Advances in Immuno-Oncology: Evaluating a Bispecific, Bifunctional Fusion Protein

Narrator:

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Your host is Dr. Barry Mennen.
Dr. Mennen:
Immune checkpoint inhibitors, specifically those targeting programmed death-1 and programmed
death-ligand 1, or PD-1 and PD-L1 respectively, have been remarkably beneficial in the treatment of a wide range of cancers. However, as we've become more experienced with these agents, we've found that not every patient responds to this immune-modulating therapy, which creates a pressing need for identifying and targeting other pathways central to cancer progression.

This is CME on ReachMD, and I'm Dr. Barry Mennen. Joining me today is Dr. James Gulley, Director of Medical Oncology Service at the Center for Cancer Research of the National Cancer Institute. On this program, we'll be focusing on the role of TGF-beta in the pathophysiology of tumor cells and how the exploitation of this pathway can potentially lead to breakthrough therapies for our patients.

Dr. Gulley, welcome to the program.

Dr. Gulley:
Delighted to be here.

Dr. Mennen:
Let's start with my earlier comment about the initial excitement among clinicians toward PD-1 and PD-L1 targeting agents, followed soon afterwards by a sense of disappointment for their limitations. What can you tell us about these limitations?

Dr. Gulley:
It's a great question. Let me start by just explaining what PD-L1 is. So, when you have an activated T-cell and it gets into the tumor and it recognizes the tumor, what it does is it sends out activation signals, including a protein called gamma interferon. This causes upregulation of PD-L1 on the tumor, and this sends a stop signal to the T-cell. So the T-cell just waits there, and if you can come in with something that blocks that stop signal, you can allow that T-cell to work. So now you can have an antibody that blocks PD-1 or PD-L1 and allowing that T-cell to really become active. What we've seen is... Across a wide range of different cancers, we've seen deep, durable, and rapid responses, and only, unfortunately, in a subset of patients. So we can get about 20% of cancers that may respond to these, but that leaves 80% of the patients that don’t have a significant decrease in the tumor size because of these. Perhaps one of the issues is there are multiple, different stop signals given, not just PD-L1, and one of those stop signals is TGF-beta.

Dr. Mennen:
Thanks for that, Dr. Gulley. Let's now focus on the TGF-beta pathway and its role in cancer development. We know that TGF-beta is an important factor in maintaining immune tolerance, but it looks like those protective functions also play a key role in shielding cancers from our own immune defenses. How does this happen?
Dr. Gulley:
Great question, again. So one of the things that we’re seeing is that there are multiple, different cells in the tumor microenvironment that make TGF-beta. These include the tumor cells themselves as well as certain immune cells in the tumor microenvironment, such as myeloid-derived suppressor cells. These cells make the TGF-beta, and this TGF-beta has a multitude of different effects. One of those effects is fibrosis, where you can get areas that become very dense and very difficult for cells or drugs to get into. Another thing is something called epithelial-to-mesenchymal transition. This is involved in metastatic process so that cancer cells have to become more mesenchymal to be able to spread and go to other parts of the body. It’s also involved in angiogenesis, so it makes new blood vessels for the tumor to grow. And finally, and perhaps most importantly for this conversation, is it is very much involved in immune suppression, so it can downregulate your good T-cells, your NK cells, and it can make the activity of myeloid-derived suppressor cells better.

Dr. Mennen:
Now, what agents targeting this pathway are currently available or under investigation?

Dr. Gulley:
There are multiple different agents that have been tested over the years targeting this very important biologic process and immunologic process. There have been antibodies that have been tried. There have been small molecule targets that have been tried with varying levels of success, and not just in cancer—I would add also in fibrosis. However, one agent that has recently come to the fore is an agent that is an antibody and a TGF-beta trap. So this agent is called M7824, and it is an agent that not only blocks PD-L1, which is so important for cancer therapy, but it also serves as a TGF-beta trap.

Dr. Mennen:
Excellent. Now, Dr. Gulley, let’s dive into one of the investigational agents we’ve just covered called M7824. It’s described as a bifunctional fusion molecule. What does this mean specifically in terms of its antitumor activity?

Dr. Gulley:
What you have is on one end of the antibody, you have the antibody binding to the PD-L1, blocking that important negative signal for the T-cells, and on the other end of the antibody, you have two TGF-beta receptor 2 molecules that serve as a TGF-beta receptor trap, so this binds to TGF-beta and will basically vacuum up the TGF-beta. Any activated, free TGF-beta will be sequestered by this method and not able to signal and do all the negative regulatory things that it does. And basically, what this allows it to do is clear out that TGF-beta so there’s no fibrosis formation, there’s no angiogenesis, there’s no EMT spreading drug resistance and none of the immune-negative influences on the T-cells,
on the NK cells, and increasing functionality of the myeloid-derived suppressor cells. So with this then, you have the ability to target these many biologic effects that TGF-beta has and completely negate them within the tumor microenvironment. The nice thing about this molecule is, because it is all in 1—you have the 2 shots on goal there—you’re bringing in this anti-PD-L1 antibody and concentrating it within the tumor microenvironment where there’s a lot of PD-L1 expression, hopefully, with an inflamed tumor, and you’re concentrating that TGF-beta activity within this tumor microenvironment.

