# RCC New Drugs: Where Do They Fit? What Does the Future Hold?

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**Overview**

This activity is designed to inform physicians about new and emerging therapies for the treatment of patients with renal cell carcinoma (RCC).

**Target Audience**

This activity is directed toward medical oncologists, surgical oncologists, radiation oncologists, and urologists interested in the treatment of renal cell carcinoma. Nurse practitioners, physician assistants, nurses, and other healthcare professionals involved in the treatment and management of patients with RCC are also invited to participate.

**Learning Objectives**

After participating in this CME/CE activity, learners should be better prepared to:

- Discuss the challenges associated with effective drug delivery to patients with glioblastoma
- Summarize the main findings of studies investigating the prognostic and predictive value of O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status in patients with glioblastoma
- Characterize the technology currently used to identify MGMT promoter methylation status in patients with glioblastoma
- State the contributions of The Cancer Genome Atlas (TCGA) researchers to the genomic understanding of glioblastoma

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## Introduction

Renal cell carcinoma (RCC) accounts for approximately 2% to 3% of all new adult cancers.[1] The median age at diagnosis is 64 years.[2] It is estimated that approximately 62,700 individuals will be diagnosed with RCC in 2016, and it will account for approximately 14,240 deaths in the United States.[3] As many as 90% of the renal tumors can be attributed to RCC, and about 80% of these RCC tumors are clear cell tumors.[4]

Approximately 65% of the patients diagnosed with RCC are diagnosed at a localized stage.[2] Patients diagnosed with low-grade RCC usually have a favorable long-term prognosis with surgery being the most effective option at that stage.[5] Unfortunately, as many as 30% of patients diagnosed with locoregional tumors experience relapse after nephrectomy.[6,7] The median time to relapse after surgery is 15 months, with most relapses occurring within 3 years.[8] Currently, there exists a need for additional options for this group of patients with locoregional disease, and the search for appropriate adjuvant therapies, including targeted therapies, is ongoing.

Most recently, vascular endothelial growth factor (VEGF) pathway inhibitors sunitinib and sorafenib have both been evaluated as adjuvant therapy in resected RCC patients with high recurrence risk in two different trials with conflicting data. In the landmark phase 3 ASSURE trial that evaluated sunitinib versus sorafenib versus placebo in an adjuvant setting, no survival benefit was noticed with either therapy when compared with placebo.[9] In this trial, patients with resected, intermediate- or high-risk RCC were randomly assigned to 1 year of treatment with sorafenib, sunitinib, or placebo. The median disease-free survival (DFS) was 5.8 years for sunitinib and 6.1 years for sorafenib versus 6.6 years in the placebo arm.[9] However, another recent phase 3 study, S-TRAC, reported extended DFS with adjuvant sunitinib treatment in patients with locoregional clear cell carcinoma at high-risk for recurrence. The median duration of disease-free survival was 6.8 years in the sunitinib group versus 5.6 years in the placebo group.[10]

One of the differences between both these trials was the enrolled patient population, ie, ASSURE included patients with earlier-stage tumors and all histologies including non-clear cell histology, whereas only patients, with higher-stage disease and clear-cell histology, were included in S-TRAC trial. Another difference was sunitinib dosage, ie, in ASSURE, the starting dose (50 mg) was lowered midtrial to 37.5 mg and further dosage reductions to 25 mg were allowed.[10] In contrast, sunitinib was administered at 50 mg in the S-TRAC trial and the dose could be reduced to 37.5 mg instead of 25 mg.[10] A comparison of both these trials provides important insights for treating patients with locoregional RCC in an adjuvant setting and also for designing future trials that are focused on evaluating adjuvant therapy.[11] Currently, a few other phase 3 trials are also evaluating the benefits of targeted therapy in an adjuvant setting, and are expected to report their results soon.[11]

While targeted therapies continue to be explored in a locoregional setting in RCC, promising results have been seen with these therapies in a metastatic setting. Several targeted therapies such as the VEGF inhibitors and mammalian target of rapamycin (mTOR) inhibitors have been approved in the last decade for the treatment of metastatic RCC (mRCC).[12] Some of the approved VEGF-targeted agents for mRCC include sunitinib, sorafenib, axitinib and pazopanib. Cabozantinib, a potent inhibitor of c-MET, AXL, and VEGFR2, was recently approved as second-line therapy for mRCC; mTOR inhibitors temsirolimus and everolimus are also approved for mRCC.[11] Immunotherapy is yet another option that has long been proven to be effective in RCC, given that RCC has long been considered an "immunogenic" tumor from the time when cytokines were used.[12] An immunotherapeutic option that is gaining wide acceptance across several solid tumors is the checkpoint inhibitor therapy. Last year, the FDA approved checkpoint inhibitor nivolumab for the treatment of patients with mRCC who have progressed on front-line anti-VEGF therapies.

