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Aptose Biosciences

Transcript: KOL and Corporate Update Event

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PRESENTATION

Operator

Good afternoon and welcome to the Aptose Biosciences KOL Data Call.

As a reminder, this call is being recorded, and a replay will be made available on the Aptose website following the conclusion of the event.

I'd now like to turn the call over to Doctor William Rice, President and Chief Executive Officer of Aptose Biosciences. Please go ahead, William.

William G. Rice, Ph.D.

Thank you, Tara.

Good day, all, and thank you for joining us. I am Doctor William Rice, Chairman, President and CEO of Aptose Biosciences. Aptose is a clinical-stage biotech company developing oral kinase inhibitors for the treatment of patients with hematologic malignancies. Today we'll hold an AML-focused KOL event and a high-level update on our clinical programs.

As a reminder, we will make certain forward-looking statements today.

At Aptose we're developing two distinct clinical-stage oral kinase inhibitors. Our most advanced molecule, HM43239 or just 239 as we call it, is a clinically validated myeloid kinome inhibitor that potently suppresses high-value targets including FLT3, SYK, JAK kinases, and the mutant forms of cKIT, all operative in acute myeloid leukemias or AML. Oral 239, as a single agent, already has delivered multiple complete remissions in a diverse group of patients with relapsed or refractory AML in an ongoing international Phase 1-2 trial. This includes highly refractory patients with wild type FLT3, or in patients harboring the TKD or the tyrosine kinase domain mutant forms of FLT3, including patients with prior failure by other approved FLT3 inhibitors such as gilteritinib and midostaurin. It also includes a patient with complex karyotype and a *TP53* mutation, and patients with mutations in the *NPM1*, *RAS*, *RUNX1*, *MLL* and *IDH* genes.

239 has received orphan drug designation from the U.S.FDA and recently received fast track designation for the treatment of relapsed or refractory AML patients with mutated FLT3.

It's noteworthy that the ongoing trial now has delivered safety and efficacy data that allowed us to select our doses as well as our genetically-defined patient populations to explore in the next stage of clinical development, which includes expansion trials planned to begin in the second half of this year, with an eye toward transitioning these expansion trials, when ready, into registrational studies.

Our second molecule, luxeptinib, also known as lux or as CG806, also is an oral kinase inhibitor. This molecule, lux, inhibits BTK, FLT3, and other important kinases. Lux is in two separate Phase 1 dose escalation trials for the treatment of patients with B cell leukemias and lymphomas, and for patients with AML, and antitumor activity already has been demonstrated in heavily pretreated cancer patients. Now, we're exploring an improved formulation, and we have encouraging data that our new G3 formulation may deliver higher plasma exposures with reduced dosages.

With this background information on our clinical pipeline, let's now introduce our key opinion leaders. It's truly a pleasure to have with us today three well known KOLs to discuss the historical role of kinase inhibitors in cancer, including AML, and in particular the potential application of Aptose's 239 molecule to the treatment of AML.

Doctor Brian Druker is best known for his role in the development of imatinib, also known as Gleevec, used for the treatment of chronic myelogenous leukemia, and this was the first kinase inhibitor ever approved. I recall when I was the head of the Drug Mechanism Lab with National Cancer Institute during the 1990s and I heard about a physician scientist developing a small molecule to target kinases. Many scientists at that time said it could not be done, because it would not be possible to create a small molecule to selectively bind to the ATP binding pocket of one particular kinase, because that ATP binding pocket is found in every kinase. Well, now we all understand that ATP binding pockets differ among kinases, and that drug selectivity can be achieved. Doctor Druker's insights ushered a revolution in cancer treatment that now has yielded many targeted kinase inhibitors for many indications, but I'll let him describe how the field has evolved.

For all of Doctor Druker's contributions to medical science, he was named a Howard Hughes Investigator and a member of the National Academy of Sciences, and I'll underscore that he has received numerous

awards for his achievements, including the Lasker-DeBakey award, the Japan award, the lifetime achievement award from the Leukemia Lymphoma Society, and the medal of honor from the American Cancer Society. Remarkably, he's also a true gentleman, and it's been a pleasure to work with him over the past two decades. You'll hear from him in a few minutes.

In addition to Doctor Druker, we're thrilled to have with us today two KOLs that actually are treating AML patients with our drug 239.

Doctor Naval Daver is a professor and hematology-oncology clinical investigator at the MD Anderson Cancer Center, who has made a name for himself as an extraordinarily knowledgeable principal investigator on many institutional, national and international clinical trials, wherein he studies a breadth of single agent and drug combination therapies that evaluate small molecules, immunotherapies, and cytotoxins. His driving motivation is to deliver to hematologic cancer patients new therapies that are better tolerated and more effective, and that can overcome mechanisms of resistance. Doctor Daver is the global PI for our ongoing clinical trial with 239, and you'll hear from him in a few minutes too.

We also have with us Doctor Brian Jonas, a professor and physician scientist from the division of hematology and oncology at the University of California at Davis, Comprehensive Cancer Center, where he leads the translational research program in AML, MDS and ALL, serves as the PI on multiple clinical trials, and chairs the hematologic malignancies working group and the data and safety monitoring committee. In his spare time, he serves on the National Cancer Network panels for various hematologic cancers, and he too is treating AML patients with 239. His insights with the response of AML patients to 239 will be very telling, and we're excited to have him here today to discuss his thoughts.

In fact, I want to thank all of our KOLs in advance for their willingness to participate and share their wisdom.

While I'm certain you're eager to hear from our KOLs, you'll first need to bear with us as Doctor Rafael Bejar, our Chief Medical Officer here at Aptose, and I will provide clinical highlights of our 239 and lux programs. This truly will represent the highlights, as the bulk of the clinical data will be presented separately from this KOL event. Following our clinical update, Doctor Druker will discuss the impact of kinase inhibitors on cancer treatment and the future needs of AML patients, and then Doctor Druker will ask questions of Doctor Daver and Doctor Jonas, particularly regarding AML disease and their experience in treating patients with AML and their views of 239.

Let's begin with the update on lux and the emerging data with the new G3 formulation.

As you recall, lux potently inhibits validated lymphoma and leukemia targets, and is the only molecule reported to potently inhibit the wild type and mutant forms of both BTK and FLT3, yet it avoids many of the kinases that negatively impact safety.

While lux is in two ongoing clinical trials, what is critical for the lux program is to transition to a new and improved formulation that we refer to as Generation 3 or G3, which is being tested in patients as a single dose. To date, we have dosed patients with 50 milligrams, 100 milligrams, and 200 milligrams of G3. In these studies, after a patient receives a single dose of G3, we've followed the plasma exposure levels over 72 hours, and then have the patients migrate to the original G1 formulation with continuous dosing, so that we may follow their pharmacokinetics and follow them over longer periods of time for efficacy signals.

Today we first present the mean and standard deviation PK curves from the four patients administered a single dose of 50 milligrams and the three patients administered 100 milligrams of G3. Seventy-two hours following the single dose of G3, patients may have received either 750 milligrams or 900 milligrams of the

original G1 formulation, depending on the the trial from which the patients were accrued. Therefore, in this plot we are only illustrating the G3 PK profile, and do not include the G1 PK profile. I'll remind you that these data represent a single dose of G3 that would not be expected to achieve the micromolar steady state levels yet.

As you can see, whether delivered as 50 milligrams in the red curve or 100 milligrams in the purple curve, lux from the G3 formulation was absorbed rapidly over the first two hours and maintained exposures through 72 hours. Indeed, we had never seen such rapid absorption with the original G1 formulation. This was very encouraging.

