[MUSIC PLAYING]

HASSANE ZAROUR: So it's my great pleasure to chair this session dedicated on spores or as Lisa told you. I think this is a great funding opportunity for the cancer center to fund translation research. So it put together multiple project dedicated to translation research. It's a great opportunity also to bound tissue from this project and to have the ability to share tissue within the spore and with the investigator interested in the translation research. And as I will give you some examples, also it's a great opportunity to fund a new project, a career development award or a project in development that may feed the next iteration of the spore.

So I'm going to start on behalf of the melanoma spore, John Kirkwood cannot make it today. And the team presents you, give you an update on the melanoma spore.

So this is the melanoma spore, an overview of this skin spore. So it has been renewed already once. So we are now in the third year of the melanoma spore. So it includes four different projects, constellation projects. So four one, two, three, and four. And core. And the core are extremely important with the administrative component which manage the spore, make decision, follow the progress of the spore. Makes decision in term of also award, career development award, that are funded during the spore.

It funds also a number of core facility, as I said, critically to bound tissue. That is what the core led by Lisa Butterfield does. Biostatistics, which is really critical because most part of this spore include clinical trials. So clinical trial design is really critical. Bioinformatic and genomics for the study performed in the context of the spore.

So the project one. Project one is led by Dr. Rini and Dr. Storkus, and it's a biomarker project which evaluate a number of biomarker in the context of an adjuvant treatment. So this project takes advantage of an ECOG multi-center adjuvant treatment for patient with high risk melanoma. So this is people with known metastatic melanoma or [INAUDIBLE] or lung melanoma [INAUDIBLE] that had been resectable. So these people are disease free but with high risk of recurrence, of relapse.

And they are included in a trial which randomizes patient is either getting ipilimumab, which is an antibody targeting the CTA4 antibodies. So if you were here two days ago at the symposium, we have heard a lot about this molecule. So two different doses. 10 milligram, which is FDA approved for advance melanoma, or three milligram per kg, or the classical high dose interferon which is a treatment that had been pushed forward by John Kirkwood a while ago, which is also FDA approved. So this trial has included this already close to actual 1,600 patients.

Then what [INAUDIBLE] does is getting tumor and blood from this trial to perform a number of biomarker study. And what [INAUDIBLE] is looking at is looking at a number of marker at the pier in the periphery. So a number of cellular population, immune suppressive cells known to dampen T cell response, including [INAUDIBLE]. There are suppressive cells anti-reg, a number of protein which have been linked to bad prognostic.

In the second aim. So with [INAUDIBLE], he does a number of gene profiling studies. So at this time when the project started, he decide to go with an RNA [INAUDIBLE] to do that. Looking also at a number of marker norms to predict prognostics like the presence of T cell infiltrate or other marker. And in the aim three, he planned to put everything together and all these marker, presented the periphery at tumor site, and hopefully identify the subset of patients who may respond or not to the treatment.

So the second project is led by Dr. Butterfield in collaboration with John Kirkwood. And this is a vaccine project using specific type of vaccines using adaptive transfer of dendritic cells that have been transfused with an adenovirus containing three different of tumor antigen. So this is basically, in summary, the trial.

So patients with advanced melanoma are immunized with dendritic cells that are transacted with these constructs, as an adenovirus that Lisa has engineered in collaboration with Dr. [INAUDIBLE] at the institution which include three different antigen, the tyrosinase which is a melanoma differentiation antigen, [INAUDIBLE], and [INAUDIBLE]. In the context of this trial, these patients are immunized three times with this vaccine and then randomized to receive or not interferon alpha post vaccine.

So the rationale of this trial is first to know, understand if this type of vaccine, adaptive transfer of adenovirus vaccine, can induce the cell response. And so there is reason to believe that this, because it contains [INAUDIBLE], we see a T cell response because dendritic adenovirus DC can also activate the NK cell. So this is a thing that it may be a good way also to assimilate innate immune response.

And the other question is also to know the impact of interferon alpha. There is a number of studies that have shown that interferon alpha can transform evidence of immune response into clinical benefits. And what is I want to know. So randomizing the patient with interferon alpha post vaccine is to know if really she can both enhance immune response and provide clinical benefit using interferon alpha post vaccine. So the aims of this trial are specific, are those ones.

