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CRIS.OQ - Curis Inc Virtual KOL Event - Reviewing CA-4948 Clinical Data in NHL & AML/MDS

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PRESENTATION

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Good morning everyone, and welcome to our Virtual Key Opinion Leader call to discuss clinical data on our first-in-class IRAK4 inhibitor, CA-4948. 12 months ago, we outlined our goals for 2020 to provide data updates from both of our ongoing clinical trials of CA-4948. Today, we're excited to provide these updates.

For the NHL study, in a presentation yesterday at ASH, we formally identified our recommended Phase II dose, which has demonstrated tumor reduction in 6 of 7 patients and robust tolerability up to 2 years. All of this in single-agent therapy in a heavily pretreated patient population. These are patients who enrolled in our study after feeling on average 4 prior lines of treatment with other therapies.

In addition, we are especially excited about the identification of 2 new biomarkers, which we expect will help us with patient selection and enrichment as we advance into the combination study of CA-4948 with ibrutinib.

For the AML and MDS study, we are highly encouraged by the data released an hour ago. While we are still in the early days of the study, just the first 6 patients, we're very excited about what we're seeing. In monotherapy and in a late-line relapsed/refractory patient population, all 6 patients have seen a reduction in blast counts. 2 of these patients have already achieved a marrow complete response. Excitement both at the company and among our investigators is very high.

Dr. Bob Martell, our Head of R&D, is joining me on the call this morning, and will be reviewing clinical data from both of these studies in more detail. Additionally, we are honored to have Dr. Amit Verma joining us this morning. Dr. Verma is Professor of Medicine Oncology at Albert Einstein College of Medicine and Director of the MDS program, at Montefiore Medical center in New York. Dr. Verma serves as one of the primary investigators on our CA-4948 Phase I study in AML and MDS. This morning, Dr. Verma will be discussing his view of the current AML/MDS landscape as well as summarizing the preclinical data for CA-4948 in AML and MDS.

Following the clinical data update, we will remain on the line for a question-and-answer period. I'd like to note that during the call, we'll be making forward-looking statements, which are based on our current expectations and beliefs. These statements are subject to certain risks and uncertainties, and actual results may differ materially. For additional detail, please see our SEC filings.

I'd now like to turn the call over to our Head of R&D, Dr. Bob Martell. Bob?

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Thanks, Jim. Good morning, everybody. I'm really excited today to talk about the clinical data and some of the biomarker data that we have. So first, I'll start with the mechanism of action for 4948. In particular, this is really focused on NF-kappaB. As you know, NF-kappaB is a dominant driver of proliferation and survival in B-cell malignancies. And also a master regulator of inflammatory cytokines that are important in myelogenous leukemias. This slide represents the 2 main pathways in cancer that drive NF-kappaB. The BTK pathway on the left and the TLR signaling pathway on the right. Now the BTK pathway, as you know, is fairly well covered by current therapies, including BTK inhibitors such as ibrutinib. There are

no approved therapies right now that really control the TLR pathway signaling to NF-kappaB. And that's where we focused our efforts on drug development.

In particular, we focused in on the Myddosome, which is a complex through which virtually a high number and percentage of signaling is traveling to activate NF-kappaB. In particular, IRAK4 is a serine/threonine kinase that is required for Myddosome signaling to reach NF-kappaB. And we've developed a highly specific and potent inhibitor of IRAK4 that we have brought into the clinic, and that's what we're going to be talking about today. This inhibitor in preclinical models can basically shut down the signaling to NF-kappaB by over 90%.

This target, IRAK4 is extremely interesting and has caught the interest of the National Cancer Institute. And they become extremely excited about this. And as we mentioned recently, in a recent announcement, the NCI has chosen the Curis drug, CA-4948 as the IRAK4 inhibitor that they will investigate.

Next slide. So to get into the clinical studies that we've run, first, I'm going to focus on lymphoma. Now lymphoma, as I mentioned, is driven by these 2 pathways, in particular by the TLR pathway as well in terms of NF-kappaB. This particular study is a Phase I dose escalating trial that started at a dose of 50 milligrams daily. Throughout the trial, we escalated dosing to 400 milligrams twice daily, that's a 16-fold increase in terms of the overall dose for patients. We found that the patients treated on the study were quite elderly with a median age of 69 years. We have a variety of malignancies. Importantly, as Jim mentioned already, these patients have highly refractory disease, in fact, a median of 4 prior lines of therapy.

