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Keeping Up With The Rapid Emergence of Strategies for Advanced Renal Cell Carcinoma

Announcer Introduction:
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Taryn:
We're in the PCE Oncology Winter Conference and moving on to a new topic: Keeping Up with the Rapid Emergence of Strategies for Advanced Renal Cell Carcinoma, and we have a wonderful speaker today, Mary Dunn, who's a Nurse Practitioner in the Division of Oncology in the Departments of Neurology and Medicine at UNC School of Medicine at Chapel Hill, North Carolina. So, welcome to Mary. Thrilled to have her with us today. She has no relevant disclosures, and these are our learning objectives; To apply guideline recommended first and subsequent line treatments for advanced RCC, to manage AEs of novel therapies for RCC based on guideline recommendations, and to integrate patient education and feedback to optimize patient experiences during treatment and survivorship. So, considerations for nonmetastatic renal cell carcinoma at initial diagnosis and I will turn it over now to Mary Dunn. Welcome, Mary.

Dunn:
Thanks, Terry. And a brief overview about kidney cancer. We could do an entire day's worth of talks just about advanced renal cell carcinoma with the explosion of new treatments for these patients, how to sequence them, the data around them, and how to manage the toxicities. So, just a little brief overview about renal cell carcinoma in general. It is one of the more common cancers affecting adults in the United States and the 2023 predictions are that there'll be nearly 82,000 cases diagnosed and nearly 15,000 people with die from renal cell carcinoma. The vast majority of renal cell carcinomas are clear cell and that's going to be the focus of the discussion. As far as treatment options today, we're not going to focus on treating non-clear cell histology today.

What we know about kidney cancer is there's been an increase in incidence. We think this is mostly due to early-stage tumors. So, if you think about it, if you go to an Emergency Department and you're having abdominal pain you're likely going to get some sort of imaging of your abdomen and we're seeing a lot of, what we call, incidentalomas, or tumors on the kidneys that we weren't looking for that weren't the cause of the abdominal pain. And risk factors for kidney cancer include obesity, tobacco use, hypertension, chronic renal failure, just to name a few. And there's also some familial and genetic components as well.

So, for nonmetastatic disease, surgery, either partial nephrectomy or radical nephrectomy, is the mainstay of treatment with traditional adjuvant therapy in selected circumstances depending on what those tumors look like. For small renal masses and nonmetastatic disease, observation or surveillance is also an option for certain folks.

So before diving into some of these systemic treatments, I want to make sure we have a little bit of a baseline understanding of what categories these medications fall into in case you're not familiar with them. So, we're going to be talking about medications that are tyrosine kinase inhibitors, and those are oral drugs that are targeted so they more precisely identify certain cells, which is different than a lot of cytotoxic chemotherapy, which is nonspecific. Speaking of cytotoxic chemotherapy, it doesn't work for kidney cancer, which is why

you won't hear me talking about it in this presentation, the same for mTOR inhibitors, also oral drugs. But what's really exploded in the setting of advanced kidney cancer are immunotherapies, so we talk about those as immunotherapy, immuno-oncology, checkpoint inhibitors, immune checkpoint inhibitors, so you're going to hear a lot of variations of the same thing. But I think it's important to have a baseline of what exactly are those and the mechanism of action. So, immune checkpoints themselves are a normal part of our immune system. They prevent an immune response from being so strong that it destroys healthy cells. Checkpoints engage when T-cells recognize and bind to other proteins and then they send these off-signals to T-cells which can prevent the immune system from destroying cancer. So, checkpoint inhibitors such as PD-1 or PD-L1 inhibitors, like we'll talk about, block the protective protein. So, just a little bit of background information there before we dive into some of these drugs themselves.

Adjuvant treatment is systemic treatment that is given after surgery for kidney cancer, and these are 3 randomized controlled clinical trials that were looking at oral medications specifically sunitinib and pazopanib in the context of adjuvant treatment following radical nephrectomy. So, the only one of these to show disease-free survival was sunitinib in the S-TRAC trial, but the majority of these were clear-cell and the relatively heavy stage tumors, right, so, pT3b, or they had known positive disease.