But these mean and standard deviation curves with G3 do not give you the big picture. I'll also present PK data from a single patient, so that we can compare the PK properties of G3 directly with those of the original G1 formulation.

Here I'm showing the PK findings from the very first patient ever administered G3. At time zero, a single 50 milligram dose of G3 was administered. Lux was absorbed rapidly, as I said, over the first two hours, and then maintained exposure through 72 hours, after which a single dose of 900 milligrams of the original G1 formulation was administered. G3 exposures can be identified with the red and white markers, while the original G1 formulation exposures are identified with green markers.

I will take the first 24 hours of PK data from each formulation, shown here in the purple boxes, and overlay them on the right side of the slide.

This graph now compares the exposures from G3, the red and white markers, to the original G1 formulation, green markers, during the first 24 hours following their respective administration. I'll remind you that lux from the G3 dose remained in the plasma at 72 hours, so the G1 actually began at a higher threshold. Overall, the exposure looks roughly equivalent among the two formulations, although 18 times more G1 was administered than G3.

To provide additional perspective, we also have data from a dose of 150 milligrams of the original G1 formulation that had been administered to a separate patient some time ago. Those exposures are shown here with the blue markers. On a per milligram basis at the two-hour time point, 50 milligrams of G3 delivered approximately 200 times the exposure relative to 150 milligram dose of G1. Yes, we find the G3 now to be very encouraging.

Where are we going with lux? Well, I'll draw your attention to the right panel to highlight our plans. During the third quarter of this year, we plan to perform PK modeling with data derived from the G3 single dose studies. The modeling can predict the PK properties of continuous dosing with G3, by modeling different dosage levels and different schedules of dosing, such as once daily versus twice daily dosing. If the modeling data are compelling, we plan to submit the data and our new dosing plan to the FDA, likely later in this year, with a plan to transition our clinical trials away from the G1 formulation toward continuous dosing and dose escalation of the G1 formulation. This represents a significant action, because transition to the G3 formulation may allow us to deliver higher plasma exposure levels at reduced doses to patients with hematologic malignancies.

Our team remains steadfast in their belief of lux. Preclinically it remains one of the most impressive molecules we've ever seen, and the team is working hard every day to execute on these important studies, so stay tuned for lux.

Now let's turn to HM43239, or just 239.

Shown here is the kinase inhibitory profile of 239, illustrating that 239 potently suppresses kinases central to the proliferation and resistance-conferring pathways of AML.

This includes potency on the wild type as well as the ITD, tyrosine kinase domain, and gatekeeper mutant forms of FLT3.

The SYK signal transduction kinase.

JAK kinases 1 and 2.

Mutant forms of cKIT.

Illustrating that 239 has the potential to serve as a multidrug therapy in a single tablet, by concurrently suppressing multiple proliferation and resistance-conferring pathways in AML.

To support the concept that 239 has the potential to suppress mutations that confer resistance to other drugs, here we illustrate that in subcutaneous models, shown across the top, and systemic animal models of AML, shown across the bottom, 239 consistently demonstrates superior antitumor activity relative to gilteritinib, a FLT3 inhibitor currently used to treat AML patients with FLT3 mutations.

With that, let me pass the microphone to Doctor Bejar so he can describe our clinical findings with 239. Doctor Bejar?

Rafael Bejar, M.D., Ph.D.

Thank you. It's a pleasure to have you all here for the call. We are extremely proud of the progress we've been able to make with 239 since we picked up the study in January.

Just to summarize some of the key points that were just mentioned, we believe that 239 is really positioned well and potentially superior to other FLT3 inhibitors, as it does inhibit all mutant forms of FLT3, kills AML cells that are resistant to other FLT3 inhibitors in the lab and hopefully in the clinic as well; and by targeting multiple different kinases, we get that combination therapy in one molecule phenotype, as was just described.

We are now going to bring you up to date with where we are with the clinical program. We are exploring molecular subgroups that might be more sensitive or potentially resistant, in relapsed-refractory AML patients, particularly those with adverse mutations, in order to help us understand the full scope of their activity.

This is a diagram that shows you were we are with the clinical study. This is a Phase 1/2 international study that includes a dose escalation portion on the left, and we have completed six different dose levels there, starting with 20 milligrams, and having cleared the 160 milligram dose level, we're currently in the 200 milligram dose escalation cohort.

But as we do dose escalation, we have the ability to perform dose exploration in a larger number of patients at dose levels that show signs of activity. To that extent we've expanded the 80 milligram dose level to 20 treated patients, the 120 milligram dose level to 12 treated patients, and the 160 milligram dose level to nine treated patients. These additional patients at each of these dose levels give us a better understanding not only of the safety and tolerability of the drug but also on the pharmacokinetic properties of the agent and the efficacy that it can have in these different dose levels.

Down below, you see a Swimmers' Plot showing the duration of treatment for different patients in the study, and I'll go over some of the responders and what their eventual outcome is in the next slide. You can also see in these PK plots that show the pharmacokinetic exposure over the first 48 hours on the middle and over a longer period over on the right at steady state, how we are getting incremental increases in dose exposure up to 120 milligrams. At 160 milligrams, where we have the fewest patients treated to date, it looks like we don't quite have a greater increase in exposure there, suggesting that 160 milligrams may be above the optimal dose at which we're getting maximum absorption at the moment.

Now, I want to highlight the responses that we've had on the study to date. As I mentioned, we're able to expand dose levels where we see signs of activity, and that began at the 80 milligram dose level. We've now seen activity at the 120 milligram dose level and at the 160 milligram dose level, as I'll mention in a moment. This slide was actually prepared more than a week ago, before we had that information on 160 milligrams.

What I want to highlight about the responding patients is the diversity of patients that we've had in the study with complete responses. They do include patients that have FLT3 mutations, including the FLT3 ITD shown there in red on the left, but also includes a patient with a FLT3 TKD mutation, that D835 mutation. It includes patients that have been previously treated with other tyrosine kinase inhibitors that target FLT3, including midostaurin and/or gilteritinib. But importantly, we've seen complete remissions in patients that have very adverse mutations. *In the FLT3-mutated group, these include mutations such as mutations in NRAS, mutations in RUNX1, and mutations in MLL-PTD as well as KRAS and PTPN11.* Some of these mutations are typically associated with resistance to tyrosine kinase inhibitor exposure.

Importantly we've also seen activity in patients who do not carry a FLT3 mutation, these FLT3 wildtype patients, as we describe them on the right. In particular, one patient that had a very adverse genotype, a *TP53* mutation along with highly complex cytogenetics, and a very prolonged remission. In fact, they stayed on study for over 14 cycles.

Now, you'll see that many of the patients didn't stay on study quite as long, and that's because five out of six of those patients went on to undergo hematopoietic stem cell transplant. That is an excellent clinical endpoint that you are able to get your patients to if you can, because it represents a potentially curative therapy. For patients with relapsed or refractory disease, it can often be difficult to put them into a deep enough remission such that a stem cell transplant makes sense. Our most recent responding patient shown there in the middle at 120 milligrams that achieved a CRi, actually just now has come off study in order to begin a stem cell transplant.

Now this is a Swimmers' lot of those responding patients that I just showed you, highlighting the depth of their response. You see that many patients actually had maturation of response, leading up to a CR, and suggesting that, despite daily dosing of 239, they don't see additional myelosuppression; that true CRs without qualification are definitely possible.

As I mentioned, over the last couple of days, we've learned that we have another patient that had a response, a patient that had a newly reported CRi at 160 milligrams, also with many adverse mutations including mutations in *NRAS*, *U2AF1*, and *SETBP1*, and this patient does not have a FLT3 mutation. This is another FLT3 wild type AML patient. Interesting that they had AML with myelodysplastic related changes, which are patients that often have these more difficult to target mutations and more difficult to treat disease. We're hopeful that the patient will improve the depth of their response as time goes on.