So the clinical outcome of the clinical trial, a specific M1. The specific M2 is looking at a number of biomarker, curating this biomarker with a clinical outcome. She's looking at the vaccine component, the type of dendritic cells, and the work with the NIH for these transcription profile of the dendritic cells using the vaccine. And she's performing also a number of transcriptional study at the tumor site and at the periphery, encouraging that with the clinical income of the patient. In the third aim, she will look at the capability of the vaccine to stimulate innate response, NK cells.

So for now, 35 patients have been enrolled. So this complete accrual has been reached, which is good. 32 of the 35 patients have completed the vaccine design, and 20 out of 35 have completed the whole protocol, vaccine and interferon. So in terms of critical response, out of the 25 patients that have been evaluated, there is some evidence of clinical response. One CR, one PR. And so this trial include two type of patient. Patient with advanced diseased first, and patient with no evidence of disease.

So in the adjuvant setting, that is five or six patient with high risk melanoma which didn't progress. So Lisa is performing, actually, the monitoring of this vaccine, and has shown some evidence of immune response post vaccine, which is good. And she's trying now to evaluate whether giving interferon alpha post vaccine has further enhanced immune response. So this is in the making, as well as evaluation of NK response to the vaccine.

So the third project is a project that I lead with John Kirkwood. So it's interesting. This project is a good example of what can happen with the spore. This was not the original project of the spore. When we rolled the spore, the project was a trial proposing to combine interferon alpha with BRAF inhibitor. And there was a strong rational basis provided by [INAUDIBLE] inferon. And one was in [INAUDIBLE] to support this.

And so I think it was received very positively by the review. However, this way was difficult to do. So it was very difficult to recruit the trial. And the reason, I believe, is patient has to be naive in term of BRAF treatment. And as you know, BRAF inhibitor have been approved and are given easily in the community. So when the patient has a mutation, is given BRAF very easily. So it was difficult for us to get these BRAF naive patients.

So we had to try to find other possibility. And that's a good thing about the spore, is give you the possibility to re-evaluate your project and to change project. So this is not negative change project if for some reason it's not feasible.

So at this time, we had this trial which has initiated and was funded by [INAUDIBLE] and an award by the Melanoma Research Alliance. And we take the opportunity of the spore to increase the correlative study performed in the context of this trial. So the objective and rationale of this trial are rather simple.

So we talked two days about the PD1. So this has really changed standard of care of melanoma, providing great benefits to 30% to 40% of patients with advanced melanoma. However, still two thirds of the patients do not respond to PD1 blockade. And the reason PD1 may not work is now really better understood following the work by Antoni Ribas. And this is following some study that he did from a treatment [INAUDIBLE] which is an anti PD1 treatment, and find out that the patient who responds to PD1 are the one that presents T cell in their tumor pretreatment. So the evidence dose of preexisting immune response is what seems to predict response to PD1.

In contrast in this case, a patient with no T cell did not respond. So I think it's a great confirmation of a concept that has been brought forward by Tom Gajewski several years ago, the concept of cold or non-flamed tumor versus inflamed tumor. So the inflamed tumor are the cells where the T cell are present who are PD1. PD1 are expressal most likely to respond.

And the question is when the tumor is cold, when no T cells are present, what do we need to make these cells sensitive to PD1 treatment? So interferon alpha is a molecule known to prime immunse response, to augment tumor antigen presentation. So the idea was let's use peginterferon alpha in combination with PD1 in the hope to hopefully convert a cold tumor into an inflamed tumor.

So the trial design was simple, a classic dose escalation. So the pembro or PD1 dose was fixed. This is FDA approved, two mic per kg every three weeks. And we used peginterferon alpha at three different dose, one, two, and three microgram. And then expanded. So there was no major adverse event. So we reached the dose of three microgram per kg per week easily.

And we expanded. So the aim of the trial, in the context of the spore, were to better evaluate immune response ir the context of this trial. Look at the presence of T cell infiltrate pre and post treatment, trying to better understand if really we are capable of converting a cold tumor into an inflamed tumor to do a number of functional study to evaluate the culture of these cells, and to look at the clonality using TCR approach pre and post treatment.

