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/personalizing-care-within-the-rcc-treatment-paradigm/29528/

Released: 03/13/2025
Valid until: 03/13/2026
Time needed to complete: 60 minutes

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

Personalizing Care Within the RCC Treatment Paradigm

Announcer:
Welcome to CME on ReachMD. This activity, titled “Personalizing Care within the RCC Treatment Paradigm” is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Chapter 1

Dr. Jonasch:
So the first section here, we have multiple sections here, and we're going to start off with the importance of risk assessment models to direct treatment.

And so our understanding of prognostic factors in renal cell carcinoma is definitely evolving. We have moved from the IMDC and MSKCC criteria, which I'm going to be talking about in the next couple of slides, to beginning to understand that there's a variety of molecular factors, including chromosomal copy number changes, as well as particular mutations that do provide prognostic information in a renal cell carcinoma. Ones that I'd really want to highlight here are 9p and 14q loss, which are associated with worse prognosis. And there are some great papers by Samra Turajlic’s group at the Crick in London, demonstrating that these are probably essential elements to enable metastasis to form. If you don't have these, you probably won't develop metastases.

There are some additional, what I would call, secondary mutations. So you have a primary mutation of VHL, and then you have these secondary mutations in BAP1, SETD2, and others that are sort of more lethal, again, like CDKN2A mutations that are associated then with more malign behavior and the increased risk of lethality.

There's some protein expressions, HIF1 alpha expression actually, is kind of interesting. It’s probably not in the tumor, it's probably in the microenvironment in the immune cells, but higher HIF1 alpha expression. We've published this a couple of years ago showing that that's negative prognostically. High Ki-67, which kind of just shows that there's more cell turnovers. It’s got somewhat of a universal sort of thing that's associated with worse prognosis. And low carbonic anhydrases 9, which is a protein that's actually driven by loss of VHL and high HIFs, but as you get more dedifferentiated tumors, this will start going down. And there’s various gene expression profiles as well. But none of these are used in clinical practice in 2025, and so what we really need to do as a field in renal cell carcinomas move from these being intellectual curiosities into something that we can really use for our patients.

Things that we can use for our patients are things like this MSKCC prognostic model. Very simple. It's 5 features that you can see here, and this was done back in the day when we were treating patients with interferon. You can see that it's associated with different prognoses. Similarly, the IMDC prognostic model has almost the same number of features. One is replaced by high neutrophil count and high platelet count, and once again, a very nice differentiation here. But what's interesting is that although this is used to differentiate in terms of how we treat people, as you can see here – or it was – now, we are kind of using the same drugs whether individuals have favorable or intermediate- and poor-risk features. And that doesn't mean that these criteria have ceased to have prognostic value. They still have prognostic value, we’re just at a time in therapeutic history, if you will, in renal cell carcinoma where now, the treatments have all converged and look pretty similar.

What we do see is that individuals who have intermediate/poor-risk features, that there's a difference between whether you give things

like an IO/TKI combination versus sunitinib. And you can see here these are Kaplan-Meier curves of survival for ipilimumab/nivolumab and the 3 IO/TKI regimens we use. But what's striking is when you then look at the favorable-risk subgroup, that there is no difference in overall survival between sunitinib and ipilimumab/nivolumab, lenvatinib/pembrolizumab, cabozantinib/nivolumab, and pembrolizumab/axitinib. So what does this mean? This means that, to me anyhow, that favorable-risk as defined by these algorithms has a distinct biology, but we aren't doing a particularly good job of developing therapies that actually speak to that biology. So it means job security for researchers, and we'll be able to hopefully come up with better ways to treat these individuals.

So in summary, we use these risk calculators because they are prognostically useful. They do give us a sense in terms of, therapeutically, that we know what to anticipate from an overall survival perspective. But they're not really differentiating between the regimens at this point in time. And it really is important, I think, as we move forward as a field that we get smarter and better.

Chapter 2

Dr. Jonasch:
Well, let's move on now to potential biomarkers and emerging endpoints. So what we're going to do now is we're going to have a panel discussion, and the question really is, for my colleagues and for anyone in the audience, is what should we be doing with biomarkers? So, Ulka, do we have anything here that you use, whether it's for clear cell or non-clear cell? What's your take on biomarkers at this point in time?

Dr. Vaishampayan:
Yeah. I mean, I think for clear cell cancer, which is the predominant one, I start with IMDC because IMDC is really what we use across the board, and it really involves patient characteristics as well as cancer characteristics. So if there's bulky disease, that's going to impact, sometimes, the calcium levels, the hemoglobin, all of that. So I think IMDC is a good baseline, but clearly it doesn't include all of the poor prognostic characteristics that we consider. For instance, the site of metastases, so liver mets, brain mets, I mean, those are bad news. Bone disease is very bad also in advanced kidney cancer. So those are things that are not quite completely factored into IMDC, but they do factor into our decision-making. Again, symptomatic disease would be another one that would factor in. So I think there is some baseline IMDC use, and then you have to factor in some other characteristics.

Dr. Jonasch:
So your biomarkers really are clinical –

Dr. Vaishampayan:
Clinical biomarkers.

Dr. Jonasch:
– clinical factors that would guide you.

Dr. Vaishampayan:
Yes.

Dr. Jonasch:
So specifically for bone metastases, how would that change your approach? Are there regimens you would favor over others?

Dr. Vaishampayan:
I think I would favor more of a VEGF TKI and IO combination for bone metastases, especially if there are multiple areas of mets. Also, the weight-bearing bones, there is an increased risk of fracture. Bone mets in kidney cancer tend to be very lytic and because of that, pathologic fractures and skeletal-related events, so to speak, are very high likelihood.

