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Collaborative Insights to Solve the Puzzle of Bladder Cancer

Announcer:
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Chapter 1

Dr. Petrylak:
So it's my pleasure to start off with differentiating molecular targets in bladder cancer. As we know, bladder cancer, of course, 90% of your bladder cancer is urothelial, the remaining portion, adenocarcinoma, small cell carcinoma, and other variants. And we know that bladder cancer can also be divided into different molecular subtypes. There's the luminal subtype, which comprises of different molecular targets, that includes FGFR, PPAR gamma. Nectin-4 is in the luminal subtype as well. And there's a basal subtype which has also a different set of markers, EGFR, p53, RB. These also are present within that particular subtype. So these are targets that we can use for urothelial carcinoma and to improve our outcomes.

So if we look at the different kinase pathways in urothelial carcinoma, there's not one kinase pathway that dominates. We see that about 20% to 30% of patients or specimens will have FGFR3, ERBB2, EGFR, NF1, PTEN, TSC2. All these seem to be at the same rate of expression, but they can be targeted. So there's no one dominant kinase pathway. And in fact, a lot of these kinase pathways have final common pathways in their signal transduction schema, as we see nectin-4, FGFR, and HER2/neu, they have common pathways with PI3 kinase, JAK/STAT, as well as the cyclins. So all of these can lead to final common pathways which lead to cancer growth.

So let's first take FGFR. FGFR3 is fibroblast growth factor receptor 3. It's a membrane-bound tyrosine kinase which is involved in cellular proliferation, differentiation, and steroid biosynthesis. There are 4 distinct subtypes. FGFR3 mutations and overexpression have been implicated in bladder cancer. And in January of 2024 the FDA granted full approval to the FGFR inhibitor erdafitinib for locally advanced or metastatic urothelial carcinoma with susceptible genetic alterations such as FGFR3 that have progressed after at least one form of prior systemic therapy. And there are other ways that we're targeting FGFR, and these include ADCs as well as theranostic approaches. So this is an important pathway in urothelial carcinoma.

Now there's an interesting paradox about FGFR. It seems that the lower-grade tumors, or the lower-stage tumors express higher levels of FGFR, Ta tumors can express FGFR in about 90% of specimens. Expression is lower in the T2 muscle-invasive disease about 10% to 20%, and mutations can occur in the extracellular or transmembrane domain of the receptor and lead to ligand-independent dimerization in this receptor. Fusions will also act by similar mechanism.

Now, we do have tissue testing for FGFR. And it's my opinion that every patient should have this testing, because of course, they could lead to a particular therapeutic approach. So the FDA-approved companion diagnostic for erdafitinib is from a company called QIAGEN. It's used in formalin-fixed paraffin-embedded tissues, and RT-PCR is used to identify the FGFR mutations.

One thing, as I mentioned before, we need to do this in all of our patients that is disappointing, is that really the rate of capture of FGFR, or the rate of testing, is lower than I would like it to be. So this is a study that took 761 patients who were post platinum for metastatic disease from April of 2019 to September 2021, 45% underwent FGFR testing, so that's really a disappointing number; 305 had tissue-based testing and 74 had blood-based testing. And of those patients, 30 patients received erdafitinib. So obviously, we're not capturing

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everybody who's eligible to receive this treatment.

Now, FGFR has a variety of different resistance pathways. We can potentially exploit these in combination therapy to potentially improve the overall outcome of FGFR. These include METF, Eph3B, the ERBB family, which can be alternated, upregulated for resistance. The gatekeeper modifications can modify the binding pocket of FGFR and prevent drug binding to that area. FGFR could also be involved in epithelial-to-mesenchymal transition that can lead to resistance. Activation of other signal transduction pathways such as MAPK, PI3 kinase, JAK/STAT, and GSK3B can also lead to resistance. So this is certainly something that can be pursued in the future in terms of synergy.