Now let's talk briefly about the safety of 239 in our experience to date. We have not had any drug-related severe adverse events, did not have any drug-related deaths, and we have not had any of the common side effects or dose-limiting effects that have affected other tyrosine kinase inhibitors. In particular, we have not seen adverse events related to elevated creatinine kinase. We have not seen adverse events

related to QT prolongation, and we have seen no observed relationship between the change in QTc and dose. Importantly we have not had any dose-limiting toxicities up and through the 160 milligram dose level, while we do have one dose-limiting toxicity of muscle weakness that was not muscle breakdown or rhabdomyolysis, and this occurred in the 200 milligram dose level.

We believe we've identified a safe therapeutic range with a broad therapeutic window, spanning the dose levels of 80, 120 and 160 milligrams, at which there were no dose-limiting toxicities encountered, despite now having treated tens of patients at these dose levels.

We're continuing to explore the safety across these cohorts as we expand them further in order to optimize the dose that we will carry forward into our subsequent studies, which I'll tell you about shortly.

Where we are today is that we've had a successful dose escalation and dose exploration phase of this Phase 1 study, where we demonstrated CRs in FLT3-mutant AML, and we've received fast track designation for treating FLT3-mutant patients. We've also selected three expansion doses that we'll take forward, as I'll describe shortly. We continue to explore molecular subgroups, particularly with adverse mutations, to identify other potential groups that we might carry forward for fast track and share with you as ongoing news flow.

Our plan will be to select 120 milligrams as our primary single agent expansion dose, with 80 milligrams and 160 milligrams as bracketing doses that we can adjust to, in order to refine our dose selection. We plan to explore this both in FLT3-mutant patients, as supported by a fast-track designation, but also in FLT3-unmutated patients with adverse mutations like the ones we just described.

The single agent studies we expect to begin in second half of 2022, and combination studies of 239 plus venetoclax in FLT3-mutated and -unmutated patients to begin in the first half of 2023.

What does that look like, in diagram form? Patients who are enrolled after this expansion phase goes live later this year will be stratified first by their mutation status, whether they have a FLT3 mutation or whether they do not, and then they will be assigned either the single agent treatment group or the combination treatment group with venetoclax once that study becomes available.

Finally, we do plan to include a triplet group of HM43239 plus venetoclax and a hypomethylating agent later on, that will enable us to then explore moving to earlier lines of therapy. The key objectives for this study will be as you see there on the right, primarily focused on safety and tolerability, but also helping us ensure that we have the right doses for our study going forward, including potential registrational studies that would follow these important expansion studies that we're doing as part of our Phase 1.

To summarize the major objectives in the AML target populations that 239 could explore, first and most important is relapsed or refractory AML patients with FLT3 mutations who have been failed by a prior FLT3 inhibitor. These patients have a great unmet medical need and really no available off-the-shelf options, so therefore the ability to rescue these patients, and perhaps send them to transplant as we now have with several patients in our study, would allow us a quicker path to registration, and that is in line with the accelerated approval plan that we have.

Then we would explore relapsed or refractory AML patients without FLT3 mutations that have other adverse mutations, such as *TP53* mutations and others we've seen, and primarily explore them both as a single agent but also in combination. This also could lead to other options for accelerated approval.

Then we'll look at relapsed or refractory AML patients in combination studies, primarily venetoclax to begin with, perhaps a triplet regimen, as that allows us to go into earlier lines of therapy, and that would include focusing on patients who are unfit for chemotherapy, who would be relegated to a

hypomethylating agent, perhaps in combination with venetoclax, as well as potentially fit patients, who would be treated with high-dose chemotherapy, again, to see if they would benefit from additional FLT3 inhibition at the time of first treatment.

I'll summarize our experience with 239 thus far. We inhibit a variety of important kinases that essentially give us the opportunity to treat multiple targets with one medication, so multi-target treatment in one medication, including some of the mechanisms of resistance that often arise to other FLT3 inhibitors. Our clinical experience to date suggests that we have an excellent safety profile associated with an excellent activity profile that would allow us to explore this further, not only as a single agent but also in combination in varieties of different populations, including those with highly adverse mutations, whether or not they have FLT3 mutations. Supporting that is our FLT3 AML fast track approval that we received earlier this year.

Our goals going forward would be to explore additional adverse genotypes to see which ones are sensitive, to go on and share this news with you in a rolling manner throughout 2022, and to plan those expansion trials that I mentioned in the second half of this year and then in early part of 2023, that will allow us to move on to registrational studies.

Enough from us. What I'd like to do now is pass it to Doctor Brian Druker, head of our scientific advisory board and obviously an expert in this area, to share his opinions about how kinase inhibitors have shaped treatment landscape for cancer in general but AML in specific, and then I'll ask him to share some of the questions that others have about 239 and AML with some of our other KOLs on the call today.

Doctor Druker, I will pass it to you.

Brian J. Druker, M.D.

Thank you very much, Doctor Bejar. It's really nice to be here and to be able to share some perspectives with you. As Doctor Rice noted, I've been involved in the development of kinase inhibitors for well over 20 years. In fact, I was in the clinic this morning and had a patient on imatinib who's been with me for 20 years. His youngest daughter is now a tenth grader, and he's just gotten to do amazing things over the last 20 years that he never thought he'd get to do.

But the reality is that CML, chronic myeloid leukemia, now has six different kinase inhibitors FDA-approved, and that gives us a whole suite of drugs to choose from. If you will get other kinase inhibitors in targets that have come along, you have EGF receptor inhibitors, of which there are four. Interesting that there are actually only two FDA-approved inhibitors for FLT3, midostaurin and gilteritinib. Midostaurin is a much more difficult kinase inhibitor to use, and I think there's lots and lots of room for improvement.

Now about a decade ago, if you go to the next slide please, one of my colleagues, who was the president of ASCO, said well CML and what Brian worked on was a pretty easy cancer; why don't you work on something a little bit more difficult? For the last decade I've transferred most of my laboratory work into AML, which I view as one of *the* most difficult-to-treat cancers or leukemias. If you look at the number of new cases, over 20,000, and that 50% of those are going to die even within the first year or two.

This is the most common adult leukemia; the five-year survival rate has been stuck at about 30% for as long as I can remember. In patients who relapse, their median life expectancy is less than six months. Despite that, we know an awful lot about the molecular drivers of AML, and FLT3 is clearly one of the top targets that have been identified over the past several decades. It's absolutely clear that we need new and better targeted agents to treat newly diagnosed as well as relapsed refractory patients with AML, but in addition what's absolutely clear for AML is that, to achieve durable and long-lasting remissions and

higher remission rates, we have to get to combinations of therapy. To do that we need well tolerated agents that can be combined.

If you go to the next slide, please.

Pretty much to summarize where we are, clearly for patients with refractory AML we need something right now. I've certainly been impressed already with five, six complete responses to single agent therapy with 239.

But more importantly, if we're going to really make an impact on this disease, we have to be able to move these therapies up, and we have to combine them to get durable responses.

But to really combine these drugs, we have to have safe drugs that are well tolerated, so they can be effectively combined and then moved up into newly diagnosed, even into patients who might be otherwise candidates for the combination chemotherapy that we currently give to our patients.

I see there is a huge unmet medical need in the field of AML, and I'm certainly hopeful that 239, as Doctor Bejar noted, can fill some of these gaps both for relapsed or refractory but then in combination, and then ultimately in the upfront setting.