These are other trials looking at different TKIs and mTOR inhibitors in the adjuvant setting, and as you can see, none of these trials showed a disease-free survival or an overall survival benefit. We don't do, at least in clinical practice, a ton of adjuvant sunitinib and you'll see why, because we have another option in the event that this is the right choice for patients. It's a relatively difficult drug to tolerate, there's lots of dose reductions because of toxicity and some people are just not eligible for it based on competing comorbidities, particularly things like uncontrolled hypertension.

So, the KEYNOTE-564 trial was looking at adjuvant pembrolizumab, which is a checkpoint inhibitor, versus placebo for clear-cell renal cell. Pembro is a PD-1 antibody, and this was looking at patients who had had nephrectomies and were considered high-risk for recurrence. So, the definition for that is that they had a stage 2 tumor with a nuclear grade of 4, or sarcomatoid features on their pathology stage 3 or higher, known positive disease, or stage M-1 disease with no evidence of disease. So, if someone had an old metastatic cyto disease that was treated and then their imaging showed that they didn't have anymore disease, they were eligible for this trial. The outcome measures was disease-free survival and what this study showed us was that criteria was met 78% for pembro versus 68% for placebo. So, the way that this is done in clinical practice is the pembro is administered every 21 days for a total of 1 year, or it is discontinued if there are significant toxicities. The overall survival data has not yet been reported and is still pending. But, this is an interesting and very long conversation that we have to have with patients about risk/benefit of doing immunotherapy following their definitive treatment because a lot of people are not quite sold on taking immunotherapy or any kind of systemic treatment after surgery that was for curative intent, and we also have to think about patient preference and what their comorbidities are because with these immune checkpoint inhibitors, people who have any kind of underlying immunosuppressive-type disease, they may not be eligible. So, it's a very long conversation about weighing the pros and cons and – and risks and benefits of doing this.

So, these are just some other trials that were looking at immunotherapy for patients with nonmetastatic renal cell carcinoma either in the neoadjuvant settings, so before surgery, or in the adjuvant setting after surgery. And as you can see there on the right column there was no disease-free survival or overall survival in these particular trials.

So, who should get adjuvant treatment? As I'm going to say a million times in this presentation, these are very long conversations to have with patients, because there is still some uncertainty in this space. We can consider adjuvant pembro in patients who meet the – the very specific criteria based on their pathology. So, clear-cell PT-3 or higher disease, known positive disease. And it's usually a collective decision between all the different disciplines, right? So, urology is involved here, they get referred to medical oncology and kind of the typical cadence we do is someone has their surgery, they have their post-op appointment, we review their pathology over in neurology and say, okay, you meet the specific criteria for this based on your pathology, we're going to refer you to medical oncology to have a discussion about whether or not this is something that's either appropriate for you, or that you want to do. And we get a set of scans between surgery and starting pembro just to ensure that they are in fact not metastatic. And that's just a little action item. So, considering adjuvant pembro for eligible patients depending on patient preference.

So, future directions and some unanswered questions in this space. Is 1 year enough for adjuvant treatment, or is it too much? Well, we don't really know the answer to that yet. Is the intensity of adjuvant therapy for resected or radiated oligometastatic disease is unknown? Is monotherapy enough? Do we need to be looking at combination therapies in this setting for these patients? Risks include more toxicity or over- or under-treating patients, so it's still unclear. Are we giving patients medications that they may not need leading to over-treatment? That's still a big question mark here.

We need different clinical trials, as you can see there. And then using the best technology to identify who will progress and who will respond. So if any of you can come up with that and send it my way that would be much appreciated.

Now we're going to talk about planning optimal first-line treatment for patients with advanced renal cell carcinoma. This landscape for

those of you who work with patients who have kidney cancer has changed drastically over the years. So, I've been doing this work since 2010. I'm a little bit of a dinosaur, but it's been fascinating to watch the change over time from patients getting sunitinib, and then everolimus, and then pazopanib, and then, what? To now, we have this whole array of treatment options that I say is a blessing and a curse because we have more options for patients and it's confusing as far as sequencing, eligibility, increased toxicity profiles, quality of life, and those types of things.

