KidneyCancer.com

KIDNEY CANCER NEWS

Brought to You in Conjunction With the Kidney Cancer Association

The Future of Immunotherapy as Perioperative Therapy in Renal Cell Carcinoma

From the International Kidney Cancer Symposium
November 5-6, 2016, Miami, Florida

Researchers are launching 2 new studies of checkpoint inhibitors as perioperative treatment for patients with nonmetastatic renal cell carcinoma (RCC), according to a series of presentations at the 2016 International Kidney Cancer Symposium. The presentations addressed recent studies of adjuvant therapy with vascular endothelial growth factor (VEGF) inhibitors and described planned perioperative trials with nivolumab (Opdivo, Bristol-Myers Squibb), which is approved for patients with metastatic RCC, and atezolizumab (Tecentriq, Genentech), which is approved for patients with metastatic urothelial carcinoma.

Lessons From Trials With VEGF Inhibitors

The current standard of care for patients with nonmetastatic RCC who have undergone surgery is observation, said Naomi B. Haas, MD, of the Perelman School of Medicine at the University of Pennsylvania, in Philadelphia. However, approximately 1 in 5 patients experience a recurrence, which leaves open a potential role for adjuvant therapy in high-risk patients.

Several trials are looking at the use of VEGF inhibitors and other tyrosine kinase inhibitors as adjuvant treatment in these patients, and 2 of the trials have reported results. S-TRAC (Sunitinib Treatment of Renal Adjuvant Cancer), which included 615 high-risk patients with clear cell RCC, found that adjuvant sunitinib (Sutent, Pfizer) improved progression-free survival compared with placebo.[1] Grade 3 or 4 adverse events were common, affecting 61% of those in the sunitinib group vs 19% of those in the placebo group.

In contrast, ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma), which included 1943 patients with either non–clear cell or clear cell histology, did not find that sunitinib or sorafenib (Nexavar, Bayer) improved 5-year disease-free survival or overall survival compared with placebo.[2] Approximately two-thirds of patients in the sunitinib and sorafenib groups experienced grade 3 or 4 adverse events.

Dr Haas pointed to several differences between the trials that might explain the difference in results. For example, S-TRAC included only patients with clear cell histology, whereas ASSURE included both patients with non–clear cell histology and patients with clear cell histology. Another difference is that S-TRAC conducted an independent central review to determine relapse, whereas ASSURE did not. The ASSURE population also included lower-risk disease in addition to high-risk disease.

Dr Haas recommended that future studies of adjuvant therapy use independent central review; the results of S-TRAC would not have been statistically significant on the basis of investigator review. She also proposed that the evaluation of adjuvant agents begin with small, single-arm trials that look only at patients within a specific risk category. She cautioned, however, that the toxicity of VEGF inhibitors makes it difficult to justify their use in low-risk patients. Further study is needed to learn which patients are most likely to experience a recurrence, regardless of tumor size. Dr Haas also recommended that future trials include overall survival as a coprimary endpoint, stating that "I do think cure is a laudable goal for adjuvant therapy."

Nivolumab in the Perioperative Setting

Lauren C. Harshman, MD, of the Dana-Farber Cancer Institute, in Boston, Massachusetts, is the principal investigator of the phase 3 PROSPER RCC trial (A Phase 3 Randomized Study Comparing Perioperative Nivolumab vs Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy), which is examining whether nivolumab is useful as a perioperative agent in nonmetastatic RCC. In addition to its proven efficacy in the metastatic setting, she pointed out that the toxicity profile of nivolumab is better than those of VEGF

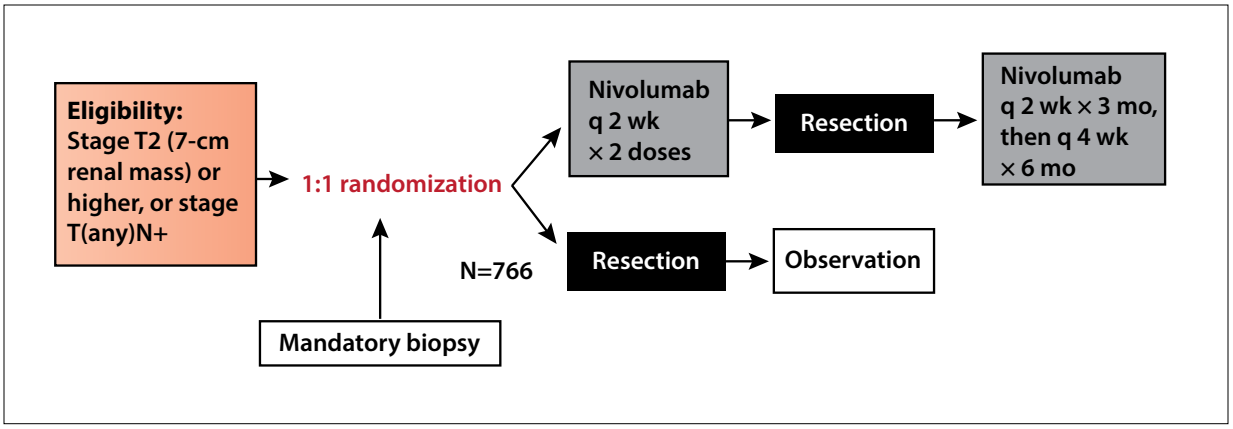

Figure 1. Design of PROSPER RCC (A Phase 3 Randomized Study Comparing Perioperative Nivolumab vs Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy).

mo, months; q, every; wk, weeks.

inhibitors or mammalian target of rapamycin (mTOR) inhibitors, making it an appealing agent for this use.

