Biomea Fusion, Inc. (BMEA)

Summary of Fireside Chat at the Guggenheim Oncology Conference 2023

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Michael Schmidt: We're back. It's Michael Schmidt with the Biotech team at Guggenheim. The next presenting company is Biomea Fusion. It's my great pleasure to welcome Steve Morris, who's the chief medical officer. Steve, welcome and thanks for joining us.

Steve Morris: Thanks very much, Michael.

Michael: Biomea is focused on the development of covalent inhibitors. Can you please talk a bit about the background of the platform and what makes it so interesting?

Steve: Sure, happy to do so … The basic approach that Biomea uses with their fusion platform technology is AI virtual reality modeling and virtual docking approach. That allows us to avoid a library compound screening, and rather identify virtual molecules that are then synthesized, of course, in the wet lab. We supplement the virtual reality approach with actual chemical structures where available, but using those in tandem, that allows us to synthesize custom scaffolds. One beauty of the approach is that, with it, again, we're not doing library screening, so we're not picking from compounds that are already out there.

This approach, the fusion platform approach, allows identification of novel chemical space, and as a result, readily protectable IP. The other beauty of this approach is the timeline from identification of target, decision to drug that target until nomination of an IND candidate is very brief. The compounds that are currently in the pipeline, the timeline was about 18 months for that process. Very efficient, good way to identify novel IP, and also a very quick way to do so.

Michael: … Very interesting. Then you're enrolling currently the phase one COVALENT-101 study. Can you just remind us of the clinical trial design? What type of patients you're enrolling and how the study's been progressing?

Steve: Certainly. COVALENT-101 is our heme malignancy first in human study. In addition to acute leukemia, we're enrolling diffuse large B cell lymphoma, myeloma, as well as CLL. All of those indications, especially the three that I mentioned after acute leukemia, DLBCL, myeloma, CLL, we have generated data indicating, as I mentioned earlier, that covalent menin inhibition has

activity in a variety of preclinical models but not reversible non-covalent inhibition.

We commenced COVALENT-101 almost exactly a year ago. The first patient dosed was in January of 2022. That was an acute leukemia patient. We are escalating in the acute leukemia cohort. We're also doing parallel distinct escalations for the other three heme malignancy indications.

Michael: Is there a biomarker approach in a plan with a study? Are there any particular subtypes of patients that you think might be particularly responsive to 219?

Steve: Right. For acute leukemia, yes, we're enriching for MLL rearranged, as well as NPM1 mutant patients. We're not excluding acute leukemia patients with other molecular drivers. Again, we're enriching for those two subsets, which have been credentialed, have the greatest both preclinical and clinical data indicating that menin inhibition is effective.

For DLBCL, we're especially keen on enrolling double and triple-hit lymphoma patients. Those are patients who have activation of MYC, as well as BCL2-plus, in the case of the triple-hit lymphomas, BCL6. These are DLBCLs that are very aggressive, that are poorly served with current standard of care lymphoma therapies. We think this is a very good population for us within DLBCL to demonstrate 219 efficacy, again, based on preclinical models that we performed with 219.

MYC and CLL, we're accepting all patients irrespective of particular driver mutations, because we've seen in the preclinical studies evidence indicative that we will likely see broad spectrum activity with 219.

Michael: Then, you've got it to presenting data from the cohort one of the study in the first half of this year. Could you just help set expectations, perhaps around the scope of the data that we'll get?

Steve: Sure, definitely… The data in acute leukemia will report roughly 20 patients. About half of those patients will be acute leukemias with a variety of driver mutations, not necessarily expected to be sensitive to menin inhibition. The other half will be MLL rearranged or NPM1 mutant patients...

Michael: Very interesting. Then, you're doing also the COVALENT-102 study in solid tumors in a KRAS mutant background. What is the mechanism of action here and also talk about what you're

trying to show in this study?

Steve: Sure. Who knew menin inhibition for KRAS-driven tumors? Again, we've generated a large body of data. We presented that over the past year-plus at various congresses, ACR, ASCO, etc. It turns out that menin is at the node of several signaling pathways that are critical for cooperation with KRAS during the tumor development process. KRAS, obviously, is critical for the genesis of KRAS-driven malignancies. KRAS does not act alone. It requires cooperating genes, like MYC, like the EP1 transcription factor JunD, like a guanine nucleotide exchange factor known as RAS-GRF1.

All three of those, cooperate with RAS, are required for RAS to cause tumor development and also to sustain tumor viability. All three of those are part of the menin signaling complexes, which we disrupt with 219. We're not directly inhibiting KRAS. Rather, we are inhibiting these cooperating pathways with KRAS. That's one reason why we see pan-KRAS activity. It's not just G12C-targeted KRAS activity, for example. It's pan-KRAS activity.

Michael: Then, talk a bit about the phase one study. What types of patients are you enrolling in that?

Steve: COVALENT-102, our KRAS solid tumor study, began enrolling patients the latter portion of last year. We're enrolling three types of KRAS-driven solid tumors, non-small cell lung cancer, pancreatic adenocarcinoma, and then finally Colorectal carcinomas.

Michael: Got you. What are you looking for in a phase one and perhaps in terms of the mutational spectrum, and then what level of efficacy are you looking forward to advance this?

Steve: Again, the activity that we saw in our preclinical studies was pan-KRAS. That's important to emphasize, because in non-small cell lung cancer, as an example, about 15 percent are G12C mutant. That's the target population for G12C-targeted inhibitors. G12C, by contrast in colorectal, is only about three percent of all colorectals. There's huge unmet need. Because we anticipate pan-KRAS activity, we are accepting any activating mutation of KRAS.

