erythroid-stimulating agents (ESAs) affords 15% to 20% ORR; for 5q deletion patients (10%), lenalidomide has 67% response rate with therapeutic duration of approximately two years. Hypomethylating agents (HMAs) have 17% ORR in lower-risk MDS patients. Unmet need in all lower risk MDS are those who have failed ESAs, lenalidomide and HMAs and still need reducing anemia. For higher-risk disease, the first option is stem cell transplant (only 10% eligible). HMAs are the only treatment option for the rest with 40% to 50% ORR and eventually all patients will stop responding Median time is about 15 to 20 months. The outlook for higher risk MDS patients failed HMA therapy is "bleak" and no approved therapy is available; 3) MDS patient size breakdown is 70%, 15% and 15% for lower, higher and very high risk, respectively; 4) the size of lower risk MDS might be over-estimated given only one-third have survival of 26 months, while two-third are 14-18 months. The latter could potentially be higher risks; 5) Dr. Raza has treated over 100 MDS patients with rigosertib during various clinical studies and she was very encouraged by the safety and the effectiveness of the drug in both the lower and higher risk patients; 6) for drug development, she sees greater difficulty in successfully developing 2nd-line therapy for higher risk MDS given the vulnerability of the patients for tolerating AEs, like myelosuppression; and 7) for drug development of lower-risk MDS, Dr. Raza is more bullish on Luspatercept (Phase III) developed by Celgene and Acceleron given the anemia improvements.
- **Action.** We reiterate our Buy rating and $10 target price. Our valuation is based on peer comparable, probability adjusted DCF and sum-of-the-parts analyses. We believe ONTX remains undervalued given its two rigosertib formulations in late stage development as potential 1st- and 2nd-line MDS therapies.

Trading Data:

Last Price (1/19/2018)	$1.77
52–Week High (4/4/2017)	$3.88
52–Week Low (12/13/2017)	$1.36
Market Cap. (MM)	$19
Shares Out. (MM)	10.77

Earnings Estimates: (per share)

(Dec)	1Q	2Q	3Q	4Q	FY	P/E
FY-17E	-1.23A	-0.29A	-0.71A	-0.61	-2.69	N.A.
FY-16A	-2.65	-1.96	-0.29	-0.80	-4.44	N.A.
FY-15A	-5.69	-4.13	-2.60	1.28	-10.54	N.A.
FY-14A	NA	NA	NA	NA	-29.41	N.A.

Source: Laidlaw & Company estimates

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Dr. Azra Raza of Columbia Medical School is a world-renowned researcher and a physician regarding MDS. She currently is the Chan Soon-Chiong Professor of Medicine and Director of the MDS Center at Columbia University. She has started her work in MDS since early '80s and has established the MDS Program along with a tissue repository containing more than 50,000 samples from MDS and acute leukemia patients. She has participated in majority of the MDS drug development clinical trials. She has seen see 40 to 50 MDS patients every week. Assuming 40 weeks per year, we estimate she sees 1500+ MDS patients per year with two-thirds have lower-risk and one-third have higher-risk disease.

MDS and its treatment landscape

Laidlaw: Could you give us a brief description of MDS?

Dr. Raza: Myelodysplastic syndromes or previously referred to as pre-leukemia are diseases which predominate in the elderly population. The median age is about 70 years. The disease really presents with low blood count (anemia) in 85% of the time, the blood count which is significantly decreased is the red blood cells. In addition, they also have low white cells and low platelets. The reason why they have this low blood count is when we look at the bone marrow, what we have been established is that the bone marrow has few hematopoietic stem cells which are responsible for hematopoiesis producing a trillion blood cells a day. Now, one of the stem cells during a process of division can acquire a somatic mutation. The mutated stem cell then divides faster than a normal stem cell and its daughters fill up the whole marrow. They're able to still differentiate and mature but they just look abnormal. That is called dysplasia, or cells are looking abnormal. They mature fully to the terminal stages but just before entering blood, many of them drop dead by a process of apoptosis and that is why the blood counts drop. As such, the marrow is getting more and more filled up with rapidly-dividing clonal cells while the peripheral blood is becoming emptier and emptier as cells die before entering blood. This is also known as ineffective hematopoiesis or the blood cells are just not healthy enough to last all the way. A third of the patients can also show problems in a daughter cell which is supposed to become a mature white cell but does not mature. An immature cell is called a blast. Up to 5% blasts are normal in the bone marrow but when that number reaches 20%, it's called acute leukemia. Therefore, a third of the patients do have this problem of a daughter cell not maturing, remaining a blast and expanding its population slowly. The thing everyone must appreciate though is that MDS patients whether they have what we call lower-risk or higher-risk disease, is risk of dying from something, leukemia or low blood counts. Whether they have lower-risk disease or higher-risk disease, whether the blast is 5% or 19% or 25%, every one of them will have a cytopenia which means a low blood count. That is the essential feature of MDS and that's what we are always trying to improve. Now, for higher-risk patients, the problem is survival, and therefore, we try to direct our treatment towards saving patients' lives and improving their survival. Lower-risk patients can live for many years but can have a poor quality of life if they are transfusion-dependent. The goal in lower-risk disease is to improve the blood counts. In higher-risk disease, the focus is on survival.

