Ascentage Pharma Group International
Fireside Chat Discussion with Umer Raffat
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TRANSCRIPT

Participants:

Dr. Dajun Yang, MD, Ph.D.
Chairman & Chief Executive Officer, Ascentage Pharma Group International

Dr. Veet Misra, Ph.D.
Chief Financial Officer, Ascentage Pharma Group International

Umer Raffat
Senior Managing Director, Equity Research, Evercore ISI

Umer Raffat:

OK, hello everyone. Thank you guys for joining. I realize it's a really busy morning and I didn't want to reschedule this after some of the news came out and I figured it's 10 at we structured it for 10 AM and we had time lined up with the management team and Ascentage. So I wanted to be respectful.
But like I shared in my prior emails, and I mentioned previously as well, I think the key goal for me was to make sure that with all the M&A activity that's happened in the space, we have a good understanding of some of the other clinical stage and mid-stage and late stage assets programs as well. So, this company in particular is in the hematology space. And it's one because my initial interest in the company originated with some of their work in the CML space because as we were spending a lot of time on Terns and Enliven and etc. But there's a path beyond that. I'll jump right in. Do you want to kick it off?

Dajun Yang:

Thank you. Good morning everyone. Thanks for this opportunity. Umer. I think that there are three key takeaway points for this discussion:
High risk MDS is going to define Ascentage as key player in this area that will potentially provide the Best-in-Disease drug for this global unmet medical need. Second, we are actually running POLARIS-1 in Ph+ALL. This is the first-line global registrational study of Olverembatinib. There's already available global data including U.S. data, doubling the MRD-negative CR rate of ponatinib. We have been even more data in combo with Blinatumomab showing oral presentation at the ASCO just a couple weeks ago by leading investigator, Dr. Elias Jabbour.
Another exciting global registration trial is the POLARIS-2 covering CML.
So, basically we have 3 potential NDA filing next year, POLARIS-1 POLARIS- 2 and NDA for HR MDS in 2027
Then opportunities expand multiple folds with Lisaftoclax as a cornerstone asset, including with proprietary BTK protein degrader APG-3288.

Umer Raffat:

Excellent. I was going to perhaps kick things off with the with the CML molecule. Could you remind us on the CML molecule, where exactly are you is it a second gen or a third gen BCR-ABL and what's novel about it?

Dajun Yang:

Our asset on the CML is the third generation BCR-ABL inhibitor, very potent against the especially T315I mutation, which is a gatekeeper define the third generation BCR-ABL inhibitor, And also is a multi kinase really broad spectrum against multiple mutations in BCR-ABL, including those compound mutations.

Umer Raffat:

Have you shown data in T315I

Dajun Yang:

Yeah, we are probably the most potent one against T315I mutations including those compound mutations on top of T315I.

Umer Raffat:

And the MMR rate is what in T315I

Dajun Yang:

MMR rates depend on the disease and the lines of a treatment we have about 50 or 60%. Umer, if you don't mind. Let me first introduce the overview of the company.
We are actually global commercial stage hematology oncology company from day one, our mission is to focus on global unmet medical need and for global market. We are very proud that now we have a two novel commercial stage products Olverembatinib and Lisaftoclax.

We are the first dual listed company on NASDAQ and also Hong Kong Stock Exchange about six years ago. We have a global issued over 500 patterns and over 1000 pending (applications) and we right now have 7 novel active compound in global clinical stage and over at least 30 FDA cleared INDs. But, more importantly, we have you know 13 global registration trials. We completed four of them, nine ongoing, and the focus is on seven compounds for global registration trials.

So, I think that the next is a little busy slide, but the key point is that we are global innovative highly de-risked, with a super late-stage pipeline.

The first product, Olverembatinib, is meant as name to overcome resistance. Sometimes we just call it Oliver. It is a third-generation BCR-ABL inhibitor already approved for CML-CP since 2021 in China. Basically we've demonstrated in thousands of patients, real world safety efficacy, especially long-term safety for some patients for nearly 10 years now. And there is the FDA and EMA cleared global registration trials covering both CML and Ph+ALL.

Lisaftoclax is a Bcl-2 selective inhibitor approved as single agent in post-BTK CLL/SLL since July last year. So, globally, we are the second Bcl-2 selective inhibitor to the market. But, in terms of single-agent for post-BTK CLL/SLL, we actually globally the first one. We have this unique daily dose ramp-up advantage enhancing safety with a low risk of DDI. We also are running two FDA and EMA

cleared global registration trials.