Rather than listening to me, I actually want to bring on our other key opinion leaders, and that will be Doctor Brian Jonas and Doctor Naval Daver, who are currently investigators on the 239 study, and I really want to get their views on both relapsed refractory AML and the results they're seeing with 239.

Doctor Daver or Doctor Jonas, if you could just start and let people on the call know a little bit about what a typical relapsed refractory AML patient is like. What kind of condition are they in? What kind of treatment options they have? How many treatments have they typically gone through when they come to see you in your clinics?

Naval G. Daver, M.D.

Sure, I'll start and then I'll turn it over to Doctor Jonas. I totally agree with Doctor Druker that AML is probably *the* most difficult of all heme malignancies. These patients usually present acutely ill, especially in the relapsed setting, and especially FLT3 mutated patients often come with elevated white counts, because FLT3 is a proliferative mutation, and these patients will often have four to five time higher than normal white count, and that usually leads to liver dysfunction, kidney dysfunction, coronary issues, 30% to 40% will present with an active infection because, even though their white count is high, they are not functional white cells and they have immune dysfunction.

The other common thing that we can sometimes see is that these patients who have had prior allogenic stem cell transplant may also be having some degree of graft versus host disease, or be on other medications that are being used to control the post-transplant immune flares.

It's a very complicated situation compared to let's say a newly diagnosed lymphoma or lung cancer. These patients already are starting at a more difficult position, so I completely agree, there's a huge need for drugs that are not only effective but are also safe, and I completely echo Doctor Druker's comment that combination therapy that can be delivered safely will be very very critical.

Doctor Jonas?

Brian A. Jonas, M.D., Ph.D.

Thanks, Naval, and thanks, Doctor Druker. I would echo everything that's been said. The patient population is very diverse, but the FLT3-mutated patients in particular, as Naval said, often present with high white counts, hyperleukocytosis, and other challenging clinical scenarios, and can be very sick or get very sick very quickly.

A lot of times, when they get to me at the academic center, they've already been through a few lines of therapy, sometimes some of the standard therapies, and they can be relatively beat up, for lack of a better expression, from the impact of all their therapies, and highly susceptible to infections. Maybe the performance status has suffered as a result of longstanding disease or potentially being relapsed and not back in remission for some long period of time. I think, to really drive home the point that was mentioned already twice now, effective therapies that are tolerable are so important for these patient populations, and to give them the opportunity to actually take therapy and have enough therapy in them to have a response, and then maybe they can get well enough to get something like a transplant that might be required for them to have any chance of a long-term survival.

Brian J. Druker, M.D.

You've both been involved in any number of drug development in AML. How difficult is it to get to a complete remission with a single agent in this patient relapsed refractory population? How often do you see that, with a single agent?

Naval G. Daver, M.D.

Brian, you want to?

Brian A. Jonas, M.D., Ph.D.

Yes, it's not a common event, the response rates in the teens and twenties are sometimes—that's—we get all excited when we see numbers like that. Often they're much lower than that. It's very challenging.

Naval G. Daver, M.D.

Yes, even to look at a drug that's approved, right, which is currently the gold standard, gilteritinib, in FLT3, if you look at the complete remission rate in relapse with single agent is about 14% to 15%. If you add CRis and CRhs, then yes, it probably gets around 25% to 30%. But I think there's definitely room to try and improve that.

Brian J. Druker, M.D.

When you look at 239, five, six patients have gone on—have received—gone—achieved a CR, several have gone to transplant. Is this typical, unusual, and what's your view on this and what you're seeing in the clinic?

Naval G. Daver, M.D.

I'd say this is very encouraging. I think couple of things, me and Brian have both used this in clinic in a number of patients, is it's been very safe, this is something we started noticing early on, even before I think the responses. We have not seen liver toxicity, we have not seen GI toxicity, cardiac issues. I mention these because these are the common ones that have been seen with other agents in the FLT3 space, gilteritinib, quizartinib, sorafenib. That's been quite positive; and then, seeing responses even at

the early dose of 80 and 120, and a number of responses, PC1 response, we always kind of joke in the academic community, right, that happens a lot, for the first patient usually. But when you have seven, eight, and it's happening consistently, I think this is a real effect. Doctor Bejar mentioned, and I'd highlight that some of these patients had received prior TKIs that target FLT3, like midostaurin and gilteritinib. To have a response after that is really really positive.

Brian J. Druker, M.D.

The two that I wanted to focus on, Doctor Jonas, I think you had the one patient who had gotten midostaurin and gilteritinib, and I'd love to hear about your experience there. But I was impressed with the *TP53* mutant patient who got to a CR. I can't remember ever seeing a patient get to CR with a single agent with a *TP53* mutation.

Brian A. Jonas, M.D., Ph.D.

Yes. Those patients have a terrible prognosis, and it's even a pretty terrible prognosis even in the first line, let alone somebody that's had extensive pre-treatment. I think I agree with you, I think that's another thing that strikes me about the data that we've seen so far is that diversity of responses, which is, I think, very impressive.

Brian J. Druker, M.D.

Doctor Daver, you mentioned a little bit about the tolerability, perhaps you can tell us—both of you tell us a little bit more about what you're seeing as far as the safety and tolerability, because again, in my view, all of you have chimed in, that combinations are essential. What have you seen in terms of your patients who are really pretty sick, how have they done on this medication?

Naval G. Daver, M.D.

Right, yes, I think that's great question, Doctor Druker, and I think that's what we have to highlight, that these patients, the median it's about second, third salvage. These are actually sicker patients and more advanced patients than were evaluated in the previous studies, many of which we were involved with and led, for example with quizartinib and gilteritinib, because those were the first major FLT3 inhibitors, so we used them in the first salvage setting, seven to eight years ago when those trials were being done, and now we have those drugs.

The people who are going on 239 are more advanced salvage. I was nervous that we would see more toxicities and difficulties in tolerability, because we know that the more prior therapies the patient has had, the more prior transplants, the more infections, the weaker they are, the higher risk. It's been very pleasant to see that it's over all been well tolerated. I think the only things we have seen are minor GI issues, some degree of diarrhea, cramping. We have not seen any significant GI, hepatic, cardiac, renal toxicity. We have seen some muscular aches and inflammation, and that's something we have seen with other TKIs, even in CML, so we're measuring that. But all in all, I think, as a single agent, we will see how the responses pan out, this is definitely encouraging. But I think it really opens the door to move quickly into combination with this drug, given its good safety profile.

Brian A. Jonas, M.D., Ph.D.

Yes, I'll echo that. In my own personal experience on the trial, the drug has been very well tolerated. My patient who responded, for example, felt better on the 239 treatment than they did on the previous treatments that they had before. Not only did they not have significant toxicity, but their overall wellbeing,

maybe that correlated with the CR, but nevertheless they felt better on the medication. I thought that was impressive.

Brian J. Druker, M.D.

I know in the past a lot of people have debated about whether the endpoint of eligibility of moving to transplant is a fair endpoint. What are your views on that one, and getting a number of these patients into remission and on to transplant?

Brian A. Jonas, M.D., Ph.D.

I think that's the goal of treating people with relapsed or refractory AML, if possible, to get them to transplant, at least that's my opinion. That's the only real effective treatment for producing a durable long-term remission, at least in our current armamentarium. Yes, that's outstanding, to see patients going to transplant on a single agent.

Naval G. Daver, M.D.

Just to echo, Brian, that's something that historically the FDA regulatory-wise did not consider a valid endpoint eight to 10 years ago, but now actually recently, and this is reflected in the gilteritinib approval as well, they actually did allow both duration of response and overall survival as well as best response capture post-transplant in patients who are on the Admiral study. I think that there has, and we have seen this in other studies as well. There is a shift to accepting that a drug that can safely get patients to stem cell transplant actually is a benefit to the patient and should be considered favor of the drug. It's a good sign.

