Adaptimmune Therapeutics plc Q4/Y 2017 Results
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Corporate Speakers

- Ad Rawcliffe; Adaptimmune Therapeutics plc; CFO
- James Noble; Adaptimmune Therapeutics plc; CEO
- Rafael Amado; Adaptimmune Therapeutics plc; Chief Medical Officer
- Gwen Binder; Adaptimmune Therapeutics plc; Chief Technology Officer

Participants

- Bin Lu; Raymond James; Analyst
- Peter Lawson; SunTrust Robinson Humphrey, Inc.; Analyst
- Tony Butler; Guggenheim Securities, LLC; Analyst
- Kripa Devarakonda; Citigroup Inc.; Analyst
- Marc Frahm; Cowen and Company, LLC; Analyst
- Soumit Roy; SunTrust Robinson Humphrey, Inc.; Analyst
- Nick Abbott; Wells Fargo Securities, LLC; Analyst
- Jenny Leeds; BofA Merrill Lynch; Analyst

PRESENTATION

Operator^ Good day, ladies and gentlemen, and welcome to the Adaptimmune Reports 2017 Fourth Quarter and Full Year Update. For your information, today's conference is being recorded.

At this time, I would like to turn the conference over to Ad Rawcliffe, Chief Financial Officer of Adaptimmune. Please go ahead.

Ad Rawcliffe^ Thank you. Good morning, and welcome to Adaptimmune's conference call to discuss our full year and fourth quarter 2017 financial results and other business updates. We issued two press releases earlier this morning, and I would ask you to please review the full text of our forward-looking statements there.

As a brief reminder, we anticipate making projections during this call and actual results could differ materially due to a number of factors, including those outlined in our latest filings with the SEC.

James Noble, our Chief Executive Officer; and Rafael Amado, our Chief Medical Officer, are with me for the prepared portion of this call. Helen Tayton-Martin, our Chief Business Officer; Gwen Binder, our Chief Technology Officer; and Bill Bertrand, our Chief Operating Officer, will be available for Q&A after the prepared portion.

With that, I'll turn the call over to James Noble. James?

James Noble^ Thank you, Ad, and good morning, everyone, and thank you for joining us today. 2017 was a transformative year for cell therapy and Adaptimmune. But before we look back at 2017, I want to share today's news that we have observed responses in a second solid tumor with NY-ESO in myxoid/round cell liposarcoma, or MRCLS, with three partial responses and one stable disease in the first four patients dosed. We will present an update on these data at an upcoming congress.

This news strengthens our conviction that we have a pipeline capable of treating solid tumors, and that our SPEAR T-cell platform has great potential for the future treatment of many cancers. This conviction is reinforced by the recent announcement at JPMorgan regarding safety in the first cohort of our MAGE-A10 pilot studies, the triple tumor and non-small cell lung cancer studies with patients who received 100 million transduced cells.

Thus far in these safety cohorts, there has been no evidence of off-target toxicity and there have been no reports of severe neurotoxic events similar to the CAR-T cell-related encephalopathy syndrome. On the basis of these data, we also announced in January of this year that the safety (sic - see press release "scientific") review committee recommended dose escalation to 1 billion transduced cells in the MAGE-A10 triple tumor study in bladder, melanoma and head and neck cancers. 1 billion transduced cells was the threshold at which we began to see responses with NY-ESO in synovial sarcoma. And Rafael will go into more detail later in the call.

Based on additional expected safety data, we expect dose escalation for the other MAGE-A10 pilot study in non-small lung cancer to be imminent. We expect to complete the first cohort of 6 patients shortly, and the next dose cohort of patients will receive 1 billion transduced cells, assuming a favorable [safety] committee review.

Our MAGE-A4 basket study across seven solid tumor indications, including bladder, melanoma, head and neck, ovarian, non-small cell lung cancer, esophageal and gastric cancers is also dosing patients.

Anticipated data readouts for 2018 include: firstly, additional safety and initial efficacy data from the MAGE-A10 pilot studies; secondly, initial safety data from the MAGE-A4 basket study to support dose escalation to 1 billion cells; thirdly, initial efficacy data from the MAGE-A4 basket study as well as additional efficacy data from the MAGE-A10 studies throughout the second half of 2018; and lastly, we anticipate initial safety data to support dose escalation in our AFP study in hepatocellular carcinoma later in 2018 with efficacy readouts in 2019.

Our focus on MAGE-A4, MAGE-A10 and AFP has been greater since GSK exercised its option over our NY-ESO program as we announced in September last year. And we are pleased to say the transition to GSK is well underway.

We have continued to manufacture and treat patients in the currently open NY-ESO study pending completion of the transition. The option exercise also extended our cash runway through to early 2020.

