While there have been very promising results with both CTLA-4 and PD-L1 agents in bladder cancer, it is time for researchers to start looking beyond that, said Alexander I. Sankin, MD.

“We are going to get to a certain point where there is only going to be so much benefit that we see from CTLA-4 and PD-L1 therapies," said Sankin, an assistant professor of Urology at Montefiore Medical Center at the Albert Einstein College of Medicine. “It is time to look for other checkpoints and understand the biology better. There seems to be a more intricate interplay and a complex relationship between the tumor biology and the host immunology than we initially understood.”

Sankin and a team of researchers at Montefiore Medical Center are investigating HHLA2, a recently defined new checkpoint “family member” that appears to play a significant role in T-cell regulation. In a preclinical study, researchers sought to determine whether the ligand was expressed in urothelial carcinoma by staining bladder cancer specimens for HHLA2 and PD-L1.

The staining provided strong evidence of HHLA2 in bladder cancer—even in tumors that also expressed PD-L1, said Sankin. In an interview with OncLive, he expands on these findings and discusses next steps in his research and what it could mean for the future of checkpoint inhibitors in the field of bladder cancer.

OncLive: What were the goals of this study?

Sankin: Immune checkpoint inhibition in cancer has really become successful and has shown to be very tolerable, leading to durable responses. The main checkpoints that have really been studied so far are CTLA-4 and PD-L1. These have been widely studied and there have been multiple clinical trials showing success.

What we aim to do is actually look at new receptors beyond PD-L1. These are receptors that are in the same family and seem to have similar biologic activity to PD-L1, but have not yet been studied in most cancer types, and especially not in bladder cancer. We were able to identify some human bladder cancer specimens from our institution and, for the
first time, we stained for these new receptors—particularly HHLA2, also known as B7H7.

What were the key findings?

We saw that not only is HHLA2 expressed in bladder cancer, but also about 66% of the tumors we looked at actually expressed HHLA2. This is an important take-home message, because PD-L1 is only expressed in about 20% to 25% of tumors, so this seems to be even more highly expressed and it might be even more biologically relevant.

Are there therapies that can target HHLA2?

There is nothing yet, but that is in the works. Right now, we have a monoclonal antibody derived from a mouse that can target this receptor. That enables us to do immunohistochemistry staining, which was the premise for my study. We are in the works of developing a humanized antibody, which could potentially block the receptor and lead to a therapeutic response.

What are the next steps in this research?

First, we are going to further characterize if HHLA2 can be used as a biomarker for predicating outcomes and perhaps disease at advanced stages—patients who are more likely to get a recurrence after treatment. We plan on collaborating with some other institutions and gathering their tissue microarrays in order to further characterize this receptor.

After that, we really want to develop cell lines, and potentially animal models—maybe even mouse models—to see if we can develop a nice model of bladder cancer tumors that express HHLA2. Then, we will see if we can block it and if they have any type of response. Ideally, following that, we want to move into human clinical studies.

Can a tumor that expresses HHLA2 also express PD-L1, and, if so, what does that mean for treatment options?

We have looked at that, we have looked at urothelial tumors that express HHLA2, and we also looked at PD-L1. In fact, some of these tumors did express both simultaneously. What is interesting is that there seems to be some geographic heterogeneity within the samples. While 1 region of the tumor expressed PD-L1, another region of the tumor expressed HHLA2. That really has some interesting implications. If a patient fails on a PD-L1 therapy, you could then possibly do a sequential therapy with an HHLA2 therapy afterwards.

What should oncologists take away from this research, at this point?

It is very early on, but there is a lot of excitement in the checkpoint inhibition area right now. We are really only at the tip of the iceberg, and there will be much more that will be developed in the next 5 to 10 years. It is very exciting.
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