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Applying Novel Strategies to the Treatment of Advanced Renal Cell Carcinoma

Announcer Open:
Welcome to CME on ReachMD. This activity titled, Sorting Through the Complexities of Managing Metastatic Colorectal Cancer: Strategies for Individualizing Treatment, is provided by Partners for Advancing Clinical Education, PACE, and supported by an educational grant from Merck Sharp and Dohme, LLC, and Seagen. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Ms. Sims:
We're thrilled to have you with us today and we have a great speaker for our topic. Today, our topic now is keeping up with the rapid emergence of strategies for advanced renal cell carcinoma. And we have a wonderful speaker, Mary Dunn, who's a Nurse Practitioner from the Division of Oncology and the Department of Urology and Medicine at UNC School of Medicine in Chapel Hill, North Carolina.

And here are Mary's disclosures.

And these are the learning objectives for this session. You'll see that she's easily going to address this to address patient and disease-related characteristics and their relevance to optimal treatment selection, develop evidence-based treatment strategies for the appropriate management of advanced RCC, and to use recommended strategies to effectively manage the adverse effects associated with novel agents for advanced RCC.

Alright, I'll now remind you that we're going to talk about considerations for non-metastatic RCC at initial diagnosis. And here's our speaker, Mary Dunn. Welcome.

Ms. Dunn:
I'm so thrilled to be here. I love talking about kidney cancer. We can have an entire conference about treatment options for management of kidney cancer, but we have to condense everything into my one presentation, so we're not going to touch on every single option that there is to treat advanced kidney cancer, but just kind of hit some of the most recent highlights and hopefully reinforce some things that you know and teach you a few new things along the way.

So, kidney cancer or renal cell carcinoma is one of the most common cancers affecting adults in the United States. This year alone, roughly 82,000 people will be diagnosed and close to 15,000 people will die from kidney cancer. The vast majority of kidney cancers over 70% are clear cell. There are other subtypes, but the majority of the treatment options that we're going to discuss today are going to kind of revolve around the treatment of clear cell renal cell carcinoma, with the little caveat there that we need more clinical trials that include patients who have non-clear cell so we can get a better understanding of how to effectively treat them as well.

Another little thing is that I work in urology and medical oncology, so I take care of patients who have had surgery for their kidney cancers, and also patients who are getting systemic treatment. So, what I see on the urology side is that we're seeing a lot more early-stage tumors, because as I'm sure all of you know, if you go to an urgent care or an emergency department with belly pain or any kind of kind of abdominal symptoms, you're probably going to get some sort of imaging test. So, we're seeing a higher incidence of kind of small renal masses being detected earlier than normal.

So, this is kind of outside the scope of this talk, but for non-metastatic or localized kidney cancer, surgery remains the kind of the mainstay of treatment with the addition of adjuvant therapy in selected circumstances, which I'll touch on. But also, for small renal masses, a lot of times we can do surveillance, depending on what the circumstances are for that particular patient.

So, this is a chart that kind of highlights some of the published adjuvant trials for tyrosine kinase inhibitors. So, adjuvant therapy is

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systemic treatment that's given after definitive therapy. So, this would be for folks who have had partial or radical nephrectomies for their kidney cancer. So, there's three randomized controlled clinical trials here and the majority was in the clear cell population, and only one of these trials, so S-TRAC, showed disease-free survival. So, this was sunitinib versus placebo. We typically don't prescribe a lot of adjuvant sunitinib, generally because of the toxicity profile and because there is now another option which we will talk about.

So, this is KEYNOTE-564. So, this was a trial of adjuvant pembrolizumab, which is an anti-PD-1 antibody, immunotherapy versus placebo. So, this was given for patients after surgery who were at an increased risk of recurrence. So, those patients who were stage II with a Fuhrman grade 4, or sarcomatoid features, or patients who were stage III or higher, or patients who have regional lymph nodes or M1 with no evidence of active disease. So, the outcome measure here was disease-free survival. And as you can see, the disease-free survival for patients who received pembrolizumab was 78% versus 67% in patients who are getting placebo. The way that the pembrolizumab is given is every 21 days. So, on a 3-week cycle for up to 1 year depending on things like tolerability. The overall survival data for this is still pending, so we don't have those long-term numbers yet.