On the study, we've had 2 patients who have had MYD88 positive disease.

Next slide. So I'd like to shift -- and before I actually get into the clinical data, talk a little bit about the biomarker data that we've got. So biomarkers, as you know, are very important for verifying target ambition and also potentially for enriching a patient population.

The first biomarker that I'd like to talk to is actually NF-kappaB itself. So the P50 subunit of NF-kappaB when phosphorylated represents activation of NF-kappaB. So this is interesting because if we might hypothesize that if NF-kappaB is active, we might think that our drug could have effectiveness. On the other hand if NF-kappaB is not active in the first place, this might be a population that may not benefit from our drug. And so potentially an enrichment strategy could be developed from that.

Also, it might be an excellent way to determine whether or not we're hitting the target. In other words, we can monitor this during treatment to see if our drug is inhibiting this downstream target.

The second major biomarker that I'd like to talk to you about today is MYD88. When mutated, this protein actually causes constitutive activation of the Myddosome and activation of NF-kappaB regardless of the upstream signaling. And this is actually pathognomonic of certain malignancies and may be a great way to enrich for patients likely to respond to CA-4948.

Next slide. So the next slide starts to show some early biomarker data from our Phase I patients. First, let me talk about the P50 biomarker. And this is the panel on the left here. This shows a picture of 2 tumors stained for phospho-P50 biomarker. The left tumor shows negligible staining, while the right has positive staining. We actually have data from 14 patients early in the study, half it turns out were negative for staining for phospho-P50 and half were positive. And below, we've shown the patients in terms of their best response on study. And you can see that all 7 of the patients who had negative staining for phospho-p50 had progressive disease as their best response on study.

In contrast, although one of the patients who had positive staining at baseline had either tumor shrinkage or stable disease on study. So this suggests this could be a potential enrichment marker for selecting patients although the data right now, we would think are not quite mature enough. Because most of these patients, as I mentioned, were early on the study, had suboptimal dosing. We did have 3 patients who were actually treated at the 300-milligram twice daily dosing, where we did have pre-treatment biopsies. And the correlation was actually perfect, 2 of the patients had negative staining at baseline, and both of those patients had progression on study. And one of the patients had positive staining at 300, and that patient had a significant tumor reduction with a durable duration on study and well tolerated.

Let me shift to the right bottom panel, here this demonstrates clear inhibition of the target by 4948. So this patient had a biopsy right before they started treatment with 4948. And then after 3 weeks of treatment, they had another biopsy of their tumor. And you can see that the 4948 completely inhibited the NF-kappaB signal. And this is exactly what we're looking for to demonstrate that CA-4948 is effective at inhibiting IRAK4.

Actually, before we switch to the next slide, let me just highlight also that MYD88, as I mentioned, is the other biomarker that we're very interested in. So 2 patients on study so far have had mutated MYD88, and actually, both of those patients had tumor burden reduction on study. So 2 out of 2 have had tumor reduction with MYD88 mutation.

Next slide. And so this next slide actually shows one of those patients. This patient actually came on very early in the study at a quite low dose of 50 milligrams. And they had stabilization of their disease, maybe some reduction in their tumor burden, they're in spike. But per protocol, they were able to escalate as we cleared higher doses. And at each dose escalation, we saw a further reduction in the tumor burden. In fact, by the time they got to 300 milligrams twice daily, the patient achieved a PR with more than 50% reduction, in fact, 67% reduction so far. This patient is continuing on study. They've had a dramatic improvement in their symptoms from their disease and is doing quite well currently. Now 2 years on study.

Next slide. So as I mentioned, this is a dose escalating study with our goal of trying to identify a recommended Phase II dose. So we've determined that based on the tolerability and the anticancer activity that the optimal dosing in this lymphoma population is 300 milligrams twice daily. And I kind of illustrated that here with the blue bars, which are patients who are treated at the 300-milligram twice daily dose. And you can see that the majority of these patients, 6 out of 7 evaluable patients here had reduction in their tumor. And again, I'd like to illustrate and point out these were highly refractory patients. So we're talking a single oral agent achieving really nice tumor reductions.

