# SEQUENCING THERAPIES IN RENAL CELL CARCINOMA

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DR. PAL Great. Well, thanks so much for that very kind introduction. On behalf of myself and Kathy, we're really thrilled to be here to discuss advances in advanced renal cell carcinoma.

MS. BURNS Happy to be here.

DR. PAL Yeah. And what we're going to do is focus on how we can best utilize immunotherapy across various settings for advanced renal cell carcinoma. But I think there's still going to be a role for tyrosine kinase inhibitors and VEGF-directed therapies in this disease. And so, we'll really try to outline the intent and current utilization of those treatments, as well.

Here are our disclosures, I'll leave those up here for just a moment.

Now, I'll focus on this slide for a second here, to put all these treatments in context. This is really the lineage of therapies that we've had for advanced renal cell carcinoma, and this all begins back in the early ’90s with the advent of high-dose interleukin-2. At that point in time, the debates that we had weren't too exciting. Interleukin-2 was really the only treatment that we had at our disposal, and I have to tell you, we would use this in a fairly limited population of patients, individuals with very limited evidence of metastasis, not a huge extent of disease, and that relegated most patients to either no therapy or perhaps very inactive agents like interferon.

Now, in 2005, I think the debates got a little bit more exciting. We saw the advent of sunitinib and sorafenib, two oral VEGF-directed therapies. In 2007, we had temsirolimus, an intravenous mTOR inhibitor for advanced disease. And, so we started having some discussions, and I'm sure you guys were privy to most of these around VEGF-directed therapy versus mTOR inhibitors. And then the conversation really got advanced, perhaps, about 2 to 3 years ago, when we saw nivolumab introduced for advanced renal cell carcinoma, a PD-1 inhibitor. So, this really complicates the debate a little bit. We had discussions around whether or not we should be using a VEGF inhibitor, an mTOR inhibitor, or a PD-1 inhibitor, across these various settings. And what Kathy and I are going to try to do today, is we're really going to try to outline some of the more recent debates that we've had within just this past year about whether or not perhaps we should be using combined immune-based therapies, a VEGF inhibitor or perhaps even a combination of both.

But as we're going through all these recent data sets, I just want you to keep in mind, two universal goals that we have for our patients with advanced kidney cancer. Number one: we want our patient's to live longer, if at all possible, and ideally we want to offer these patients a cure. And the second thing we want for our patients is obviously, we want them to live better and with a great quality of life and I think, together, Kathy and I, we certainly share these goals in the clinic.

Now this has really been a banner year for immunotherapy in advanced renal cell carcinoma. And it all began, actually, last year at ESMO when we saw

the data released for nivolumab and ipilimumab. Nivolumab, as many of you know, is a PD-1 inhibitor, ipilimumab is a CTLA-4 inhibitor, both of these are immune-based therapies. I know this has been covered to some extent in some of the other programs, but we're really going to dive a little bit deeper and discuss how these therapies are applied in advanced renal cell carcinoma.

The second big advance for us came at the GU Cancer Symposium, which was in February of this year. And that was the release of some data for bevacizumab, perhaps one of the oldest targeted therapies we've used in renal cell with atezolizumab. And atezolizumab differed slightly from nivolumab in that it's a PD-L1 inhibitor. This regimen was compared against sunitinib and we'll dive through that data. And we're going to wrap up with probably the most recent update that we could possibly provide at this meeting. This comes from Munich, just two weeks ago. Kathy and I were both there, where they released the data for a combination of axitinib, an oral VEGF inhibitor, in combination with avelumab, which is an intravenous PD-L1 inhibitor and this regimen was compared against sunitinib. We saw the first data cut there and we're going to be sharing with you some of the slides.

And, what we're going to do, in terms of organization of this talk, is I'm going to run through some of the key data points, across all these studies, and then we're going to throw it to Kathy to walk you through some of the cases that we've actually seen together in the clinic, and hopefully highlight some of the potential toxicities and management strategies thereafter.

