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Selecting and Sequencing Immunotherapies for Patients with Advanced RCC

Announcer:
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Dr. Jonasch:
Immunotherapies have drastically changed the treatment landscape for renal cell carcinoma, or RCC. Are you familiar with the most recent clinical data on immunotherapy? You’ll need to be to optimize outcomes for your patients in the first line and beyond.

This is CME on ReachMD, and I’m Dr. Eric Jonasch.

Dr. McGregor:
And I’m Dr. Brad McGregor.

Dr. Jonasch:
To start things off, Dr. McGregor, what are some of the factors that impact the selection of therapies for renal cell carcinoma?

Dr. McGregor:
Yeah, you know, this is a really pivotal question. It’s something that we struggle with every day in the clinic. You know, going back to when the VEGF/TKIs [tyrosine kinase inhibitors] were first approved for renal cell carcinoma, we had risk factor stratification that were good – developed to sort of help prognosticate patients, and now those risk factor models are actually important as we sort of think about the frontline therapies. As we look at the NCCN [National Comprehensive Cancer Network] guidelines, there’s IMDC [International Metastatic RCC Database Consortium], the MSKCC [Memorial Sloan-Kettering Cancer Center], and these are using clinical factors to help sort of prognosticate how the patient’s going to do. Most pivotal is how long has it been from the nephrectomy to the immune systemic therapy, if that’s under or over a year, and then the performance status, and then we look at different lab values, and each model looks at different ones. We look at anemia, neutrophilia, thrombocytosis, hyperglycemia, or LDH [lactate dehydrogenase], and so, you know, there’s different calculators, and we use those, and we can group patients into favorable-, intermediate-, or poor-risk categories, and if you look at the NCCN guidelines for up-front clear cell renal cell carcinoma, they actually have different recommendations based on favorable or not, and that’s based on design of trials. So for favorable disease, IO/TKI combinations, be it cabozantinib with nivolumab, lenvatinib with pembrolizumab, or axitinib and pembrolizumab are there. While as for the intermediate-risk and poor-risk disease, we have the addition of nivolumab/ipilimumab, as well as cabozantinib based on the CABOSUN. And so we have all these different options, and so often beyond just those options, how do you choose one versus the other? And that may depend on patient preferences, and unfortunately it often depends on insurance. Timing of infusions – some infusions are every 2 weeks and some as infrequent as every 6 weeks with pembrolizumab, and those different factors, and then obviously this is all for a clear cell disease.

And we start thinking about those patients with non-clear cell disease, those variant histologies. These really encompass a wide variety of tumors, very different biology. And then in that situation, it’s a whole different scenario, right, where histology-directed therapy is

becoming more and more important, though now we have data that some of the IO/TKI combinations – nivolumab and cabozantinib, lenvatinib and pembrolizumab – can be quite effective in that frontline therapy. So, you know, as we think about the frontline options, it really does involve a discussion with a patient about what's important to them in terms of where they're at in their disease course and the risk/benefits of each different approach to toxicities and as well as, you know, financial toxicities and burden on the patient as they look to start this treatment.

Dr. Jonasch:
Yeah, it's really interesting, Brad, how these very simple algorithms that we use looking at clinical and laboratory features in 2022 are still the most valuable way of stratifying our patients. Hopefully at some point in the next 5 to 10 years we're going to come up with some better molecular features, but I agree this is a very, very important way of stratifying our patients.

Dr. McGregor:
Absolutely. I think we look forward to the day when we can have molecular signatures to help say which therapy is the right one for a patient, and we're there in other diseases, and we're working hard to get there in kidney cancer.

But, Dr. Jonasch, now that we understand the factors we need to consider when selecting therapies for renal cell carcinoma, what clinical data do we actually have in this first-line setting to help guide decisions?

