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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Promising Bifunctional Agents in Immuno-Oncology: A Roundtable Discussion with the Experts

Announcer:
Welcome to CME on ReachMD! This activity, “Advances in Immuno-Oncology: Experts Discuss the Promises of Bifunctional Fusion Protein” is provided by TOPEC Global and supported by an educational grant from Merck KGaA.

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Your moderator is Dr. James Gulley, Director of Medical Oncology Service at the Center for Cancer Research at the National Cancer Institute and National Institutes of Health. Dr. Gulley is joined by Dr. Scott Kopetz, Associate Professor and Deputy Chair of Translational Research at the University of Texas MD Anderson Cancer Center in Houston, Texas and Dr. Luis Paz-Ares, Head of the Lung Cancer Unit at the National Oncology Research Center in Madrid, Spain.

Here's Dr. Gulley.

Dr. Gulley:
I am James Gulley. Joining me today are Dr. Kopetz and Dr. Paz-Ares to discuss the latest findings in TGF beta, its role in pathophysiology, and treatment advances that we hope to bring in the near future. Welcome, thank you for joining me.

Dr. Paz-Ares:
Thank you.

Dr. Kopetz:
Glad to be here.

Dr. Gulley:
So, over the last several years, we've seen an explosion in interest in the immunotherapy for cancer. This has been driven in large part by the rapid, deep and durable responses we've seen with immunotherapy agents, including anti-PD-1 and anti-PD-L1 agents. However, there are limitations with these approaches. Often this is because of other negative regulatory influences within the tumor microenvironment, so we don't see everybody responding to these. One of the new agents' pathways that is being seen to be involved is the TGF beta pathway. This pathway is what we're going to be discussing today.

Dr. Kopetz:
TGF beta is a complex pathway that has really been characterized over the years by a bit of a dichotomy. A lot of the TGF beta biology has been described in the gut where there is an exquisite need to not overreact to the antigens that we eat or the bacteria in our gut but to make sure that the immune system is still able to defend from the microbes that may be pathogenic.

In cancer, however, TGF beta is important for regulating the type of immune cells in the microenvironment and really helps to structure a more complex microenvironment that can exclude and regulate the different types of T-cells and other effector cells that are present in the environment.

Dr. Paz-Ares:

I would add that those pleiotropic effects and complex effects of TGF beta signaling—and this is lung cancer, very important—on one hand it has relative effect on the tumor cell, on the tumor itself, promoting invasion, metastasis, and of course through EMT. On the other hand, it has some effects on the immune microenvironment. It has some other effect potentially, which is relevant to lung cancer, which is actually, let's say, promoting fibrosis, which is maybe important in the context of radiotherapy here and particularly taking into account that at this very stage that we are using some PD-1 or PD-L1 agents post chemoradiation in lung cancer. So I think that is for a number of reasons a very relevant target, and I hope that we are going to show that in the years to come. And very likely intervention on the TGF beta is going to be an important component of our therapy in the future.

Dr. Gulley:
This is a good point. And, there are several other agents targeting this relevant target that are currently under investigation. There are several small molecules that target the TGF-beta receptor. These include Galunisertib, Actosertib, and there is also in the antisense, oligonucleotide, Trabederson, that is in phase II testing in melanoma. There are several vaccines that are currently under investigation that actually use antisense technology to decrease the TGF best in the local vaccine site. There's also monoclonal antibodies against TGF beta, like Fresolimumab, and this is in phase I and II testing in melanoma and non-small cell lung cancer. There's another antibody, Xoma 81, that targets TGF beta I and II. And finally, there are bifunctional antibodies that target TGF beta and anti-CTLA4 or TGF beta and anti-PDL1 that have been tested pre-clinically, that have been recently published.
There's also M7824, which is a novel first-in-class bifunctional fusion antibody that is in clinical trials. This has an anti-PDL1 antibody, that on the tail of the antibody has 2 TGF beta receptor 2 molecules.

Dr. Gulley:
So, Dr. Paz-Ares, can you tell us a little bit about M7824?