So, let's first start with the nivolumab and ipilimumab in combination. So, this is the so-called CheckMate 214 clinic trial. Keep in mind that this is a little different from the trials of immunotherapy that we had in previous years. This specifically focused on individuals who had no prior therapy. Previously we were applying immunotherapy to patients that had gotten the prior VEGF inhibitor. It took patients, also, who had reasonable performance status, keep that in mind when you're applying these therapies, patients in his study had a KPS of greater than or equal to 70%. And one of the things that we'll harp in on as we discuss this data set is the use of PD-L1 testing. I'm sure this is a question that pops up in your clinic every now and then—should my patients get PD-L1 testing in this context? And we'll touch on that later. But patients were randomized in nivolumab and ipilimumab versus sunitinib. It's really important, as you're putting orders in for nivolumab and ipilimumab, to pay attention to the dosing over here because this is actually different than what we're using in melanoma. So, melanoma, what you see is actually the flip of this. We use a higher dose of ipilimumab and a lower dose of nivolumab. Here, for renal cell carcinoma, we are using three of nivo, so that's the higher dose, per kilogram, and we're using one of ipilimumab. So, a little different there. And also, the other thing to bear in mind is that sunitinib, when it was used as the comparative arm in these studies, was given in the traditional dosing regimen. I know a lot of us in clinic right now are using sunitinib, perhaps on a 2 week on, 1 week off schedule. We're getting comfortable with other permutations, 1 week off and 1 week on, for instance. But

I have to tell you that in this study, they really held to the more traditional regimen and that's been one of the criticisms.

Now, this is the overarching study result, here. One thing that I'll point out is that this data looks at patients who are intermediate and poor risk and this uses the so-called IMDC, International Metastatic Renal Cell Carcinoma Data Base Consortium Criteria. So, this includes elements such as the patient's performance status, the time from their nephrectomy to the initiation of systemic treatment, their calcium levels, their hemoglobin, their platelet counts. It factors all these in and if you've got at least one of those risk factors, then you would fall into an intermediate, and if you have multiple, perhaps the poor-risk category. So, in that population, clear win for nivolumab and ipilimumab in terms of overall survival.

You see that median overall survival wasn't reached for nivo and ipi, versus 26 months with sunitinib. And in the bottom right table, one of the things that you'll appreciate is that there's a pretty outstanding response rate to nivolumab and ipilimumab, 42% overall. And a 9% complete response rate. So, we're actually getting some of these cures that Kathy and I are looking for in the clinic.

But I think there are some caveats to this data. I really wanted to focus on this slide here for a second. And this really underscores why it's so important to really get the risk score of your patient when you're in the clinic. So, if your patient is not intermediate or poor risk, if they don't have any of those risk factors, and by the way, there's a fantastic risk calculator on the mdcalc.com website. If

your patient has good risk disease, you see the results here. Actually the flip of what we saw in the intermediate- and poor-risk population. So, rather than nivo and ipi outperforming sunitinib, you actually see sunitinib outperforms nivo and ipi. The progression-free survival here, the response rate, it's about double with sunitinib versus what you see with nivo and ipi. So, bear that in mind. If you have a patient whose good risk, they should probably still get a VEGF inhibitor in this setting.

Now, I'll focus also here on drug toxicity. And this really underscores what I think is a really important point. I really think that with nivo and ipi, and we'll go into some of the toxicities in just a moment. If you don't have a really fantastic multidisciplinary team including gastroenterologist, rheumatologist, etc., built around you, you may want to think twice about potentially using this regimen. We always think about immunotherapy as maybe being a kinder, gentler approach for patients, but what I've highlighted here is that about a quarter of patients, you see this in red, actually discontinued nivolumab and ipilimumab on account of drug toxicity. And that's actually double the number of patients that discontinued therapy on account of toxicity for sunitinib. So, a little bit paradoxical in my mind, definitely not the kinder and gentler approach that we were hoping for.

And this slide highlights some of the toxicities that we see with nivo and ipi, again, really not a cakewalk. There's a substantial number of grade 3-4 adverse events, about 46% here. And some of the toxicities that really stand out are fatigue. That's also common with VEGF inhibitors. You also see that there's a high incidence of diarrhea. There's a high incidence of pruritis, hypothyroidism,

etc. And bear in mind, that about 60% of patients who are getting nivo and ipi really need to consider steroid therapy at some point during their treatment. So I personally am pretty heavy-handed in clinic in using steroids in this population.