Next slide. This slide provides similar data and a more focused data set on the 300-milligram twice daily patient population. Here, you can see the durability in the course throughout their therapy in terms of their tumor burden. 3 of these patients have actually been treated for a year longer and the majority of them are actually still ongoing on their therapy as is illustrated by the dotted lines here.

Now I'd just like to take this moment to emphasize, again, at our recommended Phase II dose, we're seeing this level of anticancer activity, again, pointing out highly refractory patient population, oral drug, single drug. The population is actually here unselected. So we haven't yet gone down and started to select for p50, for example. Patients found as to be well tolerated. I think an important point is that there's minimal myelosuppression with this drug. So that's really important as we think about combining this drug with other therapies that may have some myelosuppression.

It is to be determined, yes, since we only have 2 patients with MYD88 mutation, for example, whether this could serve as a single agent registrational strategy, but we do feel that it is a very solid foundation for going forward with combinations.

So let me switch to the next slide. And this is the basis for our combination approach, which we're actually going to start a clinical study within the next quarter, early 2021. But here, what I'd like to remind you is the 2 key pathways, regulating NF-kappaB, the TLR pathway, and the BTK pathway. So ibrutinib, as you know, targets the BTK pathway, 4948 is really the first legitimate IRAK4 inhibitor to be able to target the TLR pathway. So I'm showing an experiment here, what I'm actually not showing here is the monotherapy of 4948 going to the maximal optimal dose in this model. 4948 can almost completely inhibit tumor growth by itself. Here, we've used a lower dose of 4948 to be able to illustrate the synergy between these 2 molecules. And you can see at that dose, there's modest reduction in the tumor burden, but it really illustrates the ability of adding these 2 drugs together, can show a significant decrease in the tumor growth.

Now we're really excited about this. We think this is going to be an optimal combination targeting both of these parallel pathways. And so as I mentioned, we're working really hard with our investigators to get this study open and started in the first quarter.

So at that point, I'd like to pause because that's -- that completes my summary of the lymphoma data and hand it over to Dr. Amit Verma to give an introduction on our AML/MDS efforts. Amit?

Amit Verma

Thank you, Bob. Next slide. So acute myeloid leukemia and myelodysplastic syndrome are diseases that are characterized by dismal outcomes, especially in the elderly. And these diseases, especially MDS, don't have generally curable curative therapies. The only curative therapy for MDS is an allogeneic stem cell transplant. And these are diseases of the elderly, which makes it tough to do allogeneic transplants for these diseases.

The current treatments available and approved by the FDA for MDS include lenalidomide, which is only used for patients with 5q deletion; and hypomethylating agents, which include azacitidine, decitabine and an oral version of recently approved decitabine with a CD inhibitor. There is also a recent drug luspatercept that's approved for treatment of anemia in low-risk MDS. But that's about the limited number of drugs that are approved for this tough disease.

AML has more drugs that have been approved for treatment. And recently, we've had FLT3 inhibitors, IDH inhibitors, and chemotherapeutic regimens that have been approved. But still, the outcomes remain not very desirable, especially when we deal with AML and MDS in the elderly.

So IRAK4 represents a novel therapeutic target in these diseases. And this is a research that we have done in our lab in collaboration in Dr. Dan Starczynowski at Cincinnati and Dr. Boultwood at Oxford. We showed that IRAK4 can exist in 2 major isoforms: One is the IRAK4-long, which is the active full-length isoform of this serine/threonine kinase. And then there is a shorter isoform, which lacks an important part of this enzyme called the death domain. So the shorter isoform cannot transduce signals from the surface of the cell from toll-like receptors down to NF-kappaB, which Bob had talked about in the previous slides.

And when we looked at RNA-Seq data from AML samples in the tumor consortium TCGA, we found that in AMLs, the ratio of the active long isoform to the inactive short isoform was more than 1.25 in more than 50% of AML samples. So basically, what I'm saying is that AMLs, the majority of AMLs, have more of the active long isoform versus the inactive short isoform. And when we look at normal hematopoietic stem cells, we find that these cells have more of the short isoform and less of the long isoform. So we have over activation of the active isoform of IRAK in MDS and AML samples.