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Laidlaw: Next question is how is MDS being treated? Could you just break down for the high-risk versus the low-risk?

Dr. Raza: The focus in higher-risk disease is trying to improve survival but also help blood counts of course because as I said, 100% patients will have low blood counts. Right now, there is only one strategy of treatment which is FDA-approved for higher-risk MDS and that is hypomethylating agents. There are two FDA-approved hypomethylating agents, 5-azacitidine and decitabine. As I said, the focus of treatment in lower-risk disease is improving the blood count. For lower-risk MDS patients the same things also apply, the same hypomethylating agents and in addition, for 10% of lower-risk MDS patients who have a chromosome 5 abnormality, lenalidomide is also approved for treatment of these patients.

Laidlaw: Okay, great. Let's start with the low-risk patients particular for 5q deletion patients that the Revlimid is the approved treatment. What do you think are the pros and cons of this drug for treating those patients and is this drug actually more palliative or really disease modifying?

Dr. Raza: That's so important to address because so far as far as we know, for lower-risk MDS, all treatments are palliative because we have not done prospective survival trials to see if they actually affect the natural history of the disease by improving survival. Those studies would be very hard to do because these patients can live for many, many years and may die of other factors because they are elderly. Therefore, the fact that it's called a disease-modifying agent doesn't necessarily mean that in any prospective trial, it has shown to affect the natural history of the disease. However, the reason it was developed was that in fact, I am the primary person who started using – I was the first to use thalidomide in myelodysplastic syndromes. The reason was that I had already shown that cells are dying before entering blood because of excessive amounts of a protein called tumor necrosis factor or TNF that is being produced. Thalidomide had just become approved in 1998 for treatment of leprosy in the United States and this drug has an anti-TNF effect. Therefore, I was looking for anti-TNF drugs. I started to use this in MDS and sure enough, I saw 20% patients had complete remissions. I published these data in the journal of Blood and then because of its teratogenic toxicity, the company then developed an analogue - multiple analogues of thalidomide and one of them is lenalidomide. When that was tried in a Phase 1 trial by oncologists, it showed that the best responders were those who had deletion 5q. We don't know exactly what the mechanism of response is. Various proposals have been made but none have been found to be predictive of response or non-response because even within deletion 5q, the complete response rate is 67% and patients stop responding. The median duration of response is only about two years at most. So even when those patients respond, half of them stop responding within two years because there is clonal outgrowth of cells with properties that are resistant to lenalidomide. I hope this answer both parts of your question.

Laidlaw: Sure. That's very helpful and I believe both of the drugs were the first step that make the company called Celgene eventually becomes successful from that class of drug. So similar question, for lower-risk MDS patients, how effective in general is blood transfusion or using ESA, the erythropoietin-stimulating agents?

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How much of these patients, this modality can last before they get any worse and what percentage of patients really can be well-managed to fight some of these tumor modalities?

Dr. Raza: So first of all, the erythroid-stimulating agents are not FDA-approved for these indications because no prospective trial has been done but we all use them. They produce a response in 15% to 20% patients with MDS. The response takes about 8 to 12 weeks to appear and it can last anywhere from a few months up to many years in very low-risk MDS patients. However, eventually, most patients, 90-plus percent will stop responding to erythroid-stimulating agents also. Once they stop responding and the anemia starts deepening, that's the problem. To begin with, the patients who respond are ones who have a low serum baseline erythropoietin level of less than 500 and are not transfusion-dependent yet. Therefore, the anemia has become profound but they're not getting blood yet. Those are the patients who have a good 70% chance of response but those are the rarer patients. Most patients will have a higher than 500 EPO level and/or are already transfusion-dependent, so the overall response rate is about 20%.