As you can see, we also have a very rich pipeline covering multiple novel targets. Some of them can be first-in-class if successfully carried out like MDM2-p53, our dual Bcl-2/BCL-XL and also PRC2 inhibitor, which is an EED inhibitor - APG-5918. We also have moved our BTK degrader into Phase one in the U.S. and China early this year.

Umer Raffat:

Got it. OK, great. So I wanted to maybe kick things off on the on the CML side with the BCR-ABL. Just remind me, you're approved in China and what's the sort of market share in China plus when do we get Phase 3 data for U.S. filing and is that the plan?

Dajun Yang:

Yes, I think that first, we were the first and only third generation BCR-ABL inhibitor approved and also getting the NRDL coverage in China. So there are thousands of patients of available data in the real world. We were the first and the only one in the last three years. And last year both of Ponatinib and Asciminib were approved in China, but they're not getting an NRDL coverage yet. So we are the only third generation BCR-ABL inhibitor available in China. Globally, we have done the bridging study around five years ago with MD Anderson. Dr. Hagop Kantarjian and Dr. Elias Jabbour conducted it and we published a JAMA oncology paper demonstrating U.S. data in heavily pretreated patients.
We demonstrated very robust MMR rates. For the patients who failed Ponatinib, who failed Asciminib or, in some cases, patients who failed both Ponatinib and Asciminib, we achieved excellent MMR rates. These already had an oral presentation at ASCO and ASH as well as been published in JAMA Oncology. But, more importantly, also for those with the T315 mutations. So, those who patients who were fourth, fifth in line, heavily pretreated, as I mentioned, you know those who failed the Ponatinib and Asciminib or both, we demonstrated excellent MMR rates.

Umer Raffat:

OK, remind me again, timing of Phase 3

Dajun Yang:

Timing of Phase 3 for CML in our POLARIS-2 study, we already opened more than 20 countries and over 100 sites, our goal is to complete POLARIS- 2 for CML-CP patients globally early later this year or early next year.

Umer Raffat:

POLARIS-2?

Dajun Yang:

Yeah, POLARIS-2 for CML and the 6-month MMR rate is the primary endpoint for Accelerated Approval. So, basically, we're looking for NDA filing in second-half of next year.

Umer Raffat:

So, on clinicaltrials.gov, if I may, it says the study should have been completed by December 2025. Could you just give us a little bit of sense on the POLARIS-2 trial?

Dajun Yang:

Yeah, those are not actively updated. I think that those were older information. But, as I mentioned, we have those data in the U.S. and globally and POLARIS-2 is cleared by FDA, EMA, and multiple countries. This is a randomized Phase 3 trial as FDA requires a RCT, and it was a Bosutinib as a control arm at a 2 to 1 ratio, 190 patients, investigation arm and the Bosutinib arm is 95 patients. One thing important to help patient enrollment is the FDA agreed with a crossover late last year that helped our enrollment a lot.

Umer Raffat:

OK, and if I may, what's your expectation on MMR because I think this study has two parts, there's a non T315I and T315I. What's your expectation on MMR for the T315I?

Dajun Yang:

The control arm in this case is Bosutinib, which is not active against the T315I mutation. So, the Part B of POLARIS-2 is a single agent single arm with T315I mutants only in total about 48 patients. We expect the MMR rate for this particular group of patients is probably around 50%, based on our previous data and we are probably the most potent and the T315I mutation or compound mutations.

Veet Misra:

Yeah, that would that would put us as one of the more potent out there because

even if you look at the non-T315I mutations, that number in itself would be, you know, pretty acceptable.

Umer Raffat:

Yeah. I think that's really important. And I guess as we think about some of the activity we've seen from other folks on T315I, I mean, obviously even Terns had very limited data, but based the T315I as you're recruiting, are they all Asciminib experienced?

Dajun Yang:

Not all. But we include do Asciminib-experienced patients as well. We published the U.S. data, right? The patients experienced Asciminib or both Ponatinib and Asciminib basically showing how we addressed unmet medical needs and demonstrated good efficacy data and MMR rates.

Umer Raffat:

Yeah, that makes sense. And then also in terms of sort of, I know you're sort of putting these 50% (MMR) numbers out there, but I don't know if you necessarily need to hit a number that high for it to be considered fairly competitive. I guess could you put that into perspective for us as well? What's an MMR number in general that will be considered fairly competitive, even if let's say it's like a 25% MMR and addressing T35I is competitive or not.

