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# Celyad

## Update Call

## July 2, 2019

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## PRESENTATION

**Operator:**

Ladies and gentlemen, thank you for standing by and welcome to the Celyad AML/MDS Program Update Call. At this time, all participants are in a listen-only mode. There will be a presentation by Celyad followed by a question and answer session. As a reminder, today's conference call is being recorded.

With that, I would like to turn the call over Dr. Anne Moore, Celyad's Vice President, Corporate Strategy. Please go ahead.

**Anne Moore:**

Thank you Operator and thank you everyone for joining us for our AML/MDS Program Update Call today. Joining me today, Filippo Petti, our CEO and interim CFO, Dr. David Gilham, Vice President of Research and Development, and Dr. Frédéric Lehmann, Vice President of Global Clinical Development.

We will start the call with an update on our AML/MDS Programs and then open up the line for your questions.

Before I turn the call over Management for their prepared remarks, I would like to take this opportunity to remind you that this call may contain forward-looking statements including statements regarding the safety and efficacy of our drug product candidates and the manufacturing methods used to manufacture these drug product candidates, as well as statements concerning the ongoing and planned clinical development of our drug product candidates including the timing of trials, enrollment, data readout and presentation, and refer you to our regulatory filings for additional information of the Company.

With that, I'd like to turn over the call to Filippo Petti. Please go ahead, Filippo.

**Filippo Petti:**

Thank you Anne and thank you everyone for joining us today. We are pleased to announce today that the Company has achieved a steady flow of positive milestones over the past couple of weeks regarding our autologous relapse refractory AML and MDS program. On today's call we'll be discussing several of these events including an overview of the initial data for the THINK AND DEPLETHINK Phase 1 trials, an introduction to our OptimAb manufacturing process for CYAD-01 and CYAD-02, and the FDA acceptance of the Investigational New Drug application, or IND, for our next generation NKG2D-based CAR-T therapy CYAD-02.

Each of these milestones is expected to have a positive impact on our strategy for the relapse refractory acute myeloid leukemia and myelodysplastic syndrome program we couldn't me more excited to talk about.

On Slide 4 I want to give you a quick overview of AML and the seriousness of this form of leukemia, and the need for more efficacious therapies for the majority of AML patients. AML is the most common form of an aggressive leukemia with approximately 40,000 new cases each year in aggregate between the United States and Europe, yet there are a limited number of effective therapies for most patients. Many patients become resistant to chemo and only allo-hematopoietic stem cell transplant as a potential curative effect for some patients.

Unlike the case in B-cell malignancies, ideal targets for CAR-T cell therapy in acute myeloid leukemia are thought to be limited largely due to expression of many cell surface markers on highly sensitive progenitor cells that produce many of the essential cells for the blood. This does mean that the potential for toxicity is significant.

By contrast, our approach for acute myeloid leukemia is based on the fact that this patient population expresses at least one NKG2D ligand on leukemic blasts with little evidence for expression of these targets on normal progenitor cells. The tolerability of our approach to date, and indeed, evidence of the rapid return of hematological function in some patients continues to support this view. In contrast to the STFB antibody method used in classical CAR-T, the Celyad CAR-T approach uses the full human NKG2D activating receptor to recognize the family of stressed ligands on the tumor. This NKG2D activating receptor plays an important role in protecting the host from infections and cancer and provides us with the rationale that we can target multisurface tumor antigens over single target CAR-Ts.

With that, I'll turn it over to Dr. Frédéric Lehmann, VP of Global Clinical Development, who will walk you through our current CYAD-1 program. Frédéric?

**Frédéric Lehmann:**

Thank you Filippo and thank you everyone again for joining us today. I'm on Slide 5.

Indeed, this brings me to our lead program CYAD-01 which, as you all know, is an autologous NKG2D-based CAR-T that we have developed. In vitro and in vivo protocol data have proven the activity and safety of CYAD-01 in different solid cancer and hematological malignancies. We are currently conducting two clinical trials evaluating CYAD-01 in the treatment of relapse refractory acute myeloid leukemia, AML, and myelodysplastic syndrome, MDS.

The THINK Phase 1 trial is an open labels study that has completed the dose escalation segment of the trial evaluating CYAD-01 multi injections without any preconditioning chemotherapy and without any bridging anti-disease chemotherapy.

We are now focusing our efforts on evaluating CYAD-01 in two schedule optimization cohorts, assessing a more frequent dose schedule, up to six injections over two months, again, without preconditioning chemotherapy.

The second ongoing Phase 1 trial is a depleting study which is also an open label dose escalation study design. DEPLETHINK is evaluating a single infusion of the CYAD-01 following standard treatment with preconditioning chemotherapy using cyclophosphamide and fludarabine with dose and schedule which is the common regimen used in CAR-T development.

The primary endpoints of those two Phase 1 trials are safety with secondary endpoint including clinical activity and cell kinetics.