Not only was 2017 a year of clinical momentum, it was also a year of great progress towards a fully integrated cell therapy company. We have now successfully manufactured and released product for several patients in our MAGE-A4 study with manufacturing for MAGE-A10 trial scheduled to commence shortly following regulatory clearance. We also announced in January of this year that we executed an agreement with Cell and Gene Therapy Catapult to provide our own dedicated manufacturing space to secure vector supply for the medium term.

We also made great strides in building our executive team in 2017. We expanded our manufacturing team with Mark Dudley joining as Senior Vice President of Global Bio-Process and Development, and John Lunger joining as the Vice President of Manufacturing and Supply Chain Development. Our Co-Founder Helen Tayton-Martin transitioned from founding Chief Operating Officer to focus on the newly created role of Chief Business Officer, and Bill Bertrand joined as Chief Operating Officer. Most recently Sébastien Desprez joined Adaptimmune as Vice President of Communications and Investor Relations, and Paul Stead joined as Vice President Business Development. We believe the right infrastructure and leaders are in place to ensure our success as we aim to be the first company to launch a TCR T-cell therapy to treat solid tumors.

With that, I will turn the call over to Rafael for a clinical update. Rafael?

Rafael Amado^ Thank you, James, and thanks to everyone for joining this call. As James said, we have observed responses with our NY-ESO SPEAR T-cells in a second solid tumor called myxoid/ round cell liposarcoma, or MRCLS, with three partial responses and one stable disease in the first four patients dosed. Importantly, these patients tolerated treatment well with cytokine release syndrome managed following standard treatment guidelines.

We think that these data are meaningful and a further validation of the potential of our SPEAR T-cells to address solid tumors because although MRCLS is a soft tissue sarcoma, like synovial sarcoma, there are fundamental differences between these two malignancies, and I wanted to take a moment to go over some of these differences.

MRCLS is a subtype of soft tissue sarcoma called liposarcoma and is characterized by the proliferation of fat cell precursors called lipoblasts that have stopped differentiating into mature adipocytes. In contrast, the cell of origin of synovial sarcoma is unknown. The peak incidence of MRCLS is 30 to 50 years, and it is estimated that there are approximately 2,000 new diagnosis of MRCLS each year in the United States and Europe.

MRCLS arises in the proximal areas of the limbs, most commonly the thigh. The primary treatment for MRCLS is surgery with or without radiotherapy, but recurrences

are common, particularly in patients with high-risk tumors. The metastatic pattern of MRCLS is different from other soft tissue sarcoma. It tends to spread to the bone, abdomen, pelvis and other soft tissues, rather than the characteristic spread to the lung that is seen in others sarcomas like synovial sarcoma. Moreover, there's also a defining chromosomal translocation in MRCLS that drives this malignancy. This molecular signature is different from the translocation observed in synovial sarcoma.

I would like to illustrate the potential clinical benefit of our NY-ESO SPEAR T-cells by briefly outlining the clinical course of one of the initial responders in the MRCLS trial. This patient is a 59-year-old man diagnosed in 2015 with biopsy-proven MRCLS located in the retroperitoneum. He was initially treated with radiation followed by eight cycles of adriamycin plus ifosfamide and he achieved a partial response. Upon progression, he received three months of trabectedin and again achieved a response. Subsequent progression led to the participation in an NY-ESO vaccine trial, but the patient progressed and entered our trial.

His tumor biopsy at screening showed that 60% of the tumor cells being positive for NY-ESO with 3 plus intensity. He received 1.04 billion transduced SPEAR T-cells on the 10th of January and tolerated the infusion well. Post infusion, he had grade 1 cytokine release syndrome characterized by fever and rash that resolved with supportive care. Other adverse events included anemia and thrombocytopenia, which are not unusual in this patient.

At baseline, a target lesion was a firm tumor in the shoulder measuring 7.6 centimeters in longest diameter. At week four, that lesion was softer and had reduced in size by 37%, meeting the criteria for a partial response. A confirmatory scan four weeks later showed further reduction of the tumor by 48% compared to baseline with improvement of symptoms. There was high expansion of NY-ESO SPEAR T-cells detectable in the peripheral blood, a finding that has been associated with clinical responses in synovial sarcoma.

As you may recall, we have solid tumor data from our pilot study of NY-ESO in synovial sarcoma that also remains encouraging. In 2017, our investigators presented data during oral presentations at both CTOS and ASCO. Our NY-ESO SPEAR T-cells continue to be generally well tolerated in synovial sarcoma with initial efficacy observed in all cohorts, including the low-expressing cohort.

As reported at CTOS in December, 5 of the 12 patients treated in cohort 1 remain alive with a median overall survival of approximately 120 weeks. Among cohort 1 patients, there are 60% with confirmed responses at target dose, and we have seen confirmed responses in 33% of low expressors in cohort 2 and 36% of patients in cohort 4, our modified preconditioning regimen cohort.

