Incorporating New Systemic Therapies in Kidney Cancer Treatment

Presented by Eric Jonasch, MD

Abstract

In 2017, pazopanib and sunitinib remain the mainstays of frontline therapy for advanced renal cell carcinoma. Independent review of frontline cabozantinib therapy may alter standard of care for patients at intermediate and poor risk. Multiple agents show a survival advantage in the second-line setting, including nivolumab, cabozantinib, and combination lenvatinib and everolimus. Selection of subsequent therapy will depend on patient disease status, comorbidities, and resource availability.

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Over the past decade, a number of new therapies have been approved for the treatment of renal cell carcinoma (RCC; Figure 1). Most treatments are driven by clear cell histology, which represents 70% to 75% of all RCCs. Eric Jonasch, MD, Professor, Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, and Vice Chair of the NCCN Guidelines Panel, reviewed the state of the art and new systemic therapies incorporated into the 2017 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer.

Adjuvant Therapy

Three trials have been conducted in the adjuvant setting, 2 of which (ASSURE and PROTECT) showed negative results for adjuvant sunitinib, sorafenib, and pazopanib. A third trial, S-TRAC, showed improved relapse-free (RFS) survival with adjuvant sunitinib versus placebo, but no improvement in overall survival (OS). Thus, the standard of care has not been altered for adjuvant treatment of kidney cancer, Dr. Jonasch stated.

ASSURE randomized 1,943 intermediate- and high-risk patients to receive adjuvant sunitinib, sorafenib, or placebo for 1 year. No difference in disease-free survival was seen among the 3 arms, and high rates of toxicity for the 2 active treatments led to dose reductions and treatment discontinuation.¹

PROTECT randomized 1,500 patients to either adjuvant pazopanib or placebo for 1 year (ClinicalTrials.gov identifier: NCT01235962). Again, the study showed no difference in RFS between the arms.

S-TRAC randomized 720 high-risk patients to 1 year of either adjuvant sunitinib or placebo. This study showed improved RFS for sunitinib, with a median of 6.8 versus 5.6 years for placebo. No survival advantage was seen with adjuvant sunitinib.²

Two additional trials of adjuvant therapy are ongoing: SORCE, which is comparing 3 years of adjuvant sorafenib versus 1 year of sorafenib versus placebo in 1,656 patients; and EVEREST, comparing 1 year of everolimus versus 1 year of placebo in 1,218 patients. The primary end point of both trials is RFS.

“No VEGF [vascular endothelial growth factor] inhibitor in the adjuvant setting has improved OS. There are still no FDA-approved agents for adjuvant therapy, and no drug shows a benefit in high-risk patients. If ongoing follow-up of S-TRAC shows a survival benefit, the situation may change. There are ongoing trials in the adjuvant setting of immune checkpoint inhibitors, but we don’t have that data yet. My fingers are crossed. Time will tell,” Dr. Jonasch said

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Setting		Approved Agents	Alternative
First-line therapy	Good or intermediate risk ^a	Sunitinib Pazopanib Bevacizumab + IFN α	HD IL-2
	Poor risk ^a	Temsirolimus	Sunitinib Pazopanib
Second-line therapy	Prior VEGFR inhibitor	Nivolumab Cabozantinib Lenvatinib + everolimus Axitinib Everolimus	Sunitinib Pazopanib
	Prior mTOR inhibitor	Clinical trial; other approved agents	

^aMSKCC risk status

Figure 1. Lines of treatment in advanced renal cell carcinoma. Abbreviations: HD, high dose; IFN, interferon; IL, interleukin; MSKCC, Memorial Sloan Kettering Cancer Center; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

First-Line Treatment for Advanced RCC

Sunitinib and pazopanib are the mainstays of therapy in the first-line setting and are considered “preferred” for good- or intermediate-risk patients in the 2017 NCCN Guidelines for Kidney Cancer (category 1 evidence). Bevacizumab plus interferon is also a category 1 recommendation for these risk groups.

Temsirolimus remains an option for patients at poor risk (category 1), but Dr. Jonasch said its use is declining. Temsirolimus is a category 2B recommendation for select patients in other risk groups. He noted that cabozantinib may turn out to be a good option for patients at intermediate or poor risk after data from an independent review of the CABOSUN trial become available.

Sunitinib was approved for the treatment of advanced RCC in 2006, based on a median progression-free survival (PFS) of 11 versus 5.1 months for interferon- α .³ OS was not significantly different between these 2 treatments.