Dr. Jonasch:
So a great question, Brad. You know, we have a lot of information here, and we can really break this down into the CheckMate studies, which have a nivolumab backbone and the KEYNOTE studies that have a pembrolizumab backbone. So looking at CheckMate 214, which is ipilimumab and nivolumab combination, so this is a study, its primary endpoint was objective response rate, PFS [progression-free survival], and overall survival in the intermediate- and poor-risk patient population. It did handily meet its primary endpoint of overall survival and did have superior PFS and ORR [objective response rate] compared to the comparator sunitinib, but there are a couple of important points with this combination. The first are that, A, it has really good durable CR [complete response] in those individuals that are responders. B, PD [progressive disease] as best response is actually quite high – about 20% of patients did not really benefit from it. And the third is that in the favorable-risk subcategory – there's about a quarter of the patients that had that subcategory – the PFS and ORR actually were better for sunitinib than for ipilimumab and nivolumab, although the overall survival was kind of similar. So an interesting agent, definitely some side effects there that we need to consider. Cabozantinib and nivolumab in the CheckMate 9ER study had primary endpoint of PFS – see a really good PFS advantage of the combination over sunitinib – 16 months versus 8 months – improved overall survival, improved objective response rate. CR rates also kind of in the 10% to 12% range, less certain how durable they are, but PD as best response quite low, about 5% to 6%.

Moving on to the pembrolizumab backbone studies – so axitinib and pembrolizumab in KEYNOTE-426 had the primary endpoint of overall survival and PFS, and here, once again, endpoints met PFS of 15 versus 11 months, overall survival clearly favorable for the combination. Again, we have the question here – CR rates around 10%, how durable are they? Less certain than for the ipi + nivo combination.

And lastly, we have lenvatinib and pembrolizumab which was in the CLEAR study which looked at that combination compared to sunitinib – once again meeting all of its primary endpoints, clearly higher objective response rate – 71% for the combination compared to sunitinib higher overall survival. And once again, the question really is how durable are the complete responses? Are we seeing a tail on the curve?

So, in summary, we have one IO/IO combination, we have 3 IO/TKI combinations. The IO/TKI combinations clearly have very good objective response rates, very few patients progress on them. The durability of these complete responders, less certain, and ipi + nivo – really the king probably of durable response, but there is a subset of individuals that clearly don't respond.

Dr. McGregor:
Yeah, amazing packing all that into 5 minutes or less, but really highlights the data so well, and I 100% agree, I think, you know, nivo + ipi offers that ability for that durable treatment-free interval, and we don't know yet what the IO/TKI is, although at the expense of that 20% PD as best response, but it's a really exciting time as a physician treating kidney cancer to have so many options available for our patients.

Dr. Jonasch:
So speaking of exciting, what was presented at ESMO this year? Were there any interesting studies that we should talk about?

Dr. McGregor:
Yeah, I mean ESMO was really quite exciting as a physician taking care of kidney cancer, and we're not even going to get into the large data presented on the role of immunotherapy in the adjuvant setting, but we actually had some very impressive data looking at novel

approaches in the metastatic setting, and I think one of the most interesting trials was COSMIC-313. This was actually a plenary that was the first trial conducted in renal cell carcinoma with a modern comparator. So all of the studies you heard about, you know, were looking to get sunitinib. So this was a trial, primary endpoint was PFS in patients with intermediate- and poor-risk disease. Those were the only patients that were enrolled, and patients were all given nivolumab and ipilimumab at the doses seen in CheckMate 214 with or without cabozantinib. One of the key differences in this trial from CheckMate 214 is that patients didn't have to receive all 4 doses of ipilimumab to go on to receive maintenance therapy, which is more real-world experience with the regimen. And what we saw is that the study actually met its primary endpoint, and there was an improvement in progression-free survival with the addition of cabozantinib to nivolumab/ipilimumab, and as we hoped, the PD as best response was cut in half from 20% down to less than 10%. So I think very remarkable, a positive trial with a modern comparator. Overall survival data at this point remains immature and there were some notable toxicities in that 25% of the patients had grade 3 or higher ALT abnormalities, a large proportion of patients required high-dose steroids, but certainly commendable trial. I think a longer-term follow-up is really going to determine how we're going to use this regimen in the clinic because, of note, while subset – you know, it seemed like those poor-risk patients where you'd think, oh, we just need to go all in, give the most therapy – maybe didn't derive the benefits. So I think longer-term follow-up, further analysis of the data is going to be really important.

