KIDNEY CANCER UPDATE

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The Right Questions to Ask in New Trials of Immunotherapy

Based on a presentation by David McDermott, MD, at the Kidney Cancer Symposium

Now that immunotherapy is an expanding area of inquiry in kidney cancer, trials have many new questions to answer, according to David F. McDermott, MD, an associate professor of medicine at Harvard Medical School and leader of the Kidney Cancer Program and the Dana-Farber/Harvard Cancer Center in Boston, Massachusetts. These include the proper duration of treatment, how often responses persist after treatment ends, the role of tumor biomarkers, the best combinations and sequences of treatment, and what study endpoints should be used.

Regarding the proper duration of treatment, "there is probably a subset of patients who don't need treatment beyond 6 months," said Dr McDermott, pointing to data from the CheckMate 025 study. This study, which was published in the *New England Journal of Medicine* in late 2015, compared the use of the programmed death 1 (PD-1) inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) with the use of the mammalian target of rapamycin (mTOR) inhibitor everolimus (Afinitor, Novartis) in advanced renal cell carcinoma. A number of patients responded to nivolumab after just 4 to 6 months of treatment. Among the patients who did respond, "most of the responses happened early and many of them lasted off treatment," he said. These are the patients who are likely to experience continued treatment-free survival without further therapy. "We need to identify who these patients are going forward," said Dr McDermott. "We shouldn't be treating patients continuously if they don't need it."

One way to determine the optimal duration of treatment is through randomized discontinuation studies, in which patients with stable disease are randomly assigned to either stay on the drug or discontinue it. This type of trial was used by Dr Mark Ratain and colleagues in an examination of sorafenib (Nexavar, Bayer/Onyx) for kidney cancer that was published in the *Journal of Clinical Oncology* in 2006. Dr McDermott pointed out that getting patients to sign up for these types of trials can be difficult, especially in the case of checkpoint inhibitors, which have a low toxicity profile. To address that concern, he proposed assigning participants to 1 of 2 different durations of checkpoint blockade, such as 6 vs 12 months.

As for how many responses are durable after immunotherapy ends, "the answer is, maybe not as many as we might think." He referred to overall survival results from the initial phase 1 study of nivolumab in melanoma. In that trial, overall survival was "fantastic" at 2 years, with a rate of 47%. As treatment stopped, however, the curves began to trend down to 32%. "One big question for the field is, where will this curve plateau [in kidney cancer]? I don't think we know yet, and we need to follow that in all the diseases that we're treating."

Patient selection is an important part of immunotherapy. Unfortunately, the ability to develop biomarkers is complicated by sizable heterogeneity within kidney tumors. Dr McDermott pointed out that even frontline, single-agent PD-1 blockade is difficult without a biomarker. "While we don't have a marker yet, it's going to be essential for the next generation of trials."

He said that researchers are currently looking into the use of CD8+ T cells, neoepitope signature, and tumor histology as possible ways to determine who might respond to treatment. A report on the programmed death ligand 1 (PD-L1) inhibitor atezolizumab (MPDL3280A that is being published in the *Journal of Clinical Oncology* should provide additional insight into potential predictors of response.

Another question is whether combination therapy with checkpoint inhibitors will be worthwhile, or whether the side effects and costs will outweigh the benefits. A study published in the *New England Journal of Medicine* looked at a combination of nivolumab and ipilimumab in patients with melanoma and found that combining the agents improved response rates at the expense of more toxicity. "It's not just more toxicity, it's toxicity that doesn't always go away," said Dr McDermott. Many grade 3 or 4 toxicities took weeks or months to resolve, and some led to hospitalization or did not resolve. At least 7 studies are examining combinations of nivolumab, pembrolizumab (Keytruda, Merck), and MPDL3280A along with other agents in renal cell carcinoma (Table).

Table. Studies of PD-1 Pathway Blockade Combination Therapy

Study	Treatment	Setting	Phase	Status	Patients	Completion
Nivolumab						
NCT01472081, CheckMate 016	NIV + SUN vs NIV + PAZ vs NIV + IPI	First-line	1	Ongoing, not recruiting	175	October 2015
NCT02231749, CheckMate 214	NIV + IPI vs SUN	First-line	3	Recruiting	1070	January 2018
NCT02210117	NIV vs NIV + BEV vs NIV + IPI	Neoadjuvant	2	Recruiting	45	November 2018
Pembrolizumab						
NCT02014636	PAZ ± PEM	First-line	1/2	Recruiting	228	October 2018
MPDL3280A						
NCT01633970	MPDL3280A ± BEV	First-line[a]	1b	Recruiting	225	February 2016
NCT01984242	MPDL3280A ± BEV vs SUN	First-line	2	Ongoing, not recruiting	305	January 2016
NCT02420821	MPDL3280A + BEV vs SUN	First-line	3	Recruiting	550	October 2019

BEV, bevacizumab; IPI, ipilimumab; NIV, nivolumab; PAZ, pazopanib (Votrient, Novartis); PD-1, programmed death 1; PEM, pembrolizumab; SUN, sunitinib.

[a]Subgroup of patients with metastatic renal cell carcinoma.

Source: http://www.clinicaltrials.gov. Accessed November 2015.

Researchers also need to determine the optimal treatment sequence, including the possibility of using PD-1/PD-L1 inhibitors before tyrosine kinase inhibitors. A crossover trial in patients with *BRAF*-mutated melanoma is comparing ipilimumab plus nivolumab with a BRAF inhibitor plus a MEK inhibitor. A similar type of trial might be used in kidney cancer, bearing in mind that RECORD-3, which compared everolimus with sunitinib (Sutent, Pfizer), struggled with issues related to accrual and patient crossover (this trial was published by Motzer and colleagues in the *Journal of Clinical Oncology* in 2014). "We will need to consider these novel designs if we're going to try to answer these sequence questions," said Dr McDermott.

Future trials will probably need to look at landmark endpoints, specifically overall survival. This may be difficult given that many immunotherapy agents are available outside of clinical trials, but not impossible. One phase 3 trial that Dr McDermott and his colleagues published in the *Journal of Clinical Oncology* in 2005 compared high-dose interleukin 2 (IL-2) vs IL-2 plus interferon, using the established endpoint of 3-year progression-free survival (PFS). "I think we should consider bringing back this landmark PFS endpoint as a way of trying to look early at endpoints that might translate into improvements in the tail of the curve." The goal, he said, should not be simply to improve overall survival. Instead, the goal should be to improve treatment-free survival, which means considering novel endpoints. He said it will be necessary to explain the validity of these endpoints to the US Food and Drug Administration.

The possibility exists that checkpoint inhibitors might be more active before surgery than afterward because T cells that recognize the tumor are still present prior to surgery. A phase 3 trial of nivolumab before surgery vs surgery alone has just received National Cancer Institute Genitourinary Cancers Steering Committee approval and should begin next year with Dr Lauren Harshman as the principal investigator.

Dr McDermott concluded that by formulating studies to address these key questions, "we can improve the application of immunotherapy for the right patients, and improve overall survival and treatment-free survival."

Suggested Readings

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.

McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23(1):133-141.

Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2014;32(25):2765-2772.

Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.

Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24(16):2505-2512.