

KIDNEY CANCER UPDATE

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Current and Emerging First-Line Systemic Therapies in Clear Cell Renal Cell Carcinoma



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H&O Which patients with clear cell renal cell carcinoma (RCC) are candidates for systemic therapy?

BR All patients with clear cell RCC are potential candidates for systemic therapy, although some of them do not need treatment right away. The biology of RCC is extremely variable, and I would estimate that 10% to 15% of patients can likely be observed safely before starting systemic therapy. Most, however, will require immediate treatment.

H&O Which agents are used for first-line systemic therapy in these patients?

BR The 3 drug classes that are available for treating these patients are vascular endothelial growth factor (VEGF) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and immunotherapy agents.

The VEGF inhibitors that are used in clear cell RCC are sunitinib (Sutent, Pfizer), pazopanib (Votrient, Novartis), bevacizumab (Avastin, Genentech), axitinib (Inlyta, Pfizer), and cabozantinib (Cabometyx, Exelixis). Bevacizumab is administered in combination with interferon. The one mTOR inhibitor that has been studied for use in first-line treatment is temsirolimus (Torisel, Pfizer); it is given less often than VEGF inhibitors because weekly intravenous infusions are required, and it has been evaluated only in poor-risk patients. Immunotherapy historically consisted of interleukin 2 (IL-2), which can achieve a cure in 5% to 10% of patients. Now, great interest is being shown in checkpoint inhibitors to treat RCC, although none have been approved for frontline use.

H&O How safe and effective are these agents?

BR VEGF inhibitors, which are primarily what we use now, are moderately effective. They have their share of toxicities, but we can generally find a dose and schedule that will work for each patient. We also have become better over the years at managing adverse effects, and these agents rarely lead to treatment-related deaths. Nearly all patients can take a VEGF inhibitor. They do control disease, for less than a year on average, but they don't cure it—disease will eventually progress in all patients.

Immunotherapy agents are also very well tolerated, and we are just starting to learn about the effectiveness of the checkpoint inhibitors in RCC. We know that checkpoint inhibitors are not as well tolerated in combination as they are as single agents. What is most exciting about the checkpoint inhibitors is that they have the potential to offer more than just disease control. I expect that checkpoint inhibitors will be able to cure the disease of at least some patients, especially when given in combination. Several large combination trials have completed accrual, and results are just beginning to be reported.

H&O How many months of overall survival (OS) does systemic treatment add?

BR It's hard to say. Patients in these trials usually eventually receive more than one agent, so it's not a pure comparison. Median survival in kidney cancer was approximately 12 to 14 months before VEGF agents and was closer to 26 to 28 months in the initial trials of sunitinib—so these agents appear to have doubled survival time. Median survival in the CheckMate 214 trial (Nivolumab Combined With

Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma), which combined ipilimumab (Yervoy, Bristol-Myers Squibb) with nivolumab (Opdivo, Bristol-Myers Squibb), has not yet been reached, but it will likely be more than 3 years. So the introduction of new agents has increased survival from 1 year to 2 years, and we expect to see survival reach more than 3 years.

H&O Could you talk more about the results of CheckMate 214?

BR CheckMate 214 is a phase 3, open-label trial that Dr Bernard Escudier presented at the European Society for Medical Oncology (ESMO) annual meeting in 2017. For the study, 1096 patients with previously untreated advanced or metastatic RCC were randomly assigned either to nivolumab plus ipilimumab or to sunitinib. After 17.5 months of follow-up, the trial showed an OS advantage for nivolumab plus ipilimumab compared with sunitinib—the median OS times were not reached and 32.9 months, respectively (hazard ratio [HR], 0.68; 99.8% CI, 0.49-0.95; $P=.0003$). The confirmed objective response rate (ORR) across the entire group also was better with nivolumab/ipilimumab than with sunitinib (39% vs 32%; $P=.0191$), and the complete response rates were 9% and 1%, respectively. Overall, nivolumab/ipilimumab did not improve progression-free survival (PFS) compared with sunitinib, but a trend toward improved median PFS with nivolumab/ipilimumab was observed among patients in the intermediate- and poor-risk groups. Patients with elevated expression of programmed death ligand 1 (PD-L1) also had significantly better PFS with the immunotherapy combination than with sunitinib. Adverse events leading to discontinuation occurred in 22% of patients taking nivolumab/ipilimumab compared with 12% of those taking sunitinib. These data are impressive, and pending US Food and Drug Administration (FDA) approval, I expect this combination to become a standard of care. CheckMate 214 is the first trial of combination immunotherapy in RCC to release data; additional trials are being conducted that are expected to transform the field.