Now, we'd mentioned earlier that we were going to talk a little bit about PD-L1 status. And I wanted to highlight one of the critical elements here. A lot of folks will say, “Well gosh, PD-L1 testing, not ready for prime time in metastatic renal cell carcinoma,” but look at this data here. This is progression-free survival from the same trial. Now, by the data in this study, about two-thirds of patients are going to be considered PD-L1 negative. And one of the things you'll appreciate in this curve to the left is that if you're PD-L1 negative, there's really no difference in terms of progression-free survival, whatsoever, between nivo and ipi versus sunitinib. On the right-hand side, however, you're going to see that there's a tremendous difference. So, if you're really on the fence about whether or not to use nivolumab and ipilimumab, we had just discussed this in a tumor board recently, maybe PD-L1 status could potentially be helpful. And a lot of folks say well that's the progression-free survival data. We really want to see overall survival. These are the overall survival curves here. And one of the things that you'll appreciate is that even though both subgroups, PD-L1 negative and PD-L1 positive, seem to drive benefit from nivo and ipi. I got to say there's something to this, because the magnitude of benefit is really very different if you're PD-L1 negative versus PD-L1 positive. So, those were a couple of notes on CheckMate 214. Now we're going to turn it over to Kathy to run through a case.

MS. BURNS Thanks very much, Monte. We're going to tell a story about John, a patient who was 44 at presentation with no past medical history. He presented with headaches and ultimately was found, on imaging, to have a 1.6-cm cerebellar lesion as well as a 7.5-cm left renal mass. He had the first lesion resected, followed by nephrectomy. He ultimately had fairly rapid disease progression in the retroperitoneum. And he received multiple levels of therapy at that time, including IL-2, pazopanib, bevacizumab. And, then enrolled in our phase 1 clinical trial at City of Hope, which was with nivo/ipi. He presents for cycle 2, day 1 with no symptoms at all, no complaints, other than on his labs an elevated ALT of 658, varying rapid spike. No other symptoms at this point. So, at that time, we didn't have the NCCN and ASCO immunotherapy guidelines; we had the clinical trial information to guide us, where he was quantified with a grade 3 transaminitis. If we were giving this today, you would realize that at that point, grade 3, we need to permanently discontinue his I-O, initiate prednisone 1 to 2 mg/kg/day. He was watched fairly closely. He was not hospitalized at the time, but we did do his chemistries every 1 to 2 days after that. And you can see on this graphic, that the ALT, although it spiked quickly, it resolved fairly quickly on steroids. And, we've heard this a couple times this weekend, actually, but I think it's important to repeat. When you have a well-educated patient who understands how I-O works and understands how steroids can turn that off, you may get asked that question. You know, if you're going to give me steroids, is the response going to be less? And I think what we've seen is no. This is a pictorial of John's case. You can see on the X axis, that's his tumor burden in millimeters.

And this is his time. So, I don't have a pointer, but if you follow that first few, the first two vertical orange boxes are prior lines of therapy before nivo/ipi. Where you see those two orange boxes on the top, that's where he was dosed with one cycle. He had rapid regression of disease at that point, even though, which I think is the really key point here, even though he had one cycle of medication. The steroids are those blue block looking things at the bottom and you can see, over time, and that distance between the nivo/ipi and that next orange box is about 8 or 9 months of time where he had a durable response after one cycle only.

Just a couple FAQs, and again, I think we've talked about this this weekend in different programs. Endocrine and thyroid adverse events are the only class that do not require steroids. And remember for those of us who are freely using steroids in this I-O treatments, if you're giving greater than 20 mg/day over 4 weeks, you want to make sure you're prophylaxing for pneumonia. If it's for 6 to 8 weeks, you want to make sure you're prophylaxing for fungal infections and please don't forget the PPIs for steroid-induced gastritis.

This is just a pictorial of general I-O regimens, what the timing could be on adverse events. So, we can see that rash and skin come first. GI, liver toxicity, followed by hypophysitis. Thanks very much. We'll pass it over to Monte.

DR. PAL Thanks, Kathy. That was a great delineation of a case of nivo and ipi–related toxicity. Next, I'm going to talk a little bit about bevacizumab and atezolizumab. This is a regimen that I've been using for a while. We participated in a randomized phase 2 study looking at this regimen. And since then, it's actually been validated in the phase 3 trials. So, this is the so-

called IMmotion151 trial. It differs a little bit actually from the CheckMate 214 study that I referred to in terms of eligibility. So, in this study again, patients who had no prior therapy were assessed. But here, you could actually have clear cell or sarcomatoid histology. When we look at patient's pathology reports, we're going to find that about 20% or so of them have sarcomatoid features. These are really aggressive features that you can delineate under the microscope that really tend to poor prognosis. So, we'll take a look at that subset in this study. And again, in this trial, we looked at PD-L1 status.