We have observed that peak and long-term expansion of NY-ESO SPEAR T-cells correlates with clinical efficacy, and importantly our SPEAR T-cells migrate into patients' tumors after infusion, as seen in both treatment tumor biopsies. This supports

the notion that our SPEAR T-cells can convert cold tumors into inflamed tumors. The data from synovial sarcoma pilot study continues to inform development plans with our wholly-owned pipeline of products. And we, together with GSK, plan to present mature data on the differences in clinical outcomes that we have observed between cohorts 1 and 4 at an upcoming congress.

Moving on to our wholly-owned assets. As James said, we received a recommendation from the safety (sic - see press release "scientific") review committee to dose patients at 1 billion cells in the MAGE-A10 triple tumor study. We believe the 1 billion cells to be the therapeutic threshold based on our experience with NY-ESO in synovial sarcoma. The peak expansion we observed at 100 million cells is about tenfold lower than what was seen with doses above 1 billion cells. And we believe that 100 million cells is likely to be a subtherapeutic dose.

We received a dose escalation recommendation from the safety (sic - see press release "scientific") review committee as they reviewed data from three patients in the 100 million cell dose cohort in the MAGE-A10 triple tumor study in which there were no dose-limiting toxicities or DLTs.

In the other MAGE-A10 pilot study in non-small cell lung cancer, one patient experienced a grade 4 event of cytokine release syndrome, which was considered a DLT at the time. And it is worth noting that this patient had a large tumor burden. This patient's cytokine release syndrome resolved, and we are making changes to the DLT definition to exclude successfully managed cytokine release syndrome events.

At the time, however, this DLT led to expansion of the safety cohort in the MAGE-A10 lung cancer study from three patients to six patients, and we are now in the process of completing this cohort. After this, the safety (sic - see press release "scientific") review committee will review the data and make its recommendations regarding dose escalation to 1 billion cells. Across both MAGE-A10 pilot studies, there has been no evidence of target toxicity in patients who received the 100 million cells, and we have not seen severe neurotoxic events similar to CAR-T-related encephalopathy syndrome.

In our other trials with wholly-owned assets, we are dosing patients in our MAGE-A4 basked study, and we are enrolling in our AFP trial in hepatocellular carcinoma. We anticipate safety and efficacy data throughout 2018 from our MAGE-A10 studies and initial safety followed by efficacy data in our MAGE-A4 basket trial. We expect initial safety data from AFP in hepatocellular carcinoma towards the end of 2018 with efficacy readouts throughout 2019.

And now, I will turn the call back over to James. James?

James Noble^ Thanks, Rafael. These are exciting times for Adaptimmune. In 2017, we demonstrated compelling results in synovial sarcoma, further validated by GSK's option exercise over NY-ESO, and the late-breaking news of responses we have now seen in MRCLS. These data, with NY-ESO in two different solid tumors combined with the

encouraging initial safety in our MAGE-A10 pilot study, first with one of our own -- our wholly-owned assets, reaffirm the potential of our SPEAR T-cell platform in solid tumors. Importantly, we have made great strides towards becoming a fully integrated cell therapy company. This integration will put us in the best position to conduct future pivotal studies to support approval and ultimately deliver products and value for our patients and investors.

In 2018, we are on track to deliver data from our wholly-owned pipeline in up to eight different solid tumor types. With more than $208 million in total liquidity, we are funded to deliver these data and through to early 2020. We are even more confident that we will achieve our goal, be first to market with an engineered TCR T-cell therapy in solid tumors.

With that, I'd like to open up the call for questions. Operator?

QUESTIONS AND ANSWERS

Operator^ (Operator Instructions) We will take our opening question from Tony Butler of Guggenheim Securities. Tony's question appears to have been withdrawn.

(Operator Instructions) We have a question from Reni Benjamin of Raymond James.

Bin Lu^ This is Bin Lu on for Ren. So maybe first, can you talk about the durability of the responses that you saw in MRCLS?

James Noble^ I'll ask Rafael to comment.

Rafael Amado^ Yes. So this study has been treating patients for not a very long time. So we have waited until the first couple of responses were confirmed before releasing the news. So it's too early to talk about durability. We know that one patient has been -- responded after eight weeks, and then eight weeks later, was confirmed. And then the second patient was confirmed at week eight. So the first scan showed response and the second scan showed confirmation. And then the third patient was just scanned and had shown a response. And we have a fourth patient that had just had his first assessment and the tumor is smaller, but hasn't met yet criteria for response.