The logic behind using nivolumab in the neoadjuvant setting is to expand the T cells in the primary tumor, tumor microenvironment, and tumor-draining lymph nodes, allowing them to travel to distant sites and potentially eradicate micrometastatic disease. The agent might even have a long-term effect on T cells through the formation of memory cells. Because nephrectomy removes the majority of tumor antigen, many effector cells, and many cytokines, using nivolumab might induce a less potent response after surgery than before surgery. To increase the chances of efficacy, the protocol calls for nivolumab to be administered twice before surgery and for 9 months after surgery. "We believe that you need the trifecta" of presurgical priming, resection, and continued adjuvant programmed death 1 blockade, Dr Harshman said.

> "We'll also be looking at safety, feasibility, and tolerability, and we have incorporated important quality-of-life metrics."
> —Lauren C. Harshman, MD

Dr Harshman explained that the study will enroll approximately 766 patients whose RCC is stage T2 or higher or who show clinical signs of node-positive disease (Figure 1). All histologic types will be permitted, although no more than 15% of participants will have non–clear cell histology. Biopsy is mandated prior to randomization to confirm the diagnosis of RCC but will also provide important tissue for analysis of potential biomarkers.

After stratification by stage, node status, and histology, patients will be randomly assigned to nivolumab or standard care. Those in the nivolumab group will receive 2 doses of nivolumab before resection. They will also receive nivolumab for approximately 9 months after resection, every 2 weeks for the first 3 months, then every 4 weeks for an additional 6 months to "enhance patient quality of life." Those in the standard care group will undergo resection followed by observation. The lack of a placebo arm was based on much feedback from the urologic oncology community with respect to the ethical considerations of submitting patients to intravenous line placement and placebo drug administration every 2 to 4 weeks for nearly a year, when they may be cured by surgery alone. The primary endpoint will be recurrence-free survival, and a key secondary endpoint will be overall survival at 5 years. "We'll also be looking at safety, feasibility, and tolerability, and we have incorporated important quality-of-life metrics."

The required pretreatment biopsies and neoadjuvant approach make this study uniquely suited for biomarker discovery. The study will investigate questions such as whether tumor inflammation or preexisting intratumoral T cells predict nivolumab benefit, whether priming with nivolumab increases the trafficking and proliferation of CD8-positive T cells within tumors, and whether programmed death ligand 1 (PD-L1) expression adaptively increases after nivolumab administration.

The trial already has received approval from the US

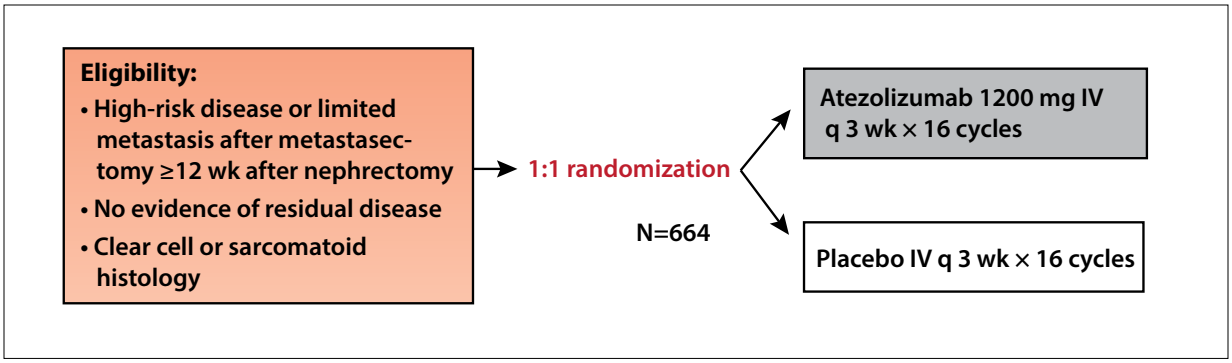

Figure 2. Design of trial to characterize the efficacy of atezolizumab vs placebo in patients with high-risk renal cell carcinoma after nephrectomy or complete metastasectomy.

IV, intravenous; q, every; wk, weeks.