H&O Which of the VEGF inhibitors do you use?

BR Right now, I use sunitinib. Cabozantinib was recently approved for first-line use on the basis of results of the CABOSUN study (Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk), which found advantages in PFS with cabozantinib; however, my take is that cabozantinib appeared to be more effective than sunitinib in CABOSUN because sunitinib

Table. Ongoing Phase 3 Studies of First-Line Immunotherapy in Advanced Renal Cell Carcinoma

Study	Groups	Identifier
CheckMate 214	Nivolumab/ ipilimumab vs sunitinib	NCT02231749
IMmotion151	Atezolizumab/ bevacizumab vs sunitinib	NCT02420821
KEYNOTE-426	Pembrolizumab/ axitinib vs sunitinib	NCT02853331
JAVELIN Renal 101	Avelumab/axitinib vs sunitinib	NCT02684006

underperformed. In any case, the decision about VEGF inhibitors will not matter for much longer—I expect immunotherapy to be the treatment of choice soon.

H&O How do physicians decide which systemic agent to use?

BR The decision is certainly based on data, but because we do not have perfect comparative data, we end up deciding mostly on the basis of familiarity—what we have used in trials or in our practice. Rather than saying there is one best drug, it is important for each physician to become familiar with toxicity and side effect management for a specific agent to optimize delivery of that drug.

H&O Do we know whether certain agents are better for specific subgroups?

BR Certain drugs probably are, but we don't know that at this point. As I mentioned earlier, nivolumab/ipilimumab seems to be more effective in intermediate- and poor-risk RCC, at least in part because of greater expression of PD-L1. We still need to learn much more about how to apply these agents most effectively.

H&O Could you discuss the ongoing trials that are looking at systemic agents for RCC?

BR Several ongoing phase 3 trials are looking at combination therapy with either 2 immunotherapy agents or immunotherapy plus a VEGF inhibitor (Table). The comparison in all cases is a standard-of-care treatment, sunitinib. The IMmotion151 study (A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma; NCT02420821) is looking at

atezolizumab (Tecentriq, Genentech) plus bevacizumab; KEYNOTE-426 (Study to Evaluate the Efficacy and Safety of Pembrolizumab in Combination With Axitinib Versus Sunitinib Monotherapy in Participants With Renal Cell Carcinoma; NCT02853331) is looking at axitinib plus pembrolizumab (Keytruda, Merck); and the JAVELIN Renal 101 study (A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer; NCT02684006) is looking at axitinib plus avelumab (Bavencio, EMD Serono/Pfizer). The results of these studies are pending; only the results of CheckMate 214 have been presented.

H&O What else should physicians know about the first-line treatment of RCC?

BR Everything is about to change dramatically. Right now, we are in a middle period in which new data are beginning to come out. Community oncologists will need to pay attention and become educated over the next 1 to 2 years because I believe the approach to metastatic RCC soon will be completely altered. Everything we've been doing for the last 10 years is likely to become outdated.

The results from CheckMate 214 are emblematic of the wave of data that is about to come, and new combinations are going to change the field.

Disclosure

Dr Rini has served as a consultant or advisor to Pfizer, Merck, and Corvus, and has received research funding from Pfizer, Merck, Bristol-Myers Squibb, Peloton, and Aveo.

Suggested Readings

ClinicalTrials.gov. A study of atezolizumab in combination with bevacizumab versus sunitinib in participants with untreated advanced renal cell carcinoma [IMmotion151]. <https://clinicaltrials.gov/ct2/show/NCT02420821>. Identifier: NCT02420821. Accessed January 23, 2018.

ClinicalTrials.gov. A study of avelumab with axitinib versus sunitinib in advanced renal cell cancer (JAVELIN Renal 101). <https://clinicaltrials.gov/ct2/show/NCT02684006>. Identifier: NCT02684006. Accessed January 23, 2018.

ClinicalTrials.gov. Study to evaluate the efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy in participants with renal cell carcinoma (MK-3475-426/KEYNOTE-426). <https://clinicaltrials.gov/ct2/show/NCT02853331>. Identifier: NCT02853331. Accessed January 23, 2018.

Escudier B, Tannir NM, McDermott DF, et al. CheckMate 214: efficacy and safety of nivolumab + ipilimumab (N+I) *v* sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups [ESMO abstract LBA5]. *Ann Oncol*. 2017;28(suppl 5).