So these are initial data. But it's unusual in a cancer patient to see tumor shrinkage in all the patients that are treated, which is why we felt this significant. But you're absolutely right that it's going to be very important to keep accumulating data and, importantly, to find out how durable these responses are.

Bin Lu^ Got it. That's very helpful, Rafael. Maybe if you can further comment, I think you mentioned one patient had their reduction in tumors from 37% to 47%, if I remember that correctly. So maybe can you comment on how -- like what drives this improvement in response? And is it because you get more T-cell expansion over time or does it -- something change in the immune system?

Rafael Amado^ Yes, it's a really good question. It's really a behavior that we've seen in synovial sarcoma as well, unlike in the CAR space where if patients are not in complete response within the first four weeks, they're probably not going to respond, at least in ALL. The pattern of response that we see in synovial, and it appears to be recapitulating in this tumor type as well, is more progressive. So it may be because there is a much lower antigenic load and the cells have to find the tumor, cause inflammation, first, because these are very cold tumors and recruit other cells. So we have seen slow responses.

As I said, the first patient did not achieve a response at the first scan. And we have seen in synovial patients that have progressive reduction in tumor size going over a year. So it is possible that there's an initial decrease and then some functional control of the tumor that occurs over time. And again, this is in stark contrast with what's seen in the CAR space.

In the patients in whom we have had a chance to look at persistence, all these patients have had really high persistence comparable to their responses -- the responders in synovial sarcoma. We don't have long-term persistence in them because it's still a short follow-up. But we would expect that in these patients, the transduced T-cells will remain detectable as we've seen in synovial.

Bin Lu^ Got it. That was helpful. If I may, just one last question from me is, so maybe just given the totality of the data generated from NY-ESO TCR, can you provide your perspectives regarding how much read-through we can glean from these results into the MAGE-A10 and MAGE-A4 TCRs? I think we understand that the expression frequency of those antigens is different. But maybe besides that, can you comment on the similarities and the differences between soft-tissue carcinoma and other solid tumors in terms of their tumor heterogeneity, tumor microenvironment and the potential for T-cells to infiltrate.

Rafael Amado^ Yes. Obviously, that's a question that we, ourselves, would like to know the answer to, but I'll give you my thoughts. I think there's a lot of discussion out there about whether TCRs can really target solid tumors and whether sarcomas are just a one-off. I think there is plenty of evidence out there that TCRs can target solid tumors of multiple histologies. We've seen responses in melanoma. We've seen them in myeloma. We've obviously seen them in soft tissue sarcoma. Other investigators out there have seen responses in colorectal cancer. They have been seen in cholangiocarcinoma.

And so I think there's evidence that it's not just mesenchymal tumors, but epithelial tumors can be treated with TCRs. I think the point that you make about what this means for MAGE-A10 and MAGE-A4, well, for us, the most important thing is to discharge the potential cross-reactivity safety issue. And we are very pleased with the trajectory that we're in so far with MAGE-A10, and we are dosing MAGE-A4 as well. And so once we discharge safety, then we would be in a really good position to start testing efficacy.

As I mentioned in the call, 1 billion cells appears to be a minimum threshold, so we're not there yet, but we're testing these TCRs in a lot of solid tumors. So we hopefully will be able to show the potential of this technology. MAGE-A10 and MAGE-A4 are quite active TCRs in preclinical studies, and our newer sort of technology was applied in the development of these TCRs. So we're quite hopeful about the potential of these two products going forward.

Operator^ We will take our next question from Peter Lawson of SunTrust Robinson Humphrey.

Peter Lawson^ I guess as you think about responses, is there -- do you think we'll get to a point where you can correlate responses with biomarkers? Or is -- you think it's still going to be an [off] kind of thing, patient-to-patient specific responses?

James Noble^ Rafael, do you want to start? And maybe Gwen can add some things after that. It's a very good question, and we're very interested in the answer ourselves. Rafael?

Rafael Amado^ I mean, the most reliable biomarker we have now is the peak persistence, so it's the maximum persistence which is observed within the first week. And there is a clear difference between responders and non-responders that we've seen in synovial sarcoma. There is also a difference in peak persistence depending on what conditioning regimen is used. But we are not necessarily at a point where, by looking at peak persistence, we can make a long-term prediction. We do know that patients that don't experience good expansion are very unlikely to respond. We are starting to look at infiltration of our SPEAR T-cells and other T-cells into tumor in post-response biopsies. And maybe I'll let Gwen comment on that and some other potential biomarkers.

Gwen Binder^ Yes. So in terms of understanding what the patient's tumor looks like, we have initiated a very successful tumor biomarker analysis program, so that we can understand what mechanisms of resistance might be to our therapy. And so we're looking at all the usual suspects, so first and foremost, understanding if there is a change in antigen expression in the patients, both at baseline and post treatment. So we can understand if there's a priority resistance or if there's resistance that develops over time. And so that includes things like looking at antigen processing machinery, looking at HLA expression, looking at antigen expression in the tumors. So that's pretty straightforward.