Dajun Yang:

I think the 25% for those who failed the Ponatinib and Asciminib who probably is sufficient, right? This is a unmet medical need, but for patients, fail one of them maybe let's say Asciminib, right, if we can hit the 30 or 40%, I think that that's also good enough.

Umer Raffat:

Makes sense. I know it's an open label trial. Do you have visibility on whether prior observations of these MMR rates are replicating in the Phase 3 as well?

Dajun Yang:

That's hard to say because this is ongoing registrational trial, but according to our experience, these are the U.S. data, with an MD Anderson leading PI that we believe and they do as well as probably the most potent one especially nowadays as more patient experience first line Asciminib and Asciminib itself, you, know requires five times dose preclinically and clinically and also five times

the cost (for T315I mutations), right? So, they basically apply to about 40% late-line CML patients, Asciminib is not that potent.

Umer Raffat:

And just remind me, what's the dose that's approved in China and what's the dose that's being used in T315I and the dose used in non-T315I?

Dajun Yang:

The approval dose is 40 milligram QOD and with the FDA per Project Optimus, we can start with a 30 milligram QOD in the investigation arm and for those who didn't get a good response, they can move to 40mg. And for the T315I mutation, patients can start with 40 milligram QOD and can also reduce it to 30 milligram, if that dose can achieve MMR.

Umer Raffat:

Oh, wow. So you're not doing that, because I felt like for Asciminib and a lot of these other data sets, Asciminib was 40 milligrams regular, but 200 milligrams for T315I! So you're not pushing the dose for T315I?

Dajun Yang:

No, just regular doses are very potent.

Umer Raffat:

So presumably the tolerability would be meaningfully differentiated regardless of efficacy because the dose is a lot lower in the T315I mutant patients, right?

Dajun Yang:

Yeah.

Umer Raffat:

But conversely, do you think you're leaving efficacy on the table by not pushing the dose in T315I?

Dajun Yang:

We don't need to. We actually showed in ASCO, we had oral presentation of second line data, where if a patient in the front line experienced a second generation TKI, the MMR rate with our drug is even higher.

Umer Raffat:

I see.

Veet Misra:

Yeah, I think that speaks to your question about the MMR for the ongoing Phase 3. We actually have real world data to show, you know, maintaining pretty high and increasing MMR rates over cycles here.

Umer Raffat:

Got it, that's super helpful. Let me transition quickly to the Bcl-2. And I know this is a target that a lot of investors are familiar with from Venetoclax perspective. I know BeOne is working on a Bcl-2 as well and on the fixed-duration regimen along with their BTK inhibitor.
So I guess my first question to you is, where are you in your development and how do you see differentiation over Venetoclax, which I would love to hear about. But also how do you see this molecule relative to the BeOne Bcl-2 as well?

Dajun Yang:

Very good question. First, we have always been competitive to Venetoclax. The number one differentiation is from day one, we designed this daily dose ramp-up, right? So, because of tumor lysis syndrome in the early clinical trial for Venetoclax, the approved label is five weekly dose ramp-up. It's actually the same even more complicated for Sonrotoclax. Sonrotoclax starts at 1 milligram and the target dose is 320 milligrams. You can see from 1 milligram to 320 milligrams is 9 weeks does ramp up.

Umer Raffat:

Can you please remind me the doses again for Sonrotoclax?

Dajun Yang:

Sonrotoclax started from 1 mg (weekly ramp-up). So 1 milligram every day for one week, OK. And then the RP2D is actually 320 milligrams. So from 1 milligram, the run up is to 320 milligrams. That's 9 dose cohorts, OK? So in their clinical trial, it takes 9 weeks or two months.

For the approved label (of Sonrotoclax), they were able to squeeze that into five weeks. So every week at the dose ramp-up with two doses, OK? So three days for one milligram, four days for 2 milligrams and then up to 320 milligrams. So that's also five weeks, but a 9 dose cohort ramp-up. That's number one, very

important point for, you know, patient convenience and also we don't need a lead-in when we combine with a BTK inhibitor.

Second, I think the more important point is that we have a shorter T-half. That's important for this class of drug because it's C-max driven, and also is a hit-and-run mechanism, right? So we have about 5-6 hours T-half where Venetoclax is about 25-30 hours, OK? So shorter T-half translates into a better safety profile and better tolerance. So, we demonstrate much lower AEs, especially Grade 3 or 4 neutropenia, thrombocytopenia or febrile neutropenia and also related to those late-stage infection SAEs.