Dr. Mennen:
What can you tell us about the clinical trial data thus far to support the efficacy of this molecule?

Dr. Gulley:
Let me tell you a little bit about some more of the preclinical as well as the clinical data for this. So, preclinically, what we have seen is you can get activity where you see better activity than just PD-1 or PD-L1 agents and better than TGF-beta agents alone, so when you give this combination, it does appear to be more active. The other nice thing that you see is it’s blocking 2 agents in 1, and because of that, when you have an activated immune environment in a tumor, you’re going to get the antibody binding there, and so you’re going to get a concentration of this TGF-beta trapping within the tumor microenvironment where it’s very important for the biologic processes. What we’ve seen with the clinical trials is, in a 19-patient dose-escalation study, we showed that:

1. It was very safe to give. You got similar side effects that you might get with anti-PD-1 agents or anti-PD-L1 agents, some degree of autoimmunity, but very low-grade most of the time and was easily reversible either just by stopping the drug or by giving low dose of steroids.

2. There were really no additional toxicities over what you’d expect from that, except for 1, and that is a very minor skin condition called keratoacanthoma. Sometimes it’s confused with a low-grade squamous cell carcinoma. Typically, this can either be excised or just watched, doesn’t need to be treated.

What we’ve also seen in that initial 19-patient study, however, was evidence of this antibody working. So we saw that both ends of the antibody worked; it bound to the PD-L1; and we could see target occupancy of greater than 80% throughout the entire dosing; and we could also see that the other end of the antibody worked, that is the TGF-beta sequestration. What we found was that when we measured levels of activated TGF-beta after starting the drug, they were below the lower limits of quantitation during the entire dosing period, so what we’re seeing here then is something that can both bind to the PD-L1 and get rid of the TGF-beta.

Now in terms of clinical activity, even though this was a dose-escalation study with only 19 patients, many of them heavily pretreated, we did see evidence of activity with 1 complete and 2 partial
responses in this initial study. There are additional data that have more recently come out though, including data in gastric cancer and gastroesophageal cancer, where we’re seeing almost a 20% response rate and about a 35% disease-control rate in these patients, and this was presented at ASCO GI this year. In addition, there were 2 presentations at ASCO in the annual meeting: an oral presentation with HPV and a presentation with lung cancer. What we found in lung cancer was, out of 80 patients treated, there were 2 different dose levels. Forty were treated at the 1200 mg dose level and 40 at the 500 mg dose level. I’m going to focus on the 1200 mg dose level because that’s the dose level going forward in all of our expansion groups, and what we found was that, of those 40 patients, we got an objective response rate of 28%. Eleven of these patients had an objective response. But if you just looked at the 27 patients that were PD-L1 positive, all 11 of those patients that responded were PD-L1 positive, so the response rate there was about a 41%. And if you looked at the patients that had a high PD-L1 expression of at least 80%, 6 out of 7 of those patients responded, so a very interesting early data in lung cancer suggesting activity—also, there’s interesting data in HPV-associated cancers. So there were 17 patients that we looked at. I should mention that the historical response rates with HPV-associated cancers with anti-PD-1 agents is about, 15 to 20%. What we saw with this group of patients was that we had objective responses in about 35% of the patients overall, and those 12 patients that had known HPV positivity, we saw a 42% response rate, a total of two complete responses and 4 partial responses—so very interesting early evidence of activity, including in frontline setting and including in those patients that have progressed on PD-1 or PD-L1 inhibitors.

Dr. Mennen:
In the HPV-associated, were they head and neck as well as genital?

Dr. Gulley:
Yes, so they’re head and neck, anal, and cervical cancers were the primary ones seen.

Dr. Mennen:
Dr. Gulley, my last question to you: Looking ahead, what are the next action steps or lines of investigation for this and other pathways in immune checkpoint inhibition?

Dr. Gulley:
I think that looking forward, really the mantra is going to be combination therapy. With this agent you’re almost doing combination therapy with 1 agent because you’re targeting 2 different pathways, but I still think there’s room to target additional pathways. We have several ongoing studies that are combining this agent with therapeutic vaccines, anti-cancer vaccines, to try and generate a good immune response in those T-cell-poor tumors and then allow those immune cells to work by blocking TGF-beta and by blocking PD-L1 in the tumor microenvironment. I think you’re going to be able to see this
potentially work as a single agent in multiple different indications. It doesn’t just have to be in the refractory setting where there’s resistance, but I think you’re going to be also able to use this perhaps to get better response rates as we may be starting to see in lung cancer and HPV-positive cancers with single agent earlier on in the disease treatment.

Dr. Mennen:
Well, with those forward-looking thoughts in mind, I’d like to thank Dr. Gulley for joining me to talk about the latest understanding of the TGF pathways, its role in solid tumor physiology, and opportunities for future treatment approaches. Dr. Gulley, it was great having you in this program.

Dr. Gulley:
It was my pleasure. Thank you so much, Barry.

Dr. Mennen:
Our pleasure.

Narrator:
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