This is one disease where PD-L1 status, at least the way we check for it, has not been proven to be a guide for therapy, so regardless of PD-L1 positive or negative, you are going to use immune checkpoint therapy, typically, as the backbone. So that is somewhat a unique feature of kidney cancer, I feel.

Dr. Jonasch:
Great. So, Brad, in terms of new trial endpoints, obviously, we're using progression-free survival. The FDA sort of wants us usually to have PFS and OS, but what about things like treatment-free intervals, quality of life metrics, and also the idea of a landmark analysis? Do you think that these should become tools that we use in practice or things that the FDA should be using for approval strategies?

Dr. McGregor:
So, I mean, I think great points. I mean, we have all these trials that are showing benefits to our patients and how do we better characterize those benefits? And this is looking at different ways of doing so, right? So I think quality of life is something that's incredibly

important, but that's really based on the instrument you're using to assess quality of life and you're asking the right questions. So I think there's a lot of effort to sort of rethink our quality life analysis and making sure we're asking the patients the right questions to get the right answers so we can better characterize how this management is really affecting the patient.

I think treatment-free survival is something that we talk about a lot, and I think it's something that, as we think about these therapies that provide durable responses, is there an opportunity to stop therapy and let the patient not have to worry about coming in for infusions once a month or taking a pill every day for maybe months or even years. So I think this will lend itself very well to the IO-only regimens because, in general, we stop at a predefined time. I think that IO/TKI regimens right now, the standard care is once you start a TKI, you sort of stay with it. That treatment-free survival has a much more challenging endpoint. And finally, I do think landmark analysis is just helpful because it gives this idea for that potential durability, right? Like, what, 2 years, 20-something percent of patients are still doing well on the same therapy. And it gives you some idea of that durability. And sometimes the situations like we see with belzutifan versus everolimus, where the median progression survival isn't that impressive – it's almost exactly the same between the 2 arms, but then you look at those tail of the curves, those landmark analyses, it really sometimes tells a little bit different story, and so it can help frame that. And I think it is really helpful to talk to the patient, right? When you see a patient in the clinic, well, this study shows that at 2 years, X percent are doing well. I think it's a very tangible endpoint patients can hold on to.

Dr. Jonasch:
Yeah, it's interesting. The hazard ratio does incorporate that information, but it's hard to sort of talk to a patient about what does a hazard ratio mean for them. And the same thing as you're saying, these quality of life instruments. We have the FKSI and the EORTC and the this and the that, and then to say to the patient, well, there's a 2-point difference in this regimen versus that regimen. What does that mean for a patient? So there's a great abstract if you're going to be looking at the abstracts on Saturday, Cristiane Bergerot has worked on trying to get something that's a little bit more tailored for patients with renal cell carcinoma. But I think we really need to work on these things because we do have equivalent-ish regimens where I don't think there's equivalent quality of life.

Chapter 3

Dr. McGregor:
All right, so you have 7 minutes to talk about every single trial that's done to change treatment for renal cell carcinoma, so buckle up. So as you think about this, I think that there was a year where every single meeting had a new phase 3 trial. And as you think about this overall, as we saw from the initial slides, we generally think about it as the IO/IO regimens versus the IO/TKI. IO/IO is really only one regiment that was nivolumab/ipilimumab and again, this was nivolumab/ipilimumab versus sunitinib. Nivolumab/ipilimumab for 4 cycles. In this trial, the nivolumab was actually given indefinitely. I think in modern trials, we're not doing that. This led to FDA approval specifically in those with intermediate- or poor-risk disease, really just because of the way the trial was designed, because that was the primary endpoint. Although, as you saw, with the extended follow-up those patients with favorable-risk disease actually seemed to derive a benefit as well with numerically superior overall survival in long-term follow-up.

The one issue with nivolumab/ipilimumab is that, yes, we think we are curing patients, maybe around 20% to 25% depending on your optimism level. But at the same time, there is a high PD as best response rate around 20%. There is some nice data that those patient's sarcomatoid features had better outcomes. Response rate up to 60%, CR rate up to 20%, although 20% PD as best response persists.

And as we see, their CR rates are independent of risk category. And these key factors here, these can be durable. So there's some really nice conditional analysis where we're showing that, hey, if you're responding at 2 years, what's your chance of responding 3 years later? And really, if you get that response at 2 years, your chance of maintaining that response for an extended period of time is over 80%.

So we really do think that not only are we providing these patients short-term benefit, but there's really a hope that we are curing patients, and they can stop therapy and not have to worry about that.

At the same time, the other trial we have of the IO/TKIs, these are all far more alike than they are different. All looked at IO/TKI with IO again for 2 years. TKI continued indefinitely versus sunitinib. The first was KEYNOTE-426 with the combination of pembrolizumab and axitinib. And what we see here is the extended final analysis. There is an improvement in overall survival in intention-to-treat population, and we see that there is a higher response rate than we see with nivolumab/ipilimumab and a comparable CR rate. And the big difference here is the lower PD as best response. So pembrolizumab/axitinib right around just over 10%, CheckMate 9ER, this is the combination of cabozantinib/nivolumab. This regimen is different in that the dose of cabozantinib is 40 mg. We figured out monotherapy is at 60 mg. This is the only trial where the dose of TKI was lower with the combination.

Again, we see a doubling in progression-free survival. We see an improvement in overall survival. We see a very low PD as best response rate at less than 6%, and we look forward to seeing the final OS results that are going to be presented in an abstract on Saturday.