Laidlaw: Okay, great. That's very helpful for us to understand. The next question is for the high-risk MDS patient and there is only one class of the drug, the hypomethylating agents (HMAs) and there're two of them. What do you see are the pros and cons in each one of those and do most of the patients eventually become refractory to these drugs?

Dr. Raza: When we say a high-risk MDS patient, this is a great matter of concern because as I told you earlier, survival is the issue. They can die very quickly also. Therefore, when dealing with a high-risk patient presents, the first question we ask is can the patient tolerate high-dose chemotherapy? If yes, then that means they could be potential candidates for allogeneic stem cell transplant and immediately that is the first choice of treatment for high-risk patients is to get a transplant. If that is not an option, which doesn't happen to be the option for more than 90% patients, then the next step is only hypomethylating agents and you have a choice of 5-azacitidine or decitabine. I always choose 5-azacitidine over decitabine because in prospective studies, azacitidine has shown improvement in survival compared to physician's choice, whereas, decitabine did not show that significant improvement in survival over placebo or physician's choice or best supportive care. Why is that difference there? Remember, 5-azacitidine is the parent drug. It is a prodrug. It gets converted in the body to the active form. It can be incorporated both into the RNA and the DNA; so when it's incorporated or it affects the RNA then it affects the proteins that are being produced in the cell which means it affects a lot of the cytokines like TNF alpha, et cetera. When it gets incorporated into the DNA then it has a hypomethylating effect in promoter sites as we expected, and then it reactivates some of the silenced tumor suppressor genes and causes the cell to die. Hence, it affects both the seed and the soil, the bone marrow microenvironment as well as the MDS cell. 5-azacitidine because of its activity on RNA and DNA affects seed and soil. Decitabine on the other hand is the analogue of 5-azacitidine. It is six times more effective in suppressing the DNA methyltransferase enzyme causing demethylation, or hypomethylation

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so it's very active on the cell but because it only has its effect on DNA, it has no effect on the microenvironment or the soil. That is why it can kill cells rapidly but then the environment is still remaining poisonous and that's why it doesn't improve (survival) – they affect the natural history of the disease which is a much longer issue. Short-term it could produce a response in terms of improving blood counts but long-term, it fails to have that desired effect of improving the microenvironment. So that's why I generally choose 5-azacitidine when I'm dealing with high-risk MDS patients except those who are going on to transplant because there, the idea is we have to kill as many blasts as possible so it's better to go with decitabine. In terms of response, 40% to 50% patients will respond. So right off the bat, 50% to 60% patients are going to be resistant to hypomethylating agents and that is called primary resistance to HMA. Then practically every patient because it's not curative, so eventually all patients will stop responding as well but if they have responded first and then stopped responding, that's called a secondary HMA failure. Therefore, what I'm saying is if we have 100 patients with high-risk disease, 40% to 50% will respond, 50% to 60% will not respond to begin with. Of those who respond, everyone will stop responding. Median time is about I believe 15 to 20 [months] and then they stop responding and then we have secondary HMA failures.

Laidlaw: Okay, great. That's a very clear for treatment landscape there. Then let's follow up with a question for the high-risk MDS patients, how would they be managed medically once they failed either refractory or relapse from the HMA therapy? What's their outlook in terms of survival and other aspects?

Dr. Raza: Outlook is very bleak because we don't have anything to offer them. We are trying and we have some clinical trials oddly and hoping that some drugs will improve survival and survival is really gloomy because it's about 22 to 24 weeks median survival afterwards. They are resistant to azacitidine or decitabine so HMA failures in high-risk MDS have a short survival with no options right now except the clinical trial.

Laidlaw: Therefore, the re-treatment usually it is ineffective or probably maybe useless in that regard?

Dr. Raza: Yes.

Laidlaw: Given that the MDS is comprised of patient with a varying risk profile based on multiple prognostic variables, do you view the future drug developments should be let's say more fine-tuned based on current risk classification such as IPSS-R subgroups or other criteria or do you think the current sort of grouping of higher and lower risk will be sufficient to develop treatments going forward or develop treatments going forward?