What about nectin-4? Well, we know that nectin-4 is strongly expressed in metastatic urothelial carcinoma. And this is from the EV-201 trial and the EV-101 study, where we did phase 1 studies with enfortumab. In prescreening, initially we were looking at nectin-4 expression as a selection factor, and this went by the wayside because practically every specimen was found to be positive by immunohistochemistry for nectin-4. About 97% of specimens showed nectin-4 expression. And a majority of patients had high levels of expression. And so pre-screening was basically taken out in terms of enfortumab. And this is the way in which enfortumab works, it binds to nectin-4, it's internalized, and then the ADC is cleaved to leave free MMAE, which causes the cytotoxic effect on tubulin.

Now it makes sense that the membrane is where the money is in terms of response. So this is a study that's looked at nectin-4 amplification in patients with urothelial carcinoma. And this seemed to predict response; high levels of nectin-4 or overexpression of nectin-4 by PCR. This showed an improvement, at least in prediction of response to enfortumab vedotin. So it’s certainly probably more specific than immunohistochemistry in this situation.

This also reminds us that nectin-4 is not only expressed in urothelial carcinoma, it's expressed in cholangiocarcinoma, head and neck cancer, breast cancer, and there are trials that are looking at the targeted therapy to nectin-4, particularly enfortumab, in these other tumor types. So this is not just a urothelial carcinoma marker.

The HER2/neu signaling pathway is also important for urothelial cancer. This has been known for a long period of time. But now we do have agents that are FDA-approved in the situation. As we know, this is part of the super family of EGF receptors, which there are different forms of dimerization. There's HER2/neu, HER3, HER2 that can dimerize, HER2 and HER4 can also dimerize. And these can lead to different activations of signal transduction pathways, and then also increased in cellular growth. In urothelial carcinoma, we see that there can be strong expression, 3+ in about 18% of specimens that have been examined, 34% of 2+ overall. So again, this is a target that we can use in urothelial carcinoma.

And trastuzumab deruxtecan is an ADC that recognizes HER2/neu. It’s cleaved by the lysosome, and then the warhead will cause DNA damage and apoptotic cell death, leading to anti-tumor activity. And the question, of course, is, and this is something that's interesting, is can we use combination therapies of antibodies to treat these patients? And are those patients who respond best to EV, the same patients that may be enriched for HER2/neu? And they've been found to be super responders, as mentioned before, by nectin-4 amplification. And these patients will also have alterations in ERBB2 overexpressed in luminal-differentiated urothelial carcinoma back to that original pathway I showed you previously, which can enrich for nectin-4 amplification. And then this is really, I think, a clue as to going forth with combination therapy in the future.

And this slide also illustrates that particular fact. ERBB2 can be amplified in the luminal subtype, and it's absolutely in the basal squamous subtype, and nectin-4 expression weakly positive correlates with ERBB2 expression. So again, this may be a way of using going forth with multiple antibodies. And this is also the fact that ERBB2 alteration may be associated with benefit to EV. I point at the top portion where the hazard ratio is 0.5 for survival in those patients who express ERBB2 and are treated with enfortumab. So this may be again, another clue as to a combination therapy.

So in conclusion, nectin-4, FGFR3, and HER2/neu are expressed in luminal subtype of urothelial carcinoma. FGFR3 expression can be measured by RT-PCR of tissue specimens. And FGFR3 testing is recommended by the NCCN Guidelines. Nectin-4 testing is not routinely performed in urothelial carcinoma specimens, and so by IHC, we should not use this to select treatment. Nearly all specimens of patients with urothelial carcinoma express nectin-4, and copy number of nectin-4 may predict response to enfortumab vedotin. And HER2/neu has a variable expression in advanced urothelial carcinoma, and its testing is recommended by NCCN Guidelines.

