Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/Community-Clinic-Translating-Data-Into-Action-Practical-Strategies-for-Optimizing-First-Line-RCC-Management/35774/

Released: 07/25/2025
Valid until: 07/25/2026
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Community Clinic: Translating Data Into Action — Practical Strategies for Optimizing First-Line RCC Management

Dr. Motzer:
In recent years, the treatment landscape for first-line advanced renal cell carcinoma, or RCC, has evolved significantly. Are you up-to-date on the latest clinical evidence and guideline recommendations? This is CME on ReachMD, and I'm Dr. Robert Motzer.

Dr. Plimack:
And I am Dr. Elizabeth Plimack. Dr. Motzer, can you give us an overview of the first-line treatment landscape for advanced clear cell RCC?

Dr. Motzer:
Yes, Dr. Plimack. There's been significant improvements in first-line treatment for RCC, and a change in paradigm that came around 2017 or 2018. For the most part, the standard of care was sunitinib, a tyrosine kinase inhibitor, which was approved in 2006. And this remained the standard of care for many years, until the IO doublets challenged sunitinib in large phase 3 trials.

The first was CheckMate 214, which compared 2 immunotherapies, nivolumab and ipilimumab, to sunitinib. The primary endpoint was in the intermediate- and poor-risk group, but patients with favorable risk were included as well. The study reached the primary endpoint showing a benefit in overall survival and response rate for ipi plus nivo compared to sunitinib, and really was the first to change the paradigm.

Now, CheckMate 9ER was a randomized phase 3 trial that compared cabozantinib plus nivolumab to sunitinib, and this showed benefits in progression-free survival, overall survival, and response, and became a good option for first-line therapy as well.

The KEYNOTE-426 compared axitinib and pembrolizumab to sunitinib, and showed benefits in progression-free survival, overall survival, and response rate, and became an equal option for first-line therapy for the TKI IO group.

Lastly, the CLEAR trial compared lenvatinib plus pembrolizumab to sunitinib and showed striking benefits and improvement in progression-free survival, overall survival, and response rate.

So now these are all options in first-line therapy for patients with advanced clear cell RCC. So all 4 of these programs are included as Category 1 options within the NCCN.

Dr. Plimack, what are some of the practical considerations that we need to keep in mind when incorporating these regimens into clinical practice?

Dr. Plimack:
Thanks, Dr. Motzer, that was a great overview.

When considering which of these to start your patient on, I usually look at 3 things. One is, does the patient need a short-term benefit? Do they need a response? Am I worried that if their disease progresses, I won't have another chance to control it? Do they have something causing a symptom or threatening an organ or structure? Those patients, I usually go to the TKI/IO combos.

And then the other is consideration for subsequent therapy. So any of the IO/TKI therapies all use a TKI in the frontline that then we typically don't use in second-line and beyond. And so selecting something that preserves the most options for later is something we sometimes think about.

Now, ipilimumab and nivolumab is one of the earliest trials. I remember participating in that with you, Dr. Motzer, many years ago, and now we all still have patients in our practice who benefited from that all those years ago, which is really encouraging. And this was shown in the long-term update—the 10-year update—presented at ASCO, which showed durable responses and patients still alive 10 years after starting this treatment, which would have been unheard of before we had immunotherapy combinations.

So if you're really looking for the best-defined long-term results, ipi and nivo may be what you reach for.

Dr. Motzer, any other comments on those thoughts?

Dr. Motzer:
Well, Dr. Plimack, I have to say that my practice pretty much mirrors yours with the same points you raised, particularly the durability with ipi/nivo.

And on the other side, the response rates with TKI/IO, including lenvatinib and pembrolizumab or cabozantinib and nivolumab, are really very impressive. And so if disease control is needed immediately, then that's certainly a good option. I also tend to use those combinations for patients with favorable-risk RCC because of the underlying kind of biology of the favorable-risk tumors and in my own experience that I've been quite successful in management.