And finally, we have CLEAR. This looked at lenvatinib/pembrolizumab. So this trial, the TKI dose of lenvatinib is 20 mg, so higher than we use with lenvatinib/everolimus, lower than the technical monotherapy dose. Highest numerical response rates, over 70%, very low PD as best response rate, and very, very impressive hazards for PFS, although with overall survival as you go further and further out, the curves get closer and closer together. But certainly, another very compelling option.

Across the board, I think the IO/TKIs offer much more rapid responses. We see an early separation of the curves, although the durability is really unknown. And as you already saw from NCCN Guidelines, now if you look at the preferred options, really any combination is a preferred option, independent of risk categories. So even though nivolumab/ipilimumab right now is only FDA-approved in the poor risk, it is an option for all risk options.

But unfortunately, as great as these results are at curing 20% of patients with nivolumab/ipilimumab, patients do progress. And so, what do we do next, right? So if a patient does progress, what we do next? And if you look at the NCCN Guidelines, it really tells us where we're at. There's no preferred regimen for if a patient progresses on immunotherapy. What to do next? What we do know, though, is things we shouldn't do. And so I think we had 2 key trials on the role of continuing an immune checkpoint inhibitor beyond progression. So there's CONTACT-03 which looked at cabozantinib/atezolizumab versus cabozantinib. This trial focused on TKI dose, so cabozantinib was at 60 mg.

Other issue is patients had received immune checkpoint blockade right before they went on trial. TiNivo-2 tried to do a different approach. They used a PD-L1 inhibitor with nivolumab. Tivozanib actually, per concerns about hypertension, was lower in the combination arm versus the monotherapy arm. And patients did not have to receive immune checkpoint as the most recent therapy. They could have had immune checkpoint, intervening TKI, and then go on the trial.

At the end of the day, neither one showed a benefit in terms of progression-free survival or overall survival, and when we look at CONTACT-03, there is no difference and increased toxicity. When we look at TiNivo-2, no difference – no increased toxicity, but numerically worse outcomes. And to me, I think that these trials really highlight the need to prioritize TKI dosing over combining with immunotherapy, and it shows that TKI does not rescue immune checkpoint blockade. Not to say we shouldn't invest in novel mechanisms of immunotherapy, but TKI plus immunotherapy is really not the answer.

In terms of dosing, we have a poster on Saturday looking at the ER data for tivo, really highlighting that they got the dose right with 1.34.

Finally, what about novel approaches? I think everolimus versus belzutifan. This is a key trial that led to FDA approval of belzutifan, a HIF-2 inhibitor. So this was belzutifan 120 daily verses everolimus, and patients progressed on immunotherapy in VEGF. It doesn't need to be sequential; it could be an IO/TKI. And what we see here is an improvement in objective response rate over 20% versus less than 4%. No CRs, but a quite high PD as best response rate at 34%. Although, as alluded to earlier, sometimes the hazard ratios don't tell the whole story. If you look at the duration in response for those patients who do respond, those 20%, it seems to be durable. This is why we see the PFS, no difference in the median PFS, but when you look at 24-month analysis, close to 20% are doing well. This did not translate into a numerically statistically significant improvement in overall survival benefit, however.

Chapter 4

Dr. Vaishampayan:
Okay. So now we're going to switch gears, and this is an even tougher topic to talk about: non-clear cell histology. Now, we've typically extrapolated from clear cell into non-clear cell, really, although all of the studies that Brad discussed were all required clear cell component as an eligibility criteria.

So for the most part, non-clear cell histology is a very mixed bag and that has been the biggest challenge because it's really a number of diseases that we put under this umbrella of non-clear cell because we don't know where to place them. And each one has its unique genetic composition, and each has its unique, somewhat, clinical features also. But because of really not knowing exactly what to do, there are clinical trials now that are specifically non-clear cell that we are trying to learn from. But it looks like both VEGF TKI and maybe IO combinations might be something to consider, and we'll see why.

So here is the NCCN Guidelines for systemic therapy for non-clear cell. Not terribly helpful. If there's a clinical trial, I absolutely look for it because there's no clear-cut, proven therapy, except for cabozantinib in papillary kidney cancer has been established in a phase 2 randomized trial. But again, there is no major curative therapies for metastatic non-clear cell that we can really tout as something that we have to treat. If the patient has some sarcomatoid features, regardless of which non-clear cell histology you're dealing with, definitely use an IO-based regimen. But that's about all we can say from this, and all of the regimens are listed there. As you can see, the same things that were tested in clear cell are listed here.

So this is the phase 2 SWOG PAPMET trial that established median PFS of cabozantinib at 9 months. There were some other MET

inhibitors that were tested in this and in terms of feasibility, some of them fell apart and did not quite make it. This is the next-generation study that is currently ongoing, so think about this if you have a metastatic papillary cancer patient where you can randomize to cabozantinib single-agent or cabozantinib plus IO-based regimen to establish if frontline combination does make sense in metastatic papillary cancer, which we don't know for sure.

This is a phase 2 trial of cabozantinib/nivolumab, so sort of that VEGF/IO combination, in 40 patients that showed response rates pretty decent, 48%. So very promising results for the combination and that's what we are trying to look at in a phase 3 setting, if the addition of IO does truly add overall survival or PFS benefit.

This is the KEYNOTE-B61 trial, which is also a single-arm study, based on response rates across multiple different non-clear cell histologies. And this actually showed fairly promising responses. So this was a combination of lenvatinib with pembrolizumab, and it showed response rates, about 50%, in majority of the histologies. And this is the PFS and OS updated recently in the last year's meeting, again showing very promising median PFS and OS results, one of the best seen and longest PFS seen in non-clear cell histologies. So something to keep in mind as the data we have.

