

# KIDNEY CANCER UPDATE

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## Choosing the Best Approach for Patients With Favorable-Risk Metastatic Renal Cell Carcinoma

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Oncologists treating patients with favorable-risk metastatic renal cell carcinoma (RCC) have multiple choices, ranging from active surveillance to monotherapy to combination therapy. So which approach is best? A series of presentations at the meeting made the case for each of these options.

### The Argument for Active Surveillance

Active surveillance is used in selected patients with RCC to avoid the toxicity of immediate systemic therapy but still provide systemic therapy at a later date when needed, said Dr Michael R. Harrison, an associate professor of medicine at the Duke Cancer Institute in Durham, North Carolina. “There’s a real danger with all of the new therapies available that more patients will be exposed to toxicity, including financial toxicity, without substantive benefit,” he said.

Although the National Comprehensive Cancer Network guidelines for kidney cancer list active surveillance as “useful in certain circumstances” when a patient has favorable-risk metastatic disease, they do not specify what those circumstances are. Determining the circumstances is especially difficult, given the nature of clinical trials.

One of the shortcomings of clinical trials is that the patients who are enrolled are fundamentally different from real-world patients, Dr Harrison noted. Therefore, the results from trials of systemic therapy—including CheckMate 214 (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma), KEYNOTE-426 (Study to Evaluate the Efficacy and Safety of Pembrolizumab in Combination With Axitinib Versus Sunitinib Monotherapy in Participants With Renal Cell Carcinoma), and COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma)—do not necessarily apply to all patients in the designated population. For example, RCC

trials routinely factor in International Metastatic RCC Database Consortium (IMDC) risk categories, which are easily measurable, but rarely factor in the speed of disease spread and the volume of disease. However, these variables may be factored into physician decision-making when

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choosing whether to use systemic therapy, and which systemic therapy to use.

The same phenomenon occurs in trials of patients on active surveillance. For example, a phase 2 study of active surveillance by Rini and colleagues enrolled 48 patients with metastatic RCC who were accrued at 5 centers over 5 years.<sup>1</sup> The researchers specifically targeted patients who were asymptomatic, had measurable or evaluable disease, and had their first documentation of metastases within 12 months of study registration. Surprisingly, the majority of patients (75%) had intermediate-risk disease and 23% had favorable-risk disease according to IMDC risk factors. The researchers found that the median time on active surveillance was 15 months, and the median overall survival (OS) was 22 months. Multivariable analysis revealed that the only factors independently associated with a favorable prognosis were the involvement of 2 or fewer organs and the presence of 0 or 1 IMDC risk factor.

Data from the prospective observational Metastatic Renal Cell Carcinoma (MaRCC) Registry study

also support the use of active surveillance in metastatic RCC.<sup>2</sup> The study included patients from 20 academic sites and 26 community sites who were accrued from March 2014 to December 2016. Of 504 patients, 143 received active surveillance. The majority of these patients (60%) had favorable-risk disease, and 38% had intermediate-risk disease.

The researchers found that the median time on surveillance was 54 months. OS from the time of metastatic diagnosis was not reached in the active surveillance population vs 30 months in the systemic therapy population.

Although few data exist to guide physicians regarding the appropriate selection of patients for active surveillance vs systemic therapy, said Dr Harrison, the results of this study suggest that “clinicians were able to select patients for active surveillance with very good results based on their clinical judgment and/or their intuitive sense.” Factors that may play a role in this decision process include IMDC risk, burden of disease, and pace of disease spread.

Dr Harrison cautioned against using the results of trials of systemic therapy to conclude that all patients must be treated; instead, clinicians should step back and ask whether a patient even needs systemic therapy.

He also recommended that prospective observational studies be undertaken to evaluate active surveillance in the context of systemic therapy. A prospective observational study with multiple sponsors, called ODYSSEY, is in the planning stages; it will be accruing up to 800 patients, of whom 20% will have been selected for active surveillance.

### The Merits of Monotherapy

“Single-agent VEGFR TKI is the best approach for favorable-risk metastatic renal cancer,” said Dr Walter M. Stadler, a professor of medicine and surgery at University of Chicago Medicine in Chicago, Illinois. “I think it should be intuitively obvious to the most casual observer,” he added with a smile.

Dr Stadler began his talk by pointing to data from phase 3 trials showing that vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) are able to improve OS in patients with favorable-risk metastatic RCC. For example, in a study published by Manola and colleagues in 2011, median OS was significantly longer with sunitinib than with interferon alfa, at 26.4 vs 21.8 months, respectively.<sup>3</sup> This result showed that sunitinib was better than nothing, he said, given that interferon alfa is “essentially a toxic placebo.” He pointed out that the population in this study was highly representative because it included patients from both academic and community sites and patients who were not part of clinical trials.