Chapter 2
Dr. Yu:
Let's jump into some of the clinical data from some of the clinical trials. So I think one of the most exciting things that has happened in this field is really for first-line now, first-line metastatic urothelial carcinoma, where, if you rewind the clock to when I started in this field, median survival was we're talking in terms of less than 1.5 years, and we've made major improvements here.

So this is the EV-302 trial. This is in previously untreated patients eligible for platinum, enfortumab, and pembrolizumab. And randomized 886 patients to enfortumab vedotin/pembrolizumab vs chemotherapy. And chemotherapy was dealer's choice; you would designate whether the patient was a cisplatin candidate or whether you would treat them with carboplatin. And it was dual primary

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endpoints of progression-free survival per BICR or overall survival.

And here you go, you can see the overall survival data. I don't think we need to spend a lot of time on this to see that there's clearly a statistically significant benefit with a hazard ratio of 0.47, wonderful P value, and essentially a doubling of median overall survival from 16 to almost 32 months. So I think that's a major impressive groundbreaking move in our field.

Now, one question that people had is, is that we used to really put a lot of time into thinking about whether a patient with cisplatin eligible or ineligible, and we had all these criteria based on kidney function, based on hearing, based on cardiac function, neuropathy, et cetera. And it may not matter that much, as much as it used to anymore, because you can see whether you're cisplatin eligible or ineligible, both of these groups of patients had a very significant benefit over a traditional platinum-based chemotherapy.

I want to draw your attention for the objective response rate: 67.7% is very impressive versus 44.4% with chemotherapy. And I think that oftentimes we don't spend enough time thinking about objective response rate, because of the field has gone towards IO and we think about durability. But one thing I want to draw your attention to is the complete response rate of 29% versus 12.5%. That's really, really impressive. And anecdotally, some of these patients don't actually relapse. So that's one thing that I want to point out there when you look at these tables, is really that the complete response rate is quite, quite impressive from this study.

When you think about treatment-related adverse events, the key things we think about are at the top there. They're really peripheral sensory neuropathy. That's because the payload for enfortumab vedotin is MMAE, monomethyl auristatin E, which is a microtubule inhibitor. And then, of course, skin changes, rash, pruritus, alopecia, et cetera, and that's because nectin-4, the target for enfortumab vedotin, is highly expressed in the skin as well.

But the thing they bring up is just the fact that some patients did discontinue, and the most common cause for discontinuing early on the trial was due to peripheral sensory neuropathy there. And it was 29.5% of patients discontinued enfortumab vedotin for that reason, whereas it was 21.4% of patients who discontinued pembrolizumab.

Again, this is just another way to show the treatment-emergent events of special interest. And again, it emphasizes the differences in skin reactions, 68.8% of any grade versus with chemotherapy is 13.9%, peripheral neuropathy of 63.2% versus 12.2%, and then ocular disorders, we know that antibody-drug conjugates, there can be a class effect of deposition on the cornea there. These usually resolve, withholding the agent over time.

The other thing to bring up that I haven't talked about yet is hyperglycemia. This tends to happen in patients of more advanced age, and especially those patients with higher body mass index. And so hyperglycemia can be something to watch out for as well.

Now, I think that one word that we use a lot, is synergism. And if you really think about it in oncology, we probably don't have as much synergism as we talk about. And I think we wish we had more synergism. Sometimes you get additive effect, but I think in this case, it's hard to deny that there might be synergism. And so one has to ask the question, and this was brought up by Matt Galsky, and that's why I borrowed his slide here, is just that he's the first one that, at least that I can remember that brought it up at the podium, although I'm sure others have discussed it before, is there something special about MMAE? Because when you look at the IO combinations with antibody-drug conjugates, we seem to have seen more, I think, dramatic results when the antibody-drug conjugate has MMAE plus IO versus maybe a different payload.

Again, it's somewhat speculative. We don't have a lot of data to support that. There's a little bit of pre-clinical data, but it's not anything that's definitive, but it is interesting that we seem to see potential more synergism in those situations.