Now, this was an interesting study that was reported at ESMO, the SUNNIFORECAST trial. And this is the study design of that study which is comparing sunitinib as standard therapy at the time the study was started, only in non-clear cell histology, again, as compared to ipilimumab/nivolumab, so only immune checkpoint combination was compared here. And overall survival was the primary endpoint. And interestingly, the combination of ipilimumab/nivolumab did show a benefit in terms of overall survival. So this is a provocative trial, again, with results that show that maybe the immune checkpoint combination does hold a lot of credibility in terms of therapy consideration.

So at present, VEGF-based therapy, VEGF/IO combinations, or now IO/IO combinations are something worth considering, and that's why the clinical trial pathway is kind of important to establish which one of these therapies we should really use.

And here is the different OS by PD-L1. Again, PD-L1 was not terribly helpful, but definitely here, it seemed to show a sliver of difference that favored the PD-L1-positive patients. So, again, something to consider in non-clear cell histology. Genomic testing may hold a role that is bigger in non-clear cell as compared to clear cell from what we know so far. There are also multiple genetic syndromes, germline syndromes, that you need to recognize and have a discussion with the patient that are in conjunction with multiple non-clear cell histologies.

So I sort of crystallize it down to these things: review the pathology, think about genomic sequencing because it may help you both germline as well as somatic, consider resection of metastatic disease. Here, surgery should maybe hold a bigger role because systemic therapy is not that great, as well as if sarcomatoid features, obviously consider the ipilimumab/nivolumab or immune checkpoint-based regimen. And in papillary cancer so far, standard frontline therapy, either cabozantinib single-agent or pembrolizumab and lenvatinib appear to be standard therapies based on phase 2 trials, so now phase 3s. And as I said, all advances in kidney cancer and other cancers, I would say, are made through clinical trials, so please help your patient and others in the long run.

So this is my pitch for clinical trials.

Chapter 5

Dr. Vaishampayan:
Kidney cancer is a multifaceted disease, and it is a heterogeneous disease. I think anybody who has dealt with kidney cancer will agree with that. There are some patients who go for years and years with barely any progression, and then there is, unfortunately, the predominant disease which is progressing rapidly unless you really are able to treat and make an impact on the outcomes.

The other thing I think that that favorable-risk group, as we as we followed it out, what it highlighted for me was that there are a proportion of people, more than half of them in fact, are dying from the disease even in the favorable-risk group. So that was an eye opener, which for the longest time, people thought, oh, you have time, you could do easily sequencing from one treatment to another, and they are not really going to have too much of a risk to their mortality. But even within the 8 years, we're seeing that.

So it takes a village to treat kidney cancer, and I think you need multiple disciplines participating and giving you input. You know, medical oncology, of course, and then pathology review. There is involvement of urology and radiation oncology for palliation, oligo mets, et cetera. Nursing, pharmacy, social work, psychosocial care, palliative medicine, of course. So you do need multiple disciplines to work together towards a common goal, which is to improve the outcome of the patient.

Multidisciplinary care has been shown to improve overall survival, specifically in metastatic RCC. This is a single-center retrospective study with all the limitations possible from a retrospective study, but basically, for the patients who were selected out for multidisciplinary care had much better outcomes. I mean, we all know that, and we should try to involve multiple disciplines in the patient's care as much

as you possibly can.

The other thing is, where do we involve surgery in this? That has become a very, sort of burning topic because we have controversial data with the initial immunotherapy, like interferon when we had lousy systemic therapy, nephrectomy – cytoreductive nephrectomy, even in metastatic disease, played a big role. Now, even with sunitinib-based regimen, that was shown to be not true, where nephrectomy did not help improve outcomes, now we think that deferred nephrectomy – so give systemic therapy first so the patient is not deprived of their main active treatment, and then considering nephrectomy. So the principle is that you leave the primary neoantigens in place so you can activate the immune system much better against multiple antigens within the tumor, and then you remove, potentially, the resistant clones. So that is being addressed with this PROBE trial, which is after initial 12 weeks of systemic IO-based regimen, any of the FDA-approved regimens you can use. You randomize the patient to nephrectomy or continued systemic therapy without removing the kidney. Primary endpoint in the study is overall survival, so think of this study if you have a patient with synchronous metastatic disease.

Other things with RCC where focal therapy can make an impact, more and more, we are beginning to use radiation therapy. Keep the systemic therapy backbone going. If one or 2 areas are progressing, you use radiation to address those. Keep going with the same treatment. So that oligo progression, et cetera, has been shown to be helpful. Sometimes, after nephrectomy, if there is one area of disease where the patient has relapsed, also that can be addressed with radiation. So radiation is beginning to have more and more impact and application in advanced kidney cancer.

This is the SAMURAI trial, which is looking at the role of addressing the primary with radiation. Again, same thing. Start with systemic therapy and then randomize patients to receive radiation to the primary instead of doing surgery, as compared to continuing on systemic therapy. So there is a randomized trial addressing that.

So I just think about the differences between IO/IO therapy versus IO/TKI. In my view, sarcomatoid features, I think, you should warrant considering IO/IO. Then also, if the patient has the reserve to tolerate severe immune-related events, because clearly, IO/IO, about 30% of the patients are likely to get significant either immune colitis, pneumonitis, et cetera, so those are the things that you need to think about. Long-term survival goals absolutely are important, good organ functions. If patient has had recent severe thromboembolic events, I may lean more towards IO/IO because it is not likely to increase their chances of worsening thromboembolism. And then any recent arterial events, so MIs, CVAs, again, may make me lean towards IO/IO.