Dr Stadler said that the difference among VEGFR TKIs is minimal, so oncologists do not need to be

especially concerned about which one they choose. A 2013 trial in the *New England Journal of Medicine* by Motzer and colleagues found no difference between OS in second-line patients treated with pazopanib (Votrient, Novartis) and OS in those treated with sunitinib (Sutent, Pfizer),<sup>4</sup> and a 2013 trial in *Lancet Oncology* by Motzer and colleagues found no difference between OS in patients treated with axitinib (Inlyta, Pfizer) and OS in those treated with sorafenib (Nexavar, Bayer).<sup>5</sup>

Dr Stadler also rejected the idea that combination treatment is better than treatment with a single VEGFR TKI. In the CheckMate 214 study, published by Motzer and colleagues in *Lancet Oncology* in 2019,<sup>6</sup> OS was better with the combination of ipilimumab (Yervoy, Bristol-Myers Squibb) and nivolumab (Opdivo, Bristol-Myers Squibb) than with sunitinib alone as first-line treatment in intermediate- and poor-risk patients. However, as seen in the 2018 publication of this study in the *New England Journal of Medicine*, improvement with the combination did not extend to favorable-risk patients.<sup>7</sup>

Regarding a KEYNOTE-426 study of pembrolizumab (Keytruda, Merck) and axitinib vs sunitinib, which was presented by Dr Brian Rini at the 2019 annual meeting of the American Society of Clinical Oncology (ASCO), survival did not differ between the 2 groups among all patients and among the patients with a favorable prognosis.<sup>8</sup> Perhaps this interpretation will change for the patients with a favorable prognosis as the data mature.

Another important fact to consider in choosing a treatment for these patients is that combination immunotherapy carries risks. In a presentation of CheckMate 214 by Dr Bernard Escudier at the 2017 European Society for Medical Oncology (ESMO) annual meeting, more of the patients who received nivolumab plus ipilimumab than of those who received sunitinib discontinued treatment because of adverse events: 22 of 547 vs 12 of 535, respectively.<sup>9</sup> Furthermore, the number of deaths was higher in the nivolumab/ipilimumab group than in the sunitinib group: 7 vs 4, respectively. “That’s not a lot, but that’s almost twice as many deaths,” he said.

Furthermore, 60% of the patients treated with the combination required systemic corticosteroids to manage the toxicity of treatment, and corticosteroids carry additional risks. “There’s an old saying,” said Dr Stadler, that “you give a patient high-dose steroids and they smile all the way down to the morgue.”

### The Benefits of Combination Therapy

Combination therapy is a well-supported treatment in patients with favorable-risk metastatic RCC, said Dr André P. Fay, a professor of medicine at PUCRS School of Medicine in Porto Alegre, Brazil. The guidelines of Dr Bernard

Escudier and colleagues for treating patients with clear cell RCC,<sup>10</sup> updated by ESMO online on February 7, 2020,<sup>11</sup> recommend the use of combination therapy with pembrolizumab and axitinib in favorable-risk patients. Alternatives to this regimen are sunitinib and pazopanib. Dr Fay pointed out that VEGF-targeted therapy produces limited responses in patients with metastatic RCC. The overall response rate in pivotal clinical studies is just 30%, and 25% of patients have progression of disease as the best response. Complete responses and durable responses are “very rare,” he said. Among those who do respond to VEGFR-targeted therapy, progression-free survival (PFS) is rarely longer than 12 months.

The treatment of metastatic RCC has recently been changed as the result of 3 studies in which combination immunotherapy—either dual immunotherapy or immunotherapy plus a VEGF inhibitor—was compared with sunitinib. CheckMate 214 used nivolumab and ipilimumab, KEYNOTE-426 used pembrolizumab and axitinib, and Javelin Renal 101 (A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer) used avelumab (Bavencio, EMD Serono/Pfizer) and axitinib. The 3 trials differed in terms of primary endpoints, risk categories of the enrolled population, and programmed death ligand 1 (PD-L1) expression, which may explain some of the differences in the results of these studies.

For example, in CheckMate 214, combination immunotherapy clearly produced an OS benefit in the intermediate- and poor-risk populations, but not in the favorable-risk population.<sup>7</sup> Although sunitinib did not produce better survival than nivolumab/ipilimumab in favorable-risk patients, initial results did show a better overall response rate (52% vs 29%, respectively;  $P=.0002$ ) and PFS (15.3 vs 25.1 months, respectively;  $P<.0001$ ) with sunitinib than with nivolumab/ipilimumab in this patient group. These differences in overall response rate and PFS were smaller at 30-month follow-up, however: 50% vs 39%, respectively, for overall response rate and 19.9 vs 13.0 months, respectively, for PFS, as reported by Dr Nizar Tannir at the 2019 ASCO Genitourinary Cancers Symposium.<sup>12</sup> Dr Fay pointed out that sunitinib was “overperforming” in this study.

Another important finding of CheckMate 214 is the high rate of complete responses (13% in favorable-risk disease) with the use of dual immunotherapy in favorable-risk patients. Dr Fay pointed out that objective responses to immunotherapy have been associated with improved OS in patients with RCC or other malignancies.