Again, the dosing here for bevacizumab is a little bit different than what you might be used to. For instance, in the context of historic use in renal cell carcinoma. We used to give bevacizumab every 2 weeks. In this trial, since it's paired with atezolizumab, it's given intravenously every 3 weeks instead at a slightly higher dose, 15 mg/kg. And, it's again compared to the conventional dose of sunitinib.

Now, bear in mind here, bevacizumab is a monoclonal antibody as opposed to a small molecule. What we see in this trial, and this is the primary endpoint of the study, is that in PD-L1–positive patients, you see this off to the left, it really looked as if there was a significant improvement in progression-free survival. This is based on response for investigators. We move the needle from 7.7 months with sunitinib to 11.2 months with the combination of bevacizumab and atezolizumab. Now many of you may be wondering, “Well, what about that subset of patients who are PD-L1 negative?” We don't have any specific data in that regard, but if you look at the curve over to the right, this is the overall

population. You see that there's a trend towards improvement in that population, as well. So, my take on this is that there's pretty consistent results in PD-L1 positive and the overarching intention to treat population in this study.

Now, one of the things that you'll appreciate in this trial is, again, response rates with bevacizumab and atezolizumab are higher than what you see with sunitinib, 43% versus 35%. But, what really stood out to me is the complete response rate here, about 9%. This is based on investigator assessment. If you look at the independent assessment, it's actually higher than that, closer to 15%. And it looks to me—this is true based on the curve on the right hand side—that a lot of the responses that we're seeing with bevacizumab and atezolizumab are pretty durable. You can see that that blue curve is really tailing off a relatively high level there. So I think there are high CR rates associated, complete response rates associated with bevacizumab and atezolizumab and certainly way higher than what I would typically anticipate with drugs like sunitinib in years past. This is the overall survival. Here, you can see that there's a compelling trend in my mind, towards improvement. We're going to see how this pans out but irrespective of how that does pan out, one of the things that really stands out to me about this regimen, is the exceptional tolerability. This is a so-called tornado plot. I've blocked out a couple of the elements here, but one of the things that you'll appreciate is that everything off to the blue is a toxicity associated with bevacizumab and atezolizumab, and in red is toxicity associated with sunitinib. Now, those of us familiar with using VEGF TKIs in the clinic know that we see a lot of hand-foot syndrome, we see a lot of diarrhea, etc. All of those endpoints

seem to be markedly improved with the combination of bev/atezo. And the other thing is, we're not seeing that same need for steroids as we are with the combination of nivolumab and ipilimumab. We saw a 60% steroid utilization with that regimen. Here, it's only about 16%, so we're not needing to kick in with steroids quite as much, which is quite nice.

So, with that background, I'm going to turn it back over to Kathy.

MS. BURNS Okay. So, let's look at the story of this regimen and it's tolerability through the eyes of Eileen. These are not the real pictures, this is a lady from Google, but she's a lovely lady with a beautiful smile, 91 years young. Diagnosed in 2011, had a radical nephrectomy. Only comorbidities of hypertension and osteoporosis. But she signed on to one of our frontline studies. At the time, atezolizumab had a number, so this was the regimen she started on November in 2014. Over the years, she did extremely well with just some varying degrees of fatigue and proteinuria. We know with bevacizumab we check urine protein every time it's given, so I think the take-home point with her example is that, one, the importance of using the older adult in our clinical trials. And, not being afraid of treating them, but also paying exquisite attention to their quality of life and their symptomatology. So, she was able to maintain her quality of life and her work as a volunteer at a beautiful museum we have in Pasadena, California. This is just toxicity grading for proteinuria, so just for the actual information it's important to know you would hold treatment if your urine protein was above 2+. Discontinue for edema or nephrotic syndrome, which never happened to her, and she had a great durable response for over 3 years. Back to Monte.

DR. PAL Thanks a lot, Kathy. I really think that case underscores the points that Kathy had noted. And also the fact, in an older patient with all these various regimens available, that regimen of bevacizumab and atezolizumab, is incredibly well tolerated. Again, not achieving regulatory approval yet, but I'm keeping my fingers crossed, so we'll see what happens there. But, in any case, it certainly would be one of my preferred choices for the frail patient.