For IO/TKI symptomatic patients, because IO/TKI, majority of your patients are going to show some tumor shrinkage, so at least you will make the patient feel better relatively quickly. Severe visceral disease, liver mets, recurrent pleural effusions, pathologic fractures, these are things where I would prefer to go with IO/TKI. No major risk of cardiac diseases helps. Brain metastases, because you are using steroids and stuff, so you want the TKI to sort of help you get some response. On patients on immunosuppression. I mean, and there it's questionable even whether you use that single IO, depending on what immunosuppressive or autoimmune conditions the patient has.

So excellent supportive care, no matter which regimen you use. This is a critical piece. Monitor the toxicities, get the patient through the treatment well, feeling as well as they can be. Maintain their quality of life. These are going to be things – and for kidney cancer, you do need to think longer term because these people are, chances are, are going to be on these treatments for a couple of years maybe, and so you want to think of the longer term, not the immediate. Don't try and push the dose. If you need to reduce the dose of the VEGF TKI because, if the patients can stay on the therapy longer and continue their benefit, that is important.

So I summarized some of the toxicities here, but of course, Brad will discuss those more in detail. And involve the dermatologists or the specialists that you need, different specialists depending on the need of the patient and the required toxicity monitoring.

Shared decision-making is another big piece of cancer care. And our kidney cancer metastatic disease – granted, we have all these multiple regimens, so our discussions are getting longer and longer, but we do need to be able to explain to the patients the mechanism and what to expect with each of the treatments. What kind of social support they are going to need, what they should ask for, what help they should get from their friends, family, whoever, and have that lined up. And of course, what to read and focus on, even in the education materials that you're giving them because, granted, the education materials are sort of like our medical textbooks. Let's face it. They have 50 things listed and none of that tells us what to focus on.

So the role of shared decision-making and planning treatment regimens is critical, and patients and their families need to be involved, whoever they think important and whose opinion they seek, and the complexity of cancer care. So they need to have all the cancer-related information. And like I said, the critical pieces need to be highlighted for them to understand.

Chapter 6

Dr. McGregor:
All right. So the title of this says safety takes a multidisciplinary village. I think that's great, but I think we also need to realize that that's

not always possible, right? I mean, I think when you need multidisciplinary care, we know that specialists can be very challenging. It's challenging in academic center. It can be very challenging to the community. So I think it does come down to really engaging with the patient, your nursing team, everyone, so you can recognize things early. Because I think if we can intervene early, we could make a huge difference.

So when you think about the toxicities of these agents, immunotherapy has one set of toxicities; TKIs have another set of toxicities. I'm showing 2 sort of key trials here. CABOSUN looked at cabozantinib versus sunitinib, and I think what we see was major side effects are fatigue, hypertension, diarrhea, and LFT abnormalities. What we don't generally see with the newer TKIs much in the way of myelosuppression. And then we look at something like single-agent nivolumab with that 025. Again, the number one side effect is fatigue, then followed by nausea, pruritus, and then diarrhea and decrease appetite. So already say just look at the most common side effects. Fatigue is number one in both arms. So fatigue, I find, is one of the more challenging toxicities to manage. But then diarrhea is certainly high up there in both arms.

So when we start looking at these combination therapies, how can we really choose which is the offending agent? How do we adjust things overall? So I think we can think about timing. I think this has been a slide that's been around a lot. I think it can help, but in no way is it definitive, right? You're going to get patients that start immunotherapy, and they get a Grade 3 colitis within 24 to 48 hours. So I don't think you can say, oh, it's too early for IO. IO doesn't follow the rules. It's never too early; it's never too late. Any time is just right for IO. It can happen at any point in time.

Now, in general we say, oh, well, some of these side effects happen earlier versus some later, but I think that's incredibly challenging. So if we look at the toxicities of the combination regimens, and we look at nivolumab/ipilimumab, 60% of patients required steroids, about 30% required high-dose steroids. We can see rash is very high up there followed by diarrhea, hepatitis, and really, this is one of the earliest trials of immunotherapy in renal cells, so I think we learned a lot and I think those numbers may be slightly different today.

And then we look at the IO/TKIs. They're all, again, a little bit more similar than they are different. Diarrhea sort of leads the pack for all of these. But then we start seeing some slight differences. Maybe some more hypertension with axitinib and lenvatinib than with cabozantinib. Maybe less severe Grade 3 with cabozantinib/nivolumab. Less LFTs with lenvatinib than pembrolizumab/axitinib. But I think there are a lot of similarities in general, anywhere from 15% to 30% need a high-dose steroid for management of immune-related adverse events with these agents.

So how do we really manage these toxicities? I think as you think about that, we manage VEGF TKI toxicities through supportive care, so antihypertensives, antidiarrheals, thyroid replacement. And then dose holds and dose reductions. And I think that's really critical to educate the patient on day zero, before they get their pills. Ulka said, it's okay. We're going to start you at this dose. This is a dose they studied in the first time, but everyone dose reduces. That's perfectly fine. So educate the patient early on.

Immunotherapy, supportive care, again, for the rash, corticosteroids as needed. We can delay, but we can't modify the dose anyway. And ultimately, at the end of the day, you just want to pick your guideline on how to manage immune-related adverse events and just use it all the time and just follow it. And the more you follow it and do this on a regular basis, it's critical.