Operator, please next slide, so Slide 6.

Reviewing our strategy for these different studies and as well our program in general, I really would like to highlight three key points of focus on why we are confident in our path forward in regard to this approach to relapsed refractory AML and MDS.

First, and as noted earlier, we are in the process of evaluating multiple treatment conditions based on the encouraging results, clinical and scientific results to date from CYAD-01, including the denser dose schedule as well as treatment following a standard precondition chemotherapy. Given the tolerability and the cell engraftment that we have reported to date, we see room to continue towards finding an optimal dose to driving additional activity with this cell therapy.

Secondly, we continue to tap into our deep expertise and knowledge in cell therapy manufacturing and an all-in-one vector approach which is providing tremendous flexibility (inaudible) and certainly efficiency in the design of novel CAR-T cell therapy with a memory-like phenotype for increased persistence and CAR-T potency.

Third pillar is that we are optimizing all CAR-T therapy approach to include RNA interference through short hairpin RNA or shRNA to modulate the expression of the NKG2D ligands to help extend the persistence of the cell therapy.

We really strongly believe that those three key drivers of our program will help to enhance our autologous NKG2D-based CAR-T cell therapy to potentially deepen the breadth, the frequency and the duration of the clinical response in these refractory, highly rapidly progressing patient populations.

Please, Operator, go to the next slide for Slide 7.

Turning to our THINK AND DEPLETHINK trials, and the first part of the focused strategy I just described, we recently presented data collected to date from our Phase 1 THINK trial for the CYAD-01 program in

AML and MDS at the EHA conference in Amsterdam. The most significant point I would like to highlight in regard to the data of that THINK trial is that we observed that this (inaudible) injections monotherapy without preconditioning is well tolerated even at denser schedule from the what's called (inaudible) of the trial evaluating up to six time 1 billion of cells. Overall, the THINK trial, including the dose escalation segment, we have observed encouraging preliminary antileukemic activity in 6 out of the 13 patients evaluated per trial protocols, so approximately 50%. Out of those six patients, four patients exhibited an objective response of complete remission.

We also reported at the EHA encouraging preliminary data from the dose escalation cohort of the Phase depleting study, so evaluating CYAD-01 post preconditioning chemotherapy. Initial results from the trial have shown that the regimen was well tolerated and led to a better cell engraftment of the CYAD-01 compared to the dose escalation segment of the THINK study at same dose with our preconditioning chemotherapy.

Next slide, please, so Slide 8.

These initial findings have created a real great excitement amongst our Celyad team and looking ahead we continue to focus on the THINK and DEPLETHINK trials, but in particular we are in the process of increasing the dose of the CYAD-01 in Cohort 11 of the THINK trial to evaluate up to six infusions of 3 billion of CYAD-01 without preconditioning chemotherapy. Currently, we expect preliminary results from Cohort 11 of the THINK schedule optimized schedule approach to be available during the second half of this year, 2019.

In addition, following initial safety data from the first dose level of 100 million of cells injected post preconditioning in the DEPLETHINK trial, patient recruitment for Cohort 3 evaluating 300 million of cells post preconditioning, it's ongoing and results should be available and are expected for the end of 2019.

Lastly and that will be discussed by Dr. Gilham, we are also excited to announce today the opportunity to assess the impact of our new optimized process called OptimAb manufacturing process for CYAD-01 in the next cohort called Cohort 4 of the DEPLETHINK trial under the same and therefore current IND application for CYAD-01.

I would like now to turn over the discussion to Dr. David Gilham, Celyad's VP Corporate—of R&D of Celyad. David?

**David Gilham:**

Thank you very much, Frédéric. Hello to everybody and thank you for joining us today on this call. For the next few slides I'll talk over our OptimAb process to try and bring a little more color and background to where we are in terms of this process development.

As we progress through our trials, these data presented at EHA raised a highly relevant point concerning our clinical development pathway. What has become clear is that as we have progressed through our CAR-T dose escalation stage, it is also clear that the average tumor burden for patients has also increased. We feel this is a likely response to the good safety and tolerability of our products, but of course also means that interpretation of clear signals remains a challenge.

However, given that we are currently treating patients with potentially high tumor burden, it seems obvious that providing our CYAD-01 cells with a greater opportunity to fight tumor is sensible. We have been working over the last year on approaches to increase the potency of CYAD-01 and many of these were discussed at our R&D Day last March.

We are now excited to tell more about these developments, the first of which is highly relevant to CYAD-01 and is the OptimAb process, which brings together the best attributes from previous manufacturing processes at Celyad including and 8-day cell culture, so this is two days shorter than the current culture process; the utilization of an NKG2D blocking antibody; and thirdly, a selective PI3 kinase inhibitor that helps to enrich with T cells with a memory-like phenotype. This process has been developed in response to the increased understanding of the role of memory cells in CAR-T cell therapy, and stems from our in-house R&D and manufacturing capacity. We are pleased to announce that this amendment achieved regulatory approval earlier than anticipated and provides us the opportunity to bring CYAD-01 OptimAb more quickly to patients.