Dr. Paz-Ares:
Okay, so that's a very interesting compound. Actually, it's a bifunctional agent. On one hand it's a typical monoclonal antibody against PD-L1, very, let's say, available now, I would say, but it's fused to a trap, which is actually able to trap the TGF beta. you are having this bifunctional ability to engage on the one hand PD-L1, on the other hand TGF beta. So by doing that you're kind of interfering not only on TGF beta at the tumor level, but also you can intervene on the microenvironment.

Dr. Gulley:
So I was honored to be part of the Phase I dose escalation study of M7824 where we did the first-in-human study. It was a safety study Phase IA where we enrolled 36 patients who had advanced cancer,

a variety of different cancers, and we started with doses as low as 0.3 mg/kg and went up to as high as 30 mg/kg, and we recently published the first 19 patients up to 20 mg/kg dose level, but what we found was that it was safe to give. We could see virtually the identical side effects to what you'd expect with PD-1 or PD-L1 inhibition with the addition of keratoacanthomas or benign skin condition. In addition, what we looked at was the pharmacodynamics, and what we saw was that not only did we get saturation of the receptor occupancy on the PD-L1 side of the molecule, but actually, we also got a decrease in the TGF beta. All activated TGF beta was below the lower limits of detection throughout the entire dosing period. We also looked at preliminary evidence of activity, and in this very advanced patient population—some of them treated with very low doses—we did see a one complete response and two partial responses suggesting that there is preliminary evidence of activity there, and this led to multiple expansion cohorts. We also determined that the best dose to use going forward would be the 1,200 mg flat dose.

Dr. Paz-Ares:
Sorry for that. The three responses you see, in which tumor types they were? And also they were at the highest dose level or...

Dr. Gulley:
So these responses were seen at a variety of dose levels.

Dr. Gulley:
And it wasn't just at the highest dose level, and we saw this in MSI high pancreatic cancer.

Dr. Paz-Ares:
Right.

Dr. Gulley:
We saw this in cervical cancer, and we saw this in anal cancer, so we did see responses across a range of different tumors.

Dr. Paz-Ares:
Right.

Dr. Gulley:
So, one of the expansion cohorts was in GI cancer. So, Dr. Kopetz, could you share with us some of the data that's come out of the GI cohort that was presented at ASCO GI?

Dr. Kopetz:
Certainly. So in GI, I think there's been two efforts. One was an expansion cohort in colorectal cancer,

and another was an effort in gastric gastroesophageal. In the gastric gastroesophageal cohort, this was enrolled primarily in Asia. It's a 31-patient cohort and encouragingly had a 19% response rate, and there was another—or 35% disease control rate overall. The activity was durable as well. The reports and the updates from the cohort are still a bit immature, but responders are continuing on for the most part. Toxicities were similar to what you had seen in the Phase I dose escalation, so I don't think any surprises there—a few autoimmune side effects, a little bit of fatigue.

So similarly, the colorectal cancer expansion cohort was done, and this was looking at a refractory patient population there was one remarkable responder that was on for well over a year, and she had microsatellite-stable colon cancer. This was not a very immunogenic-looking tumor as we would classically think, but importantly, she had a subtype of colorectal cancer that we defined based on RNA profiles, what we call CMS4, but really is a very mesenchymal-defined subgroup, and that's about 20% of our patients, so it's in a minority of patients, but this is really the subgroup of colorectal cancer where TGF beta is very active, where there's an engaged immune system it appears but is the tumor microenvironment that is in hospitable to an immune response. So this is encouraging as leading to expansion studies looking in CMS4 for further activity.