Dr. Raza: No. I think that current IPSS revised classification is not the most accurate especially we tend to overestimate lower-risk disease patients. Why do I say that? Because if we classify 100 patients as having lower-risk MDS, what we see and over and over, like MD Anderson has shown it, a Spanish group using over 800 patients just confirmed their finding. What we find is that if we classify 800

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patients as having lower-risk MDS, a third will survive for 18 months median, a third will survive for 26 months median but a third will only survive for 14 months, yet we are calling the patient whose survival is a median of 18 months and that whose survival is 14 months, we are calling both of them lower-risk MDS. How is that possible? Well, because the biology can be very different even though morphologically and cytogenetically, they look similar. In other words, we overestimate clearly the patient who had a 14-month median survival definitely needs some more intervention and is really high-risk disease. We are just calling them low risk, so there are a lot more high-risk patients miss-grading as lower-risk disease is what I am saying.

Laidlaw: Maybe just a follow-up on that, is there a clear way, for example, using biomarkers or other aspects currently to separate the patient with a 36-month outlook versus the 14-month outlook so people can develop therapies for each of those groups that – or better serve these patients?

Dr. Raza: Sadly, no. That is one of issues that we don't have surrogate markers that would identify patients who having very bad disease or not. So right now, I mean that's what IPSS-R tried to do is to go, okay, not 5% blasts but 2% to 3% blasts, 3% to 5% blasts, 1% to 3% blasts. It's crazy. I mean one man's ceiling is another man's floor. [In order to better adjust the prognostic system], that means that the whole classification has changed so we need better biomarkers in terms of genetic profiles. I am the one who published in the New England Journal of Medicine in 2011 that if there are mutations in one of five genes: p53, ASXL1, EZH2, ETV6 then patients can have a worse survival if they have the mutation. However, half the patients will still do well, so it's not as if we can say, "Okay, this gene is it," so except p53 is associated with a poorer survival but not necessarily universal. So, no, there is no specific biomarker. There's no specific surrogate marker or genetic profile. There are combinations of things, patients have high blasts and assessing risks of whole host of things together tell us whether there the risk is high or low, not any single one or two markers.

Laidlaw: Maybe just a little bit follow-up on the biomarker question as any new biomarkers to be used for prognosis and maybe for detecting treatment efficacy in drug development in the MDS?

Dr. Raza: I mean everybody and their grandmother is trying.

Laidlaw: So, if we recap at this point, what do you see the general unmet medical needs in treating lower-risk patients and also for treating higher-risk patients and whether that'd be first or second line settings?

Dr. Raza: So, to except in lower-risk MDS patients, first line of treatment is erythroid-stimulating agents, 15% to 20% response. Second, if the patient has deletion 5q which 10% patients have, there's a 67% chance of response and then they stop responding within two years. Third, we have hypomethylating agents where the chance of response is only 17% in lower-risk MDS patients. So that's the lower-risk MDS which means basically, the unmet need is all patients who have failed erythroid-stimulating agents, all patients were not deletion 5q and not responding

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to hypomethylating agents. That's the unmet need and the real issue is how do we improve anemia in these patients? For higher-risk disease, we can take the first step is transplant. If that's not possible, we go with hypomethylating agents. If patients fail hypomethylating agents, whether primary or secondary failures, we have no other option. That is the unmet need here.

Laidlaw: Roughly 30% of the MDS high-risk patients will progress into AML and is there some sort of pharmaceutical solution on the horizon that potentially could slow down or try to solve this problem?

Dr. Raza: Well, I tried to point this out earlier that 70% patients who have high-risk MDS will also die within six months but not of AML and only 30% will die of AML. So, AML is not the only problem in high-risk MDS patients. It's the bone marrow failure is happening very, very rapidly. The count drops so fast you can't keep up with transfusion. That's the real issue in high-risk MDS. I mean all we are trying to do is palliate and prolong. If we can prolong by 2.5 months, the drug will be approved by the FDA. That's what everyone's short-term goal seems to be but everyone who is interested in studying the disease is trying to understand what can we do to improve the hematopoiesis which is causing the cells to die so fast.

Laidlaw: What's sort of breakdown in terms of number of patient percentage between the very high risk within the high-risk MDS populations?