Brian J. Druker, M.D.

Do either of you have any final thoughts about 239 and where you think this will land?

Naval G. Daver, M.D.

I think that we have to be cognizant of the fact that this is still a competitive space, there are other effective FLT3 inhibitors that have been around for eight to 10 years, gilteritinib, quizartinib are probably the most effective single agents, and in combinations with venetoclax showing activity.

I think the paths here are, one, to see how we can continue to hopefully generate responses after prior TKIs, as we saw Doctor Jonas's population. But that's still a big area of unmet need. We get a lot of referrals at MD Anderson for patients who have gotten midostaurin induction, then got gilteritinib, single agent or combo, and then failed, and they then have no option. There, any activity, even 20% to 30% would be better than zero, which is what we have currently.

Then the other would be, as Doctor Bejar showed, to move with combinations, because we do have combination data with gilteritinib venetoclax, with quizartinib venetoclax, but it is quite myelosuppressive. That may be a class effect, that may be seen when we combine other drugs with venetoclax, but if it's not, then that could really open up a path to move 239 ahead quickly.

Brian?

Brian A. Jonas, M.D., Ph.D.

I agree. I don't have a whole lot to add to that, but I think the combination therapy, especially with venetoclax combinations, as you point out, are not necessarily easy to give, especially in a relapsed refractory patient, for example. But even in the front line, unfit patients. I think if the drug ends up being as well tolerated as we're seeing so far in combination therapies, that would be also a very exciting and I think something that would be maybe able to distinguish it more from some of the other drugs that are out there.

Brian J. Druker, M.D.

Wonderful. Thank you both for sharing your perspectives on this exciting advance in the treatment of AML. Doctor Bejar, I'll turn it back to you.

Rafael Bejar, M.D., Ph.D.

All right, thank you, and thank you, all, for great discussion and participation here. I think it's wonderful to hear your personal experiences and your thoughts about the drug going forward.

Just to recap our future plans here before we get to questions. HM43239 has already shown itself to be a drug. It's clinically validated, in having treated both FLT3-mutated and FLT3-unmutated patients and having achieved CRs. We plan to continue our current phase of the study, where we explore different dose levels to get a better sense of their activity and exposure in patients, and use that to refine our subsequent studies that are going to come later this year, and that includes that single agent trial that I mentioned, both mutant and unmutated FLT3 patients with adverse mutations, with a single agent, and then in combination with venetoclax, something that we highly anticipate being able to do and move the drug forward with.

Our plan is to start with 120 milligrams as our single agent dose, and then backet that with 80 and 160 milligrams as tolerated, perhaps even allowing patients to dose-escalate, should they need to, after an initial cycle of therapy at a lower dose.

Data permitting, we will then request allowance to move additional genotypes into this high-need category for potential accelerated approvals, and ultimately plan what our registrational studies will be based on this experience that'll come with these subsequent expansions.

Ultimately, we're looking beyond that and we're looking to see what our plans for commercialization might be, and that is to include as many patients with AML as possible, as long as we learn about which are likely to respond. That includes FLT3-mutant, but also could include FLT3-unmutated patients, having seen the activity that we've noted thus far. As we move into earlier lines of therapy, that also could include treating patients who are fit or unfit, as well as relapsed refractory patients, not just in first line but also in second line and beyond.

Then with luxeptinib we're very excited by this early data that we've gotten with G3. It really does hold further promise for this drug and for our ability to move forward. We'll continue to explore G3 and then hopefully move to continuous dosing as soon as we have a better understanding of the ideal dose with which to do that, leading us to getting higher exposures with less drug, less pill burden, and less drug to manufacture.

At this point I will again thank our key opinion leaders, Doctor Druker, Doctor Jonas, and Doctor Daver. I think it's a really illuminating discussion. Very much appreciate having you on the call with us. We will move on and open it up to questions.

Operator

Thank you, Doctor Bejar.

Our first question comes from Gregory Renza from RBC. Gregory, you may go ahead and unmute your line.

Gregory Renza, M.D.

Great. Thank you very much. Thanks to Bill, the Aptose team, and the physician experts for joining us today. Very helpful presentation and dialogue.

Maybe to kick off and maybe to the panel, if I may, you covered a great deal of attributes about 239, both on the efficacy potential as well as the safety set. I'm just curious if you could help boil down some of the maybe just the topic area of the profile that you are excited about. Certainly helpful to hear about the safety and of course the combination potential, the diversity. But maybe just helping us understand that area that is most exciting to you, and then on the flipside maybe some commentary on some of the greatest risks to the profile that you think are worth considering. Thank you.

Naval G. Daver, M.D.

I can start. I think that the greatest risks are obviously in this very high-risk population is the efficacy parameter, that's something that is going to be compared. I think one of the things we have to be very careful of is, when we look at the profile of these patients, we really have to match apples to apples, so we're going to see that a lot of these patients are going to have had prior TKI, and I think we have to compare that, and there is data now being published from our group and from others, of outcomes in prior TKI-exposed patients with drugs like gilteritinib and quizartinib. I think looking at it in that apples-to-apples comparison will give us a fair view, because the 239 is going to get a much heavier treated exposed population.

I think the greatest opportunity is, as both Doctor Jonas and I mentioned, is really if the safety continues to be this encouraging, to move quickly with combinations, initially in salvage with venetoclax and then really up front with the established FDA-approved backbone of HMA venetoclax in both FLT3 and maybe even in non-FLT3-mutated populations.

Gregory Renza, M.D.

That's really helpful. Perhaps, Doctor Daver, if I could just follow up, your mention on the muscle weakness finding, and I believe Doctor Bejar talked about a DLT at the 200. Perhaps you could just expand a little bit about the quality of that, and Doctor Bejar, any additional information you have on that finding, in addition to no rhabdo present, that would be very helpful. Thank you.

Rafael Bejar, M.D., Ph.D.

I can take that. Yes. We did have, in our dose escalation cohort at 200 milligrams, one patient that developed muscle weakness during that first cycle of treatment. One of the things that we worry about, when you see muscle weakness, is that there are all sorts of different potential causes. Was it due to muscle damage or muscle breakdown, so we explored that extensively and did not find any evidence of that. If anything, it had more of a myasthenia gravis-type quality, and ultimately the patient did come off study, and did have some improvement after they came off study, and then moved on to the next therapy, so was lost to follow-up.

I would point out that this patient actually had one of the highest exposures that we've seen on the study to date. I think it was the second-highest exposure of any other patient treated at this 200 milligram dose level; and in part influenced our decision, having seen activity at 2.5 times lower dose, to focus on our expansion studies at 80, 120 and 160, so that, were this to be something that might crop up again, we'd be less likely to see it at these dose levels.

We have a couple other cases of unrelated muscle weakness, but, as Doctor Daver mentioned, these patients come to us with a lot of comorbidities, and it's not unusual to see this even in patients who are treated with other agents.

Gregory Renza, M.D.

That's great. Thank you for taking my questions, and congrats on all the progress.

Operator

Thanks for the questions, Gregory. Our next question comes from Li Watsek from Cantor Fitzgerald. Li, you may go ahead and unmute your line?

Li Watsek

Oh, hi, guys. Thank you very much for the update. For the Doctors, can you talk a little bit about the clinical bar for 239 perhaps in relapsed and refractory AML patients that failed FLT3 inhibitors?

The second question is, I know it's small numbers, but how are we thinking about the dose response here? In the extension cohorts, what do you need to see there to select the going forward dose? You select 120 mg as the primary dose, so just want to understand what's the reasoning behind that.