Now, one of the newer items that we should be aware of is the fact that nivolumab is now available as a subcutaneous dosing schema. And so this can be substituted for IV nivo in patients who are either receiving cabozantinib and nivolumab, or for patients who are on the ipi/nivo program and have completed the doublet aspect of this while they're receiving nivo monotherapy. It may be a good alternative for some patients who prefer not to receive IV medications or in whom scheduling is an issue.

Now we're going to use some patient cases to demonstrate how to apply clinical evidence and guideline recommendations to daily practice. Here's the first case.

A 59-year-old African American woman is diagnosed with clear cell RCC. She undergoes a left total radical nephrectomy in December 2019, but 9 months later, she develops metastatic disease to both lungs and bulky disease in her mediastinum with retroperitoneal involvement as well. Now, the diagnosis is made of stage IV RCC, clear cell histology with metastasis to the lung and retroperitoneum. She has a good performance status. Her hemoglobin, neutrophil, and platelet counts are within normal limits, but she does have hypercalcemia.

So this is a patient who I would probably consider nivolumab plus ipilimumab for. This is a patient who has intermediate-risk RCC by the international criteria. She otherwise has good performance status. She's really quite stable. And based on the durability of response, the survival benefits that have been established long term. And the favorable quality of life for patients who are completing treatment, this would be probably my preferred option for this patient.

Dr. Plimack:
Yeah, I agree. She is young, and so the long-term goal is long-term overall survival, and ipi and nivo—the data that we've seen, provides the longest reach towards that long-term survival. We can actually see how many people are still alive and doing well, many treatment-free, out at 10 years. So that makes absolute sense.

In terms of convenience, most of our 59-year-olds are still working, they may have to take time off of work for longer infusions. And the ability to switch from intravenous after the first 4 doses to a subq regimen does yield some convenience for this patient.

Dr. Motzer:
So this would be a discussion between the treating physician and the patient, because it would also be reasonable to treat this patient with a TKI/IO. And there's no clear consensus among those 4 programs that one is definitely right and the other is wrong. So I think it's really kind of a preference from the treating physician.

Certainly, patients should be informed of the risks with different side effects, the treatment plan, and then a decision is made with which program suits the needs of the patient best.

Mid-tag

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Robert Motzer, and here with me today is Dr. Elizabeth Plimack. We're discussing the evolving first-line treatment landscape of advanced clear cell RCC.

Dr. Plimack:
Now, let's move on to our third topic, another patient case, this one with very aggressive disease in a poor-risk setting. This is a real case, presented with permission, of a man who was 50 years old when I met him. He had just underwent a right nephrectomy 6 months prior. Pathology was a T3 high-grade, 5% rhabdoid features and 20% necrosis.

His second scan showed a 12-cm retroperitoneal mass. At that time, his hemoglobin had dropped to 10.8 and his platelets were up to 823. Because of the rapidity with which this mass presented itself, we all agreed he needed a response and started lenvatinib 18 mg daily with pembrolizumab 400 mg every 6 weeks.

His first scan showed a deep partial response with the gradually decreasing lesions over the subsequent 2 years. Over those 2 years, the toxicity he experienced was hypothyroid requiring replacement, and at the beginning, severe hypertension requiring a dose reduction of lenvatinib to 14 mg daily, as we already had him on maximal antihypertensive therapy.

At the 2-year mark, he had achieved a complete response and we made the decision at that point to discontinue lenvatinib and pembrolizumab after 2 years of both in the setting of this complete response.

He's been off therapy for 1 year. He's asymptomatic, and remains without evidence of disease on imaging.

Tell us what you think about this case.

Dr. Motzer:
Well, I think this really is a good example for the high efficacy associated with the TKI/IO programs. Whether it be lenvatinib/pembrolizumab, axitinib/pembrolizumab, or cabozantinib and nivolumab, they are characterized by high response rates. And this patient you were concerned was going to get into trouble and really wanted to get disease control early, so it seems very appropriate to treat this patient with a TKI/IO.