So, understanding the role of risk in the treatment of metastatic kidney cancer. So, we put people into risk categories. So, these risk categories were developed to classify patients in to groups with corresponding prognoses. The higher the score on their risk calculator, the poorer the risk and they have decreased survival. As you can see here, these are the criteria. So, performance status, time from initial diagnosis to targeted treatment less than a year, hemoglobin, calcium, platelets and neutrophils. This has not been updated in the era of all of these different types of combination modalities and ICI modalities. So, I imagine sometime in the future this may change, but the overall survival data that goes along with these risk factors are, so, patients with favorable risk, the overall survival is about 43 months, for intermediate risk, 22 months, and for poor risk, 8 months. About 75% of patients who are being considered for first-line therapy for advanced kidney cancer have at least 1 risk factor, which automatically puts them in the intermediate risk category, so that's a large portion of patients.

This is a little snapshot of the current therapeutic landscape for metastatic kidney cancer for first-line therapy. We do their risk stratification, and we say, okay, based on their risk stratification, what makes sense for them in the first-line setting? It's always a good idea to talk about clinical trials with your patients, and whether or not they are available at your institution or other institutions because that's how we learn more about best treatment practices and such. If there are no clinical trials that are available or that make sense for your patients, then these are kind of the things that we recommend. So, for favorable risk first-line, axitinib plus pembro, cabo plus nivo, or Lenvatinib plus pembro. As you can see these are all combination therapies. First-line recommendations of just a single agent TKI are not there anymore, which is kind of weird, which is why I'm a dinosaur. For intermediate or poor risk, you can also see here, and these are not listed in any particular order, that they're all combination therapies of either a TKI and a checkpoint inhibitor, or 2 different immunotherapies together. So, we're going to go through some of the data here and things that might be helpful for you in clinical practice.

Let's talk about surgery. What about surgery for patients who have advanced disease? Especially in the context of people with favorable risk disease. CARMENA was a trial that was a cytoreductive, or debulking nephrectomy. So, essentially what that means is taking out the tumor and the kidney in the context of advanced disease. So, it was looking at surgery followed by treatment with sunitinib versus sunitinib alone. This trial had a lot of issues, unfortunately. So, the primary endpoint was overall survival with a couple of secondary endpoints there, but there was very poor accrual to this trial. So, there was less than 1 patient per center, per year. All of these patients were intermediate or poor risk, they have very large tumors. Kind of rough shape. So, basically what this showed us was sunitinib alone is noninferior to cytoreductive nephrectomy plus sunitinib.

There was another clinical trial called SURTIME that looked at this as well, cytoreductive nephrectomy, in this context and that trial closed early due to accrual. But this is very, very patient selective and very surgeon selective. What might make sense for people to have a debulking nephrectomy in the context of advanced disease? I like pictures, so I like this slide. If you look at the first on here where you see there might be a couple little pulmonary nodules, but that big old renal mass there, minimal extrarenal disease, and they have a good performance status. That might make sense, because then we might be able to put this person on surveillance. Like, if they only have a handful of really small pulmonary nodules, we might be able to delay their systemic treatment. The middle picture, larger pulmonary nodules, intermediate risk disease, moderate extrarenal disease, and then, kind of the last picture there, lots of lung mat, big tumor, extensive extrarenal disease, very large primary. So, does it really make sense in that context?

Thinking about systemic treatment. The CheckMate 214, ipi-nivo as I call it, versus sunitinib. So, you'll see a lot of these trials are the medications versus sunitinib. A lot of them are compared to sunitinib, which is one of the older drugs that we really don't use anymore for advanced renal cell carcinoma in the setting of having all of these other options. For allcomers, so the all-risk intent-to-treat that nivo plus ipi showed a greater median overall survival. So, roughly 66% versus 38% over sunitinib. However, this trial was really the primary focus were patients with intermediate and poor risk disease with looking at favorable risk disease as kind of an exploratory afterthought. That's why nivo was not approved for first-line setting for favorable risk disease because it was really looking at intermediate and poor risk disease, which is kind of what this slide here shows.

KEYNOTE-426 is first-line pembro plus axi, so a checkpoint inhibitor plus the tyrosine kinase inhibitor versus sunitinib. And what it showed there was for all-risk, pembro-axi had a greater median overall survival versus sunitinib. Looking at more recent data at a median follow-up of 43 months, pembro-axi showed a greater survival 46-months versus 40 months, which was statistically significant.

We, at least in clinical practice – love to hear how you all practice – we do a lot of pembro-axi in the first line setting for our patients.