Rafael Bejar, M.D., Ph.D.

I can take the last part of that question first. I think one of the advantages we have with the trial design that we're working with is that we explore multiple patients at different dose levels, not just the three plus three that you get in dose escalation. It gives us a better understanding of not only the safety but also the PK and the efficacy. Noting that we are not getting substantially greater exposures above 120, we selected that 120 would be the go-forward dose, with the caveat that we might be able to adjust that for certain patients who aren't achieving the desired exposure. I think that is a good balance between the safety that we've observed at these dose levels, the efficacy that we've observed as low as 80 milligrams, and the likelihood that we'd be able to treat a greater number of patients successfully by going slightly above that minimally effective dose.

That's our thought. Now, the beauty of the expansion studies is that they have some flexibility built into them, so that if 120 after treating additional patients doesn't seem like the ideal dose, we'll have the ability to adjust that.

As you may know, the FDA now is very interested in ensuring that companies have done a good job of dose exploration in early-phase studies, before they're treating large number of patients and settling on what may be a too-toxic dose of their drug for an eventual regulatory approval study.

We're hopeful that this exploration we're doing now will pay off in the long run. Might take us a little bit longer to get through it, but it'll get some better understanding and a more solid grounding when we select our final dose.

Naval G. Daver, M.D.

I think to the first question, it was really teasing out the importance of responses in prior TKI-exposed patients. I think we need more numbers. Just to see activity in prior TKI-exposed off the bat is already encouraging. Now we have to look at it with more patients and see if this is 20% or is this 40%, where those response numbers will fall. I think that's what's going to happen in the next stage of development, where we're probably going to want to have a dedicated number cohort of patients who've had prior gilteritinib, for example, and try to get an actual percent response, so to see if that could be a path for early registration potentially, if we do see activity.

Rafael Bejar, M.D., Ph.D.

Just to echo that point, we are enriching our FLT3-mutant cohort for patients with prior treatment, at least 50% have to had a prior FLT3 inhibitor in that cohort, so we do want to make sure we have enough numbers there to explore it adequately.

Operator

Great. Thank you for the questions, Li. Our next question comes from John Newman from Canaccord. John, you may go ahead and unmute your line.

John Newman, Ph.D.

Hi guys, thanks very much for hosting the call, and just had a few questions. The first one, I don't know if there would ever be a reason to continue dosing 239 during stem cell transplant, given the safety profile. I'm assuming that most TKIs are stopped, really any drug treatment is stopped before transplant because you have to ablate the patients. Curious if that's something that has really ever been tried, I'd be curious to hear a response from the physicians on the call.

Then just a quick second question is just, have you identified any agents besides venetoclax that could be interesting in combination next year? Thanks.

Brian J. Druker, M.D.

I'll let the AML experts weigh in, but I don't know that drugs have been used during conditioning for transplant, but there's a huge opportunity to use a well-tolerated agent after transplant as a maintenance therapy to prevent relapse. Perhaps one of the two experts or both would weigh in on that.

Naval G. Daver, M.D.

I think Doctor Druker's point is a good one. There's a huge—well, there's emerging data already showing that sorafenib, which is what we call a first generation, is a good drug but has a lot of issues with tolerability. But even with that agent post-transplant, now two randomized case studies, one from China one from Germany, have shown eventually an overall survival benefit, and we think we can do much better if we have a drug that's actually more specific, more potent to FLT3, and better tolerated. I think that's where of course gilteritinib is being evaluated but could also be a path for 239.

Now there is some data, actually, our center has been looking at sorafenib for many years in ongoing study with conditioning. Some of the preliminary data that Doctor Popat, who's the vice-chair of our transplant group, has presented looks encouraging.

Again, if it's a very safe drug, maybe it could definitely go into maintenance post-transplant, but there may even be a role to add it to the conditioning regimen. It's a much harder regulatory path, I think that's something that could be done as an extension after you have an FDA approval, but it is an interesting thought.

Brian A. Jonas, M.D., Ph.D.

I echo what Naval said on the aspect of adding additional drugs to conditioning. That is an area of investigation, not just with small molecule inhibitors but there are immunotherapies and things like that, and so obviously done on the clinical trial and they really in the setting. Then I think the role of maintenance after transplant is very important and clearly there's data showing improved outcomes such as the sorafenib trial, as was mentioned. But clinically in practice, these drugs are not easy to administer, and I think that's—and obviously if you can't administer a drug that has been shown to benefit, then the patients are going to not get that benefit, and I think that's really a big issue, and the quality of life aspect of things as well, so. I think, yes, maintenance after transplant is another really great opportunity.

Operator

Thank you for the questions, John. Our next question comes from Matt Cross from AGP. Matt, you may go ahead and unmute your line.

Matthew Cross

Hi all. Thanks for the update today. Just one question on each program here. Starting with 239, just wanted to go over the response levels that you're seeing, very preliminary at this stage I know, but across dose levels. Just was curious, I know, Doctor Bejar, you commented on that you're not really seeing substantially greater exposures at doses above 120, looking at the 160 and the 200. Is there anything else you can flesh out there about the exposure trends you're seeing, and maybe as we look and project what we think may happen as you expand those cohorts at 160, 120 and possibly 200? Is there anything you can say about the mutation profile and that element of patients at 120 or 160 that have not responded? We emphasized who is responding, but whether how much that plays into the equation of who's not, and what could be addressed by expanding the number of patients you're looking at.

Rafael Bejar, M.D., Ph.D.

Thanks, Matt, that's a great question, and I think that one of the things you can learn about the drug in a clinical study beyond the safety and efficacy is you can learn a lot about the target patient population that's best served by it. That involves looking at those patients that maybe don't respond.

I think, to Doctor Daver's point earlier, the patients on the study are very heavily pretreated, not just with prior FLT3 inhibitors but all sorts of varieties of other agents, including some experimental agents. It becomes difficult to tease out whether or not their resistance is due to a preexisting mutation or prior selection for resistance in a more general way. But we are taking a look at this. I think what really surprises me is that some of those mutations that I would expect to be more consistent resistance mutations, like the RAS pathway mutations and *TP53* mutations, haven't necessarily been absolute barriers to response. That gives us hope that we'll be able to treat some of these more challenging patients to treat, and, as we get into earlier lines of therapy, see even greater activity than we're seeing now in those less heavily pretreated patients.

We are exploring that further, and to your question about the PK, the reason that we're taking the time to do this additional expansion is to really understand that better. Like most drugs, there's a lot of variability between individual patients, and you don't really get a full picture of that after just treating a handful.

I mentioned that we don't see what looks like greater exposure at 200 milligrams, yet one of those patients had one of the highest exposures we've seen on study to date, suggesting that there's a lot of variability at that dose level. Some patients have actually had lower exposures than patients at even lower dose levels.

We'll need more numbers in order to make more firm statements about dose-response relationships, or even dose-toxicity relationships, and we're taking the time to get that information so that, when we finally get to the point of wanting to move to that next regulatory step, we'll have that data to back us up and won't be asked to go back and have to repeat it.

Naval G. Daver, M.D.

I want to piggyback on that as well. We didn't talk about it, but the mutations that Doctor Bejar is mentioning are typically ones that are known to be resistant to gilteritinib, so both Catherine Smith and our group have published now papers in *Cancer Discovery* and *Blood Cancer Discovery* showing that people who have been treated with gilteritinib at the time of relapse, about 35% of them have emergent RAS-MAP kinase mutations, which in fact drive resistance, and even if you look at them pre-treatment, patients who have a higher allelic burdens of RAS don't respond. There were two patients at least who had a RAS or a RAS-MAP kinase mutation like PTPN11, who responded to the 239, and then there was one who had an MLL which also is historically associated with resistance to FLT3 inhibitor single agent or duration of response, if not resistance.