Now, let's update you with the most recent data that we have at our fingertips. This comes from ESMO 2018. Again, just 2 weeks ago in Munich, they had the unveiling of this data for a combination of axitinib with avelumab. So, we've had a lot of different trials looking at combinations of these small molecule tyrosine kinase inhibitors, or other VEGF inhibitors with immunotherapy. But one of the neat things about them is that, I've put together this little summary here. You can see that we're achieving complete response plus partial response rates that are in the ballpark of around 40 to 50%. And beyond that, if you look at the clinical benefit rate, which tacks in those patients who have disease stabilization as well, it's almost 100% of patients that are deriving benefit from these therapies, so pretty outstanding.

And the goal that we're trying to achieve when we combine a small molecule TKI with an immune-based agent, is to see whether or not we can generate somewhat of a plateau here. And really take the durable responses that we see with immunotherapy, in that middle graph, and associate that with

perhaps the higher progression-free survival that we see with TKIs, and really raise the bar for out patients.

So, this is the JAVELIN Renal 101 study that looked at axitinib with avelumab. Again, this trial didn't differ much in terms of eligibility, from the trial that you saw previously. Here, not necessarily, set your focus on patients with sarcomatoid elements. But patients were randomized in a 1:1 fashion to either axitinib or avelumab. Axitinib is dosed 5 mg twice daily. You're probably used to using axitinib in clinic in sort of a flexible fashion. You start at 5 mg twice daily. If the patient's tolerating it, you can go up to 7 and then to 10. If not doing so well, you can dose down. Avelumab is given at the flat dose of 10 mg/kg, intravenously every 2 weeks. That, of course, is the immune component of this regimen. And this regimen was compared against sunitinib, at again, the standard dosing.

What we saw in this trial, and this was the primary endpoint, is that when you look at the independent review and the PD-L1 positive group, there's a pretty marked extension in terms of progression-free survival: 7.2 months with sunitinib versus 13.2 months with this combination of axitinib with avelumab. So, I would say very compelling data.

I'll point out on the next slide, over there, that if you look at the overall population, not just those individuals that are PD-L1 positive, but PD-L1 positive and PD-L1 negative, you can see here again, a fairly profound benefit in terms of progression-free survival – 8.4 months and we're moving the needle up with axitinib and avelumab to 13.8 months.

I will say that, perhaps, what needs a little bit more review is the PFS based on investigator assessment as well as the PFS – the overall survival in the population. Here, what we see is that there's not a huge separation between these curves at this point in time. So, the OS looks as though it might be trending slightly towards improvement with axitinib and avelumab, but we're going to have to wait and see how this data pans out over time. Right now, the overall survival data from this trial is a bit immature.

Now, in terms of treatment-related adverse events, I think that axitinib isn't necessarily a drug for the faint of heart. It does have a fairly significant side effect profile associated with it. We do see diarrhea, we see hypertension, hand-foot syndrome, etc. With avelumab we see the typical array of immune-related adverse events. Diarrhea can be lumped into that mix. I think one of the problems and dilemmas that this sort of regimen presents is how do you really generate those toxicity attributions? When you start a patient on axitinib and avelumab, when they do develop diarrhea, how do you tease out whether that's immune-related to start steroids? How do you know whether or not it's related to the tyrosine kinase inhibitors? Do you stop that instead? It's something that we're facing in the clinic and I'm not sure we have a fantastic answer for you, but we're dealing with each of these on an individual basis. These are those immune-related adverse events that I was referring to, so you see that there's a fair incidence here of colitis, liver-related toxicity, liver function test abnormalities, and so on. Not so different when you compare it to some of the other immune-

based regimens. You see that the total frequency of immune-related adverse events is around 38% here.

Now, with that background, I'm going to let Kathy run us through a case of a patient that we treated with axi/avelumab recently.