We believe this updated process maintains a high level of manufacturing reliability required to support our clinical development, and based research data from our in vivo experiments, the OptimAb manufacturing process led to an improved antitumor activity in the highly aggressive AML model.

On Slide 10, as you can see on the charts on this slide, aside from the clear benefits of a shorter process time, the OptimAb approach results in a product that maintains an earlier memory phenotype. In the left panel, we can see that that OptimAb process results in an increased frequency of T cells expressing CD62L or L-selecting, a marker associated with homing which is frequently expressed on memory T cells.

In the right-hand panel, a deeper analysis shows that the cells produced by the OptimAb process have a larger portion of naïve and central memory T cells with a reduced effect there and differentiated memory cell phenotype. These phenotypes are considered by many in the field to be indicative of cells that have an increased antitumor activity.

Moving to Slide 11, looking at the preclinical data we have shown here, which is based on conditions where the dose of CYAD-01 is reduced to have minimal activity—that is a stress test model—these data suggest that the OptimAb manufacturing process utilizes CYAD-01 mediates an improved survival in this aggressive THP1 AML model as compared to CYAD-01 cells produced using the previous manufacturing process which we refer to as the mAb process.

In addition, based on these conditions, CYAD-02 has the potential to even further enhance the antitumor activity beyond that seen with CYAD-01 where both are manufactured using the OptimAb manufacturing process.

To discuss our CYAD-02 program, I'll pass back to Filippo Petti, our CEO.

**Filippo Petti:**

Thank you David. On Slide 12, and based on the benefits that we believe OptimAb offers, including improved antitumor activity in AML models, we will be treating all future patients in the relapsed refractory AML and MDS program with either CYAD-01 or CYAD-02 manufactured using this new process. We recently submitted CMC amendment related to the Investigational New Drug application for CYAD-01 to regulators both in the United States and Belgium, which was accepted just a few days ago. Our plan is to treat the first patient with CYAD-01 manufactured using the OptimAb process in Cohort 4 of the DEPLETHINK trial by August. We expect to have the initial clinical data for the OptimAb manufacturing process from Cohort 4 of the DEPLETHINK trial by year-end 2019.

Just to emphasize, our ability to produce amendments that pass regulatory scrutiny is based upon our capabilities around R&D and manufacturing that eliminates the time delays associated with outsourced manufacturing in R&D activities. We are truly fortunate to have the infrastructure and relevant knowledge in-house.

On Slide 13, as we introduced at our R&D Day earlier this year, CYAD-02 is our novel next generation NKG2D-based CAR-T candidate. This new therapy utilizes Horizon Discovery's shRNA SMARTvector technology which is designed to deliver efficient knockdown with high specificity for NKG2D ligands MICA and MICB. The single shRNA modulates the expression of both ligands which translates to encouraging increase in in vitro proliferation, in vivo engraftment and antitumor activity. This platform complements our all-in-one vector approach in the design, the discovery and the development of next generation CAR-T candidates. Thus far, CYAD-02 has shown encouraging preclinical data of increased CAR-T cell expansion, persistence and antitumor efficacy.

On Slide 14, I'd like for you to take a look at the two programs side-by-side. They are very similar in terms of being NKG2D-based therapies; the difference is that CYAD-02 benefits from the shRNA technology. As a result, we believe these similarities and the preclinical work we have performed to date comparing CYAD-01 and CYAD-02 have positioned CYAD-02 to benefit from preclinical and clinical work we are already performing for CYAD-01 in regards to our safety and potential to optimize dosing.

On Slide 15, we are very excited today to announce that the FDA has accepted our IND application for CYAD-02 for the treatment of relapsed refractory acute myeloid leukemia and myelodysplastic syndrome in such a short turnaround. This will allow us to move ahead with our planned Phase 1 trial to evaluate the safety and clinical activity of CYAD-02 with preconditioning chemotherapy of cyclophosphamide and fludarabine in the United States and in Europe in early 2020. We believe this to be the first example of the clinical testing of a shRNA targeting the expression of two independent genes that provides some insight into the opportunities afforded by this technology.

Moreover, the rapidity of the regulatory review we are certain is associated with the confidence that the clinical history of shRNA brings. I am very excited by the prospects for this program as we believe CYAD-02 is just the beginning of what our shRNA platform has to offer for the development of novel CAR-T therapies.

On Slide 16 I wanted to just quickly review and update the autologous relapse/refractory AML and MDS clinical program. Looking ahead, we now have several new milestones pending and we believe that they now carry even more potential impact for the program and our company. By the end of 2019 we hope to have provided new data from the THINK and DEPLETHINK trial, including initial data from the OptimAb manufacturing process in patients treated in Cohort 4 of the DEPLETHINK trial. In addition, we are in preparation to initiate our Phase 1 CYAD-02 study in early 2020 with initial data from the program expected by mid-2020.