And so the field of checkpoint inhibitors have also been looking very aggressively at these questions as well. So for example, in about 10% of patients, you do see loss of Class 1 and that mirrors what we see in our patients as well.

But we're also looking more deeply at the tumor to understand intrinsic and extrinsic mechanisms of resistance. So that means, in terms of extrinsic mechanisms, understanding what the immune contexture is in the tumor. And so that's things like looking at Tregs or myeloid-derived suppressor cells and trying to understand, if you have higher levels of these types of cells in the tumor, does that change the ability of the patient to respond to our therapy or not?

One possibility is that, if our product is sufficiently potent because of the affinity of optimized T-cell receptor, our T-cell product might be less susceptible to these types of suppressive mechanisms. But that -- we don't know the answer to that question yet. And we're also looking at intrinsic mechanisms of resistance, so that's -- those are things like what the tumor actually produces, so things like TGF-beta or upregulating the adenosine pathway, and -- or levels of chemokine receptors and so forth. So it's a long project, but we're actively looking at those correlates along with the serum biomarkers that Rafael mentioned.

Peter Lawson^ And then just on manufacturing. I like the progress that's been made there. Do you think you're going to get to quicker turnaround times and shorter [brain-to-brain] or is it still around what 28 days or so?

James Noble^ I'll let Ad answer that one.

Ad Rawcliffe^ So I think, at the moment, we have a turnaround time of roughly five weeks. And that split into two weeks at the manufacturer, and we are still using 14-day sterility and it will have escape -- nobody has noticed that the rest of the industry is moving towards a more rapid sterility -- has moved towards a more rapid sterility. And we plan to be implementing that this year.

So I think with that, we would be down at the sort of levels that some of the competitor companies are seeing. And obviously, Novartis' process is most like ours. And so at that point, we'll certainly be competitive for -- from a clinical trials perspective. And I think, as well, there's incremental improvements that can be made to reduce that further. But we're very pleased with the progress that we've made in our Navy Yard facility in terms of being able to manufacture very successfully for our MAGE-A4 trials and for our other internal assets.

Peter Lawson^ And just finally, how is enrollment going for MAGE-A10, MAGE-A4? That's the last question.

Rafael Amado^ So this is Rafael, again. I think the question was about enrollment, is that correct?

Peter Lawson^ Yes. How is enrollment going for MAGE-A10 and MAGE-A4?

Rafael Amado^ Yes. So the limiting factor has been mostly the stagger required and the need for safety review after we complete our cohort to define -- to obtain a recommendation of dose escalation. We're pleased with how things are going. And in fact, we are now screening patients, identifying them early, even when they are in prior therapies. We are [apheresing] many patients before they are ready to be treated so that the cells are ready at the time of progression. And we have, I think, what we believe is a good number of patients identified in both MAGE-A10 and MAGE-A4 to sort of keep

the pace of the trial going. So I think the efforts that we've made over these past couple of years have paid off.

Operator^ We will take our next question from Tony Butler of Guggenheim Securities.

Tony Butler^ I have three questions, if I may. I'll just ask them all three together. James or Rafael, the question around MAGE-A4, MAGE-A10. I'm curious if, in fact, you have a bias to a tumor or a histology, or is really the goal simply to think about the marker, MAGE-A4 or MAGE-A10, on a variety of tumors and perhaps being able to develop a tumor-independent therapy based upon MAGE-A4 or MAGE-A10 as being that marker? That's question one.

And then question two, either Rafael or Gwen, I wanted to ask about persistence of cells and the net amount of cells in vivo in which one may need to obtain or there may be a threshold for efficacy. So the question is, as you dose escalate, how many -- is it the net number of cells that need to be present in order to create efficacy? And let's assume that TCR is optimal, or is it the net amount of cells, which need to be present. They grow out to a certain time point, 30 days, 60 days, I don't know. Or is it both?

Rafael Amado^ Those are great questions, Tony. I think in terms of the first one, there's a variety of tumor types in both programs. And obviously, there's the option, if we see that the responses or the activity is histology independent, to attempt to develop this product in a way that we obtain a label that is defined by the expression of the marker, rather than the histology and, as you know, the expressions for that in the MSI-high tumors for checkpoints, which I think it was kind of a landmark development plan that potentially could be applicable to other products.