Another important differentiation is the drug - drug interaction, right? So among the three approved Bcl-2s, we are the ones that lowers risk of DDI.

We are not a substrate of P-gp or BCRP. So, those are important differentiation points. Because most of the hematology, oncology patients are elderly, they need to combine even in like the case of the BTK inhibitor, Ibrutinib. But they need reduce dose (of the BTK inhibitor) and also antifungal drugs in late stage infection. Those are concerns, right? So, those are the key differentiation.

But I think more importantly as we are in 2 FDA and EMA cleared global registration trials, GLORA and GLORA-4, I think we're very excited. Also, its important to describe the impact globally with the GLORA-4 study.

I think first we have to realize that globally, there's no target drug approved for HR-MDS, right? There's about 10 plus for AML but zero for HR-MDS so far. We are doing the only global registration trial on HR-MDS. Sonrotoclax is not on HR-MDS either, OK? They are doing, as you mentioned, a registration trial combo with their zanubrutinib and only in CLL. So, they're not in AML or MDS for sure. And Abbvie failed in the Verona trial announced last year. So, we are in the frontline for the HR-MDS.

This is very important. This is a frontline patient registration trial and there’s no competition. Basically, the Verona trial failed, Sonrotoclax is not in MDS.

We are the only global Phase 3 registration trial and we just had a really excellent advisor board meeting at EHA. Most of the MDS experts are very excited about this trial. They all want to help patients with MDS globally. Enrollment is moving very fast and very well. So, we're looking for potential completion late this year or early next year and again, potential NDA filing in 2027.

Umer Raffat:
Got it. NDA filings in 2027, OK, there's a few trials I want to make sure we go through. Let me just go step by step. Number one, can you walk us through the data maybe put up the slide on for Lisaftoclax in HR-MDS, what the prior

treatment was, the duration of treatment, how many patients, CRs and if there was any myeloid suppression seen?

Dajun Yang:

Yeah, we published this and actually had an oral presentation at ASCO two years ago. Those are all U.S. and Australian data. So two important data points. First just focus on HR-MDS. We show the OR in newly diagnosed MDS patients 80% ORR and the CR rate about 40% OK. I think that those are very impressive data.

Second, we also took the Venetoclax failed AML patients, OK? The naive patients have about the same efficacy. But more importantly, we have Venetoclax failed AML patients. We got an OOR about a 31.8%. I think this actually was surprising, right? Because it's the same target, same pathway. How come, you know, in Venetoclax failed AML patients, Lisaftoclax works?

I think in terms of MOA, we have to realize that most of the Bcl-2 inhibitor resistant mechanism is not because of new mutations, but because of MCL-1 upregulation and also Bcl-xL. So, basically the downstream pathway is the one causes the resistance.

So we did the resistant cell lines exposure to Venetoclax or Lisaftoclax. We did the profiling analysis. Actually, the downstream profilings are not exactly the same. This is maybe the explanation why Lisaftoclax works when just in combo with AZA in Venetoclax-failed patients.

But I think that in the real world we want to get it better. That's why we also have a clinical trial planned for a combo with our Olverembatinib, because it's a multi-kinase inhibitor that also can down regulate MCL-1.

We already demonstrated excellent data including that presented at EHA just last week for pediatric Ph+ALL. We demonstrated excellent safety and some efficacy in early data - excellent efficacy data with the combo of Olverembatinib and Lisaftoclax.

Umer Raffat:

But just so I'm clear, Phase 3 that's ongoing is AZA combo, correct? And this data we're looking at here is AZA combo as well. So then could you just give us a sense for how would your monotherapy have looked versus AZA combo?

Dajun Yang:

The efficacy of Lisa in AML - the overall CR/CRi rate is about 72%

Umer Raffat:

Monotherapy CR in AML is 70 to 72%?

Dajun Yang:

For AML, you have to combo with AZA. AZA is a standard of care for AML/MDS

Umer Raffat:

What about MDS as monotherapy?

Dajun Yang:

You have to combo with AZA as well. That's also considered a standard of care. AZA for MDS, OK? So, the combo with AZA is considered like a single agent.

Umer Raffat:

Have you ever run a monotherapy?

Dajun Yang:

I don't think that it's allowed, right? Because the AZA is a backbone for AML and MDS, although the ORR or CR rate is low. So, you have to, especially in HR MDS, you have to do a combo with AZA.