Dr. Raza: 70% have lower risk, 30% have high risk. Out of those 30%, very high risk would be 15% of the entire MDS population.

Laidlaw: How are the very high risk MDS patients being managed medically at this point?

Dr. Raza: We don't have any effective treatment.

Her thoughts and experiences about rigosertib

Laidlaw: Recently, Onconova is developing rigosertib which is targeting RAS and associated signal transduction. Could you provide us some of your understanding and maybe your experience about this drug and possibly any potential advantage of this drug if it gets approved in the future?

Dr. Raza: I want to say first of all that I am probably the single investigator in the world who has treated over 100 patients with rigosertib. There are three areas I want to mention rigosertib in so I started by using the intravenous drug and I've treated about 35 patients with it in the Phase I and II trials and then I also did a big trial of oral rigosertib pill in the lower-risk MDS patients and now I'm doing the very-high-risk trial with the INSPIRE trial with rigosertib. So, my experience is as follows, for lower-risk MDS, I think it's a fantastic drug. I am very anxious and very excited that once the INSPIRE trial shows good results and Onconova receives some serious backing that they will allow me to conduct the lower-risk trial with the oral rigosertib. We saw 35% complete transfusion independence. I just reported it in December of 2017 at the ASH meeting that the response rate

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for ESA-resistant patients can be as high as 35% and I think that's a very, very amazing number for lower-risk MDS to gain transfusion independence. In fact, I have two patients who I think basically got cured of the disease. I also reported one patient who is six years out, lower-risk MDS, p53 mutation, six years out with rigosertib, transfusion dependent. That is dramatic but that one was with combination of rigosertib and erythroid-stimulating agent. I think my experience, lower-risk MDS, oral rigosertib, very exciting. I'm following these patients still. I treated over 60 patients with this drug with lower-risk MDS and I'm excited to restart the drug as soon as Onconova is able to support this trial.

The second area is where rigosertib has been used in all MDS patients in combination with hypomethylating agent, azacitidine and that study also shows 35% response rate in the doublet trial and now Onconova has plans to take it to first-line treatment randomizing patients between the doublet versus azacitidine alone. So, it's a very exciting time for the oral drug which can be used in lower-risk MDS patients as well as combo with azacitidine, again both places, 35% response rate, very exciting.

Third is patients now being treated with the intravenous formulation. This is the INSPIRE trial. You know that the trial – the Phase III had failed but now the INSPIRE trial is ongoing in a selected subset of patients where the survival is the issue. As you know, I have been saying all along that in higher-risk MDS that's what we are – our goal is to improve survival and it seems that when we look back at the failed Phase III data that the patients who almost doubled their survival compared to the placebo arm were those who had very-high-risk disease and were primary HMA failures. So, as I told you, 50% to 60% patients with very high risk or higher-risk MDS will be primary HMA failures and these are the patients who seem to have – they don't respond to azacitidine but they seem to respond well to rigosertib and that makes sense because one strategy is not working, the other will work and that's a very good proof where survival was very short but INSPIRE trial is testing this. Now, the latest result that I believe the company announced and you know about is the fact that the committee has reviewed the data and found it exciting, interesting. They didn't stop the trial. They want the trial to continue but they've asked to add more patients to bring more power and it's only a question of statistical significance will become much more clear and direct if we add more patients. So, they've asked to add more patients and I think the company is aggressively going forward to do that.

Laidlaw: It seems that you have a very great experience on this drug. Should I assume that if this drug gets approved, you will use it at least initially in the higher-risk second line settings, would you use this drug as a monotherapy which is the study was conducting right now or you may even consider use this one along with other sort of treatment modalities and hopefully that can do even better?

Dr. Raza: Too early to say that right now.

Laidlaw: Rigosertib is a RAS-targeting therapy, and how valid do you think this approach potentially treating MDS? and is there any other molecular target currently you think was also valid for potentially treating MDS?

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Dr. Raza: No. I can't answer those questions. There are all the targets that are there. RAS has been a known target for a long time. MAP kinase is a target. *Jagged1* is a target. *Notch1* is a target. I mean there are all kinds of targets. Yes. so, whether a target is [clinically validated will be not be fully determined] until we understand much more about how the downstream signals and pathways are being affected by these targets, I don't think we'll be able to develop effective therapies. I mean a lot of pathways are being targeted right now and RAS is a good one. That's my answer.