That is, again, small numbers, but biologically is very interesting and could start differentiating 239 from gilteritinib and quizartinib, if we continue to see that.

Matthew Cross

Perfect. That's exactly what I needed. Thanks, Doctor Bejar and Doctor Daver.

Then just briefly on lux, wanted to address similarly on a PK angle, very helpful to see some of the comparison in this single dose setting between the G3 and the G1 exposure levels, it looked like, across patients the 50 and the 100 milligram G3 were in the same ballpark, and I know you're expanding to look at 200 as well. Just wanted to review the rationale, given that it looks like the 50 and 100 milligram doses, you're getting exposure levels that are, again, in the same ballpark as the 750 or 900, so dose change here is great, from a pill burden perspective, but is there a ceiling there that you think you can push past with looking at 200, or what—any additional context on that, those take-aways at this stage, would be super helpful.

Rafael Bejar, M.D., Ph.D.

I think one of the reasons for exploring different dose levels with G3 is really to get more information about how to model it in continuous dosing. Because that's going to be the next step. After we get this data, we'll look at the PK parameters associated with G3, and then try to predict what it will look like when we give it continuously. Even those small differences, after a single dose, can really add up. As you saw, there was still drug left over after 72 hours, and those small initial differences with dose could lead to very different steady state differences in concentration. Our goal is to get to higher exposures through this dose escalation mechanism, so we can truly test the efficacy of the drug at exposures we haven't been able to reach with G1. I think if you look at the PK curves of G1 that we've published previously, there is a ceiling there, that, as we went from 750 to 900, for example, we didn't necessarily see more drug get in. On a per milligram basis, G3 is definitely doing better, and these small differences that you see with a single dose may actually translate to more meaningful differences in steady state down the road.

That's the reason for exploring it. I think if we just did a single dose and said well, they're roughly equivalent, let's go, we wouldn't necessarily have that understanding that we need in order to do more accurate modeling. We'll take the time to get a few additional patients at 200, get that data together, do the modeling, and then push the continuous dosing.

Matthew Cross

Makes perfect sense to me. Thanks, Doctor Bejar. Look forward to seeing you guys around the ASCO-EHA track.

Rafael Bejar, M.D., Ph.D.

Absolutely.

Brian J. Druker, M.D.

Thanks, Matt.

Operator

Our next question comes from Joe Pantginis at H. C. Wainwright. Joe, you may go ahead and unmute your line.

Joseph Pantginis, Ph.D.

Hey, everybody, good afternoon, thanks for taking the question.

First, I just wanted to ask the Company if you could provide any comments around the ease of manufacturing of G3 of lux and are there any rate-limiting steps that we'll need to be aware of, to be able to have all the ample drug supply that you need for your plans and beyond.

Then second, and more importantly obviously, everyone's talking about the profile of 239, Aptose has always been very good with the visibility around, and especially the slides, where their particular drugs hit the kinome on those kinome trees and which dots are more red than others, and how big the dots are, et cetera. I know the slide's not up right now, but obviously you're hitting a lot more of the kinases that we talked about. Maybe for the physicians on the line, when you consider the broader hits that 239 is having, so far, the safety profile's been discussed already, but do any of those particular kinases give you pause or potential concern with longer-term exposure?

William G. Rice, Ph.D.

Perhaps I can start with the G3, the manufacturing. We have an ample supply of the drug substance, because you'll remember when we were manufacturing the G1 and G2, we were having to manufacture the drug substance so frequently, very expensive, and then making the capsules also for the G1 and G2. It looks like we are going to be able to deliver much less API / drug substance in the G3, to be able to support these exposures that we want to achieve. That's greatly reduced our need for the amount of drug substance that we produce.

You also asked about the manufacturing of the drug product, so that's the G3 capsule. It's a relatively simple procedure. Once we identified the excipients that were included, it's a self-emulsifying process. It's relatively simple to manufacture, we've been able to manufacture at least two manufacturing runs with the

GMP material now. It appears to be stable over time, so we don't see that as a problem right now. We will have to continue to manufacture over time, as we hopefully expand out into these continuous dosing studies as we get to the later part of this year and early next year. But at this point I don't see that as being a show-stopper by any means, whereas it would have been with the G1 G2.

Then I'll let somebody else talk about the 239, and the kinases. Doctor Bejar, did you want to talk about that one?

Rafael Bejar, M.D., Ph.D.

Yes, and Doctor Daver and Doctor Jonas jump in. I think that agents that are very very highly selective, that target really only one kinase, may show a lot of activity potentially in untreated patients, because that target is active in that disease. However, these cells can quickly evolve other mechanisms to get around that, and you heard the discussion about NRAS and MAPPK pathway mutations that can do just that, they can bypass FLT3 signaling. But if there are other mechanisms that are in play that cells are using in order to do that kind of bypassing, having a little bit broader activity can be helpful. If it's too broad, then, as mentioned in your question, then you can hit kinases that are important for toxicity and targets that you don't necessarily need in order to kill the cell, but that might lead to toxicity off target, like EGFR inhibitor, inhibition can lead to skin problems, HER2 inhibition can lead to cardiac issues and so on.

I think having a sweet spot, where you have a good breadth of activity against important kinases are are not hitting those that are more relevant for toxicity, is the spot to be. We've shared that kinome tree. I think we'll have to take a closer look at it to see if there's anything there that might be concerning in long-term studies so far, but we surely haven't seen that to date in multiple patients or anything like that in the study.

William G. Rice, Ph.D.

Just a quick addition to that. When we were looking around at molecules, we were looking for molecules of course that could inhibit the FLT3, because it's one of the major drivers of AML. We all wanted a FLT3 inhibitor. But we also wanted one that inhibits all different forms of FLT3 that have been tested thus far, so that that could minimize the resistance.

But no one wanted just another FLT3 inhibitor because it's insufficient. We wanted a molecule that also could suppress some of the downstream pathways: the JAK-STAT pathway, the RAS-ERK-MAP kinase pathways, as well as some of the AKT pathway, without having to directly target PI3K or AKT. So that's what we were looking for. We actually saw this molecule a number of years ago, before we ever licensed it in, and we thought, that's going to be an impressive molecule, if it's safe because of the kinases that it hits and the pathways it affected. That was the reason we brought the molecule in. It did hit those pathways, it suppresses the right pathways, but thus far it's been very safe.

Then I'll pass it over to the other physicians, if they have any other comments.

Brian A. Jonas, M.D., Ph.D.

I would just say real quick, we know from lots of lines of evidence at this point that AML is an oligoclonal disease, often at presentation. Having broader activity theoretically is advantageous, and so I think that's one distinct advantage that allows maybe targeting of some of the minor clones at the same time.

Rafael Bejar, M.D., Ph.D.

Great point. Many of the patients with FLT3 mutations relapse without that FLT3 mutation, in part because they've selected for those clones that don't have it. If you can have some broader activity against both your mutant and nonmutant cells, it might help suppress some of those potentially emerging clones.

Joseph Pantginis, Ph.D.

Thank you, gentlemen.

William G. Rice, Ph.D.

Thank you, Joe.

Operator

Our next question comes from Matt Biegler from Oppenheimer. Matt, you may go ahead and unmute your line.

Matthew Biegler

Oh, hey, guys, thanks for taking my questions. One for the Docs. Are you guys seeing any anemia-related side effects? That's obviously an issue with a lot of targeted agents in AML. If you are, what's your confidence as you start thinking about a venetoclax combination, considering you're probably going to be dealing with pretty frail patients?