Food and Drug Administration (FDA) and the Consortium of Independent Review Boards (CIRB) and will begin as soon as it has been approved by the Cancer Therapy Evaluation Program (CTEP). Dr Harshman encouraged her colleagues in the United States, Canada, and selected countries in Europe and South America to join the PROSPER RCC team and enroll eligible patients in the trial.

Atezolizumab in the Postoperative Setting

Sumanta K. Pal, MD, of the City of Hope Comprehensive Cancer Center, in Duarte, California, presented the design of a planned study of adjuvant atezolizumab called IMmotion 010.

The study will enroll 664 patients with high-risk clear cell or sarcomatoid RCC who have undergone surgery and for whom a biopsy sample is available for PD-L1 assessment (Figure 2). High-risk RCC is defined as follows: stage T2, grade 4 disease; stage T3a, grade 3 or 4 disease; or stage T3b or higher, disease of any grade (including node-positive disease). Selected patients with fully resected metastatic disease also will be eligible.

Participants will be stratified by disease stage, PD-L1 status, and geographic region. They will then be randomly assigned in a ratio of 1:1 to either 1200 mg of atezolizumab or placebo every 3 weeks for 16 cycles. The primary endpoint will be investigator-assessed disease-free survival, and the secondary endpoint will be overall survival.

"We're hoping to make this a very correlative-rich clinical trial," said Dr Pal. To that end, the researchers will be evaluating PD-L1 expression, T-effector signatures in archival tumor tissues, quality of life, and surgical complication rates.

Dr Pal said that one strength of the atezolizumab study is that it has a placebo arm, in which an inactive treatment will be administered intravenously. The control group in the PROSPER RCC trial, by contrast, will undergo observation. He said that patients in the observation arm may eventually enroll in a second study and receive a VEGF inhibitor.

> "We're hoping to make this a very correlative-rich clinical trial."
> —Sumanta K. Pal, MD

Another limitation of PROSPER RCC is that it does not include an arm for nivolumab without neoadjuvant therapy. "We may be left asking, what is the true benefit of neoadjuvant treatment?" said Dr Pal. Even if neoadjuvant treatment should prove to be effective, physicians will need to strive to ensure that it is used. For example, one study found that even though level 1 evidence supports the use of neoadjuvant treatment in bladder cancer, only one-third of patients in community-based practices were receiving it several years ago.[3] "It remains to be seen in the context of renal cell carcinoma—especially once this data is out there for clinical utilization—whether or not urologists and medical oncologists will collaborate." A study of Society of Urologic Oncology members found that urologists were reluctant to use neoadjuvant treatment in bladder cancer for reasons that included prolonged diagnosis and referral, marginal benefit vs adjuvant therapy, and possible delay in surgery.[4]

Another factor in trials of neoadjuvant therapy for RCC is that not all patients who receive systemic therapy may go on to surgery. In a now-completed study of neoadjuvant sunitinib for RCC (Sunitinib in Treating Patients With Kidney Cancer That Cannot Be Removed by Surgery), only 43% of patients went on to surgery as planned.[5] Finally, the use of neoadjuvant therapy requires referral to a medical oncologist before surgery—something that often does not take place.

Discussion

In a discussion of PROSPER RCC, Mohamad E. Allaf, MD, of the Johns Hopkins Hospital, in Baltimore, Maryland, said that results with adjuvant treatment have been disappointing but that sound preclinical data support the efficacy of neoadjuvant dosing. "I believe the answer here is to support the PROSPER trial," he said.

Robert G. Uzzo, MD, of the Fox Chase Cancer Center, in Philadelphia, Pennsylvania, pointed out that community practitioners may have some difficulty enrolling their patients in PROSPER because of the need for preoperative biopsy; the need to delay surgery for neoadjuvant therapy; the possibility of preoperative lymph node pseudoprogression, which complicates the question of whether lymph node dissection is required; and toxicities that may include immune mediated adverse events or even alterations in creatinine. Patients may be reluctant to enroll in the IMmotion atezolizumab trial because of the placebo design.

"It's a great privilege to be able to have 2 trials that are tremendously important," said Dr Uzzo. "I'd like to advocate that people consider both trials, but recognize that there are practical limitations to multiple trials in this space that may make one trial more easy to accrue to than then other, especially in the community."

References

1. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med.* 2016;375(23):2246-2254.

2. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet.* 2016;387(10032):2008-2016.

3. Bergerot P, Sonpavde G, Nelson R, et al. Trends in neoadjuvant chemotherapy (NAC) use for muscle-invasive bladder cancer (MIBC): an updated report using the National Cancer Database (NCDB) [ASCO abstract 4540]. *J Clin Oncol* 2016;34;(15)(suppl).

4. Cowan NG, Chen Y, Downs TM, et al. Neoadjuvant chemotherapy use in bladder cancer: a survey of current practice and opinions. *Adv Urol.* 2014;2014:746298.

5. Rini BI, Garcia J, Elson P, et al. The effect of sunitinib on primary renal cell carcinoma and facilitation of subsequent surgery. *J Urol.* 2012;187(5):1548-1554.