Others in development MDS treatment programs

Laidlaw: Let's talk about a little bit the pipelines currently in development from other companies.

Dr. Raza: I don't know of any great drugs that are coming around. I mean anything that works in AML is tried in MDS. For example, venetoclax (Venclexta) is an obvious example as the trial started, the combination of Vidaza (5-azacitidine) and venetoclax, I had two patients on the trial and within four days, there was panic and they asked us to hold the drug because the myelosuppression was too much. So now that trial is on hold. I mean there are just not enough agents. If you try to use aggressive cytotoxic agents in higher-risk MDS patients, you end up with extreme myelosuppression even lower cytopenia then patients just die. So that's why I love rigosertib for higher-risk MDS because here is a drug which is not doing that. It is not causing the severe myelosuppression that is seen with all these other agents and yet, it is able to prolong survival by somehow affecting the clones so it's actually having an effect on the natural history of the disease.

Laidlaw: Okay. That's good to know and I think probably that's one of the reasons as we examine that the landscape and discovered that fewer drugs were targeting higher-risk MDS probably just because the patient was very vulnerable. So, if let's look at the lower-risk MDS, there's a little bit as more drug developments in that front. Was there any product so far, you've seen or you understand that you think you like and why or if you're excited.

Dr. Raza: Well, I am excited about the Celgene drug, Luspatercept right now and that is specifically targeting a subtype of lower-risk MDS, refractory anemia with ringed sideroblasts. It seems to improve their anemia which is a good thing. That is one drug, Luspatercept, to be excited about. The Syros' trial 1425, the SY-1425 which is a RARα agonist, all-trans retinoic acid analogue, that hasn't turned out to be great. They reported their data in ASH meeting and there was what I believe only one complete responder out of 50-plus patients so it's not looking that great.

Laidlaw: We also noticed that there are at least two so the next-generation HMA which one is the oral azacitidine and the other one is decitabine developed by different companies. What's your thought about in general sort of next-gen HMA agents? Does this class of drug need a lot of improvement or simply just try to fine tune to treat different patients? What's your thought?

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Dr. Raza: My thought is that Celgene is developing the oral azacitidine but by another indication, they have chosen is one of thrombocytopenia, that is, to try and improve their platelet count because they have to distinguish that as a different kind of drug. Its biological activity is different than azacitidine because otherwise, they can't patent or they can't use the patent. So, I think that the indication they're going for is an important one. It's thrombocytopenia because we don't have any drugs for thrombocytopenia but they're having a difficult time because lower-risk MDS patients with thrombocytopenia were transfusion-dependent, not a very small percentage and that population they're trying to develop because that was the only population that had the unmet need. So, it's taking them a long time. I mean oral azacitidine trials have been going for many years, not that exciting to me.

Laidlaw: First of all, we really appreciate your participation and to help us out here. thanks to all the participants in this conference call.

Dr. Raza: Thank you. Bye-bye.

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Anticipated milestones in 2018 and beyond

Product	Indication	Event	Timing	Importance
Rigosertib	Myelodysplastic syndromes (MDS) - high risk	Potentially complete Phase III (INSPIRE) patient recuritment	**1H19**	***
		Potentially report Phase III (INSPIRE) top-line results	**2020**	*****
		Potentially finalize Phase III study design for oral formulation azacitidine combination as first-line treatment and with possiblbe SPA designation	**2018**	***
		Potentially start oral formulation azacitidine combination Phase III study as first-line treatment	**2018**	***
	Pediatric RASopathies	Potentially start Phase I study	**2018**	***
		Additional business developments	**2018**	****

***** / ***** Major catalyst event that could impact share price very significantly while *** event is more informative*

Source: Laidlaw & Company and company presentation

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Major Risks

Clinical study failure could have a major impact on ONTX share value. Given the study design of the ongoing rigosertib INSPIRE Phase III study was based on outcomes from retrospective analysis of a prior failed Phase III clinical study (ONTIME), there are certain inherited risks beyond that of a typical Phase III study as post hoc analysis could potentially identify any favorable features based on the set criteria for analysis. Also, given rigosertib is the only clinically advanced asset in ONTX's portfolio, negative results of the Phase III and additional clinical studies could have a materially negative impact on the shareholder value.