Turning to Slide 17, in summary, we have delivered on several milestones for our autologous relapsed/refractory AML and MDS program over the past 12 months. The data from the THINK and DEPLETHINK trials to date have provided us with greater understanding of NKG2D and the opportunity to focus on dosing, scheduling and assessing various conditions for the cell therapy that will help drive development of CYAD-01 and CYAD-02.

We are also excited to bring the OptimAb manufacturing process to the DEPLETHINK study next month and to future trials. In addition, the recent FDA acceptance of our IND application for CYAD-02 allows us to plan for a Phase 1 trial of our next generation candidate and build a broader data set for an autologous NKG2D-based program for the treatment of relapse/refractory in AML and MDS that leverages an OptimAb manufacturing process.

We believe that we remain on course with respect to taking the optimal NKG2D approach into Phase 2 clinical testing in the relapsed/refractory AML situation. We feel that the updates provided here show that

the safety profile of NKG2D CAR-T to date supports the development of a more aggressive approach to drive an increased durability of clinical responses. The CYAD-01 OptimAb amendment fits seamlessly into our current trial schema with readouts starting year-end 2019. These readouts kicking off from year-end will allow a series of gating steps that should provide us our internal threshold to be reached and would initiate an expansion towards Phase 2 development. We feel that setting up sequential steps each increasing the expected potencies of the approach enriched for success in generating maximal clinical responses in the AML patients with truly awful prognosis and no effective treatment options while maintaining patient safety.

I would also like to draw your attention to Celyad's next milestone in solid cancer. In a couple of days we will present an update on the allogeneic and autologous NKG2D-based CAR-T candidate in refractory metastatic colorectal cancer in at the ESMO World GI Congress in Barcelona, Spain. We will highlight preliminary data from CYAD-101, our investigational non-gene edited allogeneic and donor derived CAR-T therapy that expresses the NKG2D CAR of CYAD-01 and the novel inhibitory peptide TIM, our T cell receptor inhibiting molecule. That provides an opportunity to knockdown and reduce signaling of the TCR complex.

Before we open the call for questions, I would like to commend our team's hard work over the past few months. We believe that the company has a number of exciting developments in process and our clinical pipeline is flush with near-term and long-term milestones. We look forward to providing clinical updates to our AML and MDS program over the next several quarters.

With that, I will turn the call over to the operator for any questions. Operator?

**Operator:**

Thank you. We will now be conducting a question and answer session. If you would like to ask a question, please press star, one on your telephone keypad. A confirmation tone will indicate your line is in the question queue. You may press star, two if you would like to remove your question from the queue. For participants using speaker equipment, it may be necessary to pick up your handset before pressing the star keys. One moment, please, while we poll for questions.

Our first question comes from the line of Peter Lawson with SunTrust Robinson Humphrey. Please proceed with your question.

**Male Speaker:**

Hi everyone. Congrats on the progress and manufacturing and IND acceptance. This is Min (phon) on for Peter. I guess just really quick, I think year-end we're going to be getting data from Cohort 11 of THINK and 3 of DEPLETHINK, but they don't be treated—these patients won't be treated with the new OptimAb process, is that correct?

**Filippo Petti:**

Hi Min. Thanks for the question. Yes, exactly. Those patients who are being enrolled and recruited for Cohort 11 of the schedule optimization of the THINK trial as well as the Cohort 3 of the DEPLETHINK trial will be treated with CYAD-01 cells manufactured with the mAb process, and it's not until the first patient of Cohort 4 in the DEPLETHINK trial that we'll be able to treat patients using the updated OptimAb process.

**Male Speaker:**

Okay, thank you. What's the thinking around using the OptimAb process for some more dense scheduling? I guess will you guys be looking to do that later, and possibly the study design for CYAD-02, will that start with the higher density dosing schedule?

**Filippo Petti:**

I'll take your questions in order. In terms of being able to perhaps a schedule optimization with the new process it's something we're certainly looking to maybe bring into that approach into the THINK trial. We'll look to maybe see what some initial data looks like from the Cohort 11 as that unfolds in the second half of 2019, some initial data from the OptimAb process from the Cohort 4, and then think about if there's additional patients we should be recruiting for evaluating the therapy with regards to an OptimAb manufacturing process in the schedule optimization approach. That's certainly top of mind.

With respect to your second question, on one of those slides you'll see we're actually going to kick off the CYAD-02 program looking at three dose levels, dose escalation. The first dose level is at 100 million cells injected once, followed by 300 million cells injected once, and lastly, the third cohort will be evaluating 1 billion cells of CYAD-02 injected once following preconditioning chemotherapy of cyclophosphamide and fludarabine.

**Male Speaker:**

Great. Thank you.

**Filippo Petti:**

Thank you, Min.