Dr. Gulley:
Fantastic. So one of the other pieces of information that's emerging is in HPV-positive cancers. You can see TGF beta dysregulation in many patients with HPV-associated cancers, so this led us to enroll patients in our dose escalation Phase I study, and we're presenting 17 patients. And what we saw that these patients had anal cancer, cervical cancer and head and neck cancer. 12 of these 17 had known HPV positivity, 4 were untested and 1 was negative. So the majority of patients had some decrease in their tumor, and 35% of the patients had an objective response overall. And of the 12 patients that were known to be HPV positive, we had a 42% response rate. Now, just to put this in context, what is out there in the literature with PD-1 and PD-L1 inhibition in HPV-positive cancers is somewhere between 16 and 20% response rate, so we find this early signal with limited numbers of patients promising. And we actually have a Phase 2 study going on looking just at HPV-positive cancers at the National Cancer Institute.

Additional data that came out at ASCO is the data on lung cancer. And, Dr. Paz-Ares, could you comment on that?

Dr. Paz-Ares:
Yes. There is a Phase 2 study where 80 patients had been included, treated at 2 different dose levels, 500 mg and 1,200 mg total dose, and the efficacy was very clear there. Overall, among the 80 patients, response rate was 23.5%, which is somehow a bit better of what you would expect with PD-1 or PD-L1

agents alone in this setting without making any restriction by PD-L1 expression. And more importantly, when you go and analyze the subgroup of patients with high dose, 1,200 mg, response rate is actually 27%, 27.5% as compared to 20% on the low dose, 500 mg. More importantly, if you concentrate on the PD-L1 positive tumors, response rate is exceeding 40%, and it's actually exceeding 70% on those tumors which are very high with PD-L1 expression using the 80% cutpoint, which is actually with this assay corresponding to the 50% positivity with 223C assay. So the data in terms of event-driven responses like PFS, NOS, are also pretty incredible I would say, even, of course, immature, but incredible particularly at the 1,200 mg dose particularly on those patients which are PD-L1 positive.

Dr. Gulley:
Thank you very much, very interesting data. So I think that what I am seeing is preliminary evidence of activity with this anti-TGF beta trap molecule that also blocks PD-L1 alone, and I think that perhaps we're going to see this in patients who have immune systems that already recognize their tumors such as highly mutated tumors like lung cancer or patients who have viral-associated cancers like HPV-positive cancer. I think, also, there's a potential for, as you mentioned, those tumors that are immune deserts. Potentially, one could use this and perhaps in combination with other agents to get the immune system to recognize this. And I just want to mention one quick study that recently opened at the National Cancer Institute where we're combining a vaccine approach with this M7824 to see if we can get the immune system to recognize the cancer and then allow those effector cells to be functional within the tumor microenvironment. We're also adding in IL-15 and an IDO inhibitor in sequential cohorts to try and break the back, and we're doing this in prostate cancer, which is a typical T-cell poor tumor where we don't see activity with PD-1 and PD-L1 inhibition unless the patient is MSI high. So I think the interesting thing about this approach is not just that we're targeting 4 agents that target 5 different pathways but that we're trying to do these combinations quickly to get the answer quickly to see does this work or not. In 3 sequential cohorts we'll get our answer very quickly.

So, any closing comments for our audience?

Dr. Kopetz:
I think I share your enthusiasm for the target and the opportunities. I think, as you mentioned, the next wave is really understanding the right setting for agents like this that target TGF beta. It's about kind of patient selection, understanding the biology, understanding where TGF beta is playing a really critical role, and I think also in what combinations is a TGF beta response kind of productive. So I think it was brought up radiation as one, and I think a lot of excitement about radiation combination studies moving forward as well.

Dr. Paz-Ares:

And I fully agree with your comments and your prospects for the future. I would say I would favor particularly on PD-L1 highs, maybe the setting of tumor which are immune deserts to see if you are actually able to get some lymphocytes inside. And also very attractive for me would be on the Stage III setting. We are starting our chemoradiation immunotherapy all together trials.

Dr. Gulley:
So we've had an insightful and exciting discussion today on the role of TGF beta and potential opportunities to use this M7824 to target cancer. I've been delighted to be here with you both. Thank you so much.

Dr. Paz-Ares:
Our pleasure.

Dr. Kopetz:
Likewise.

Announcer:
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