Without a Ras-targeted drug being clinically successful and approved, this molecular target has not gained sufficient clinical validation and therefore has greater uncertainty. Although the relationship between Ras mutations and tumorigenesis was known for a few decades, there are no drugs that target Ras that have been approved. Given Ras has been characterized as potentially "undruggable", there are potentially greater clinical risks for a Ras targeting therapy compared to drugs that target other more proven molecular targets or development platforms.

Product may not be approved or reach anticipated sales. Although ONTX's current pipeline products, especially the leading rigosertib, have exhibited the potential to generate positive clinical outcomes from current and future trials; it remains too early to project whether any of these products would be approved by regulatory agencies. Even if the products were to enter the market, sales could be significantly below projections due to the specific product label under approval, physician consensus for prescribing the drug, changes of treatment paradigms, entrance of competitors, and the possible changes in pricing flexibility and payer reimbursement. A revenue outlook below expectations could also negatively affect ONTX shareholder value.

Additional financings could dilute shareholder value. Although the company had ~$8MM cash by the end of 3Q17, ONTX most likely would need more financial resources going forward if they want to complete the rigosertib clinical developments and potentially expand and further develop their additional pipeline. Should the future operational expenses, especially from R&D and COGs, increase significantly, products not receive FDA approval, or product revenue not reach expectations; the company might need to issue new equity to raise additional cash. Under such a scenario, the share value of existing shareholders could be diluted.

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Figure 1: Income Statement

Onconova Therapeutics - Income Statement

($'000)	2015	2016	1Q17	2Q17	3Q17	4Q17E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
Revenue													
Rigosertib sale										16,200	50,708	122,096	218,574
Non-product revenue	11,456	5,546	210	324	110	190	834	523	2,050	2,100	1,000	500	0
Total revenues	11,456	5,546	210	324	110	190	834	523	2,050	18,300	51,708	122,596	218,574
COGS									0	1,620	5,071	12,210	21,857
Net revenue									0	14,580	45,637	109,886	196,717
Total net revenue								523	2,050	16,680	46,637	110,386	196,717
General and administrative	9,533	9,178	2,116	1,779	1,728	1,693	7,316	7,551	8,230	8,889	9,422	9,799	10,093
Research and development	25,895	20,071	4,886	4,614	5,141	5,192	19,833	20,143	22,560	25,041	26,794	24,115	24,597
Marketing and sales									22,000	23,540	24,717	26,447	27,770
Total operating costs and expenses	35,428	29,249	7,002	6,393	6,869	6,886	27,150	27,694	52,790	57,470	60,934	60,361	62,460
Operating Incomes (losses)	(23,972)	(23,703)	(6,792)	(6,069)	(6,759)	(6,696)	(26,316)	(27,171)	(50,740)	(40,791)	(14,296)	50,025	134,257
Change in fair value of warrant liability		3,988	(1,549)	3,474	(210)	140	1,855	(2,468)	(450)	(400)	(350)	(350)	(350)
Interest expense							0						
Other income, net	(35)	62	0	11	8	10	29	45	50	54	60	66	72
Net loss before income taxes	(24,007)	(19,653)	(8,341)	(2,584)	(6,961)	(6,546)	(24,432)	(29,594)	(51,141)	(41,136)	(14,587)	49,741	133,979
Income taxes	16	14							0	0	0	18,404	49,572
Net Income (Loss)	(24,023)	(19,667)	(8,341)	(2,584)	(6,961)	(6,546)	(24,432)	(29,594)	(51,141)	(41,136)	(14,587)	31,337	84,407
Net loss attributable to non-controlling interest	44												
Net loss attributable to Onconova Therapeutics, Inc	(23,979)	(19,667)	(8,341)	(2,584)	(6,961)	(6,546)	(24,432)	(29,594)	(51,141)	(41,136)	(14,587)	31,337	84,407
Accretion of redeemable convertible preferred stock													
Net loss applicable to common stockholders	(23,979)	(19,667)	(8,341)	(2,584)	(6,961)	(6,546)	(24,432)	(29,594)	(51,141)	(41,136)	(14,587)	31,337	84,407
Basic and diluted net loss per share	($10.54)	($4.44)	($1.23)	($0.29)	($0.71)	($0.61)	($2.69)	($2.03)	($2.91)	($2.00)	($0.65)	$1.33	$3.57
Shares of the basic and diluted net loss	2,274	4,427	6,771	8,999	9,851	10,771	9,098	14,571	17,571	20,571	22,571	23,571	23,671
Margin Analysis (% of Sales/Revenue)													
Costs of goods									10%	10%	10%	10%	10%
R&D	83%	165%	1008%	549%	1571%	891%	877%	1444%	401%	49%	18%	8%	5%
SG&A	226%	362%	2327%	1424%	4674%	2733%	2378%	3851%	1100%	137%	52%	20%	11%
Operating Income (loss)	-209%	-427%	-3234%	-1873%	-6145%	-3524%	-3155%	-5195%	-2475%	-223%	-28%	41%	61%
Net Income	-210%	-355%	-3972%	-798%	-6328%	-3445%	-2929%	-5658%	-2495%	-225%	-28%	26%	39%
Financial Indicator Growth Analysis (YoY%)													
Total Revenue	1332%	-52%	-86%	-86%	-93%	10%	-85%	-37%	292%	793%	183%	137%	78%
G&A	-37%	-4%	-33%	-15%	-13%	-13%	-20%	3%	9%	8%	6%	4%	3%
R&D	-48%	-22%	-16%	-17%	29%	11%	-1%	2%	12%	11%	7%	-10%	2%
M&S										7%	5%	7%	5%
Operating Income (Losses)	-62%	-17%	-22%	-16%	15%	4%	-7%	2%	91%	9%	6%	-1%	3%
Pretax Income	-62%	-18%	15%	-52%	335%	20%	24%	21%	73%	-20%	-65%	-441%	169%
Net Income	-62%	-18%	15%	-52%	335%	20%	24%	21%	73%	-20%	-65%	-315%	169%
EPS	-64%	-58%	-54%	-85%	140%	-24%	-40%	-24%	43%	-31%	-68%	-306%	168%