So, who should we consider adjuvant treatment for, for those who are at a high risk of recurrence? Patients with clear cell with T3 or higher on their pathology, patients who have M1 disease who are without evidence of active disease within 1 year of treatment. And this is really a very much an example of shared decision-making, because urology is involved in this in the postoperative setting. And then we get our medical oncology colleagues involved. And of course, the patients, because it involves really assessing their comorbidities, are they even candidates to get immunotherapies. I'm sure many of you are prescribing and/or managing folks who are getting different types of immunotherapies. And you know, it's certainly not a one size fits all, including all the social situations, where having to come to, you know, come to the clinic every 3 weeks to get infusions, and all the other kind of barriers to care. So, it's a big decision-making process, especially in the context of not having that long-term overall survival data yet. Sometimes patients are fine going on a surveillance protocol, which is – would be standard of care if they choose not to get adjuvant treatment. We monitor high-risk folks, usually every 3 months for the first year with imaging to make sure that they don't recur.

So, our action item here is to speak with eligible patients, as we talked about, about the potential risks and benefits of adjuvant pembro. So, there's this kind of theoretical question of: Can this potentially eradicate any micrometastatic disease that our imaging studies just aren't sophisticated enough to pick up following surgery?

Okay, so now we're going to talk about planning optimal first-line treatment for patients with advanced kidney cancer. And my goodness, how this space has exploded. So, I tell people I'm a dinosaur. So, I've been in this role since 2010. And when I first started, I think I had sunitinib and pazopanib, and a handful of other things. And then single-agent nivo came along and then, you know, in the following years, this space has just exploded. So, I say that it's a bit of a blessing and a curse, and you'll see why in subsequent slides.

So, before we even consider which regimen to put people on, we have to be mindful of what risk category they fall in. So, this risk category stratification system was developed to classify patients into groups with corresponding prognoses. So, you see all the criteria that we use: the performance status, time of diagnosis to recurrence, and different lab values, so hemoglobin, calcium, platelets, and neutrophils. So, what you do not see on the list is LDH, that does not come into play. So, what we know is that the higher the risk category – the higher the score, the poorer risk and the decreased survival for these folks, as you can see here. So, we kind of break people into three different categories depending on their risk factors. So favorable risk, intermediate risk, and poor risk; 70-75% of patients with whom we're selecting first-line therapy for, have at least one risk factor, which kind of automatically slides them into that intermediate-risk category. But there are 20-25% of folks who present and are favorable risk. So, with favorable risk, we know that the overall survival is about 43 months, intermediate risk is roughly 22 months, and high risk is much lower at 8 months.

This is the current therapeutic landscape for kidney cancer – metastatic kidney cancer in the first-line setting so we risk stratify people, and then based on their risk stratification, we then take all the other factors that we have to consider that you all know: comorbidities, social determinants, patient preference, other medications that they're taking for their comorbidities, etcetera, and then decide what is the best step for them. So, you can see here, the vast majority, or everything actually in the first-line setting that we would recommend is some form of combination. So, as you all know, with the more cancer-directed medications you throw at people, the higher risk they are for having toxicities and side effects. So, a lot of really good nursing and provider education has to come into play here and you'll hear me harp on that a little bit. But now, you know, in this world of newer agents and combination agents, the targeted plus immunotherapy sequencing, and even kind of picking that first-line treatment can be a little tricky. We do, if patients are eligible and interested, always encourage people to consider clinical trials when applicable and available.

Ms. Sims:
So, here's a case. Now, this is Robert, a 58-year-old with advanced RCC receiving cabo/nivo. He reports grade 2 LFT elevation after 3 cycles of therapy with nivo/cabozantinib. His AST is 66 and his ALT is 160. He's asymptomatic and otherwise tolerating therapy without other AEs.

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Ms. Dunn:
So, yeah, one of the things I've kind of mentioned along the way are this concept of overlapping toxicities when people are taking combination regimens for their kidney cancer, a lot of times these drugs can have the same side effects. So, one kind of classic example is hepatitis. So, tyrosine kinase inhibitors and immune checkpoint inhibitors can cause hepatitis at roughly the same time points. So, what do we do? It's a little bit of a crapshoot. So, depending on what they're on, like, the easiest thing typically is to stop their tyrosine kinase inhibitor. The half-life of axitinib is really, really short, for example. So, if axitinib is the one that's causing it, then the LFTs will go back down rather quickly. However, if it's unclear, the best course of action is to stop, hold both agents, and just recheck.

