

# KIDNEY CANCER UPDATE

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## Combination Immunotherapy in Renal Cell Carcinoma

Based on a presentation by Charles G. Drake, MD, PhD, at the Kidney Cancer Symposium

Several approaches to combination immunotherapy are being investigated in kidney cancer, according to Charles G. Drake, MD, PhD, a professor of oncology, urology, and immunology at the Johns Hopkins School of Medicine in Baltimore, Maryland. These include combining a checkpoint inhibitor with a tyrosine kinase inhibitor (TKI), with a second checkpoint inhibitor, or with radiation therapy. In some cases—but not all—the results of animal studies have offered insights into the use of these agents in humans.

### Checkpoint Inhibition Plus a TKI

Regarding checkpoint inhibition plus the use of a TKI, Dr Drake said that in 2008 his team at Johns Hopkins was the first in the world to treat a patient with a programmed death 1 (PD-1) inhibitor—in this case, nivolumab (Opdivo, Bristol-Myers Squibb). That patient was a complete and extreme responder, he said, and is still alive. Given this long history with PD-1 inhibitors, it is logical to combine them with other agents that have been shown to be effective: TKIs that target the vascular endothelial growth factor (VEGF) pathway.

Looking back to the experience with animal models, Dr Drake pointed to an unpublished study by Hans Hammers and his own laboratory in which the combination of a PD-1 inhibitor and sunitinib (Sutent, Pfizer) was found to be more effective at shrinking tumors than either agent alone in an orthotopic mouse model of kidney cancer. “You can see a fairly nice additive effect, sometimes bordering on synergy,” said Dr Drake, who pointed out that research from other groups has produced similar results.

These encouraging results in animals led to studies of the combination in humans. Dr Drake pointed to preliminary results from a phase 1 study by Amin and colleagues presented at the 2014 American Society of Clinical Oncology (ASCO) annual meeting. In this trial, 48 patients with kidney cancer that was progressing on either sunitinib or pazopanib (Votrient, Novartis) were crossed over to receive the other TKI in combination with nivolumab.

“The response rate looked like it was better [with the combination] than with either a PD-1 or TKI agent alone,” Dr Drake said. He pointed out that although mouse studies had predicted tumor response rates in humans, they had not offered any insights into toxicity. In humans, the toxicities of the 2 agents were additive or possibly even synergistic, with grade 3 or 4 adverse events occurring in 82% of patients taking sunitinib/nivolumab and 70% of patients taking pazopanib/nivolumab. The rate of hepatic dysfunction was such that the pazopanib/nivolumab arm had to be discontinued. “That is a question that we face going forward in these kinds of cases, where you see really nice responses like this in patients with rapidly progressing disease. Is the risk of this toxicity worth the potential benefit?”

### Combination Checkpoint Blockade

Dr Drake next spoke about combining checkpoint inhibitors, pointing out that Alan Korman was one of the first to study these combinations in mice with cancer. Dr Korman found that in certain animal models, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors had very little effect and PD-1 inhibitors had only a modest effect. A combination of the two, however, worked synergistically and was able to cure the mice.

Dr Korman’s research did not reveal any benefit from the sequential use of CTLA-4 inhibitors and PD-1 inhibitors, suggesting that parallel combination might be useful. One possible explanation for the synergy of this parallel combination is that anti-CTLA-4 agents may be more effective on CD4 cells and anti-PD-1 agents may be more effective on CD8 cells.

As Hammers and colleagues showed in a phase 1 study presented at the 2014 ASCO meeting, the combination of nivolumab and ipilimumab (Yervoy, Bristol-Myers Squibb) indeed showed encouraging antitumor activity and acceptable safety in patients with metastatic renal cell carcinoma, whether nivolumab or ipilimumab was given at a higher (3 mg/kg) or lower (1 mg/kg) dose.

## Checkpoint Inhibition Plus Radiation Therapy

Another combination that has been tested in both mice and humans is checkpoint inhibition plus radiation therapy. Several studies have described the synergistic effects on local and distant tumor control when immunotherapy is combined with radiation therapy. Andrew Sharabi, working in Dr Drake's laboratory, discussed the biological and mechanistic rationale behind this combination, as well as the potential ways in which radiation might activate the immune system, in an article that was published in *Cancer Immunology Research* in 2015. "When you radiate a tumor, the antigen-presenting cells wind up picking up and presenting the tumor antigens in a pro-immunogenic way in the tumor-draining lymph node," he said.

In one study that Dr Drake conducted with Jing Zeng as the first author, the investigators placed tumor cells into the brains of mice. "When the tumor cells are in the brain, that's a fairly tolerogenic environment, and neither radiation therapy nor a checkpoint inhibitor alone was found to be effective." What the investigators found in this study, however, was that the combination of PD-1 blockade and localized radiation therapy resulted in long-term survival.

"Everything in the world has both a plus side and a dark side," however, said Dr Drake. On the negative side, delivering radiation to a tumor increases the number of CD4 cells that dampen an antitumor response, pointing to unpublished work in the laboratory by himself, Yuki Muroyama, and Tina Ceccato. "We thought that radiation plus PD-1 blockade would be a good idea, but we have to keep in mind the possibility that this will induce regulatory or expand intratumoral T cells."

In an unpublished study by Dr Drake's group using mice with prostate tumors, a combination of radiation therapy with a depleting anti-CTLA-4 antibody was able to halt tumor growth, whereas radiation alone had no effect. Although the depleting antibodies of mice are different from those of humans, Dr Drake theorized that

using an experimental reagent such as mogamulizumab might produce a similar effect in humans. "When we give this depleting regulatory T cell (Treg) antibody, we do not deplete the Tregs in the mouse's gut, skin, liver, or lungs. So there's a hope that perhaps that can be translated to humans and not lead to systemic toxicity."

He said that Dr Hammers has designed a trial in which patients with oligometastatic kidney cancer receive radiation therapy followed by a combination of CTLA-4 and PD-1 blockade and then PD-1 monotherapy. Although anti-CTLA-4 agents may not deplete CTLA-4 in humans the way they do in mice, there is a possibility of seeing the type of synergy that is revealed in the mouse models.

## Conclusion

"So we can see that these mouse models are at least a little bit predictive," said Dr Drake. Checkpoint inhibition plus TKIs worked in both mice and humans, although studies in mice did not predict toxicity in humans; combination checkpoint inhibition worked in both mice and humans; and it remains to be seen whether checkpoint inhibition plus radiation therapy might work in humans. "We hope to see the sort of synergy that we saw in the mouse models," Dr Drake concluded.

## References

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