I do want to talk about the DESTINY-PanTumor02 study design, as we were talking more about antibody-drug conjugates. Dan brought up trastuzumab deruxtecan there. And so this was a study for second-line patients with advanced solid tumors. They had to be HER2 2+ or 3+ by immunohistochemistry. And they did allow prior HER2-targeting agents in this study since some of these cancers are treated with other HER2-targeting agents. But you can see there, there were bladder cancer patients in here as well, and objective response rate was really what we're looking for. So I'm just going to emphasize bladder, although you can see t all the other tumor types there as well, like endometrial, ovarian, et cetera. But you can see very significant response rates, especially for the 3+ populations. And you can see most of the patients had shrinkage of tumor, and there were patients on the swimmer plot that had a very nice, long, durable response there. So something to bring up.

Safety is as expected with trastuzumab deruxtecan, which has been around for a while and used in other diseases like breast and gastric cancer there. It tends to be nausea, fatigue, some GI side effects, and then some myelosuppression type of issues there. But the one thing I want to draw your attention to is pneumonitis. I think that's the one side effect that can be very dangerous. We all have to be on high alert for it, and it is a unique side effect that you can see.

I do want to talk briefly about mutations. So we always talk about quantifying HER2 by immunohistochemistry, by ISH, but HER2 mutations, there are activating mutations. And the question has always been, will these agents still work for them? Now, there's not as

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much data because they're not as common, but when they do occur, and as you can see, I highlighted urothelial here again since we're talking about bladder cancer, these patients can respond as well. And so this is just a basket study looking at patients with HER2-activating mutations here with trastuzumab deruxtecan, and there might be something to do with these HER2 mutations leading to better internalization of these antibody-drug conjugates.

Now, as we stay on the theme of HER2, I want to bring up disitamab vedotin, which was an agent that was studied early in China. And then they did combination type of therapies with toripalimab, and they saw very, very dramatic effects, especially in the HER2-high populations, but the HER2-low populations seemed to respond as well. And so this is just from 20 patients. This is a phase 2 study, and was really the initial 20-patient lead-in, run-in of the study there. As you can see, I think it was about 30% of the patients were HER2-high, which is 3+ or 2+ ISH positive, and about another 70% were HER2-low. But you can see here at the bottom there on that waterfall plot there that there's responders kind of across the board, and there's a nice spider plot there as well. So pretty good data; early on though, so we've got to see a lot more data there.

I'm going to move on real quickly to FGFR and the THOR studies. Erdafitinib, we know, is FDA-approved. There was a couple second-line studies here. One in patients that were previously IO treated. It was erdafitinib versus taxane, and one that was previously IO naïve, and it was erdafitinib versus pembrolizumab. And I'll just show you that it was a very significant survival benefit there for erdafitinib versus taxane chemotherapy for those who are IO treated there. And then the safety data is as expected with erdafitinib, the nail changes, the hyperphosphatemia, the stomatitis, diarrhea, these are all things that we've seen before with this FGFR inhibitor that's a pan inhibitor of FGFR1 through 4.

And here's the cohort of patients that were studied that had not received prior IO. And as you can see here, there's no survival benefit; median overall survival is essentially the same between these 2 populations there.

All right, so I just want to do some wrap-up take-home points here for this talk. Enfortumab/pembro is a new standard of care for first-line treatment of locally advanced metastatic urothelial carcinoma. Trastuzumab deruxtecan does have accelerated approval for HER2 3+ urothelial bladder cancer and for other solid tumors as well. Other HER2 antibody-drug conjugates like disitamab vedotin have promise and are being studied, both for HER2-high and low tumors. And erdafitinib is now FDA-approved for patients with FGFR3 genetic alterations, mutations in particular, with superiority over taxane chemotherapy in second-line and beyond, although it wasn't better than pembrolizumab.