MS. BURNS Let's tell the story of Robert. Robert was a 77-year-old male diagnosed in 2014. He had his nephrectomy and developed mediastinal lymph nodes and some lung mass subsequent to that. So, he was treated by us in June of 2018, not long ago, with avelumab/axitinib. We're using his story to highlight one of the more unusual side effects that you can see with I-Os. He developed a left-sided facial droop. No other neuro symptoms, no other complaints. And, we originally thought his differential was related to the axitinib with either thrombosis or stroke. His head CT was negative. MRI was negative of his head. We are blessed in City of Hope to have lots of great practitioners. We referred him to neurology. The neurologist suspected myasthenia gravis. So, in your brain, you're going back to your medical training. What is myasthenia gravis? An autoimmune disorder of the proteins in the postsynaptic membrane of the neuromuscular junction. So, presenting symptoms can be weakness, eye droop, muscle weakness that kind of comes and goes, at times. The drug was withheld. He had marked improvement in his symptoms with the regular treatment you would see with – from myasthenia gravis, which is physostigmine. And he was able to resume his therapy 3 months later on lenvatinib and everolimus. Back to you, Monte.

DR. PAL Thanks, Kathy. You know, it's really interesting. We had a medical student in clinic that day with me when –

MS. BURNS That's always good.

DR. PAL -- he presented. Yeah. That sounds very helpful. He actually, sort of hinted toward myasthenia gravis and so, I guess the point there, is if you can bring a medical student to your practice, do it. That often times can help with your general medicine.

So, you know, I just wanted to highlight one thing that lingers with us. Right? So, we talked about all these exciting regimens that either look at dual checkpoint inhibitors, or a combination of targeted therapy with immune therapy. But I still think that down the line, there's going to be a role for use of tyrosine kinase inhibitor monotherapy. There's still going to be subset of patients where we want to focus, for instance on use of cabozantinib or sunitinib. And, I'll walk through some of the relevant data there.

This is the CABOSUN clinical trial. We had a brief word on that this morning. The cabozantinib is a drug that doesn't just inhibit VEGF, it inhibits two distinct targets, AXL and MET. These two molecular targets, really, we think drive and offer a pathway for resistance in kidney cancer. So, by targeting those elements, we are bound to see some clinical improvement. The drug is already and has been approved for some time, in the second-line setting and beyond for renal cell carcinoma, based on a phase 3 clinical trial. This is a randomized phase 2 experience that was done by the Alliance Cooperative Group, that was really attempting to pivot cabozantinib to the frontline setting. Patients in this

study, unlike previous trial of cabozantinib, had no prior therapy. They had clear cell histology. And just like in the Checkmate 214 Study, there was a real focus here on patients with intermediate and poor-risk disease. So, the primary endpoint of the study was progression-free survival.

Here are a couple of the toxicities that we see with cabozantinib. I wanted to jump right to this to underscore the fact that the tox that we see with cabozantinib is really not so distinct from the toxicity that we see with sunitinib and pazopanib. We have a fair incidence of TKI-related diarrhea. We have a fair incidence of hand-foot syndrome, stomatitis, etc. But all are fairly manageable and I think we all, in this room, probably have some fair comfort level of managing TKI-related toxicity, having been exposed to them for more than a decade now.

Here's the clinical data from the CABOSUN clinical trial. First, the primary endpoint which was progression-free survival here. What we see is a significant improvement in PFS with cabozantinib versus sunitinib. You may look at this curve and say, “Well, wait a minute.” The data for sunitinib and cabozantinib seems to be, perhaps, a little bit subdued relative to the other data sets. Again, this was an intermediate and poor-risk population. So, that's why see, for instance, PFS are just 5.3 months with sunitinib therapy, 8.6 months with cabozantinib.

So, where do I use cabozantinib nowadays with all these newer regimens at my disposal. I think this subset analysis from the trial is really helpful. If you look at this forest plot off to the right-hand side of the slide, one of the particular

subsets that I'm always plagued with is that 20% of patients in my clinic who have bony metastatic disease. And this probably has something to do with cabozantinib targeting MET and targeting AXL, but one of the things that we see here is that the benefit of cabozantinib, it really holds in those individuals who have bone mets. And that's something we don't necessarily see with many of the other agents that we have in our practice.

I'll also say that, again, this was a small study, 150 patients. Hard to really glean anything about overall survival, but there is somewhat of a trend here. So, all in all, I think the cabozantinib still represents a very reasonable option in the frontline setting for our patients. And with that in mind, I'll have Kathy present a case.