So, these are just management algorithms. I won't read this to you, but this just kind of goes into if there's overlapping toxicities, what do we do with which drug depending on the severity of the toxicity? And it can be tricky. And it's more of an art than a science.

So, this just goes through what we do with hepatitis. With people who are on two agents who, with both agents can cause this, so, depending on the grade and depending on the drug. So, for Robert, we would hold both, so he kind of falls into this middle category here of AEs of unknown etiology. We don't know. So, holding both agents. And then management of hepatitis depending on the grade, always getting our GI colleagues involved if we feel like we need their expertise.

And then looks like we're going to wrap up the case study here.

Ms. Sims:
Here's our final aspect of Robert's case. Both agents were held, and LFTs were rechecked a week later, ALT improved to 45 down from 66, and AST improved to 116 down from 160. He resumed therapy the following week, with one dose reduction of cabo to 20 mg daily, and nivolumab dosing remained the same. Serial LFTs remained grade 1 and asymptomatic.

Ms. Dunn:
Nice, thank you. So, this is just a handy tool, I think you could take a QR screenshot of this from your computer. So, a nice handy tool that goes through the NCCN clinical practice guidelines in oncology for managing immuno-related therapy toxicity. It's so nice to have like on your phone, in your pocket, quick and easy reference guide. If you can't remember all the things you have to do based on grade, it's nearly impossible to remember, and incorporating your pharmacy colleagues in here too. We have a clinical pharmacist who's embedded in our clinic who's super helpful with helping to manage these AEs. But this is a nice tool that's out there for those of you who are interested.

So, just kind of a take-home about the importance of education here. So, they're unique to immunotherapy driven by that immune response. The majority of people are not going to have severe immune-related adverse events. They have a very variable profile, and they can affect any organ. We know that they can also overlap with similar tyrosine kinase adverse events. So, we have to do dose holding, dose reduction, sometimes just kind of like I said more of an art than a science in determining how we treat this, and educating patients at every single touchpoint you have with them to ensure that they understand to please report anything that's out of their norm because it could be the onset of something unusual.

Alright, so our action plan is speaking with eligible patients about potential risks and benefits of adjuvant treatment with pembro; selecting our optimal first-line treatment for advanced kidney cancer using risk stratification, disease characteristics, and patient preferences; strategizing post-progression treatment sequencing and considering prior treatment history, evidence, side effect profile, comorbidities, preference, and other social determinants; controlling immune-related adverse events with steroids, other medications, and best supportive care; and then optimizing communication with patients around potential for adverse events and what to do in case of new issues with, there's a list here, but I say with anything.

Ms. Sims:
I've seen patients who are on hemodialysis because of their kidney cancer surgery. Patients don't feel well necessarily. How do you control their hypertension and manage that while they're getting chemo or immunotherapy plus hemodialysis. And Mary, I wonder if you've had a patient with this scenario?

Ms. Dunn:
I do have a handful of patients on hemodialysis for a variety of reasons; some from their kidney cancer or because of their kidney cancer, quite frankly. And when patients are that complicated or complex, have uncontrolled hypertension, sounds like kind of a poor performance status, having to balance things like diet in relation to their renal function, I bring in my colleagues. I bring in my pharmacy colleagues. If the hypertension is very poorly controlled, I bring in cardiology. And I'll get our oncology dietitians involved as well. I think it's important to know as a provider, what my limitations are, and I think the best thing that I can do to serve my patients is to make sure all of the people who could potentially help with this rather complicated scenario, get on board if you have access to those folks. Thanks for the question. That's tough.

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Ms. Sims:
We have one more question from Lindsay, and I think probably other people also had the same question. How do you decide if you can restart ICI therapy after holding it for immune-related – ?

Ms. Dunn:
Yeah. So, that's based on if the AE goes way. So, if it goes back typically to a grade 1 or completely resolves, and they're having – and the drug is controlling their cancer; in other words, their scans are still stable because they're off for a period of time, so because of an AE that we're treating, sometimes we feel like we need to restage them in order to ensure they're not having like significant disease progression off drug. But if grade 1 or completely resolved, then we can restart, or – what's the word I'm looking for – rechallenge patients with the same drug, if they feel comfortable with that. So yeah, that's definitely something that we do.

Ms. Sims:
I want to thank Mary Dunn, our speaker. Mary, you've done a fantastic job today and UNC is lucky to have you. Thank you so much for sharing your knowledge with us on renal cell carcinoma. Great to have you.

Announcer Close:
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