Another trial looking at first-line combination therapy was nivolumab and cabozantinib. For those of you who've been practicing and taking care of patients with advanced kidney cancer, you know that nivolumab was kind of the drug that shook everything up, right? We had isle 2 and then we had the TKIs and a couple of mTORs and then nivolumab came along and it's like everything exploded with immunotherapy, and then different TKIs, and then combination therapies. So, we got to give a little love to nivo here for kind of setting the stage for this explosion here. So, if you look at the data here, it did show that the combination of nivo-cabo had a greater median overall survival versus sunitinib in this trial.

The way that the nivo is given, when it was first FDA approved it was every 2 weeks, which, as many of you know, can be problematic for our patients who have social issues, transportation issues, like coming every 2 weeks can be a bit of a burden. It's not every 4 weeks. The thing to remember here with the combination therapy, the FDA-approved dose of cabo, if you're using cabo as a monotherapy, is 60 mg, but in combination with nivolumab, the recommended dose is 40 mg, and that's – the cabo is taken once a day. And this just shows some more data about that particular trial.

So, for allcomers, improved overall survival by 30% compared to sunitinib, which is pretty darn significant. And then the other combination that is approved in the first-line setting. So, lenvatinib, which is a tyrosine kinase inhibitor, plus pembro, or everolimus versus sunitinib in advanced renal cell carcinoma. So, this was 3 different treatments. So, lenvatinib plus pembro, lenvatinib plus everolimus and sunitinib. The overall survival data is not year reached, but lenvatinib plus pembro did show a median progression-free survival of about 24% versus 9% for sunitinib.

What we can see in the subgroup analysis is how things are favored depending on their risk category. You can see that for favorable risk, it's a little bit of a draw there. For intermediate risk, favors lenvatinib and pembro. And for poor risk, favors lenvatinib and pembro. The way that this is dosed is pembro is given 200 mg every 3 weeks or can be given 400 mg every 6 weeks. And then the lenvatinib is 20 mg daily, and we'll talk about doses of lenvatinib because that is a high dose.

In breaking up these trials into these categories here, so that you can see the ipi-nivo, axi-pembro, cabo-nivo, and lemvatinib-pembro. Just to point out one of the most important things here about the ipi-nivo trial is that the favorable risk disease was really kind of a – a secondary datapoint. It was really looking at intermediate risk and poor, which is why that's approved in the first line setting for intermediate risk and poor and not favorable risk disease. But other things to highlight – treatment discontinuation due to adverse events. These aren't really small numbers, right? So, we have to be very mindful about educating patients about toxicity profile.

And we'll get into this later, but the concern for overlapping toxicity profile once you start combining things, especially if they have similar side effect profiles, which one is causing which toxicity is always the question. So, be mindful about that.

And these are just extrapolated data. So, looking at cross-trial comparison of response in the intent-to-treat populations. We can't directly compare these things because this is just data that's extrapolated, and these are not trials that have been conducted head-to-head. But just to give you an idea of overall response rate of every trial.

And this next slide looks at what the dosing are, which we talked about a little bit. With the ipi-nivo, the nivo is given with the ipi, but the ipi is only given for 4 doses and then that one goes away. And the nivolumab stays. For pembro-axi it's pembro and the axi is 5 mg bid. The axi can be titrated up if patients are tolerating it. Sometimes we do increments of, like, going up to 7 mg bid, 10 mg bid. It's rare that I have a patient who can tolerate 10 mg bid, either monotherapy or in combination therapy. That's not something that's terribly common.

And how long do we keep people on these treatments? For most people with advanced renal cell carcinoma, we keep them on treatment until it stops working. So, in other words, we scan at certain intervals. So, depending on what treatment they're on, if their scans show significant progression of disease, and that's a bit subjective depending on who's interpreting that. Or if they have intolerable toxicities that either can't be well-controlled with best supportive care, or we re-challenge them and they end up having the same toxicity.

For pembro and nivo, so these checkpoint inhibitors, there's thought that there might be a maximum dose scheduled for that, so, for 2 years. But we do have patients who can continue on – It's not a lot of people that we keep on the same treatment for 2 years in the setting of advanced renal cell carcinoma, so we don't always get to this, but in other cancers – so for example, I also treat people with urothelial cancers. I do have folks who were on single-agent checkpoint inhibitors for a long time, and we stopped them after a couple of years, and they are doing well. So, just something to consider there.