That's the first question, and then I had a follow-up for Management on maybe just qualitatively, can you talk about the types of patients you enrolled into the 120 and 160 mg cohorts? Did you enroll less FLT3-mutant patients in those cohorts and might that explain maybe the topline differences in what we're seeing in response rate, granted we are dealing with very small numbers, obviously, but just any way you could speak to that would be great. Thanks.

Naval G. Daver, M.D.

I can start with the anemia question. No, we have not seen any significant signal, at least to my knowledge, with 239 and anemia per se. Actually, with most FLT3 inhibitors, gilteritinib and quizartinib, we haven't seen anemia as much. We do see more neutropenia with for example quizartinib, which also hits KIT, which is an important pathway for normal neutrophil and platelet development. Now in combination with venetoclax, we're doing a lot of studies at MD Anderson and in the U.S., combining different drugs with venetoclax, and there is definitely cumulative myelosuppression, and it depends on the drug. With FLT3 inhibitors, gilteritinib, quizartinib, we do see more significant cumulative myelosuppression. With IDH inhibitors, for example enasidenib and ivosidenib, we do not see that much cumulative myelosuppression.

I think that it just depends on the properties of the drug, and it'll be very—it's usually obvious very quickly, within eight or ten patients, that we know this is going to lead to significant cumulative myelosuppression, we're going to have to do a lot of things to adjust it, it may still be effective, but it won't be straightforward and easy, or it could actually not have significant myelosuppression.

I'm hoping that with 239 we see what we're seeing with IDH, where we don't see much myelosuppression beyond what we see for example with HMA venetoclax standard therapy.

Rafael Bejar, M.D., Ph.D.

To follow on with that, once patients achieve remission and you follow them, the leukemia's out of the picture. Before then it's very hard to determine whether the cytopenias are due to active disease or the drug that you're giving. But we have had patients that have been able to continue to take the drug daily for weeks on end, including one patient over a year, where they didn't see any additional myelosuppression. We've had no grade 3 adverse events of anemia, and certainly not in patients who have achieved response. From that standpoint it's not particularly myelosuppressive, outside of the context where the patient's bone marrow is already challenged by either existing disease or perhaps another agent.

(Multiple speakers)

… Management, could you just repeat that real quick?

(Multiple speakers)

… makeup of the different cohorts and might that explain the difference in response rate.

I think the way the study is designed, we want to make sure that in those expansion cohorts, that we have at least 50% of the patients with a FLT3 mutation so that we don't bias at all one way or the other. I have to look back to get the exact makeup of each of those different cohorts, but I don't think it's necessarily that.

One thing that we have seen over time is that gilteritinib has made greater penetrance into the patients that we've seen. We're seeing more patients with prior pre-treatment. In particular in Korea where some of our sites are, and where some of our patients have been treated, gilteritinib was not widely available when the study opened in 2019; however, as of March of this year, gilteritinib is now reimbursed by the national health system, becoming more prevalent in the patients treated there. I think we're going to see more of these heavily pretreated patients with that greater unmet medical need, and perhaps the response rate over all will be a little bit lower. But interestingly, if you look at the response rate of the FLT3-treated patients in our population, small numbers, but it's 50%. That's really impressive, and over all in the 80 milligram cohort the response rate, including the wild type patients, was about 25%. Perhaps there is a difference over time in the patient population that we're treating, but I think as we get to larger numbers we'll get a better sense of what that efficacy is.

Matthew Biegler

Got it. Thanks, guys.

Operator

Thanks for the questions, Matt. Our next question and final question comes from Soumit Roy from Jones Trading. Soumit, you may go ahead and unmute your line.

Soumit Roy, Ph.D.

Hi, thank you for taking the question. Congratulations to the panel for the comprehensive presentation.

Doctor Bejar, if you can just read through it, how many were there evaluable patients in the 120, 160 and 80 milligram cohorts, and was there anything other than the (inaudible) difference other than the

gilteritinib pre-treatment (inaudible) difference or age or anything else that stood out, accounting for the difference in the response rate?

Rafael Bejar, M.D., Ph.D.

Good question, no, we haven't formally looked at those measures, as to whether they might account for a difference in response rate. I think it is just stochastic variation at this point, given the small numbers of patients that we've had.

Remind me, the very first part of your question?

Soumit Roy, Ph.D.

The number of evaluable patients in the 80, 120, 160 …

Rafael Bejar, M.D., Ph.D.

We haven't reported it as the number of evaluable patients. We really treat it as an intention to treat, so to speak, and we've told you the number of patients who received drug. Now it is true that some of these patients didn't necessarily make it to be evaluable for safety, meaning they had a complication or something else that perhaps their disease progression, where they didn't necessarily finish that first cycle. Technically speaking, they wouldn't have been evaluable for that first response, but we've just shown the numbers of treated patients. I think later on we can consider doing a more nuanced example, but I think it's a fairer, less cherry-picking way of presenting the data, and that's what we've shown.

Soumit Roy, Ph.D.

Okay. Then one last question is, given the visibly conservative nature of FDA taking recently, do you think a later-line patient would have to move into a randomized Phase 3 to be the registration trial, with median OS as the primary endpoint, or …?

Rafael Bejar, M.D., Ph.D.

I think it's a great question. I don't think the FDA was saying that you have to do that. I think the FDA was saying that you have to be very careful about what your dose is in that patient population, and what your confirmatory study is going to look like, that you really have to do your homework before you propose to do a single-arm registrational study. However, if the patient population has great unmet medical need, as these patients certainly do, then I still think that that fast path to approval is going to be the most appropriate thing, both for patients and for the FDA, as long as you have a good plan for following that out and getting to full approval, that you've thought about ahead of time, even before beginning that single agent study.

I think that what the FDA was telling us is that there is a way to do it, and you have to do your homework and you have to lay the groundwork for that; but that it's still an important path.

Soumit Roy, Ph.D.

Thank you.

Naval G. Daver, M.D.

I want to echo that as well, with—oh, sorry, but just with the FDA. I actually don't necessarily think in leukemias they have become more conservative. If anything, I think they are now seeing the benefit of targeted immunotherapies and trying to get these drugs approved very quickly. As you all know, nine drugs have been approved in AML in the last 4.5 years, right, and many of them are actually single-arm studies when they were approved, with eventual confirmation; venetoclax, IDH inhibitors now, gilteritinib even right before the full case the survival. I think in a major area of unmet need post relapse gilteritinib, any drug that shows any efficacy with a good safety, I think safety is going to be what they really focus on there, that we're not doing any harm, and we're having some benefit. I think that would open the path for early approval with then a larger study, probably in an earlier line as single agent or combo, to confirm that.

Yes, I think major unmet need in a rare population of AML will be treated very different from breast cancer or lung cancer where absolutely they want full Phase 3 randomized data up front.

Soumit Roy, Ph.D.

Thank you and congratulations again.

Operator

Thank you for the questions, Soumit. This concludes our Q&A session. I will not turn it back to Doctor Bejar for closing remarks.

Rafael Bejar, M.D., Ph.D.

Thank you, Tara, and thank you, all, for your participation on the call. Discussion has been outstanding, I really appreciate the insight from Doctor Daver, Doctor Jonas and Doctor Druker, and the questions were excellent questions too. They raised some excellent points that we didn't have a chance to cover in detail. We'll have more information for everyone down the road, as we collect the more nitty-gritty fine-tuned clinical data, so apologies to those who submitted questions we weren't able to get to with question-and-answer session. We hope that those are answered in a subsequent presentation.

Once again, thank you, all.