We obviously would love to be able to see activity that would allow this product to be developed in that fashion. I think we would have to show that it is reproducible and that it is across a sufficient number of tumors, so that one could then extrapolate that it's only the expression of the antigen that determines response. It would require a critical number of patients of each histology to satisfy that requirement. But obviously, I think it would be a much more fruitful development program, and we are mindful of that and we will make sure that we adapt our studies to enrich for histologies that may be lagging behind in terms of recruitment in our trial. It is the case that there may be unevenness in the types of tumors that come into our protocol. And we are trying to even that by seeking out sites that have a preponderance of patients of a given histology that may be lagging behind in enrollment.

So I think, whether we choose a single histology or a histology agnostic pathway will depend on what we see. But we are going to attempt to look very broadly across all the tumor types that we selected to look at -- to look for activity.

I think in terms of the second point, what we have observed is that at 100 million cells, first of all, we see the cells, which I think is a great finding. So we are able to pick up the cells. The persistence of cells is actually remarkably consistent with the dose. So it is

about a lot lower than what we see at 1 billion cells. And so it sort of works out to be a proportional number to the cells that we've infused. The difference is that when we infused 100 million cells, they are very short lived in peripheral blood. So we see the cells expanding. They peak at a level that, again, is a lot lower and then they disappear after a short period of time.

So my sense is that there is a threshold number of cells that need to expand that is required for the expansion to continue and for the cells to be sufficient in number to traffic and to be able to find antigen and expand further. And that appears to be higher than 100 million, which, as you know, is a different number in the CAR space probably because the accessibility of the cells to the antigen and the antigenic tumor load is so different between tumor -- solid tumors and heme malignancies.

Anything to add Gwen?

Gwen Binder^ No. I think that's exactly it. It's about being able to find the target antigen. In solid tumors, it's more difficult.

Operator^ We will take our next question from Robyn Karnauskas of Citi.

Kripa Devarakonda^ This is Kripa on for Robyn. She apologizes for not being able to be on the call. I have a couple of questions about safety. So just wondering if you've finalized your preconditioning regimen? Or is that still a variable as you go through the different trials? And have your studies given any insight into the triggers for neurotox, given the low levels of neurotox you see, especially in comparison to the CAR-T? And one more quick question. Is there any reason to expect that you might see any sort of delayed adverse events?

Rafael Amado^ Yes. So let me start with the first. So the preconditioning that we have chosen in these trials are the same as in cohort 4 of the synovial sarcoma study. So just to remind people about that -- those doses, it's 600 milligrams per meter squared times three of cyclophosphamide so three days, and then three days of fludarabine 30 milligrams per meter. And so we chose that for the MRCLS trial, and we chose that for the MAGE-A4 study and for the MAGE-A10 study except for the lung cancer study. So the lung cancer study was written when we thought that cyclophosphamide alone perhaps could be sufficient. And so we had an initial cohort of cyclophosphamide, and so those patients were treated with cyclophosphamide only.

Now we planned, in the dose escalation to 1 billion cells, to move into the combination of fludarabine and cyclophosphamide that I just described. So the 1 billion cells is going to be given with fludarabine because now we've learned that cyclophosphamide alone is insufficient and that's data that comes from the synovial sarcoma study. So that's the preconditioning.

Having said that, there is emerging data from the synovial study comparing cohort 1 and cohort 4 that we're going to describe at ASCO that perhaps suggests that there should be

further refinement on condition -- on preconditioning. But clearly the conditioning we're using in cohort 4 is active because we are seeing responses in MRCLS and we are seeing responses in synovial sarcoma. The question is whether it's optimal. So that's what I'll say about preconditioning.

In terms of neurotoxicity, there really isn't much to say because we have not seen neurotoxicity. And we see some symptoms that sort of map to, let's say, the MedDRA code of neurotoxicity like tremors or somnolence, but they are all explainable by medication or some other factors. And there's nothing that resembles the neurotox that's seen with CAR, neither encephalopathy or some of the more serious events.

In terms of delayed adverse events, with this technology, in really one word, it's about the acute events that are seen post infusion whether they are the classical events of cytokine release syndrome or, again, neurotox or graft versus host disease or some other event. And when one is dealing with a new product, like MAGE-A10 or MAGE-A4, you always watch out for anything that could resemble end-organ toxicity that's mediated by cross-reactivity.

As I said, so far, dosing at 100 million cells, we have not seen that in -- with any of our new products. It is unlikely that once the patient recovers the counts something could happen. Obviously, we won't know until we follow these patients longer. But in general, at least our experience with NY-ESO is that it's very rare to see toxicities once the patient has recovered his or her counts.

Operator^ We will take our next question from Marc Frahm of Cowen and Company.

Marc Frahm^ So one, Rafael, can you maybe talk a little bit about what you've seen in screening in myxoid in terms of the NY-ESO positivity, frequency of being positive, intensity relative to synovial, things like that? And then, also just as we think about -- you mentioned there's potentially the threshold-affected ability in cells. So as you clear these first patients out of 1 billion cells, just talk about the process of evaluating like whether you should -- of how you'll evaluate whether you should just dose expand at 1 billion or continue to try to dose up to a higher level?