So this is not a mutation. This is an active isoform. And when we compare it to traditional mutations that are seen in AML, for example, FLT3 is seen in about 1/3 of cases, and then there are a lot of epigenetic mutations like TED, DNMT, IDH and so on and so forth. When we look at MDS, the major group of genes that are mutated in MDS include splicing proteins.

Next slide, please. So the reason splicing proteins become important in the IRAK pathways, they are the 2 major splicing proteins that are mutated in MDS, are SF3B1 and U2AF1. So invert that I previously mentioned with Dr. Dan Starczynowski that was published last year, we showed that when you have this U2AF1 splicing mutation in hematopoietic cells, this splicing mutation leads to overproduction of the active form of IRAK, the IRAK long isoform.

We also have shown that the other splicing mutation, the SF3B1 also leads to overexpression of the long active isoform of IRAK4. So we have shown a link between a splicing mutation that's commonly seen in MDS and less commonly in AML; two an overexpression and activation of the IRAK innate immune signaling pathway. Furthermore, we showed with a variety of experiments that when we block IRAK4-L either with genetic means or with CA-4948 in cell lines as well as patient-derived xenograft models, we can inhibit the MDS and AML malignant clones by inhibiting IRAK kinase.

So the panel on the left shows an example of leukemic colonies, where we genetically knock down IRAK4, and we see a nice significant reduction in leukemic colony growth. And on the right side, the panel basically shows immunodeficient mice, where we xenograft MDS and AML samples and follow them over the course of time after dosing with CA-4948. And as compared to vehicle controls, the IRAK4 inhibitor leads to a reduction of the malignant clone in immunodeficient mice.

So these data point to the potential of inhibiting IRAK4 in these 2 diseases and provided the preclinical rationale for the clinical trial testing CA-4948 in MDS and AML, the clinical trial that Bob will show you initial results from was done in a relapsed/refractory setting, which is a particularly bad prognostic group of MDS and AML.

To give you an example, when patients with MDS become relapsed or refractory to hypomethylating agents, there have been a multitude of studies that have shown that they have a dismal overall survival. We are talking of overall survival less than a year as seen by multiple groups. So this is a tough patient population with not too many therapeutic options.

Next slide. So now I hand it over to Bob to tell you the results of the preliminary clinical trial results.

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Thank you, Amit. Appreciate it. So we are extremely excited to present the early exciting preliminary data here today for the AML/MDS study that Amit mentioned. So if you go to the next slide.

So this, again, it's a Phase I study. It's a 3-plus-3 dose escalating design. We're actually able to start at the 200-milligram twice daily dose based on our lymphoma experience that I just described. The population here, as you can see, is quite elderly with a median age of 72. And also, as Amit mentioned, heavily pretreated. The median number of prior therapies was 3. It was distributed between 4 AML patients and 2 MDS patients. And both of these MDS patients were actually high risk MDS.

The study has escalated quite quickly. We actually went through the 200-milligram dose level with 3 patients. No DLTs were seen there. So we were able to escalate up to 300 milligrams twice daily. Again, we enrolled 4 patients there, and none of them had a dose-limiting toxicity. So we're currently escalated in treating patients at 400 milligrams twice daily. So the study is ongoing. And on the next slide, I'd like to show some of the early results.

So as Jim mentioned, basically, of the patients who -- of the 5 patients who were morphologically evaluable for blast reduction, all of those patients had a significant blast reduction, which is quite striking. And in fact, already 2 of these patients have achieved marrow CR, bringing their blasts back into the normal range, although one of these patients is continuing on therapy. So this has been extremely well tolerated. We're extremely encouraged by this finding and look forward to continuing on with this study in identifying a recommended Phase II dose here, expanding, getting more information. And also, as Amit mentioned, thinking about particular patient populations that within this group might be subsets that are extremely sensitive, for example, patients with splices on mutations or patients with overexpression on the IRAK4 long form.

So I'd like to just finish by putting this into context, so -- and emphasizing that. So Amit mentioned, this is an extremely difficult-to-treat disease, especially when the patients are refractory like this. We're still in the dose-finding phase of this study and have already seen this impressive data. Again, this is an oral drug, which is great for elderly frail population. It minimizes the visits to the hospital, allows patients to be treated much more efficiently.