MS. BURNS Okay. Final case study is Patrick. Patrick's a great guy. He's a 64-year-old male. He works as an auto mechanic. He was diagnosed with a pT3a clear cell renal cell carcinoma, had a laparoscopic nephrectomy back in June of 2015. I first met Patrick after he had had some restaging scans and was immediately deferred into our emergency department where he was found to, unfortunately, have progression to the brain, mediastinum and bone. At that time, he had significant pain. He needed some more urgent brain radiation, but ultimately, I believe it was that January, he started on cabozantinib. He had quite a bit of fatigue in the beginning and I think part of it was the cabo, but as well, he had just finished brain radiation. So, he did dose reduce his cabo from 60 to 40 within the first month or two. His pain was improving. He was getting a little bit more functional. He was trying to get back to work. And ultimately, by May, he

had developed a fairly significant, I would say, grade 1, almost a grade 2, hand-foot syndrome. I know in the literature you see it as hand-foot skin irritation or PPE, but for him, that was a really important problem because he was an auto mechanic and used his hands all day. In the RCC trials, PPE was reported in 42% of cabo patients. Eight percent had a grade 3. Of course, as we've learned this weekend, in other places, we withhold cabo for a grade 2 and we wait until it improves to a grade 1.

This was a guy, and I don't want to get into any gender issues, or slam anybody, but this was a guy who's a fairly macho guy and the thought of putting hand cream on was not top on his list in a day. But he realized that this was a very big problem for him and he needed to earn his income. So, we had a fairly intense patient education moment where we gave him all the data, 10% urea cream, sleeping with gloves on. You should have seen his face. But he did it and he improved significantly and ended up doing very well, which, I think, hearkens to the fact that, as providers, we want to start strong, provide a really close system of patient and family teaching and feedback.

The other thing that I've learned as I work with these drugs is to help patients understand that dose reduction is not a failure on your part at all, that this is part of treatments. Reporting, education, and support. And I also think what we've learned is the management and support of patients who are on oral therapies can be, at least, as challenging as IV treatment, as well. Back to Monte.

DR. PAL Thanks Kathy. I love those points. I think you've outlined our clinical strategy very nicely there.

So, we've walked you through, what I think are probably, the four most relevant data sets in recent years looking at dual checkpoint inhibition, looking at combinations of VEGF inhibitors and I-O. And, finally, wrapping up, with the place of where TKIs still sit in our clinics. I definitely think there is still a role for agents like cabozantinib as monotherapy.

But we just wanted to spend a moment kind of walking you through what we feel is being, potentially, the future of treatment of metastatic renal cell carcinoma. If you look at NCCN guidelines, one of the things that we fully acknowledge is that we're not necessarily curing our patients, unfortunately, for the most part with advanced disease, so clinical trials still remain at the very top of our list. And with that in mind, some of the things we're looking at are novel combinations, adjuvant treatment. We already focused primarily during this talk on clear cell disease, but there's a lot of patients that we see, especially in academic practices, who have nonclear cell kidney cancer that we need to focus on. And finally, there's all this attention on frontline therapy. We wanted to address some of those studies that we're doing in the second- and third-line setting.

So, I think we're right on time here. I'll spend a couple of moments going through a couple of studies that I'm running. This is a study looking at adjuvant therapies. So, for patients out there with localized disease, who have nephrectomy, one of the things that you'll acknowledge in the NCCN guidelines is

there's an option for adjuvant sunitinib therapy. I'll tell you firmly, this is not something that I believe in. I have a discussion around adjuvant sunitinib with patients in the clinic, but the data doesn't speak to necessarily any improvement in overall survival. And the data that does suggest some delay in cancer recurrence, really adds about a year after a year of therapy with what I perceive to be a pretty toxic drug. So, we'll have a discussion around that therapy but what I really try to emphasize is the role for adjuvant trials of immunotherapy. This is a study that we're running at the City of Hope, but it's an international trial. I'm running this with Axel Bex from the Netherlands and Rob Uzzo from Fox Chase Cancer Center in Philadelphia. And it's probably available at many of your centers. It takes patients who have high-risk disease, who have had resection, so these are patients who are staged as pathologic T3 and beyond. It can also take this really high-risk population of patients who've had metastesectomy. We still try to offer our patients who have a solitary lung met, the solitary liver lesion, surgical resection if possible. Those patients would also be category for this trial. And the study also allows for patients with sarcomatoid features. And we're randomizing them in a 1:1 fashion to either atezolizumab or placebo. This is a study that should be running for maybe about another year or so. And I think we'll glean a lot of important information from this. So, I hope you'll consider referring patients to studies such as this.