In the landmark CheckMate-025 study, anti–PD-1 antibody nivolumab demonstrated improvement in median overall survival (OS) when compared with everolimus (25 vs 19.6 months). Significantly greater objective response rate (ORR) was also observed with nivolumab versus everolimus (25% vs. 5%; $P < .001$).[13] In this study, benefit with nivolumab was observed irrespective of the patient's PD-L1 status. Emergence of checkpoint inhibitors in RCC has further lead to evaluation of these therapies in combination with other therapies. Combination therapies exploit the possibility of synergistic activity and overcome the difficulty of delivering multiple agents sequentially as monotherapy owing to further decline in performance status and comorbidities. For example, two phase 3 trials plan to compare the combination of axitinib plus avelumab (a PD-L1 inhibitor) or pembrolizumab versus sunitinib as first-line therapy in advanced RCC.[14] Moreover, the combination of bevacizumab and PD-L1 inhibitor atezolizumab is being evaluated in an ongoing, phase 3 trial comparing this combination versus sunitinib as first-line therapy.[15] Recently, the combination of yet another multikinase inhibitor, lenvatinib, was approved for mRCC in combination with everolimus; several other combinations continue to be explored.

Given the rapid pace at which newer agents are being developed along with various rationale combinations being tested, patient selection will play a key role in ensuring treatment

optimization. Co-development of predictive biomarkers will gain further traction in the coming years to enable precision medicine. Luckily, most large trials are mandating tissue and blood collection for future biomarker-based studies. Rapid developments that promise better outcomes for RCC patients make it an exciting time to be in this field.

*Toni Choueiri, MD, director of the Lank Center for Genitourinary Oncology, associate professor of Medicine at the Harvard Medical School and co-leader of the Kidney Cancer Program at Dana-Farber/ Harvard Cancer Center provided his insights and point on view on the recent and emerging advances in the treatment of RCC.*

**Moderator:** What are some of the current unmet needs in the treatment of RCC, specifically advanced RCC?
**Dr. Choueiri:** What I want to say is that despite advancement, despite patients staying on therapy longer, despite patients living longer, there are new unmet needs. The unmet needs in this day and age still involve around mechanisms of progression while on VEGF-targeted therapy. Targeting VEGF/MET and AXL with cabozantinib and combining delicately VEGF and mTOR inhibitors with lenvatinib and everolimus may provide a partial answer. The space post-PD1 inhibitor, (post nivolumab) is another unmet need.

**Moderator:** Findings from the S-TRAC study contradict those from the ASSURE trial that did not show any positive outcomes with sunitinib in the adjuvant RCC setting. What could be the likely reasons for these differences in results and what, in your opinion, is the final takeaway from both these studies for clinicians?
**Dr. Choueiri:** Yes, both adjuvant studies—one has three arms ASSURE—placebo, sorafenib, and sunitinib. S-TRAC has two arms—placebo and sunitinib—totally different outcomes. One is positive for disease-free survival—S-TRAC; one is negative—ASSURE. I think, at this point we are trying to digest the results, but there are some subtle differences in inclusion criteria such as S-TRAC, allowing only clear cell; S-TRAC allowing starting at just the highest dose. S-TRAC also has a slightly higher risk population. So, could this explain the differences? There was some subgroup analyses from ASSURE that included higher-risk patients and only clear cell and also did not find any difference. What could be the difference is the dose intensity that was received. Because at the end of the day the dose that was actually received, let's say over a unit of time—per week, per month—could be higher on S-TRAC because patients were not allowed to start at the lower dose. At least we know that in the metastatic setting, dose intensity can matter.

**Moderator:** With recent approvals of nivolumab, cabozantinib, and lenvatinib/ everolimus combination, all in second-line setting, what advice would you offer to clinicians on sequencing therapy in advanced RCC?
**Dr. Choueiri:** So, this is something that people ask us all the time—nivolumab, cabozantinib, and the combination of everolimus and lenvatinib, all second-line setting—what advice you offer to clinician. Each of the 3 new strategies did beat everolimus for the primary endpoint, but they have not been compared head-to-head. The side effects are different. Nivolumab is very well tolerated. With cabozantinib and the other combination, you have to know how to manage side effects. You have to have experience in managing TKI side effects and be comfortable with it, which we have been doing that for many years.

The other thing, the interesting thing about cabozantinib, and the combination of lenvatinib and everolimus, is there are very few patients that blow through therapy directly. While on nivolumab [it] is around 30% to 35%. So you may be able to hold the disease better with a rapidly progressing patient with large tumor burden.

**Moderator:** In your opinion, what are some of the immediate needs with respect to biomarker research for RCC treatment? What role will biomarkers play in optimizing RCC treatment in the near future?
**Dr. Toni Choueiri:** This is relevant to the work we do, the immediate need with respect to biomarker research. There has been so many biomarker research around bevacizumab, even outside renal cell cancer. The problem is despite nice and solid body of work, it did not show that the biomarker is able to translate into clinical use. Some patients with the "negative" biomarker can still have some benefit from therapy.

We were hoping that, for nivolumab, PD-L1 expression would be of predictive significance, and it was only of prognostic significance.

**Moderator:** Are there any other immunotherapies beyond anti-PD-1, anti–PD-L1 and anti-CTLA4 that are emerging for the treatment of advanced RCC?
**Dr. Choueiri:** Absolutely. Many companies have a pipeline with other immune strategies (CTLA-4, TIM3, LAG3, CD27 and others) that will be explored. This may just be the tip of the iceberg.

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