“We are moving the bar up with antiangiogenic treatment, but we are not curing patients,” Dr. Jonasch said.

A phase III trial of pazopanib versus placebo in treatment-naïve or cytokine-pretreated patients with advanced kidney cancer showed improved PFS but not OS.⁴ A separate phase III trial, COMPARZ, met the primary end point showing noninferiority of pazopanib versus sunitinib. Survival did not differ between groups. Pazopanib had a more favorable adverse event profile compared with sunitinib.⁵

Temsirolimus was compared with interferon- α versus combination temsirolimus and interferon- α in a phase III study of 626 patients with ad-

vanced RCC and with poor- or intermediate-risk features.⁶ Temsirolimus improved OS compared with interferon- α or combination temsirolimus and interferon- α ; median OS was 10.3, 7.3, and 8.4 months, respectively.

The phase II CABOSUN study of first-line cabozantinib versus sunitinib in 157 patients with untreated clear cell RCC and with intermediate- or poor-risk features found that cabozantinib significantly improved PFS (8.2 vs 5.6 months, respectively; $P=.012$) and achieved a 34% reduction in the median rate of progression. Rates of adverse events were similar between the arms.⁷

“Cabozantinib was approved in the second-line setting, and it may get frontline approval. Independent review of the study has not yet been performed,” Dr. Jonasch said. “The data need careful vetting to see if it will find a place in the frontline setting.”

Second-Line Treatment

In the 2017 NCCN Guidelines, nivolumab, cabozantinib, and lenvatinib plus everolimus are all listed as category 1 options for second-line treatment of advanced RCC after previous VEGF inhibitor therapy. These 3 treatments showed improved OS versus everolimus. Axitinib and everolimus are also second-line options.

Nivolumab was approved in November 2015 for patients in whom tyrosine kinase inhibitors (TKIs) failed. Approval was based on a study of 821 patients randomized to receive nivolumab versus everolimus with a primary end point of OS (25 vs 19 months, respectively; $P=.002$, for nivolumab).⁸

Objective response rates were 25% for nivolumab and 5% for everolimus. There was a dichotomization, with 35% in the nivolumab group having progressive disease as the best response versus 28% for those on everolimus.

“Responses to nivolumab can be deep and prolonged, and even look like a cure,” Dr. Jonasch said. “This is good for responders, but it leaves other patients high and dry. My personal practice [with nivolumab] is not to be lulled into a false sense of security. Be careful with [nonresponse]. If there is evidence of progression at 6 months, I switch therapy. Patients can develop brain metastasis or progressive bone lesions with little notice,” he emphasized.

New Systemic Therapies in Kidney Cancer

Reviewing OS by subgroup showed that patients at poor risk responded best on nivolumab relative to everolimus. This group may have the highest level of programmed death ligand-1 (PD-L1) expression, he added.

Cabozantinib was approved in April 2016 for patients who experienced disease progression on TKIs. In a phase III study evaluating cabozantinib versus everolimus in 658 patients treated with at least one prior TKI, median PFS was 7.6 versus 3.8 months with everolimus, a highly statistically significant difference ($P=.001$). OS also favored cabozantinib, at a median of 21.4 versus 16.5 months, respectively ($P=.0003$).⁹

Lenvatinib plus everolimus is the most recent treatment to gain FDA approval in the second-line setting. Lenvatinib inhibits VEGF receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), RET, and KIT. Approval was based on a phase II study of lenvatinib versus everolimus versus the combination of the 2 drugs in 153 patients with metastatic RCC. An independent review showed robust results for PFS favoring the combination

arm—12.8 months versus 9 months for lenvatinib and 5.6 months for everolimus. OS was 25.5, 18.4, and 17.5 months, respectively.¹⁰

Axitinib was approved in 2012 in the second-line setting based on a study comparing the drug with sorafenib. Median PFS was 6.7 months for axitinib versus 4.6 with sorafenib. A subgroup analysis according to prior regimen showed a median PFS of 4.8 months with axitinib after sunitinib versus 3.4 months after sunitinib.

Everolimus was approved in 2009 as second-line treatment for patients previously treated with sunitinib, sorafenib, or both drugs. In the phase III RECORD-1 trial, median PFS was 4.9 months versus 1.9 months for placebo. OS was no different between everolimus and placebo.¹¹

Key questions regarding second-line treatment are:

- Can we predict which patients will benefit from these new agents?
- Emerging data suggest that the degree of immune filtrate (“hot tumors”) may be associated with nivolumab response; is this correct?
- Where does this leave mTOR monotherapy?

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