Getting to the dose adjustments, just to show you how common it was. So I put an axitinib/avelumab in here as well. This was no PFS benefit. It actually is one of the better tolerated, probably because of the PD-L1, less immune-related adverse events. But if we look at this overall, the patients who needed dose reduction, even with cabozantinib/nivolumab where you start at 40, over 50% of the patients required a dose reduction. With lenvatinib/pembrolizumab, close to 70% required a dose reduction. Then, we start looking at breakdowns of needing stopping therapy. I think that goes down much lower. It's probably one of the lowest for our cabozantinib/nivolumab, higher for lenvatinib/pembrolizumab.

And so I think, again, this emphasizes the need to talk with our patients very early on. I tell patients, listen, this is a marathon not a sprint. I want to keep you on the highest dose that you can tolerate. I think there is some justification to start with a dose that we used in the trial, so with lenvatinib I start at 20; for cabozantinib I start at 40; for axitinib I start at 5. And I think if they can tolerate it, you stay, and reduce if they don't. I have a hard time starting at lower doses. In the second-line setting, we actually have a trial 18 and 5 lenvatinib/everolimus versus 14 and 5 lenvatinib/everolimus, and it actually seems like the numerically better outcomes were starting with lenvatinib 18/5 and, actually, better quality of life as well. Potentially, with better disease control.

So as an idea of how to do this, as you look at the IO/TKI regimens, a lot has been published most on axitinib just because it has the shortest half-life, so it's the easiest to figure out. But I think at the end of the day, as you look at diarrhea, hepatitis, the important thing is if you're at all concerned, just tell a patient to hold, right? I tell patients, hey, if you feel weird, just hold it and give me a call. So if there's concerns, hold it for Grade 1 to Grade 2. See what happens. You stop the TKI and things should get better within 24 to 48 hours, even with the longer half-life it can happen pretty quickly. If things are very severe, that's when you bring the patient in. Often with IO/TKIs, you think about doing an endoscopy, especially if there's any uncertainties.

Hepatitis, similar. Again, I think this is something that we get scared about a little bit more, less likely to rechallenge. But again, same

point. If they come in with their IO and their hepatitis is Grade 1-ish, I'm generally like, you know what? Let's just hold everything. I'm going to hold the IO today because I don't want to do something to push us over the edge. There's no harm in delaying overall. But again, the main point is, hold the TKI, see what happens, and understand that it doesn't happen overnight. Even with axitinib it can take 3 to 5 days, so just watch and look at those trends. So ultimately, management of toxicities is multidisciplinary and you need to use it to optimize success.

And finally, what about belzutifan? Belzutifan is not a TKI. This a HIF-2 inhibitor. It does not have the TKI side effects. It has very unique side effects. Anemia, which is managed with dose reductions, actually consider ESAs, and we have hypoxia. Patients won't tell you they're short of breath. They have to check their pulse ox. It will be low. And it's a very unique side effect to educate our patients about. Then again, as I alluded to, anemia, you can use EPO. Provided they have good iron stores, it works well.

This unique toxicity profile, I think, allows it to be combined with other agents well. And so I think trials are ongoing. There's combinations of lenvatinib with belzutifan, cabozantinib with belzutifan, and novel HIF-2 inhibitors with TKIs. So I think this is going to be coming soon to an earlier line near you.

Chapter 7

Dr. McGregor:
This is a 74-year-old woman who presents with anemia and hematuria, and imaging demonstrates a large enhancing exophytic left-side adrenal mass with extension into the renal vein. She undergoes nephrectomy for this T3a RCC. She doesn't get adjuvant therapy and she undergoes surveillance, and 3 years later demonstrates multiple bilateral pulmonary nodules, the largest measuring 1.1 cm in size. She has excellent performance status. She has some mild anemia, but she emphasizes that quality of life is important to her.

So, Ulka, what first-line therapy would you consider for this patient? And what discussion are you going to have with this patient about treatment?

Dr. Vaishampayan:
Okay. So except for anemia, the patient has no other actual IMDC risk factors, and even the anemia, I mean, the hemoglobin is somewhat borderline. 10.9 is not too bad, and definitely no symptoms related to that. So with lung-only metastases and relatively low-volume disease, this patient is expected to be pretty close to being a favorable-risk patient. And because of that, I think talking about the long-term goals, since this is a relatively asymptomatic patient again, I would have a discussion about considering IO/IO regimen in this patient. And if the patient is very concerned about the side effects, et cetera, of the possibility of doing the combination IO/IO, then I would go to a VEGF TKI and IO combination. But pros and cons to each approach, and this would be a situation that is perfect for shared decision-making to try and align the patient's goals with what you can discuss longer term. And the VEGF TKI/IO combination allows the patient to have both some response right away, as well as long-term outcomes, potentially.

Dr. Jonasch:
So, Brad, if I told you this patient has 4 lung metastases. So it's not clear here and they're not symptomatic, but they're small, 4, the largest still measuring 1.1 in cm in size. Would you consider referring this patient to radiation oncology?

Dr. McGregor:
Yeah. I mean, I think that's one of the key questions, right? What is the role of local therapies? Or even, what's role of systemic therapy? I think we have nice data from Brian Rini that our observation approach with close follow-up can be utilized in some of these sort of more indolent courses. Lung-only mets, over 2 years since the nephrectomy, has really borderline anemia, I think a surveillance approach is not unreasonable to get a better sense of disease status. I think without randomized trial, we always feel better if we do something more, so with those 4 mets, if our radiation oncology colleagues can zap those with limited toxicity, I think that's certainly very compelling. And there's trials that are ongoing right now trying to answer will this definitely improve outcomes? I think maybe in things like prostate cancer, we know it does. I think in renal cell, it hasn't been nearly as well established. The more I get, the less optimistic I am. I think we have pretty good data for surgery, that less than 3 mets, lung-only, surgery can potentially be a cure in about a third of patients. I still don't know the answer yet for radiation. But I do know that radiation does work in renal cell. This idea that renal cell is radioresistant, that's not true provided you are giving effective doses of radiation and collaborating with your colleagues.