Single agent, historically, single agents really don't work well at all in these diseases. And I think finally an important point that I also made with lymphoma, but I think it's really important here, and that is that there is minimal myelosuppression with this drug. And this disease, in general, is characterized by myelosuppression in the first place. And a lot of the therapies that you utilize to treat the disease cause myelosuppression themselves. So this represents an ideal opportunity for a combination as well in these difficult-to-treat patients.

So again, we're extremely excited, but preliminary and look forward to advancing this study.

Let me hand it back to Jim to finish up the call.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Excellent. Thank you, Bob. So we're going to head into the Q&A session. And if you have any questions, please raise your hand in the software, several of our analysts have dialed in. So as you submit your questions, we'll be able to see them. I will then read them for the audience, and then I'll direct the appropriate person to answer the question.

QUESTIONS AND ANSWERS

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

So the first question is from Yale Jen at Laidlaw. He's asking, in the NHL study, are there -- have there been any patients that have been treated with ibrutinib beforehand and failed? And then second, in the AML and MDS study, have the long spliced IRAK4 form being -- have a -- I guess it's a question about the long isoform of IRAK4. Have we seen any of those patients so far? So Bob, actually, I'll point to you for those.

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes. So for the NHL study, we have had several patients who have been treated with ibrutinib before. In general for many of the NHL patients that have come on to the study though, probably the majority have not been treated by ibrutinib.

The second question related to the long-form of IRAK4, this is a really important question that we're asking, and Dr. Verma is here working closely with us as well to help understand the levels of that in our patient population. We're working right now to evaluate and confirm that. Those data will be presented at a future presentation.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Okay. Thanks, Bob. So next question is coming from Alethia Young at Cantor. Why do you think -- why do you need to think about a subgroup if you're seeing activity that looks so broad-based across the population. And frankly, I don't know, Bob, if you want to start that but maybe Amit can chime in on that, too, because that was really his research.

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

So I'll start. And you may be right. And hopefully, we may be able to see enough activity in unselected patients to achieve registrational strategy here, but we still also have the option of looking at a more focused population if a subset is extremely sensitive to the drug. As -- and I'll let Amit comment as well, but we don't know -- we know that the long-form of IRAK4 is present in a broad spectrum of these diseases. We don't know exactly where the right cutoff might be, maybe even a larger population. But Amit, why don't you comment on that?

Amit Verma

Yes. Thanks, Bob. So it's an interesting question. We do see the long isoform in SF3B1 and U2AF1 mutants. But we also see the long isoform in other subgroups of AML and MDS that don't have splicing mutations. And we do not know the exact answer of why certain cases have it and certain cases don't. It seems to be -- isoforms are governed by alterations in RNA-binding proteins and the splicing machinery is actually composed of numerous proteins that could be audited. So we are still trying to find answers why non-splicing mutant AMLs and MDS can also have overexpression of the long isoform, but we do see it.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Yes. One of the things I'll add to that also Alethia, is we're learning a lot more about the IRAK4 expression, as Dr. Verma indicated. But also recall that the drug targets for 3 as well. So that could also be part of the story. But we are very pleasantly surprised to find that we had such a broad-based look in the data, such a great response among the patient population.

As I go further down, this is another question from Alethia Young. And Amit this one is for you. Is there any hypothesis around potential durability based on your modeling?

Amit Verma

Yes. So far, our experiments, preclinical experiments have been restricted to a lot of in-vitro experiments in cell lines as well as primary patient samples. And also some patient-derived xenografts with MDS and AML, primary samples, which are extremely tough to do because these cells don't survive that well in mice, in foreign environments in the mice. But from our published data, we saw quite a significant reduction in inhibition of the malignant clone. And that's all we can sort of conclude right now. It seems like a good target. It seems like the drug works in-vitro as well as in-vivo. One more thing that I can actually add to this is, in terms of durability and resistance mechanisms, there was a very nice study published by Dr. Dan Starczynowski in Science Translational Medicine last year, where he showed that IRAK4 can be an escape mechanism for resistance against FLT3 inhibitors. So that study, again, hints at the important role of this pathway in leading to recovery or resistance of sales from other agents. So that's how we know right now.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Okay. Excellent. Thank you. We also have a question from Soumit Roy at JonesTrading. This is a question really for Bob. What kind of response or blast reduction would you see in ibrutinib in phospho-p50 positive patients?