Rafael Amado^ Yes. So the screening pattern is interesting because, in the literature, the numbers that are quoted are about half the patients expressing NY-ESO. And myxoid/round cell liposarcoma is actually a mixed tumor. It has these adipocytes and then it has a round cell component. And those round cells are actually prognostic. The more rounds cells there are, the worst the patient does, and that threshold is about 5% of round cell component. By the time the patients get screened for our studies, they all have a decent component of round cells in histology. And that tends to be more resistant to treatment.

Luckily, the expression of NY-ESO is seen uniformly in all of the cell types, which is such an important in terms of being able to effectively treat the tumor. And we have seen that the expression of NY-ESO seems to be higher in the patients that we have screened.

And it may be because the literature referred to patients de novo, these are surgical specimens, and that when the patients are more advanced, perhaps, the frequency of NY-ESO is higher. So it's 70-plus percent of patients that are positive and the intensity tends to be quite high. So that's what we've observed with our assay -- our immunohistochemistry assay.

In terms of a threshold effect of 1 billion, so that really comes from the synovial sarcoma experience, and what we are learning with our own TCR. Just if you are referring to MRCLS, in MRCLS we are not dose escalating because it's NY-ESO, and we already have enough safety with NY-ESO. So we're treating patients at a target of 5 billion, sometimes we don't make sufficient -- we don't make 5 billion cells and we treat, provided that we've made at least 1 billion. So the range is between 1 and 6, where we tend to target 5. And in the dose escalation trial --

Marc Frahm^ Yes. For the threshold, (multiple speakers) for more the MAGE-A10 and MAGE-A4.

Rafael Amado^ For the MAGE-A10 and MAGE-A4, yes. So those -- I mean that threshold, again, comes from synovial sarcoma. And for instance, the patient I described received 1 billion cells and responded. So I think there's a good chance that if these products are going to be active, we may see something in the next cohort.

James Noble^ If your question -- sorry, it's James here. If your question is, if we get efficacy at a 1 billion cells, will we get at 5 billion? That is the design of the protocol at the moment, so -- in both MAGE-A10 and MAGE-A4.

So the three levels of dosing are 100 million, which is the initial safety dose, the 1 billion, at which we hope, if it's the same as NY-ESO, that we get some responses. And then we still anticipate that we -- the third arm, the third leg of it will go up to 5 billion. So that's the intention at the moment. But obviously, we have to look at all the data.

Operator^ We will take our next question from Soumit Roy of SunTrust Robinson Humphrey.

James Noble^ If Soumit has had his questions answered by Peter Lawson, who had a question earlier, maybe we can move on.

Soumit Roy^ Sorry. Yes, my question was answered by Peter. Thank you, thank you.

James Noble^ Fantastic. Thanks, Soumit.

Operator^ We will move on to our next question from Jim Birchenough of Wells Fargo.

Nick Abbott^ It is Nick in for Jim this afternoon. Going back to the lung patient that had a grade 4 CRS, did that patient show robust T-cell expansion? And if that's the case, does it suggest, perhaps, the need for individualized dosing based on tumor burden?

Rafael Amado^ Yes. So that patient developed CRS starting on day one prior to the first sample that was drawn for persistence, so we continue to draw persistence samples, but we observed very minimal levels that disappear very quickly. But the patient had received high-dose steroids before the first sample was drawn. So it's very difficult to interpret the persistence in that particular patient because he was put on a protocol for treatment of severe CRS.

In terms of individualized dosing based on tumor burden, I don't really think we are there yet. We've seen responses with -- in patients that had high tumor burden where CRS was relatively mild. And so, it's not all about tumor burden, it's about expression levels, it's about the ability of the T-cells to penetrate the tumor. And I think it would be very difficult to actually do experiments where we could come up with dosing according to tumor burden.

For one thing, the measurement of tumor burden in cancer patients is very imprecise. And it would be quite complex to do that. It's not even done in the CAR space where it's easier to measure, for instance, in leukemia according to blast counts. So I don't foresee that being a way of dosing going forward.

Nick Abbott^ I guess, maybe just a follow-up then. Were there any baseline characteristics of this particular patient that allow you potentially to identify similar patients that may not be a good candidate, particularly for a much higher dose?

Rafael Amado^ I mean, I think that when people have publicized -- or published their parameters that correlate with CRS, tumor burden does come up. I think when we have a patient that has large volume disease and has high expression, and the cell dose is high because we've been able to manufacture a high cell dose, then obviously, one has to be vigilant.