And then in terms of non-clear cell, we had another trial looking at the role of IO/TKI with lenvatinib and pembrolizumab in non-clear cell or variant histology renal cell carcinoma and really reinforced what we'd seen with data presented for nivolumab and cabozantinib, where in those patients with variant histology renal cell carcinoma, specifically excluding the chromophobe disease, there was a 50% objective response rate, and really highlights the role of, you know, that we can do these trials in this variant histology renal cell carcinoma and that we can achieve better outcomes for these patients.

And at ESMO we saw data from the KEYNOTE-B61, which is a single-arm, phase 2 study that was evaluating pembro plus lenvatinib as first-line treatment for that same population. So this studied patients with advanced, untreated renal cell carcinoma with variant histology, and they were given lenvatinib and pembrolizumab, and they had close to 150 patients, which is quite remarkable. And what we saw is an impressive response rate overall with objective response rate approaching 50% in the initial analysis, and we saw activities in papillary, unclassified translocation similar to what we saw with cabo nivo; chromophobes stand a same-level response. Now, it wasn't zeroes, but it was only 13%. This data really does highlight that we can do more in those patients with variant histology renal cell carcinoma.

Trials are possible, and through these trials, such as this one and others, we can hopefully continue to make progress and supports the ongoing trial, the cooperative PAPMET2, which is looking at cabozantinib and atezolizumab versus cabozantinib in those patients presenting with de novo papillary renal cell carcinoma.

Dr. Jonasch:
Yeah, it's amazing that we're finally now getting to a point where we're able to, A, sort of look at the so-called non-clear cell population and have some effective agents and, B, really being able to start understanding that in that broad category there are certain subsets that benefit differentially from these combinations. For example, papillary renal cell carcinoma patients are benefiting from combinations like lenvatinib and pembrolizumab or cabozantinib and nivolumab in ways that, for example, chromophobe does not, which, of course, leaves us with that unmet need in the chromophobe population, but clearly progress.

And it's really cool to see how we're finally getting therapies for what we call a non-clear cell histology, and we're beginning to get this idea that treating papillary differently from chromophobe differently from other of the less common histologies is probably going to be important in the next couple of years."

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Eric Jonasch, and here with me today is Dr. Bradley McGregor. We're discussing selecting and sequencing immunotherapies for patients with advanced RCC.

Dr. McGregor:
You know, as we just heard, you know, with COSMIC-313, we had quite a bit of immune-related adverse events [irAEs].

So, Dr. Jonasch, what do we need to keep in mind as far as immune-related adverse events when we're discussing these regimens with our patients?

Dr. Jonasch:
Yeah, probably the listeners are familiar with irAEs to a significant degree. I think one of the key things when we're treating individuals with these IO/TKI combinations is how to distinguish between whether this is an IO complication or a TKI complication and how to address that. And one of the key practice points is that when you have an individual that has a moderate level AE, which could be from both, the great thing is you can hold the TKI, and you can take a look at whether or not that adverse event diminishes, and that way you

can modulate and titrate the TKI to be able to manage it. It's different from an IO/IO combination where you know it's obviously all IO. But the things that we really are looking for here, we're looking at the diarrhea, we're looking at the transaminitis, and we're looking at nephritis. These are the ones that I'm really thinking about when I'm treating my patients, and being familiar with these adverse events and managing them is critically important. But the other thing that sort of gives us, I think, a little bit of comfort is that there are data out there that suggest that individuals who develop an irAE are more likely to have a response, so it's a little bit like what we saw with TKIs; those who had hypertension had a better response. Here, we're seeing that evidence of activation of the immune system. Even if it's not exactly what you wanted at that moment in time, it is associated with a higher probability your patient doing better.

Dr. McGregor:
Yeah, absolutely, and for those patients IO/IO alone, I think we both have patients in the clinic that had to stop immunotherapy for a treatment-related adverse event, and, you know, they can go on and do quite well off therapy for an extended period of time. So I think better understanding of immune-related adverse events and who gets them is important, but as you said, we may not be able to avoid those because they may be associated with the efficacy that we're obviously looking for.