**Operator:**

Thank you. Our next question comes from the line of Raju Prasad with William Blair. Please proceed with your question.

**Raju Prasad:**

Thanks for taking the question and congrats on your progress. How should we be thinking about the year-end update as it pertains to go-forward dose and kind of Phase 2 trial design? Do you think that you'll have enough data to kind of say that the OptimAb process with PI3 kinase inhibition is the way you're going to go and then (inaudible) regimen and things like that? It seems as though you'll have a lot of data over small numbers in different kind of iterations and just wondering how that may impact kind of timing moving forward.

**Filippo Petti:**

Sure. Thanks for the question, Raj. Look, I would say from if we take it in two buckets, from the OptimAb standpoint, and one of the reasons why I think in terms of timing we'll get some initial data from the Cohort 4 by year-end. It's not until we get I think into Q1 where we see that longer three-month duration that we're looking for for us to think about how we would plan into a potential Phase 2 program.

That being said, kind of going into Q1 is also based on the fact to your point earlier, we are trying to make sure that we have a robust data set for Cohort 4, and as you saw on one of the slides, we're looking to enroll at least 9 patients in Cohort 4 of the DEPLETHINK trial for us to make an educated guess at that

dose with the OptimAb process for us to really have the data set that we believe that we will need to take forward in terms of what a Phase 2 development plan would be using that approach following preconditioning therapy.

On the other hand, I think we'll also wait to see what the readouts are from the schedule optimization Cohort 11 as well as Cohort 3 to make an assessment on how we think about those trials and the path forward.

I would say in general the idea is to really build a larger data set of patient numbers by year-end, in particular around OptimAb, and then going into next year, into the first half of 2020, really here we think about the idea between 01 OptimAb in Cohort 4 as well as the 02 trial trying to build a larger data set around an OptimAb manufacturing process in general.

**Raju Prasad:**

Great. Then just a quick follow-up. Is there any specific engraftment or persistence profile that you're aiming to see with these patients? Is it just kind of hopefully increasing it over what you see thus far? Just given kind of the targets you're trying to hit as far as CRs in AML. Just kind of curious your thoughts there.

**Filippo Petti:**

Yes. No, it's a good question. As you saw at the update at the European Haematology Association meeting a few weeks ago, we're seeing improved engraftment of the cells following preconditioning chemotherapy and in particular the cells going out to, in terms of persistence, 40 days, 40 days-plus as compared to our monotherapy where we know the cells persist for around seven days or so. So, we are encouraged with the fact that layering on 01 following preconditioning chemotherapy is helping out with that overall persistence.

Maybe I'll turn it over to David to provide you some thoughts around what we anticipate the OptimAb kind of following conditioning and how that may have an effect on persistence.

**David Gilham:**

Hi there, Raj. It's a good question. The models that we're working with are immune-compromised mice and so there are caveats, of course, concerning how T cells engraft in those animals. There are pseudo-models of preconditioning, but allowing for that caveat what we certainly see is an increase of peak and a greater duration of expansion of the T cells in those mice really driven by we think the OptimAb process. Indeed, there's another subsequent improvement in terms of the persistence in those models with the CYAD-02 as well over and on top of that.

We're hoping that we'll see an increased persistence, but in terms really relating back to your first question is that we'll be layering on the information from these OptimAb studies on top of the information we already have which will inform us in terms of what we expect to see in terms of persistence but also clinical response.

Also, just to round off on that really, unlike the CD19 CAR approach which was really bedeviled in early days where the preconditioning chemotherapy has a very significant effect on the tumor, what we've seen in our EHA data using a suboptimal dose of cells, we could see in two cohorts of patients that cyclophosphamide and fludarabine really had a very negligible effect on the tumor blast in those patients with advanced relapsed/refractory AML, which really suggests that any signals we get as we go through dose escalation and bringing in the OptimAb must really be due to the T cells that we're infusing. The sad thing for the patients is the fact that this chemotherapy regime has really quite minimal effect on the tumor

but it does mean that the background readout for us in terms of understanding the effect of the T cells will be clearer.

**Raju Prasad:**

Great. Thanks for the color and looking forward to seeing the data later this year.

**Filippo Petti:**

Thanks, Raj.

**David Gilham:**

Thanks, Raj.

**Operator:**

Thank you. Our next question comes from the line of Jim Birchenough with Wells Fargo. Please proceed with your question.

**Male Speaker:**

Good morning. It's Nick on for Jim this morning. I just wanted to go back to the 02 design (inaudible). You said that, I think that they'll get a single infusion of cells at the three dose levels you outlined. Is this because you feel like that this product conforms more to a typical CAR-T protocol that we see which is a single dose of cells, or is this really a dose escalation safety, and if that's the case why not have an opportunity to receive a second dose after the (inaudible) theory?

**Filippo Petti:**

Nick, thanks for the question and, look, I will certainly turn it over to Fred to provide some additional thoughts there.