I must say that the guidelines for treatment of CRS have really improved and evolved, and the majority of patients are treated quite successfully like this patient was. This patient had -- was already in the ICU and was -- the reason -- the definition of grade 4 is the requirement of ventilatory support. But that was done also preserve the airway because the patient had high tumor burden in the shoulder, neck and so on. So it's unclear whether it was the CRS that led to the criteria that actually made the definition of grade 4.

And so I think the answer of that is one should be vigilant if there are some of these factors that I measured. But in qualified centers, such as the centers where we operate and most gene therapy is done, there are already very clear algorithms for treatment and initiation of tocilizumab and secondary agents, including steroids. And it's been a long time since we've heard of fatal events of CRS, and I think it's just because the whole field has learned how to manage this.

Nick Abbott^ And my second question is, are you tracking what therapy these patients are receiving post MAGE-A4 and MAGE-A10? Honestly, I'm thinking more of a checkpoint inhibitor in checkpoint-sensitive tumors?

Rafael Amado^ We track pretreatment. In these Phase 1 studies, we're not tracking post-treatment. But I can tell you that all the patients that we're enrolling have received checkpoints, unless they have an indication where checkpoints are not approved. So they're all checkpoint progressors, if you will.

Nick Abbott^ Okay. And then last question is, what should we be expecting throughout the year in terms of perhaps new INDs and new technologies, and obviously, we note the encouraging progress reported by your collaborator at Bellicum for their inducible activation switch?

James Noble^ It's James here. I don't -- we're not expecting any new INDs this year. We hope to have our next new target IND next year, if everything goes well. But so it's going to be data on MAGE-A10, MAGE-A4 and, we hope, some safety data on AFP this year. I don't -- I wouldn't expect to see any other data this year.

Operator^ We will take our next question -- apologies, go ahead.

James Noble^ We'll take the last question from Ying Huang.

Operator^ Ying Huang, your line is open.

Jenny Leeds^ This is Jenny for Ying. We've just been getting a lot of questions from clients about, I guess, how you guys are controlling for on-target but off-tumor toxicities. So maybe if you could just remind us kind of you in process -- your internal process for selecting the binding motifs that are specific for the peptide to kind of minimize your off-tumor tox?

James Noble^ So I'll ask Gwen to comment in detail. But as you know, following the cross-reactivity we observed in 2011 and 2012 with MAGE-A3, we developed a complete new system which we have published. And we can send you the publications on that, if you like, because they're published. So they go in great detail. But I'll ask Gwen to explain a little bit about the way we determine the motifs.

Gwen Binder^ Yes. So I think a good place to start is by just starting with the basics that targeting -- with TCR engineered T-cell therapy, you have the ability to select tumor targets that are actually specific for tumors. So you can actually pick a target and through -- we have a target validation program where we very carefully will screen many normal tissues and look at expression of genes on tumor tissues. And then select targets that are only expressed in tumors. And so with our MAGE-A10, MAGE-A4 programs and also NY-ESO, these are cancer/testis antigens that are not expressed on any normal cells, non-cancerous cells, except for cells in the placenta and during embryogenesis.

So now with the toxicity that James mentioned, that was -- that's a situation where -- it was that the TCR recognizes a peptide that's presented in the context of HLA. And so we now carefully screen each of those peptides to make sure that we understand what the consensus binding sequence is of the peptide. Prior to the MAGE-A3 event, we just screened the sequence of the peptide against the human genome. And now we actually screen the consensus binding sequence, so it weights each of the amino acid residues. And so, we use that to find out if there's any other proteins that might have a different sequence but the TCR will still recognize.

And so we do that for all of our T-cell receptors as well as screen against the panel of B cell lines that represent the vast majority of the HLA profile in the population -- the world population in order to look for any alloreactivity as well. So we have probably -- we have the most comprehensive preclinical screening program for T-cell receptors.

And I just want to -- one final closing comment is that, right now, in the field of CAR T-cell therapy, it's extremely difficulty to find proteins that are expressed on the surface of target cells that are actually tumor-specific. So this is on-target off-tumor toxicity is going to be a pretty common and ongoing in the problem in the CAR field, but it's something that is less of an issue for us in the TCR field.

James Noble^ Thanks very much, everybody. So extremely good set of questions today. And we're very pleased to be able to present data on a new cancer and to give you an update on progress. This is still a year where we are expecting to be very data rich for the company. We're going as well as we can and to have discovered that we have got responses -- or to relay the responses in three out of four MRCLS patients in the way we've to do today, I think, lends creditability to the concept of the TCR platform having broader applicability in solid tumors.

So it's a very exciting year. We're just at the beginning of it. And I look forward to further discussions at our next releases. Thank you very much.

Operator^ Thank you. That will conclude today's conference call. Thank you for your participation, ladies and gentlemen. You may now disconnect.