Chapter 3
Dr. Plimack:
So we're going to talk about sequencing targeted therapies. And this first algorithm, I'm going to go through quickly only because, as Dan said, there are just so few people now, at least in this country where there's access, that can't get to EV/pembro. So the first part of this talk is for those folks who can't get it. And then, of course, there's reasons that they can't get it that then make some of these algorithms not good choices either. But really, this is sort of harkening back to where we were before, where you do divide cisplatin eligible and ineligible. And then this platinum ineligible category, which is very small, people who really can probably not tolerate much and they can get pembro or atezo still. For cisplatin ineligible, it was gem/carbo, maintenance avelumab. And then for cis eligible, it was gem/cis followed by maintenance of avelumab, or now we have nivo/gem/cis where you get both together. And probably that's where we would go for the cisplatin eligible patient who for some reason, can't get EV/P. Once they have disease progression, we have a big bucket. That's the bucket we're going to end up in after EV/P also, and we'll talk more about how to choose those therapies.

So this is EV-301. This is just the enfortumab vedotin, and this is before the EV/P phase 3 readout compared to investigator's choice chemotherapy. And this is just to remind us that there's a benefit of EV by itself over chemotherapy. So that is in our bucket armamentarium if we don't spend it in the front line with EV/P. And then there are these biomarker-directed options that you've heard about already. So trastuzumab deruxtecan requires 3+ IHC testing in the panel on the left. I wrote here 12% incidence in UC, but today I've heard anywhere from 50% to 80%. So in my practice, it does feel like it's 12%, but we'll turn that question to both of you at the end of this talk and we'll see what you think. And then for FGFR right now, it's erdafitinib. Again, we saw some interesting data in the rapid oral that there might be better versions of this, but patients must have a susceptible FGFR mutation or fusion, and that is estimated to be 10 to 15% which sounds about right to me. The one on the left, of course, is intravenous. The one on the right is oral.

Okay, so when EV/P is not used in the front line, how do you sequence? Usually you give first-line chemo and an ICI, immune checkpoint inhibitor, either together, nivo/gem/cis or in sequence, your platinum combination followed by maintenance avelumab or pembrolizumab, we used to use when we did that.

And then you have to sort of know your biomarker. So this is why, in the beginning of metastatic disease, it's a really good idea to get your full set of testing on the tissue that you have. There are reasons to biopsy progressing lesions, to get fresh tissue to look for a change in biomarkers. But in general, I like to get the sequencing early, early, so I know I can kind of set up my strategy. And I think patients like knowing sort of what might be next for them as an option.

So if they're biomarker positive, they get biomarker-directed therapy, which we'll talk about. If they're biomarker negative, they get EV. I

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put the question mark pembro. I think a lot of us just kind of want to keep it going and add EV and see what happens. But again, receptor occupancy was brought up. Maybe the pembro is
kind of still working, and you don't need to actually give more of it to get that kind of that synergy that Evan spoke about.

So first-line standard of care is EV/P for almost all and second-line therapy is now really a data-free zone. Here are the second-line options, platinum-based chemo, biomarker-directed therapy, taxane, or a clinical trial. So harkening back to way back, these are the first-line data with our favorite dose-dense MVAC, gem/cis, and gem/carbo. Those response rates are shown here. And now, since we know these are active, we just kind of moved them to the post EV/P, hoping that they'll work. We don't have data on how well they'll work, but I think a lot of us do that. And in the EV-302 study, a lot of people did do that. So of those who progressed on EV/P and got subsequent therapy, almost 80% got a platinum combination. So some people who enrolled patients to the study were doing as next line.

Practical considerations for platinum. So after EV/P, do they have neuropathy? Platinum causes neuropathy. Slightly different mechanism, but it can cause long-term neuropathy in 30% to 40% of patients. Carboplatin has the same incidence, but the severity of the symptoms is typically milder and the onset is later, so that might be a reason to turn to gem/carbo in this space. And both are subject to a coasting phenomenon, which is worsening after-treatment cessation. So things to consider.