Really, in terms of the initial dose levels, we're leveraging that of the DEPLETHINK trial and the work that we've done so far in CYAD-01 and how we think about where we can quickly get a signal in terms a dose escalation with respect to a single injection of the therapy, and I think provides us an opportunity by mid 2020 to really test out the thesis of 02 with respect OptimAb manufacturing but also this ability to layer on the shRNA targeting MICA and MICB.

I'll turn it over to Frederic who can provide some additional thoughts around the study design for 02.

**Frédéric Lehmann:**

Thank you. It's a very specific and nice question. Indeed, CYAD-02, the dose escalation study, is conducted that you have a dose escalation post preconditioning therapy which is a standard, again, the same one that is in DEPLETHINK cyclophosphamide 300 milligrams per meter squared three times—three days consecutive, and fludarabine 15 milligrams per meter squared, and you do a dose escalation.

Now, what's going on with patients who after one month approximately, according to the protocol, have some—are not progressing? You have different options which is proposed per protocol. Indeed, if the patient is in complete remission, we could go to—the protocol authorizes (inaudible) like a lot of other

protocols in the CAR-T field to go to a bridge to allogeneic transplants. The seven elements for patients who are not progressing, it's the proposal that indeed, as you are proposing, that why not to propose to the patient a second 'injection' so new preconditioning and reinfuse the situation.

The third option, which is embedded into the protocol, so for nonprogressive disease, for patients, for example, who are not eligible for allograft or for patients who have some difficulties with the preconditioning—remember, AML patients, elderly patient population—in that context we are also authorizing to have a consolidation treatment with multiple infusions of the CYAD-02 without any preconditioning chemotherapy.

Obviously, all of that is autologous CAR-T so from the apheresis at baseline we are producing enough of CAR-T cells CYAD-02 to be open to all the momentum and all the possibilities. Obviously, with the increase of the engraftment that it's the (inaudible) of this shRNA on MICA and MICB and going to more early stage memory, central memory and stem cell-like CAR-T, crossed fingers that such kind of better engraftment and better potency will do the 'job' after one month after the infusion with the CYAD-02.

**Male Speaker:**

Thank you, Frederic. Phil, just a follow-up then. We're going to be aggressive with 01. We have 02. Is it your sense, then, that in the second half of next year that you would be willing to combine all of the data and maybe pick the winner, which one would assume would be 02 if everything works out well, to move forward? Or would you consider—do you think you would need to take both of these programs forward in the second half of next year?

**Filippo Petti:**

It's a good question, Nick. I think as we look at both programs, I think the backbone here is OptimAb and I think it gives us a better sense of what that manufacturing process has to both candidates. There is obviously an opportunity to see through the dose escalation what we hope to have—at the end of the 02 program we'll get a sense at that similar 1 billion dose level for both programs to tease out is there any differences here between the two candidates. I think to your point, we'll let the data come in, but to decide exactly which one we plan to push forward into maybe a Phase 2 development plan. It could be one, it could be both. Could we leverage maybe some of the findings in 02 in terms of the background of the patients? Is there subtleties between the two products? I think it will kind of be based on data and the facts coming in but an opportunity for us to make a decision I think broadly between both processes that are anchored by an OptimAb manufacturing process.

**Male Speaker:**

Okay. Thanks. I'll jump back in the queue for our other questions.

**Filippo Petti:**

Thank you, Nick.

**Operator:**

Thank you. Our next question comes from the line of Gary Waanders with Bryan, Garnier & Company. Please proceed with your question.

**Gary Waanders:**

Hi there. A question on the memory-like phenotype of the cells using the OptimAb process and how the dose of these more potent and sort of longer persisting cells might correlate with the data that you've got from the mAb manufacturing process. Have you got or can you retrospectively analyze the cells that have already been administered to patients and kind of quantify the variation between patients in terms of the make-up of the memory-like cells? Can you compare that to what you're intending to dose and sort of the effective dose levels? I guess what I'm also trying to get at with this is what might be the potential safety implications of giving a higher effective dose of these more potent cells? Thanks.

**Filippo Petti:**

Sure, Gary. Thank you for the question. Maybe I'll turn it over to David to provide some thoughts and maybe Frederic with regards to both the phenotype and the profile of the cells for in the clinic setting.

**Frederic Lehmann:**

I would propose to start—Frederic speaking—from the clinical point of view. I love the kind of very specific questions and it's very intriguing and interesting.

I can refer you to the presentation that we have done with the initial THINK data that we have done by David Salmon at the ASH last year where clearly don't talk about correlation with such a kind of few number of patients, but out of the very few patients where we had at that time three objective response, so three complete remissions, indeed intriguing it take like that more than biological correlations, intriguing those three patients were the patients where the CD8 CAR-T were the highest 'enriched' in terms of central memory phenotype. That was actually data that already initially at that time was (inaudible) at the brainstorming and the thinking about the importance of this phenotype approach and type of cell.