And then as a feature TKI/IO, there's these chronic TKI-related toxicities, including hypertension, which we commonly see with lenvatinib, and requiring a dose reduction. But nevertheless, there was a very favorable outcome with this patient in a complete response. So a really good example of progress we've made with this type of therapy in advanced RCC.

Dr. Plimack, let's turn to treatment-related adverse events. What can you tell us about the toxicity profiles by drug class in first-line advanced clear cell RCC?

Dr. Plimack:
Yeah, that's a great question and a great point. Whenever we are presenting the treatment options in the first line to our patients, we always have to inform them about the potential risks. I generally separate the risks into immune-mediated adverse events and TKI-related adverse events.

With the immune-mediated adverse events, we really emphasize that anything can happen, any tissue in the body can become inflamed, leading to symptoms. And so anything that doesn't feel right, they should call us so that we can consider what's going on, bring them in for evaluation, potentially steroids if needed. So the key to mediating irAEs, immune-related adverse events, is really close communication and really getting people in quickly to evaluate them.

When talking about TKI-related toxicities, I emphasize that most people get something, and for some, it can be uncomfortable and lead to symptoms that limit them. Our goal is to mitigate those through supportive care and a dose reduction.

So common immune-mediated adverse events are pneumonitis and colitis, and common TKI-associated adverse events are hypertension, diarrhea, fatigue, hoarse voice, and skin, hand, and foot reactions that we watch for carefully.

So Dr. Motzer, what are your tips and tricks for monitoring for and managing the treatment-related adverse events that are a risk with all these combination regimens?

Dr. Motzer:
Well, before starting treatment, we do a close assessment to identify comorbid conditions. And prior to treatment, provide education with fact cards and personal teaching in terms of the drugs and their potential side effects. And then close monitoring when patients are on treatment, particularly at first, making sure that patients know that if there are any concern of adverse events or new signs or symptoms, that they certainly reach out and let us know. And we closely monitor these with the clinical practice nurse playing a large part in that.

In terms of management, we'll manage as the medical oncologist, because we've had a lot of experience. But certainly if they become more detailed or serious, we call in specialists. So we work frequently with the nephrologists or cardiologists in managing hypertension for drugs like lenvatinib or cabozantinib. If it appears that there's an immune-related adverse event, we generally have rheumatology

see the patient and dermatology as well for rashes.

So close vigilance and call in other specialists in a multidisciplinary approach when these adverse events occur.

Dr. Plimack:
So Dr. Motzer, I agree with all those things. It's a team effort between the care team, the extended care team, and the patient. I usually emphasize that the goal is for us to mitigate these adverse events so that they can achieve a nice cancer response, response to their treatment, while living their life and enjoying life and not suffering more than a little inconvenience from the side effects. That's our goal.

Dr. Motzer:
Well, I agree with those principles completely, Dr. Plimack, and it's important to try and manage toxicities and continue treatment whenever possible.

Well, this has certainly been a great conversation, but before we wrap up, Dr. Plimack, can you share your one-time take-home message with our audience?

Dr. Plimack:
Thanks, Dr. Motzer. I agree, it's been great. So my take-home message is that we are fortunate to have a plethora of options for our patients presenting with renal cell carcinoma that's metastatic. In the first-line setting, we have multiple TKI/IO combos and ipilimumab and nivolumab. We have made progress in the convenience of dosing, and progress in managing adverse events really carefully in order to achieve the best possible response for each patient, many of which I'm happy to say, are durable.

Dr. Motzer:
Yeah, I agree with that completely. I think the treatment has really evolved dramatically over the last 10 years, for the better for our patients. I do also want to highlight, though, that we still need to do better, and so there is a role for clinical trials and continuing investigations to see if we can result in even better outcomes for our patients.

And that's all the time we have today. So I want to thank our audience for listening in, and thank you, Dr. Elizabeth Plimack, for joining me and for sharing all of your valuable insight. It was great speaking with you today.

Dr. Plimack:
So great speaking with you as well. Thanks for having me.