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes. Thanks, Soumit. That's a really great question. And actually, the answer is, not really known. The use of p50 as a potential biomarker for ibrutinib is not well characterized. We do know that p50 -- phospho-p50, obviously, the in cart of NF-kappaB is a key indicator of activity of NF-kappaB, but this particular biomarker hasn't been well characterized.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

And I would add to that, Soumit, so remember, the idea is that both pathways, both BTK inhibitors and IRAK4 inhibitors, the toll-like receptor pathway, are really coming at NF-kappaB from a different place, but they should be additive. So our hope would be going into combo therapy that, yes, as we can show so far in our data, we're hitting those patients that have flagged positive for phospho-p50. We expect that there would also be an additive effect by adding BTK to that, so that the 2 together would mirror what we saw preclinically, which is both of them together should be better than either on its own.

The next question is coming from Alethia Young at Cantor. Any difference with the activity between AML and MDS patients?

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes. So let me start, and then I'd actually like Dr. Verma to opine on this question. So we did see both the MDS patients and the AML patients with blast reduction. So I think we would expect to see activity in both. As Amit mentioned, the IRAK4-L is prominent in both of these groups of malignancies. But let me hand it over to you, Amit.

Amit Verma

Yes. Yes. Bon is correct, this pathway, and DLR MYD88 and NF-kappaB IRAK pathway seems to be active in both AML and MDS. So preclinically, we see pretty significant activity with either genetic or pharmacological inhibition of this pathway.

The clinical results, I guess, it's early days for the clinical trial. It looks very encouraging. But as the trial accrues more patients, I think, we will see if there's any differences between AML and MDS. I guess it's too early to say right now.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

So the next question is from Chad Messer at Needham. So he's asking -- and Bob, this is a question for you. Do we know what the biomarker status is for the Waldenstrom patient who got the dose escalations?

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes. So in terms of the MYD88, yes, this patient was positive for MYD88 mutation. As I mentioned, there were 2 patients that were positive for MYD88, and both of them had a tumor reduction. This one patient with the Waldenstroms is the one that I showed in detail. We actually did not have a -- archival tumor sample, enough tumor sample to test the p50 in this case, although we would expect that to be strongly positive based on our understanding of MYD88 activation of this pathway.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Yes, it's a point, we're taking 2 points there, Chad. On the 2 biomarkers, phospho-p50 and MYD88. In phospho-p50, roughly half of the patients have had samples gathered so far and tested. Obviously, most of those are going to be at the very low doses. We were encouraged that even in low doses, phospho-p50 looked to be quite predictive. But if your phospho-p50 was not active, meaning NF-kappaB was probably not playing as key a role in your disease, those patients all progressed, 7 out of 7.

On the other hand, even at low doses, if you were positive for p50 and it was playing a role in your disease, even at low doses, the drug was having an impact that 6 of the 7 of those had tumor shrinkage or stable disease. Obviously, that was very exciting, early days. On MYD88, it is even more strong, but it's -- they're only 2 of them. So we want to be careful not to make too much of that biomarker, but it is exactly what we would have expected based on the scientific thesis. That is that if you can block the TLR Myddosome axis of that pathway driving NF-kappaB, you should be able to provide some patient benefits. So we were very pleased that it seems to be so clear in the 2 patients that were MYD88 positive.

Question. Let's see, another question from Chad at Needham. What does NHL dosing data 300 milligrams at the recommended Phase II dose tell us about MDS or AML, if anything? Is there anything you learned from that NHL data that were announced yesterday that translates through a read-through to what we saw today?

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes, potentially, I mean, it gives us some guidance in terms of where we may end up with dosing. I wanted to point out, though, that in the AML/MDS population, these patients, again, extremely difficult to treat. And we do know that there is a significant dose dependence here. And that's why we have continued to dose escalate based on the fact that we had no dose-limiting toxicities at 300 out of 4 patients. And so it's possible that we'll end up with a different recommended Phase II dose for the AML/MDS population. But I think it does give us some guidance as to where we may end up.