Selecting first-line appropriate treatment, putting people into risk categories. We have to do that in the beginning so that we can make sure that we are appropriately prescribing treatment for them. For favorable risk it's pembro-axi, nivo-cabo, or pembro-lenvatinib. And for intermediate or poor risk we consider all of those in addition to ipi-nivo or cabo monotherapy. And of course, anytime we're picking any kind of treatment for patients, we have to be very mindful of their preferences. So, thinking about things like traveling to get their infusions, adherence to oral therapy. So, axitinib is twice a day, whereas other TKIs are only once a day. So, thinking about things like

that.

As nursing professionals, you know the complexities of these treatment-making decisions and all of the nuances that have to go on and the discussions that we have to have with patients and their caregivers about what makes most sense for them. Not just the data and the overall survival and the things that we read about as far as the statistical stuff. At the end of the day, it's the person sitting in front of us and they're so much more than just their cancer diagnosis. We have to be mindful of everything else that's going on in the background to make sure that we are aligning our treatment recommendations with their goals of care. And that's just a little summary of the action I have there.

Treatment options for patients with progressive kidney cancer after 1 or more previous lines of therapy. It kind of becomes a circus after this, but I will hand it off to Taryn to go over a case study.

Taryn:
Here's a case. Mary is 61 years old with metastatic RCC. She presented with intermediate risk RCC metastatic to the lung and liver at the time of diagnosis. She underwent right radical cytoreductive nephrectomy with adrenalectomy, cholecystectomy and partial hepatectomy. She began therapy with a VEGFR TKI plus ICI combination. At her first scan after 3 months on the VEGF TKI plus ICI combination, she showed progression in the lung and local recurrence in the nephrectomy bed.

Dunn:
The therapeutic landscape of kidney cancer, second line and beyond, is absolutely dizzying. So, if you look at the NCCN guidelines for what are the options for second line, it's an extraordinary list. So, there's absolutely no way we can cover all of that unfortunately, but we are going to highlight some important data so that you are at least familiar with some of what the options are.

We are going to talk about cabo. This was the METEOR trial, so this as cabo versus everolimus after patients had had a VEGF TKI. Five percent of the patients had received a previous therapy with immunotherapy. The overall response rate with cabozantinib was 17% versus 3% with everolimus alone. Data about cabo from trials that were done before this show that we think it actually works well, specifically in patients who have bone metastases. One take-home message I like to point out with cabo is that we have to dose reduce this a lot because of toxicities, diarrhea, and hand-food syndrome. So, the starting dose is 60 mg, but we can dose reduce to 40 mg or 20 mg depending on kind of what's going on with your patients and then rechallenge them.

This was lenvatinib plus everolimus, or single-agent lenvatinib, or single-agent everolimus. But what this study showed us was that the overall response rate with lenvatinib plus everolimus was 43% versus 6% with everolimus alone, so that's pretty significant there. The dosing here is lenvatinib 18 mg and everolimus 5 mg.

Something I like to point out here is that 30% of patients had to discontinue therapy because of adverse events. So, again, when we're combining therapy, there's an increased risk of having toxicities.

The sequencing VEGF TKIs following front-line immunotherapy. So, people who've had immunotherapy up front, what are some potential options for them? There's lots but these are the few we're going to kind of touch on here. This was assessing the dosing of lenvatinib because lenvatinib 20 mg or 18 mg can be a little difficult to tolerate and we find that we have to dose reduce that some. This as a post-approval study, so after that – that combination got approved. Most of these patients were intermediate and poor risk and noninferiority could not be claimed based on the overall response rate. So, essentially, lowering the dose to 14 mg didn't really make a difference in the endpoints that they were looking at.

Tivo, so this is tivozanib versus sorafenib, which is a very old drug, in advanced renal cell carcinoma after prior VEGF TKI. So, patients had to have at least 2 to 3 prior therapies and at least 1 VEGF TKI in order to be eligible for the trial. And what it showed was that the overall response rate was 18% with tivo versus 8% with sorafenib. The dosing on this is a little weird. So, it's 1.34 mg everyday for 21 days and they get a 7-week break.