Dr. Jonasch:
Yeah and, you know, so many different treatments coming out and varying degrees of availability internationally and regionally. Dr. McGregor, what are some of the regional considerations for the treatment of renal cell carcinoma?

Dr. McGregor:
Yeah, I mean, you and I are both very fortunate that we practice in the United States where, you know, we probably are able to get drugs into the clinic the fastest through the FDA and the accelerated approvals based on early data, but that's not the same everywhere. And so there certainly can be a significant lag in when a drug combination or a new drug gets approved in the United States versus where it may be approved elsewhere, and that can be quite challenging. You know, it really gets to the understanding of what the FDA views as important. It may be slightly different from what the EU views as important in terms of outcomes and confirmatory data, and as trials are developed and, thinking about this, it's really important to say is how will this trial lead to approval not in the US but globally so we're not limiting that approval to just one small population. And then obviously the delayed approval can sometimes make some of these trials more challenging to understand, you know, if – based on where patients are enrolled, what may be available second line or third line. If it's different, that can obviously sort of cloud some of the – specifically the overall survival data as we look at some of these trials. So I think this is something that is certainly evolving. Every single meeting now it seems like this is something that's being brought up more and more is how we can sort of harmonize guidelines so that we can have access to these drugs and these novel therapeutic regimens across the globe, not just in one area of the world.

Dr. Jonasch:
Yeah, great points, and I guess at the end of the day, if the therapy provides a clear, powerful improvement for key parameters compared to comparator agents, this ends up becoming an easier sell, I think, for regulatory agents and for, you know, value propositions around the world, and I think the great news is that a number of the regimens that we are talking about demonstrate this and demonstrate the value for our patients.

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

Dr. McGregor:
Yeah, I mean, I think it has been a great discussion. I think take-home message really is that doublet therapy in the frontline setting is really the mainstay of treatment, and it's really based on clinical factors right now, and I think – I hope that through continued work and also trials that will be done, we may be able to, as you pointed out, have some nice sort of biomarkers to help choose the right therapy for our patients.

I mean, I think it's certainly a very exciting time to be a GU medical oncologist treating patients with kidney cancer, and we have so many different options we can discuss with our patients at this point in time, and I think what we've seen overall is it's clear that, you know, intensification of therapy in the frontline setting is critical, and doublet therapy really is the mainstay of therapy, be it a double immunotherapy combination or an IO/TKI combination. I think further studies are ongoing, and I think that they're going to help us in multiple ways. I hope through the studies that are ongoing we may find biomarkers so we can have that discussion with our patient, hey, based on what we see in your tumor, this has the best chance to offer you a response. And I think, also, we have trials ongoing. We saw the first triplet data with nivolumab, ipilimumab, and cabozantinib, and there's ongoing trials looking at building on lenvatinib and pembrolizumab with another CTLA-4 inhibitor or the HIF-2 inhibitor belzutifan. And I think these trials will hopefully continue to move the needle forward because I think what we're hoping now is with these treatments is that there is a minority of patients that we may be providing that durable long-term control, and we want to do that for more of our patients, and I think it's only through ongoing trials and

collaboration with our patients that we're going to do that.

Dr. Jonasch:
Yeah, great points, Dr. McGregor, and having the right therapy for the right patient at the right time is something that we're slowly getting closer to. But also, I think my take-home is that we need to involve the patient in this decision-making. And the concept of shared decision-making is something that's really, I think, emerging and evolving in oncology and making sure that the decision of which treatment, because there's a number of different treatments available, the patient chooses, informing the patient in a way that they're able to make the best choice for themselves, and also when the patient's on therapy, enabling the patient to adjust treatment, to hold therapy if necessary, to inform the treating team of their side effects, actually really ends up making the patient do better, live longer, and feel better. So really, really exciting time, completely agree, and looking forward to seeing what the next 5 or 10 years are going to bring.

Unfortunately, that's all the time we have today, and I want to thank our audience for listening in and thank you, Dr. McGregor, for joining me and sharing all of your valuable insights. It was great talking with you today.

Dr. McGregor:
Absolutely. It was a pleasure speaking with you and a great discussion.

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