Now, indeed, as we know, the relationship of the safety and the clinical activity, so the bioactivity and mainly with the cytokine release syndrome we may always wondering if we have an adequate clinical impact on the disease but therefore with higher safety toxicity for the patients, and so therefore, the safety margin is quite short. That's why in the context of CYAD-02 and with discussion with the authorities, we are restarting in this new IND a quick 3-plus-3 study design where we restart the study at the dose which is, as mentioned by Filippo earlier, we start at 100 million of cells, flat dose for the first infusion. That's the reason why this type of study design has been developed as such.

Long-term persistence impact on the safety, this will be obviously highly scrutinized with a lot of clinical guidelines into the protocol in all those Phase 1 units that will participate to our study and we will monitor that as for all the rest of our program quite carefully.

David, do you want to add some other, more scientific flavor on that?

**David Gilham:**

Yes. Thanks, Frederic. Hi there, Gary. The safety really around T cell therapies in generally and certainly how we're thinking is really two levels. The first is really not talked about very much in the field and this is the short-term (inaudible) associated with infusion of any cells in the (inaudible) circulation. They tend to go directly to the lung and locate there for a period of around 6 to 24 hours. One of the—certainly how we see it and I think it's certainly true from other trials as well is that cell dose is important. The higher the cell dose, actually the greater level of transient lung toxicity such as hypoxia or shortness of breath is seen and so one of the rationales of actually using cells with an increased memory phenotype, and we think increased

potency, is actually that we can give a lower dose of cells and so we're hoping to actually reduce some of the evidence of the short-term lung toxicity that really bedevils most cell therapy trials.

The second thing, of course, is longer term response and particularly, I'm sure, you're thinking about cytokine release and neurotoxicity. We've see no evidence of neurotoxicity at the moment and I guess we presume possibly like others in the field that that particular feature is really associated specifically with CD19 for reasons that remain not entirely clear.

The CRS situation, of course, we'll be monitoring this and in terms of looking at the short-term response of these cells, but if these cells really are more of a memory phenotype, and of course we can only assess this on the cell surface markers that the T cells have, then presumably we would expect a slightly different kinetic in terms of the cytokines that will be produced from those cells. At the moment, the CRS we tend to see is quite short-term, fairly short timepoints after infusion of the cells, which we think is an on-target effect, but of course they're continuing to measure. What I can say from the animal studies is that we've seen no evidence of any adverse toxicity whatsoever really in those mice.

(Inaudible) it doesn't really say very much I'm afraid, Gary, but the main thing is actually avoiding this short-term lung toxicity and we're very keen to have as low a dose of cells as possible to try and avoid that quite acute toxicity that's quite common in most T cell trials.

**Gary Waanders:**

Lovely. Thanks. Thanks very much.

**David Gilman:**

Thank you, Gary.

**Operator:**

Thank you. Our next question comes from the line of Sandra Cauwenberghs with KBC Securities. Please proceed with your question.

**Sandra Cauwenberghs:**

Hi. I would like to actually expand a little bit on the previous question on the memory-like phenotypic cells. With regard to refractory relapsed AML I understood that this observation that you have specifically in your previous trial on the higher density of these memory cells, is this something that has been observed as well in larger AML studies with regards to constitution of immune cells inside of these tumors? Linked to that question is actually the possible application in other types of cancers, so is this something that you think is very specific for AML or MDS, or do you think it could potentially benefit as well the CRC program? Thanks.

**Filippo Petti:**

Hi Sandra. Thanks for the question. David, Frédéric, would you like to provide some thoughts there?

**Frédéric Lehmann:**

Frédéric will speak first and certainly David will come to you and to add more scientific flavor. But, yes, smart question and rapid answer is there is certainly some discussion internally the thing about the fact that some early step-phenotype like central memory, etc., could be also more impactful in terms of tumor homing

and infiltrations which we do know are some of the hurdles in the context of solid cancer indication development of cell therapy. So, yes, there is some discussion ongoing to think about using that for the OptimAb process, not only as discussed by a previous discussion in the context of things, so without preconditioning and back to hematologic malignancy but why not, therefore, also in the context of solid cancer indications. This is under contemplation and we will certainly follow-up on that. Most certainly, our strategy, and again as discussed by Filippo a few minutes ago, let's first see what are the preliminary data of this open label dose escalation study in the context of DEPLETHINK where the OptimAb data will be the first data that will be generated, and then rapidly with CYAD-02 in that context, and therefore OptimAb process equals early stage type of CAR-T cells, does that make sense to go in solid cancer like refractory metastatic colorectal cancer patients?

To finalize on that point, even again I would like to re-highlight the concluding remark of Filippo about all current data with the CYAD-01 'old process', so the mAb process in the context of metastatic colorectal cancer, the SHRINK but also the allogeneic non-gene editing TIM technology, that those technology at ESMO-GI on this Friday by an oral presentation by an important person in the field who is Eric Van Cutsem and stay tuned about this.