The other point that is relevant, at least in preclinical models, we've shown that 219 has very potent cytotoxic activity, even in cancer cell lines that are KRAS mutant that are resistant to G12C-targeted inhibitors. We are accepting patients who have seen a G12C-targeted inhibitor for that matter. Any KRAS investigational agent have failed that agent. Those are accepted into the COVALENT-102 study.

Michael: Again, when are you expecting to update investors on this study?

Steve: … What I will say is that there's a huge unmet need there. We're talking about large patient populations. Recruitment, the enrollment has gone very rapidly, so the timeline will be short, but again, we haven't messaged as to when we would have a data release.

Michael: Right. Then, I know you guys have talked a lot about diabetes as well. Again, it seems hard to comprehend how broad this drug might work and in what different spectrum of indications, but reminds of the mechanism of action in diabetes and what we've seen so far.

Steve: There's a 15-plus year peer-reviewed literature credentialing menin as the regulator of beta cell numbers. It turns out, by the age of 30, an individual has the beta cell pool. They have essentially for the remainder of their life. That's why if you lead an unhealthy lifestyle, you don't exercise, you gain weight, etc., you put constant pressure on that beta cell pool. Ultimately, you exhaust it. That's why you develop type two diabetes.

There are some notable exceptions to the statement I just made. You have the beta cell pool by the age of 30, and that's what you have for the remainder of your life. One such exception is pregnancy. As you know, some women, when they're pregnant, develop gestational diabetes. Why does every woman not develop gestational diabetes? It's been shown that as pregnancy advances, especially in the second and third trimester, prolactin levels progressively ramp up. In a science article in 2007, prolactin has been shown to down regulate menin expression.

That takes the breaks off beta cell replication and actually allows beta cells to increase in number, and as a consequence, insulin secretion to increase. In the setting of pregnancy, that indeed is what happens. Again, prolactin down regulates menin. That allows beta cell numbers to increase and the glycemic burden imposed by the growing fetus is therefore controlled. Only when that physiologic response does not work correctly does a woman develop gestational diabetes.

What we're doing with 219 is basically pharmacologically recapitulating what happens physiologically with prolactin in the setting of pregnancy. We've done diabetic animal models, for example, with 219 and shown we can revert animals with very high levels of glucose with as short as a two week dosing of 219 to normal glycemia. Intriguingly as well, the glycemic control is sustained, and you would expect that…Beta cells are long lived. Elegant studies have been done showing that the half-life of a beta cell is 10-plus years. This could potentially be a functional cure for diabetes. It's blue sky. We have to prove it. Again, if we can increase beta cells, the fact that

they are long lived could elicit long-term glycemic control.

Michael: Then, you also started phase one here recently. Can you talk about the trial design, and what it will show at the initial data readout later this year?

Steve: Sure. The diabetes study is in two portions. The first portion, phase one -- this is a phase one, two study -- phase one was a healthy volunteer portion in which we did single ascending doses in healthy volunteers, basically just to confirm safety. That has been completed. The phase two, we're dosing BMF 219 in type two diabetics. We will, at the end of this quarter, release top-line data from the healthy volunteers, as well as the initial two cohorts of type two diabetics in that multiple ascending dose portion of the phase one, two study.

Michael: Very interesting. We'll monitor that as well. Then, maybe the last couple of minutes, you have a second program, BMF-500.

Steve: That's correct. Yeah. This is also a covalent small molecule inhibitor. The target there is FLT3. The tyrosine kinase that is a driver mutation and approximately 30 percent of acute myeloid leukemias. We anticipate IND filing and commencement of the first in human study with BMF-500 in the middle of this year.

Michael: FLT3, there's a number of agents out there. We've seen data, I believe, in AML from at least three of them. Again, where do you see room for differentiation, and what's the unmet medical need that the drug addresses?

Steve: Sure. The reversible FLT3 inhibitors, as you mentioned, there are several approved, and they clearly benefit patients with FLT3 mutant/AML. Having said that, the percentage of the population that achieves a meaningful benefit is small, and the duration of that benefit is short lived. We think with a covalent menin inhibitor, that we can increase CR rate, we can increase durability of response. One aspect that is a little bit longer term in the corporate thinking is that, ultimately, we'll combine proprietary pairings, for example, with BMF 219 or menin inhibitor, as well as BMF-500, or FLT3 inhibitor in acute leukemia.

There is a substantial subset of acute leukemia patients that have dual, for example, NPM1 mutation with coexisting FLT3 mutation. A single combo approach to address that population would be very attractive. That's a longer-term thinking as to how we would position these assets.

Michael: Then, I think you're targeting IND in the first half of this year. Is that correct?

Steve: Yeah, that's correct. As I mentioned, the plan is to file the IND sometime in Q3...Sorry, Q2, and begin the first in human studies in the middle of the year.

Michael: Will this be primarily in refractory AML, or will you look at other?

Steve: It will be relapsed refractory acute leukemia. We will be enrolling both FLT3 mutant, as well as FLT3 wild-type patients. The reason to enroll the FLT3 wild-type patients is that we think, based on preclinical data, that at least some wild type FLT3 patients could well respond to covalent FLT3 inhibition as well.

Michael: Very interesting. A lot's going on. We'll look forward to the...Their first data will be in AML on the menin inhibitor. With that, I'll thank you and appreciate it.

Steve: Yep, definitely my pleasure. Thank you.

Michael: Thanks.