And honestly, it gives you a sense for the fact that we're probably already fairly close to our recommended Phase II dose with the AML/MDS population since we've already explored that dose to some extent in this group of patients. And I think we're nearing final stages of honing on where we might end up.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Yes. And let me add to that as well, Bob. I think when you look at the 2 data sets in aggregate, there are a couple of messages that you can take home. Of course, the NHL data set was dosed in dose escalation. So there were a lot of subtherapeutic doses before we got to the range of 300, where we saw 6 of 7 patients doing well. And then, of course, in AML and MDS, we started at the therapeutic dosing. But the 2 combined, the data so far suggests what we were hoping, which is, it appears as though the drug is hitting the target period. And that the target matters. If you can

hit that target and turn down IRAK4, you're going to have a very positive impact on tumors. We see that in the NHL data. And of course, we see that even more strongly in the AML/MDS data because, of course, we've been dosing at therapeutic doses from the get-go. But the 2 in combination for us give us a great deal of optimism. And as Bob said, the biomarkers moving forward, allow us to really enrich the population of patients, both clinically and frankly, hopefully, at some point, commercially, will allow us to enrich that patient population and determine and advance which patients will be amenable to IRAK4 therapy.

The next question is coming from Ed White at H.C. Wainwright. This question is for you, Bob, why did one patient leave the AML study? And when would we start planning to enrich the NHL study for biomarkers? This is a longer set of questions. Could the enrichment -- and you've got a lot of questions. Could the enrichment be part of the current study? Or would you need to initiate a new study for that? And then lastly, what would you need to see in Phase I that would give you confidence in starting a Phase II? And when could a Phase II monotherapy study begin? So Bob, I'll hand it to you.

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes. So we haven't released extended details on the patients in the AML study. So I'm not going to comment on that. So basically, the -- as I mentioned, all of the patients but one is ongoing, and all of them have had very good tolerability as well as minimal, if any, myelosuppression. So I think that's all I'll comment on that for now. We'll give much more detail on this at upcoming presentations.

The second question, enrichment strategy is part of the current study or initiating a new study. So that's a great question actually for either of the studies. Right now, we're collecting information, as I mentioned already about a couple of biomarkers that could be potential enrichment strategies. One that we feel very encouraged by is the MYD88 mutation. So far, we don't have a lot of patients there, but this really fits that hypothesis of patient selection and in terms of expanding that study, we're currently expanding it. And in particular, focusing on populations that have MYD88 mutations. And so that is one way that we are starting to enrich this. It's possible also that we could launch a separate study that would target that population specifically, but that hasn't been started yet.

And yes, I think that addresses the question. Do you want to add anything, Jim?

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

No. I thought that was really well said. Yes, I just hammer home. We all agree. We're very pleased with the data set that we see so far. Obviously, it's early days in both studies, but these preliminary data really seem to fit well with what we were expecting. And in fact, AML/MDS, it was even better than we were hoping, which is great.

Another question from Soumit Roy, JonesTrading. Do you envision a triple combo with ibrutinib, lenalidomide, 4948? Or is there something about the safety profile that wouldn't allow a triple combination?

Robert E. Martell - *Curis, Inc. - Head of Research & Development*

Yes. Let me comment on that. So I think very possible. There are some data that the combination with these with an IRAK4 targeting maybe beneficial. We're going to start with the double combination, as I mentioned, based on the rationale that these are 2 parallel pathways that are really the key areas responsible for NF-kappaB activity. But our overall development certainly could consider a triple combination. As I mentioned, the safety profile of this drug could certainly allow that.

James E. Dentzer - *Curis, Inc. - President, CEO & Director*

Okay. Excellent. I'm looking down the list, making sure that we've answered a lot of the questions. So a lot of the questions are asking some of the similar questions that we've heard before.

No. I think we've got it. So I think with that, why don't we end the Q&A session. I'd like to again take the opportunity to thank the team, thank the patients who have enrolled in this, and the clinical investigators who have been involved. I think our partners at Aurigene for helping us with this study and get to this point. It's a very happy day for Curis, a very happy day for the patients on the drug. And a special thanks to Dr. Verma, who's groundbreaking research last year that was published has really turned out to be an area of great excitement for us and for patients.

So thank you, everybody. Have a terrific day. Thank you for joining us.

Amit Verma

Thank you.