I'll also note that, again, in the setting of nonclear cell disease, we talked about a couple of data sets that encompass sarcomatoid histology. Sarcomatoid may be potentially best addressed with immune-based therapy, but there's a lot

of other subsets out there. About 20 to 25% of kidney cancer is characterized as being nonclear cell. And about 10 to 15% of those patients have papillary kidney cancer. And to date, we really don't know what to do for this subset. There have been a lot of trials using drugs like sunitinib, for instance, that show a very, very poor progression-free survival, sometimes on the order of just 1 month, if you can believe it, with that drug. So, what we're trying to do is raise the bar a little bit. We know that sunitinib can potentially be associated with substantial toxicity. And, it doesn't address one of the underlying mutations in papillary kidney cancer, which is mutation in the MET proto-oncogene. So, what we're running through SWOG, is a trial that I'm leading with Primo Lara from UC Davis and Brian Shuch who just moved to UCLA from Yale. This study should be open at many of your centers. It's open through NCORP and all NCTN sites. This study is randomizing patients to either the control arm of sunitinib. Again, we know the data is poor for sunitinib. We just have no other choice, hence our control. And we're comparing it against three other MET-directed therapies, cabozantinib, crizotinib and savolitinib. So, for the 15 to 20% of patients who are going to have papillary kidney cancer, I urge you to consider this trial.

Now we talked about some combination-based therapies of bevacizumab with atezolizumab, axitinib with avelumab, for instance. Again, we're trying to link the VEGF and I-O-based therapies together. But I think, clearly, we have a long ways to go. One of the things that you'll acknowledge from my slides is that we're not rending benefit to 100% of patients. There's still about 20 to 30% of patients who are going to progress right through these therapies, so we need to raise the

bar there. So, what we're doing in this trial, is we're combing cabozantinib, which I'm convinced is probably the best VEGF inhibitor that we have to date, with atezolizumab, the drug that you saw evaluated in the adjuvant study and the beva/atezo study. And, we're doing a dose escalation cohort which we recently presented, and then expanding into cohorts of renal cell carcinoma, bladder cancer and so on. So, I know that we might view the frontline clinical trials base in kidney cancer as being dry. A lot of these trials are done. But, there's still strong interest in looking at novel combinations and this is one of several that's out there. And it's a study that we're running with Neeraj Agarwal of the Huntsman Cancer Institute, but we have recent activation at Karmanos and Detroit and a handful of other sites around the country.

And the last study that I wanted to address is another international study that I'm running with Danny Heng from Calgary and Javier Puente from Madrid. And this is a study that fits into that second- and third-line space. So, again, I mentioned that there's huge amounts of enthusiasm. I think all companies want to see that their jugs migrate into that frontline setting. It's understandable. There's huge attrition as you go from frontline to second-line to third-line therapy. But Kathy and I have plenty of patients who progress beyond those agents and need a clinical trial. So, this is an FDA-mandated study that looks at lenvatinib and everolimus. This is an FDA-approved regimen. And what we're doing is, we're comparing a lower dose of this regimen to a higher dose to see whether or not we can potentially render the same benefit with less toxicity. So, this is a study that's ongoing.

There aren't too many sites throughout the US to be honest with you, but the study is open in Dallas. It's open in Florida and a handful of other locations. So, I urge you to consider this one, as well.

And with that, I'm going to turn it back over to Kathy.

MS. BURNS I appreciate you letting me have the last slide, and I hope you'll indulge me for just a minute. I want to publicly thank Monte Pal for his exquisite collaboration and partnership. He's been a mentor to me in my last three years at City of Hope, and I very much appreciate it.

DR. PAL Oh, thanks.

MS. BURNS Most of all, I'd like to thank our incredible patients and their families for their continued interest in clinical trials and research. Without deviation, progress is not possible. Thanks very much.

DR. PAL Thanks. Would you believe it, Kathy? We finished with a-minute-and-a-half to spare. So, it looks like we've got a little time for questions, I believe?

MS. BURNS Don't leave me hanging.

DR. PAL Okay. Oh, oh my gosh. Thank you. Great. Any questions? Looks like we might have answered everything. Okay. All right.

MS. BURNS Thank you very much.

DR. PAL Thank you.

**[END]**