Dr. Jonasch:
Yeah. So the study that you're referring to that Brian Rini published in *Lancet Oncology*, I think in 2016. So it showed that individuals, in the opinion of the investigator, didn't need to initiate systemic therapy. The median time to progression was 9.5 months, and the median time to actually initiating therapy was 14 months, so there's real-world evidence. The interesting thing there, these were obviously favorable-esque-risk patients. The median survival was less than 40 months, so maybe in 2025 that's a little less amazing. So the jury's a little out on how long one should observe. But yeah, I agree with you, Ulka. This is certainly a person you would have that conversation with about IO/IO therapy. But it's going to be shared decision-making. What are the goals of the patient?

So this patient started on cabozantinib/nivolumab. She developed some diarrhea. She takes occasional treatment breaks. Nodules have gone away to the large part. She continued response. But we don't have a parallel universe. We don't know whether IO/IO or radiation would have been a better choice.

Chapter 8

Dr. McGregor:
All right, so this is a case of mine. 48-year-old-man with minimal medical problems presents to primary doctor with scrotal pain and swelling. He has a history of a DVT. No real active meds. He gets his labs. His hemoglobin is markedly elevated at 16. Otherwise, normal CBC and CMP. CT chest shows innumerable pulmonary nodules up to a cm in size, indeterminate bone lesion, liver lesion, and biopsy confirms that clear cell RCC. He has a huge primary with a horseshoe kidney with his varicocele that's going down into his testis from just the size. So very, very symptomatic disease in need of a rapid response.

We start him on first-line lenvatinib and pembrolizumab, and within 6 months of therapy his pain is better, his varicocele is improving. The lungs have actually all disappeared and then he starts progressing. And so now he has new kidney lesions as well as new pulmonary lesions. So what second-line therapy in a patient with relatively short response to lenvatinib/pembrolizumab would you think about as a second-line option?

Ulka, I guess this is for you.

Dr. Vaishampayan:
Okay. So, yeah. This is a really tough patient because they've already declared themselves very quickly resistant to both the VEGF TKI and an IO regimen. So I would probably go towards – I mean, we don't know how they tolerated this, but assuming it was decent, it's still a very short time of response. I may want to go to a HIF-2 alpha inhibitor at this point because, just to change the MOA, mechanism of action, and look at if that has better efficacy in this patient.

Dr. McGregor:
Eric?

Dr. Jonasch:
My first instinct would have been cabozantinib, but we do have real-world evidence that individuals who get started on lenvatinib and pembrolizumab, who then do get cabozantinib salvage, they have a fairly short progression-free survival. The thing I'm concerned about with belzutifan is, for those who do respond, they have a long duration of response, but there is a 34% PD as best response. And having said that again, I have multiple patients who have aggressive disease like this, who have then treated with belzutifan, who have had tremendous response. We just don't know how to categorize – We don't know what the molecular underpinning of these people are. They have some sort of HIF-2 addiction, which results in their diseases being aggressive. But the problem is, if you get it wrong for these people, you're in trouble.

I would do cabozantinib, and if they progress on cabozantinib, I would then go to belzutifan. But I think going to belzutifan is very reasonable.

Dr. McGregor:
So, yeah, this was a situation where he was young. His disease had been of liver, bone, and that actually looked better. So, like, his disease almost evenly progressed relatively rapidly. It actually didn't look as aggressive as it did initially. And with the marked elevations and his hemoglobin presentation, we were hopeful maybe belzutifan may play a role. So we elect to start belzutifan. The approval for belzutifan is for patients who progress on IO and VEGF; it doesn't have to be IO followed by VEGF.

So scans at 8 weeks shows stability of lesions. Hemoglobin starts to drop from 14 down to 10.5, and then 4 weeks later, he calls with new headaches, progressive fatigue, but no shortness of breath, and so the nurse tells him to check his pulse ox and it's 86%.

So, Eric, you're the HIF-2 expert here. How would you manage these events?

Dr. Jonasch:
Yeah. So in general for my patients that I do start on belzutifan, I tell them to get on to Amazon and order a pulse oximeter. You can get them for less than $15 and they work. And so, that way the patients can actually proactively check this. But for those who don't, for this individual, what I typically do here is I ask them to hold the drug. The drug has a half-life of less than a day. Their oxygen level will go up quite quickly, and then dose reduce from 120 down to 80.

If you look at the studies, a lot of people do get on oxygen, but I don't think that this is absolutely necessary here. The other interesting paradoxical thing is that if they're at 86% at rest, most of the time when they walk around, their oxygen saturation actually improves. It's

because the mechanism of this is likely V/Q mismatch or central hypopnea, which is improved with moving around. So that's how I would approach this.

Dr. McGregor:
Yeah. So that's exactly what we did. We held it, and he felt better within 48 hours. We reduced dose and he keeps on there.

Dr. Vaishampayan:
So you rechallenged with the lower dose?

Dr. McGregor:
Yeah.