And then looking at KEYNOTE-146. So, response to lenvatinib plus pembro by previous therapy. Looking at this, interestingly enough, when we kind of break down the objective response rates into categories, we see that the patients who had not received prior immunotherapy had a 53% partial response and 41% stable disease. For patients who had had prior ICI therapy, they had a 63% partial response and about a 30% stable disease, which is not bad.

Looking at novel targets. So, I don't know how many of you are familiar with the drug called belzutifan. It's currently FDA approved for patients who have tumors related to von Hippel-Lindau disease. So, either CNS tumors, renal cell tumors, or pancreatic tumors. This was looking at belzutifan in patients with metastatic clear-cell renal cell carcinoma, not necessarily in the context of VHL status. So, what we see here is that there is a pretty decent number of folks who had a partial response. So, that's the green there on the waterfall. It's a relatively small trial, so in – in a 55. So, there's definitely some more research that needs to be done in looking at belzutifan in

patients who have advanced kidney cancer, but not VHL syndrome as well.

What we know about belzutifan, and I have some experience with this because we have a VHL center at UNC, is that anemia is pretty common, as well as hypoxia. So, these patients need to be monitored closely for hemoglobin numbers and also make sure that their pulse ox is checked when they come in for their visits.

Considerations for treatment after progression. Options for second line therapy and beyond are guided by what did they already received, what is the strength of evidence, what's the toxicity profile, what toxicities did they have with their prior treatment, what are their comorbidities that could preclude them from going on to X, Y, and Z therapy, patient provider preference, of course, financial concerns, all of the psychosocial stuff that you all are aware of, and then various therapeutic options can be used to sequence therapy progression depending on what patients previously received. There is a lot that is still lacking as far as data for how do we sequence these agents, and that's what we really need to be focusing on a lot of research instead of just, I don't know, we're going to try this. But that's the way that it is for right now.

Management of treatment related adverse events for patients with renal cell. This is where a lot of really important nursing education comes in. So, for tyrosine kinase inhibitors, the most common side effects are things like fatigue, hypertension, hand-foot syndrome, anorexia, diarrhea, thyroid dysfunction. For the mTORs like everolimus, things like rash, hyperlipidemia, and stomatitis. But the immunotherapies have like a whole different side effect profile. Basically, I tell folks that anything that ends in an -itis can happen. These immunotherapy adverse events can affect any organ. The major driver of these adverse events is cytokine and so the activated T-cells kind of flood the system and things can just go a little bit haywire. So, basically, an over – overdrive of the immune system, which can lead to these adverse events.

So, the timing varies greatly for what these potential adverse events. So, as you can see, it can be as early as 4 weeks. So, that's after 1 dose of most of these, and can be prolonged. Like, we've seen months and months and months after people have been on immunotherapy that these things can pop up.

The fatal IRAs are rare. You can see kind of some of the percentages here. However, when they happen, they are absolutely devastating. I think one of the most important take-home points here is nursing education, what I really try and drive home to my patients is, if there is anything different about you, we need to know about it, because these things can present very subtlety and patients might not think anything of it. Like, oh I just had a little episode of diarrhea. No no no no, we need to know about all of the things because it could be an early onset of one of these potential adverse events and they need to be handled quickly.

What this shows is that in this particular report colitis was the most reported adverse event for ICIs, but myocarditis was the most fatal. And then immunomodulary agents to manage these things. So, steroids. So, basically steroids are going to suppress the immune system, right? So, that's usually our go-to is oral steroids, high dose. We can add mycophenolate, which is also an oral drug, and then if things are not managed well with high-dose steroids, we may need to add other biologic agents. So, all of these things are FDA approved to treat certain immune disorders. So, things like rheumatoid arthritis, ulcerative colitis.

Let's say someone has refractory colitis that's not responsive to steroids, we keep them on the steroids, but we add something like infliximab or bivatuzumab in order to better control the colitis.

The treatment goals of these adverse events are to control the symptoms early and effectively. So, again, that good nursing education. Call us, call us, call us if there's anything going on. To minimize recurrence, to minimize the immunosuppression and exposure. So, we don't want to have people on high-dose steroids for eons and we also have to make sure we're controlling their symptoms. And then, maximize benefit of ICI agents for cancer treatment. So, this balance affect that we're always doing between – walking a fine line between treating people's cancer and making sure we're also not making them very sick with the treatments that we're giving them.