In KEYNOTE-426, patients in the favorable-risk group had a better overall response rate with pembrolizumab/axitinib (66.7%) than with sunitinib (49.6%).<sup>13</sup> In addition, the median PFS was longer with pembrolizumab/axitinib (17.7 months) than with sunitinib (12.7 months)

in favorable-risk patients. The data on OS were not sufficiently mature for conclusions to be drawn.

The results of KEYNOTE-426 are supported by data from Javelin Renal 101, in which patients were positive for PD-L1.<sup>14</sup> In this study, response rates were better and median PFS was longer in the favorable-risk patients taking avelumab plus axitinib than in those taking sunitinib. Dr Fay said that combination immunotherapy is “the standard of care” in favorable-risk patients.

Regarding real-world data, Dr Daniel Heng recently published data based on IMDC risk that compared dual immunotherapy and immunotherapy/VEGF combination in patients undergoing first-line treatment.<sup>15</sup> This group reported that although PFS and OS were similar with these 2 strategies, the use of first-line immunotherapy/VEGF may impede the response rate with subsequent VEGF therapy. A limitation of this study is that it did not look specifically at the favorable-risk subgroup.

Although most of the data regarding the treatment of RCC deal with clear cell RCC, Dr Fay emphasized that patients whose RCC has a sarcomatoid component require an immunotherapy-based regimen. Of patients whose RCC has a sarcomatoid component, 7% to 16% are classified as having a favorable prognosis and therefore require combination therapy.

As for toxicity, Dr Fay pointed out that many oncologists assume that combination therapy is more likely than single-agent therapy to produce toxicity. “However, when we see data from patient-reported outcomes in CheckMate 214, we see that we have a lower risk for clinical deterioration” in patients who receive combination therapy vs sunitinib.<sup>16</sup>

Another concern is financial toxicity, which might become less of a problem if patients were able to discontinue immunotherapy once the strategy proved effective. Oncologists do not yet understand when patients can safely stop taking these agents. Dr Fay called for better ways to define prognosis in RCC, and to “develop biomarkers and genomic signatures that will help us to select the group of patients that we could de-intensify treatment and not use a more aggressive strategy.”

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## Commentary

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The optimal management strategy for patients who have metastatic RCC with IMDC favorable-risk features is a matter of active clinical discussion, as was highlighted recently at the Kidney Cancer Association's 18th International Kidney Cancer Symposium. For patients with favorable-risk metastatic RCCs, which are slow-growing and angiogenesis-dependent, clinical management options include surveillance imaging alone without treatment, treatment targeting the VEGF pathway, dual immunotherapy

with ipilimumab/nivolumab, and combinations of immunotherapy plus a VEGF inhibitor. Because of the varying clinical outcomes of these management options, treatment decisions ultimately depend upon patient preferences and oncologist recommendations.

Often, when a patient has favorable-risk metastatic RCC, the decision to initiate treatment is made after a discussion of what can be expected from surveillance alone. Oncologists and patients generally evaluate the rate of tumor growth over time, and tumor proximity to critical life-sustaining organs. As Dr Harrison outlined in his part of the debate, undertaking surveillance without treatment is in itself an active decision. Surveillance programs to monitor tumor growth are often the best decision for patients who wish to avoid treatment-based side effects and who have relatively small or asymptomatic tumors in non-life-threatening locations.

The patients who decide to start treatment often have different motivations and goals. For patients who are young and motivated to obtain a complete response, Dr Stadler highlighted the results of CheckMate 214, which showed the highest complete response rate with the combination of ipilimumab and nivolumab, at 13% among those with favorable-risk disease. The patients in whom complete responses develop are also the ones who have the most durable responses. For patients who wish to pursue a complete response, ipilimumab/nivolumab remains a viable option.

Immunotherapy/VEGF inhibitor combinations are the newest type of treatment to gain FDA approval, with efficacy demonstrated across metastatic RCCs that have favorable, intermediate, or poor IMDC risk characteristics. In the subset of patients with favorable-risk tumors, Dr Fay emphasized that improvements in both disease control rates and PFS were achieved with pembrolizumab/axitinib in the KEYNOTE-426 trial, and similarly with avelumab/axitinib in the Javelin Renal 101 trial. The initial OS endpoint at the early cutoff for KEYNOTE-426 was statistically significant across risk subtypes, but time and further maturation of the data will show the actual OS benefit of the pembrolizumab/axitinib combination among patients with favorable-risk metastatic RCC. It is not yet clear to what extent the combination will expose patients to further side effects.

It remains critical to identify the goals of treatment in discussions of management strategies with patients who have favorable-risk metastatic RCC. As the options for management strategies increase, any patient with this category of disease should have a straightforward discussion with his or her oncologist to clarify which option is optimal, on the basis of the patient's own treatment goals.