Umer Raffat:

OK, got it. So in the Phase 3 that's ongoing, GLORA-4, which is AZA add-on versus AZA monotherapy, what do you expect AZA monotherapy to do for the primary endpoint and what do you expect the active arm to do?

Dajun Yang:

Excellent question. And based on the old data and the real world, AZA alone in MDS is probably about 30% ORR, CR is about 15%. Those are the consistent data across, you know, countries. OK, so we have demonstrated that, in combo with Lisaftoclax, we can achieve an ORR of 80% and CR of 40%.

Umer Raffat:

OK, got it.

Dajun Yang:

Basically, it is more than double AZA (for efficacy).

Umer Raffat:

Yeah, but the primary endpoint is overall survival and would you have survival data by next year?

Dajun Yang:

Excellent question. So you know FDA requires OS for all the AML and MDS trials, right? But, we have discussed with the FDA and last year they agreed CR as a dual primary endpoint, and so CR can be used for Accelerated Approval.

I think that that's excellent news. That's important. And, of course OS will be required for full approval. So I think that maybe I forgot to mention the reason we can say we can have an upcoming NDA filing for Accelerated Approval is that's based on the CR rate next year.

Umer Raffat:

So, OK, so basically you're saying you can more than double the AZA CR rate. Is that reasonable? And you can be at least 30% plus, you're thinking 40%, but even if it's 30%, that's doubling of CR rate, right? And doubling of ORR. What's your expectation on early Hazard Ratio on overall survival when the CR comes out? I realize it'll be immature, but what will be the effective rate like when we have 10% deaths or 20% or 30%?

Dajun Yang:

That's hard to say. let's focus on the dual primary endpoint, right, CR and OS, right, CR for Accelerated Approval and OS for the full approval. But, more importantly, I think we have to realize that for HR-MDS, there's no target drug approved in last 20 years - a lot of challenges, right? This is almost as difficult as a pancreatic cancer.

Umer Raffat:

Yeah, makes sense. One last thing, could you remind us the last time you showed data for HR-MDS was at ASCO 2025, right, EHA, was there an update?

Dajun Yang:

We had an update not on the GLORA-4 trial, but we had an update of MDS/AML patients in the real world at EHA and also in combo with Olverembatinib in

Ph+ALL patients, as well as Olverembatinib alone in Ph+ALL. We can double the MRD-negative rate, right? And, also combo was Blinatumomab. We got almost 100%, ORR and more importantly, you know, a high 80% MRD-negative rate. But in terms of MDS/ AML, we actually demonstrated real-world data again for patients who failed Venetoclax, you know, in HR- MDS and the bridging to the CAR-T as well.

Umer Raffat:

OK, excellent. Again, CR data by mid next year? Late next year. What's the timing?

Dajun Yang:

Hopefully mid next year.

Umer Raffat:

OK. One last thing, I know we're at time, but I do want to touch up on the BTK degrader pretty quick. When can we have data and why do you think you wouldn't have as much of bleeding issue?

Dajun Yang:

First, we are in Phase 1 in US and China and we got this you approved from pre-IND to IND with the FDA in about 8 months, OK? Based on the pre-clinical data we compared it both with BeOne and Nurix, where we were more selective and more potent. And, of course I cannot have an answer to your question about bleeding right now, but I think based on the pre-clinical data showing more selectively is probably important. Another, of course, consideration for us is the combo with our best-in-class Bcl-2 inhibitor, Lisaftoclax, right?

So, there are many BTK inhibitors and degraders out there, but I think of for a lot of cases, including fixed duration CLL or DLBCL, maybe the combo of a BTK degrader with a better Bcl-2 inhibitor would be, you know, have an impact and help patients as well.

Umer Raffat:

Excellent! Veet, I want to make sure we catch anything we may have missed.

Veet Misra:

No, I think Umer, there's just, as the CFO of the company here, I'd say there's a disconnect in value that we're experiencing in the market. And I hope you know what Dr. Yang shared in terms of our momentum here, and our layout as a

company - we're a fairly sizable company. We're over 820 employees right now, over 130 of which are in the U.S. And we're looking to - I say we have a very strong clinical team in the U.S., including a long history of execution. I'd say we have everything here in the U.S. but commercial. And that's something that's kind of the next chapter for us.

Umer Raffat:

Yeah, outstanding. Thank you guys for making time. Thank you so much.