These are general guidelines for management of immune-related adverse events. Really depends on the grade, the degree of severity of the particular AE. We can do observation if it's grade 1. For grade 2, we consider holding drug, dose reducing drug, best supportive care. For grade 3, we're discontinuing all kinds of stuff and adding steroids. And for grade 4, those are life-threatening, requires hospitalization and everything gets stopped, and the vast majority of the time the ICI is permanently discontinued.

Taryn:
Here's a case study. James, 51-year-old with advanced RCC receiving cabo-nivo. He develops grade 2 LFT elevation after 3 cycles of therapy with nivo-cabozantinib. His AST is 66 and ALT is 160. He is asymptomatic and otherwise tolerating his therapy without other IAEs.

Dunn:
This is just an example of potential overlapping toxicity. So, tyrosine kinase inhibitors and ICIs can cause hepatitis, and unfortunately,

like, roughly at the same timepoint. So, in order to figure out what is causing the problem in the context of hepatitis, we typically stop both of the medications and then recheck LFTs to see what's going on. And the recheck of the LFTs I typically like to do it within a week, some people do 2, but diarrhea and hepatotoxicity, as we see here, tend to be the highest-grade IRAs with combination therapy. So, just being kind of mindful of lab monitoring and making sure patients are reporting any kind of GI symptoms. What do we do as far as supportive care when these things happen? Well, it really depends on the grade and patient symptoms, and those types of things.

Management of overlapping toxicity. So, for James, if you look at the AEs etiology, unknow, he'd be a grade 2 on those LFTs and we'd have no idea which one is causing it, so we hold both agents, recheck labs. If things get better, then we can restart agents one at a time.

And this is just an ASCO guideline recommendations, which you can look up. There's ASCO guidelines, there's ONS guidelines, there's all kinds of guidelines about how to manage these toxicities, which has been very helpful because, you know, when we first started using these drugs it was kind of like, AH, out all the things are happening all at once. But there's lots of guidelines that you can look up to use in your clinical practice.

Taryn:
And our case study continues. James begins both agents. They were held and LFTs were rechecked a week later. The ALT improved to 45, the AST improved to 116. He resumed therapy the following week with a 1-dose reduction of cabo to 20, and the nivo dosing remained the same. Serum LFTs remained grade 1 and asymptomatic.

Dunn:
So, that's good for James. When doing this work and managing toxicity, sometimes it's both an art and a science. So, just understanding that following those guidelines is important, and making sure that you're targeting those guidelines to the person sitting in front of you, because it can be a little bit tricky.

So, there are NCCN clinical practice guidelines in oncology for management of these toxicities, which you can go to ClinicalOptions.com to find this really cool tool that you can download, and it's an app so that you don't have to, you know, go to a textbook like a dinosaur like me to look these types of things up. Just stressing the importance of education. These immune-related AEs are unique to immunotherapy. Most people do not experience them. The vast majority of people don't. They are very variable as far as onset and things like that. They are not as predictable as chemotherapy side effects. As we've discussed, TKIs and immunotherapy adverse events can overlap, which makes management a bit more complicated. We have to dose hold and dose reduce all the time to figure out which drug is causing which side effect, and then patient education, patient education, patient education is huge, and caregivers. And that's just a little action item. So, basically any changes to your health we need to know about it.

And then, we're going to kind of go through our action plan. Consider adjuvant pembro for eligible patients who meet criteria, depending on patient preference. Identifying risk stratification, disease characteristics, patient preferences to help select optimal first-line treatment for advanced renal cell carcinoma, all of which are combination therapies. Consider treatment history, as well as evidence, side effect profile, all the things that we've talked about. Having to use steroids or other biologic agents to control AEs to maximize time on therapy and benefit with these agents. And then, educating patients about reporting anything.

Another little nursing education take-home point I'd like to drive home is that letting patients know that they should not be put on steroids for other reasons, like if they were to have some sort of, like, asthma flare or something, to call us first because steroids, in the context of being on immunotherapy, is like, kind of counter intuitive to what we're doing. So, just letting all of their other providers who aren't their oncologists know that they're on these medications so that we can all be on the same page and do good collaborative management.

Looks like we're wrapping up with some more questions.

Taryn:
Mary-Ellen, thank you for a great presentation on a tough subject, but thank you so much for breaking it down for us.

Announcer Close:
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