David, more information, solid cancer.

**David Gilham:**

Yes. Hi there, Sandra. Just to really go into a sort of rote of context, of course I'd like to say that we were brilliant and we're the leaders and the only people to work in this space but I would be lying, of course.

The idea of using cells with a less differentiated phenotype is really being considered for probably 13, 10 years now. The issue is how to develop and generate these cells within a clinical grade compliance system, because the manufacturing processes that we all use, they're really there to try and drive as many cells as possible so we can actually infuse the patients with enough cells that we think we'll be able to populate the patient and have an effect.

We've been following certainly the work of others, and this work has really been ongoing now for around about a year or so, if not perhaps a little bit longer, where we've been looking at ways to look at our process and we can really base this on the fact that because we have strong control over our manufacturing process and a high level of success, very few manufacturing failures, it means that we can really start to dive more into that manufacturing process and try to alter or manipulate some of the specific characteristics.

After quite some time, we've worked and we feel that this PI3 kinase combination with the eight days of culture really gives us a reproducible, more earlier stage memory phenotype and this is really entirely consistent with the observations in the field. I don't know but certainly other companies and colleagues, they're already working hard to try and take this approach into clinical testing.

We're really—I think we're following the field but we're also quite close to the lead because this is quite an early stage in terms of testing this approach in the clinic.

**Sandra Cauwenberghs:**

Thanks.

**Operator:**

Thank you. Our final question comes from the line of Stéphanie Put with Degroof Petercam. Please proceed with your question.

**Stéphanie Put:**

Hi. Good afternoon. Thank you for taking my question. Most of them have been answered but I would like to elaborate a bit for clarity on two points. First, it's certainly safe to say you will let the data come in and then evaluate where you want to go for the Phase 2, but could maybe give us some more information on where you see the cutoff, for example, in the THINK and DEPLETHINK trials? Could there be a chance that you will add additional cohorts for more information, maybe to get a more robust data set on OptimAb?

Then, secondly, have you planned already to use the OptimAb protocol already in the solid tumor program, or is that also something to be evaluated upon the data set in AML? Thank you.

**Filippo Petti:**

Hi Stéphanie. This is Filippo. Thank you for the questions, and I think very pertinent questions as well. I think from our perspective in how we look to the program around 01, OptimAb and 02, let's say, again, we'll look to see how the initial data comes out. There be a little bit of a timing between when we begin to see the initial data from this Cohort 4 and when we begin to see initial data from the 02 program, and with that there may be an opportunity for us to assess additional cohorts, to your point.

One of the things we've talked about here as well that was captured in the slides and in our press release is that the ability to really define what perhaps may be the best preconditioning chemotherapy for AML patients continues to be top of mind for us. Now, we're currently in the process of looking at more standard lymphodepletion regimen with cyclophosphamide and fludarabine. What we know, as David pointed out earlier, that cyclophosphamide and fludarabine have very little impact on AML cells and the disease, and so for us, as we gather in our initial data, could we look to maybe tweak the DEPLETHINK to continue to optimize around preconditioning? I would say that that perhaps is one potential opportunity for us, and that may, again, feed into the 02 program, and I think we'll take advantage of that perhaps as we begin to see the data.

I think the second point is a good one as well. For us, as you know, we'll be seeing an update of our solid tumor program for the treatment of metastatic colorectal cancer later this week at the ESMO-GI conference for both the SHRINK and the alloSHRINK study using our autologous and allogeneic candidate CYAD-101. There, it remains a good question. If we begin to see some activity that we're encouraged by, could there be an opportunity to recycle into the solid tumor programs using an OptimAb process? I think that is still under consideration, but it's certainly something that we've discussed as a management team and really thinking about how do we bring the most potent product, cell therapy product to the solid tumor program as well. It is certainly for us an opportunity to maybe circle back into the solid tumor program and thinking about next steps there.

We'll learn more over the next coming months with regards to the overall solid tumor program, particularly around metastatic colorectal cancer and decide what manufacturing process we should be looking at for that program.

**Stéphanie Put:**

Thank you.

**Operator:**

Thank you. We have reached the end of our question and answer session. I would like to turn the call back over to Mr. Petti for any closing remarks.

**Filippo Petti:**

Very good. Thank you very much, Operator. With that, we'll bring the call to a close. To briefly recap, we are very satisfied with the progress made in our clinical development programs across a number of different trials that we have within the relapsed refractory AML and MDS program. We believe our platform of technologies have provided us with a number of opportunities to drive near-term and long-term value for our stakeholders. We look forward to providing updates over the next several quarters to folks.

Thank you again everyone for joining the call and we look forward to speaking with you again soon.

**Operator:**

Thank you. This concludes today's teleconference. You may disconnect your lines at this time. Thank you for your participation and have a wonderful day.