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Source: Bloomberg LP; Company reports; Laidlaw & Company estimates

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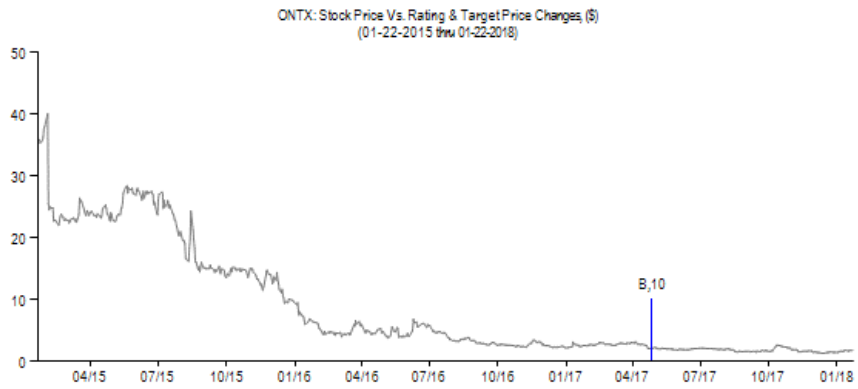
Additional information available upon request.

‡ Laidlaw & Company has received compensation from the subject company for investment banking services in the past 12 months and expects to receive or intends to seek compensation for investment banking services from the company in the next three months.

RATINGS INFORMATION

Rating and Price Target Change History



3 Year Rating Change History

Date	Rating	Closing Price ($)
04/27/2017	Buy (B)	2.13

3 Year Price Change History

Date	Target Price ($)	Closing Price, ($)
04/27/2017	10.00	2.13

Source: Laidlaw & Company **Created by: Blue-Compass.net**

Laidlaw & Company Rating System*		% of Companies Under Coverage With This Rating	% of Companies for which Laidlaw & Company has performed services for in the last 12 months	
			Investment Banking	Brokerage
Strong Buy (SB)	Expected to significantly outperform the sector over 12 months.	0.00%	0.00%	0.00%
Buy (B)	Expected to outperform the sector average over 12 months.	66.67%	29.41%	1.96%
Hold (H)	Expected returns to be in line with the sector average over 12 months.	1.96%	0.00%	0.00%
Sell (S)	Returns expected to significantly underperform the sector average over 12 months.	0.00%	0.00%	0.00%

ADDITIONAL COMPANIES MENTIONED

Celgene (CELG: Not Rated)
Acceleron (XLRN: Not Rated)

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