Chapter 9

Dr. Vaishampayan:
Okay. And then our last case is of non-clear cell histology. So 62-year-old man who presents with moderate back pain. His imaging shows a right renal mass that's 5.3 cm and bulky lymph adenopathy in the retroperitoneum. This is actually my case. Largest lymph node is 4.5 cm. His imaging shows small lung nodules bilaterally, the largest one was 1.2 cm. Biopsy of the lymph node and renal mass showed RCC with papillary features. It was Grade 3 out of 4. His labs were normal, and performance status is 1.

What frontline therapy would you consider for this patient?

Dr. McGregor:
Yeah. So I think the first thing I would do is I want to get path review. RCC with papillary features is a very big term, and so I think now we have really good pathologists that can give us a much better answer, and so that may be a clear cell. So I think getting a path view, maybe genomics to help better establish this, could help out. At 62 with a lower burden of disease, if this is clear cell, you may be really pushing towards the nivolumab/ipilimumab. To your point, I think this is just a shared decision-making, right? I think papillary RCC, I think nivolumab/ipilimumab is reasonable. I think an IO/TKI is reasonable. I think he has some back pain, so I guess you worry a little bit about that PD with nivolumab/ipilimumab, but I think it just comes down to that discussion with the patient.

Dr. Vaishampayan:
No. I think that's a very good point. Like my first thing was path review, which is critical for non-clear cell. So assuming it is still papillary, Eric, do you have any other input?

Dr. Jonasch:
I would typically treat these individuals with an IO/TKI, and I am impressed with the B61 data with regards to the objective response rate and the progression-free survival. The SUNNIFORECAST study, the challenge with that study is that the comparator was actually standard of care, which what did turn out in the majority of cases to be sunitinib, so that's a pretty weak comparator. And again, these are non-randomized data, but I like the lenvatinib/pembrolizumab data, and I totally agree. I would say that all patients with non-clear cell, quote/unquote, disease need to get NGS because these papillary, you can see in FH-deficient, you can see them in a lot of different things. You can get fooled. There's a biphasic psammomatous hyalinizing as well. I mean, there's a whole bunch of things that you need to be looking out for.

Dr. Vaishampayan:
Okay. So this patient received cabozantinib and nivolumab, and he tolerated the therapy fairly well. He had some hand-foot syndrome that required holding the therapy for one week. By the way, lots of patients don't make the connection that the medication is causing this. They just talk about blisters. So it's important to ask them leading questions about this stuff, because otherwise they're thinking they just need to go see their podiatrist or whatever, and hand-foot may or may not occur on the hands and feet. It can sometimes be on the scalp, on the genital areas, so it's important to recognize that.

And then, we talked about skin care, moisturizing, and the patient's symptoms improved. And at 12 weeks he showed a response with some lung nodules resolving and the lymph node mass is down to 2 cm. So cytoreductive nephrectomy was considered at that time and the patient is currently enrolled on the PROBE trial. He got randomized to no nephrectomy and at this point, a year later, he continues in remission with the lymph node mass continuing to shrink and the kidney mass is down to about 2.8 cm. So that's where we have.

Chapter 10

Dr. Jonasch:
Here's a question for you guys: Would you use subcutaneous checkpoint-blocking antibodies?

So my perspective on this is that at MD Anderson, we're actually starting to burst at the seams from a physical infrastructure perspective and we'll probably have to build more buildings to be able to infuse patients. So being able to administer something in the clinic as opposed to having to send them for chair time, there is an advantage. What are your guys' thoughts on this? Are you going to be adopting it when it becomes available?

Dr. Vaishampayan:
Yeah. I mean, I would be extremely in favor of adopting it because if I was given the choice, I don't want an IV started on me. So I think just for that reason, to not have to start an IV on the patients. Because timing-wise, I don't know how much time it saves. Maybe the prep time is less because you don't have to get under a hood and make the bag, it is a subcutaneous that you can just draw up. But actually giving the injection, at least for nivolumab sub-q, it's about 10-minute duration, and people have argued 10-minute versus 30-minute infusion. But the matter of starting the IV, which has a number of issues for multiple patients, how many pokes are they going to need? Are you going to get a good vein? All of that. I think it avoids that. So I would be very much in favor.

Dr. McGregor:
Yeah. I mean, it just comes down to it's an option, right? So I think that shared decision-making. Some patients are terrified of the idea of a shot and much rather have an IV. So I think it's fantastic that we have an option that can make life potentially easier for some of our patients and be able to offer that to them.

Dr. Jonasch:
And this last bullet down here. So never fear, next year I think GU-ASCO is going to be much more exciting, as will probably, ASCO and ESMO. We've got a whole bunch of trials that are actually maturing. They didn't read out at this GU-ASCO, but we've got a lot of stuff. When's PROBE going to read out?

Dr. Vaishampayan:
I don't know. It needs to complete accrual. It's at 170 right now out of 360, so appeal to everybody. If we can get it done and finished, we will get some answers on the role of cytoreductive nephrectomy.

Dr. Jonasch:
It's really important. It's going to be interesting to see, also, compared to the SAMAURI study. I mean different modalities, but similar principles.

Dr. Vaishampayan:
And there's a similar study in Europe called NORDIC SUN that's also looking at the cytoreductive nephrectomy question.

Dr. Jonasch:
Yeah. And then all of these other trials, we've got belzutifan being sprinkled into everything, and we've got new TKIs like zanzalintinib that are being tested, et cetera. And there's also some new HIF-2 alpha inhibitors, like the Arcus' casdatifan. So lots of things happening. That's not even getting into – we haven't really started using bispecifics to any great degree. There's CAR-T. There's a lot of things happening that are sort of bubbling up.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education. To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.