So this treatment has included now 26 patients. So a significant number of these patients were pre-treated CTRA4. So second or third line patient. So this was put together by [INAUDIBLE] taking care of this clinical trial. So with evidence of patient respond to these treatments. So this is the summary of these treatments. So now we are like 38% of response, which is in the range of PD1. So we obviously don't do much better than PD1 alone, and we need to understand better that we observe that when the responsive cure they are prolonged. We need to better understand here for the people who respond if in some cases interferon alpha may not have induced even bigger progression.

And is that something we need to evaluate better? The interferon alpha has also a dual effect as all the cytokine can be beneficial. But in some cases it can also have some negative effects. So we need to understand that better.

But the good thing is when the responsive cure, they are prolonged. So this is noticeable in this graph. And interestingly, a number of patients, at least one patient, had to stop treatment because of major autoimmune side effect. He made an autoimmune varieties. And this patient, although treatment has been stopped more than a year ago, still had a disease that keep on regressing although he has not received the treatment for more than a year.

So the project four is a project which evaluate an institute approach using a chemoimmunotherapy approach for skin cancer. It's a project by Dr. Falo in collaboration with Dr. Aquirof and Dr. Devar. And so the objective of this trial is to use an intratumoral immunization using microneedles that have been engineered by Dr. Falo. And a mix of chemotherapy Dr. Rubisin and [INAUDIBLE] receptor free agonist.

So if you were here two days ago, we had the great opportunity to host Dr. [INAUDIBLE], which introduce the concept of immunogenic cell death, and has shown that a number of immunotherapy not only acts in killing tumor cells but in promoting immunogenicity, what she called immunogenic cell death. And that's what Lou Falo wants to do using this combination, and hopefully stimulate immune response in this patient.

So he has engineered needles, microneedles, that are biodegradable when you put them on patient's skin. And he called them, with Dr. Ribisin and [INAUDIBLE] which is a [INAUDIBLE] receptive free agonist. So this is the trial that he has designed and which has been recently FDA approved, though the dose escalation phase where he put an increased dose of Dr. Ribisin, and then followed by a dose expression phase. He would have to do that for each component of the vaccine for the [INAUDIBLE] independently, for the [INAUDIBLE] receptive ligand, and then with a combination.

So this trial [INAUDIBLE] lagged behind. This has started only a few months ago. So this will be a challenge for the spore to be able to get meaningful results before the end of the spore project. So that's the spore together. So I talk about the outcome. So again, this project is really lagging behind.

So I'm going to end up by putting on emphasis, I think, on which is the next important part of the spore, really the capability of fund career development award, or development project. So career development award. And I engage you when you receive the email calling to really answer to this call. So really fund project. We want to increase the depth and the breadth of the spore, looking at different things.

We are really heavily immonologic. So if you are working in another area, you should really apply. We are looking really for that. And we had a number of success story that earlier investigator, young investigator, that were funded by the spore and managed to get funding. So one of the last example is [INAUDIBLE] in the program, who was funded by this spore and managed to get a DOD grant for three years.

So this is great for us. It's great for you. So I encourage you to do that. Another thing is this is a development project. So the spore has to be renewed and has to come with new projects. So we use this type of award to try to fund new idea that maybe may come as full project in the new spore iteration.

And I will give you a few examples. So here, for example, [INAUDIBLE] we funded the project that used oncologic virus. So that's something we never did in the spore. It's a mass made [INAUDIBLE]. But this could be possibly a full product in next spore iteration.

Greg [INAUDIBLE]. I think it was a great opportunity for us to introduce study of metabolism. I think it's an important parameter that modulated immune response to cancer. I think this is really a growing area on which we didn't focus. It's a great way for us to get into.

Laura Ferris, who was measuring the outcomes of a skin cancer program in western Pennsylvania. So that's also a patient outcome in epidemiology. That's something we didn't do. So this is good. It's interesting. Hopefully this may develop into a full spore project.

Karen Anderson with the imaging study which also very interesting. And Dr. Benos, which is a big data analyst. She's using a computer [INAUDIBLE]. So this may also develop into a project, and hopefully develop also into a core to support the next iteration of the spore.