So pathways for consideration of platinum after first-line EV/P. This is complicated. I just sort of made this to say you really kind of think about the neuropathy. This is probably like the first question. So many people, as Dan showed, emerge from EV/P with neuropathy. If it's ADL-limiting, you're going to be more cautious, maybe give carbo/gem. Consider that if they had prior dose dense MVAC in their past and have never been exposed to gem, you could try gem alone without carbo. Just go a little slow. And then if they have no neuropathy, your options are really much wider in terms of all of the platinum combinations.

Okay, practical considerations for taxanes. Same thing. So the reason that we think there's neuropathy is from the MMAE payload in enfortumab vedotin. It's a microtubule inhibitor. So as paclitaxel. The mechanism of neuropathy is probably similar for these; it's depicted on the left. And so we really, I think, have to be careful when we move to taxane in this space.

So after EV/pembro, it’s kind of similar consideration. If they're biomarker negative, you consider platinum. If they're biomarker positive, you can still consider platinum, but you have a lot more options in terms of biomarker-directed therapy.

Chapter 4
Dr. Plimack:
So interprofessional approach to unique adverse events. So these drugs, whenever we get a new drug, it's super exciting, and there's such a learning curve. I remember the early days of IO where we couldn't tell the difference between irAEs and something else, and it was all very confusing. So hopefully we can kind of walk you through things to think about in terms of adverse events and management.

So for EV and pembro, there are 4 big toxicities that I think about. There are others. But of course, pembro has its own tox and EV has its own, but the ones that come together in this synergistic fashion seem to be hyperglycemia, skin toxicity, neuropathy, and pneumonitis. And you can see hypoglycemia hits first in the first month, then the skin toxicity kind of comes on next, and then we really start to get neuropathy, and sometimes pneumonitis out at 6 months.

So hyperglycemia, how do we counsel our patients? How do we monitor them? And how do we manage them? Well, the mechanism of this is unknown. It's likely an insulin resistance. We know risk is higher if the A1c is greater than 6.5 or they have a high BMI. And we also know to just hold the treatment, especially the EV, if glucose is greater than or equal to 250. So we check before each cycle. Counseling pretreatment, we optimize glycemic control. We send them back to an endocrinologist to really tighten up their control. And then on-treatment monitor, we check before each infusion, and then we know to hold. If it's severe, we could consider steroids as it could be type 1 diabetes from pembro. But there have been cases with EV where folks are in diabetic ketoacidosis on insulin drips, and there's some level of insulin resistance in those rare cases. So we do try to prevent this.

Skin toxicity. So here's a wicked rash that we saw in clinic. Pretreatment counseling, we warn people. We remind the patient to report rash and use sunscreen. On treatment, we always ask them about rash, because they might not show it to you if your exam is limited. So do a careful skin exam. Always rule out mucosal involvement. Whenever someone has a rash, or someone calls saying, I have a rash, be sure to ask about that. Stevens-Johnson is rare, but you don't want to miss it if it's starting to emerge. And then rash-emergent therapy, we use a lot of topical steroid creams. It's hard if the rash is all over the body to like cream up every day. We treat itch symptomatically, hydroxyzine. We do often hold the dose of EV and sometimes reduce. And for refractory or extensive cases, we use systemic steroids, and we've actually had really good luck with dupilumab, which is a biologic therapy used for eczema that can kind of just resolve these rashes really beautifully. So our dermatologists, again, are really tight partners with us. And that's part of the messaging here; you need endocrinology for the diabetes, you need dermatology for the rash. And then we'll get to neuropathy.

So the reason we talk so much about neuropathy is that it is , as you saw, the most common reason to have to stop treatment, at least stop the EV in EV/pembro. And it can be irreversible and it can be debilitating. So it's sobering. It’s one of the toughest ones, I think, for

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us. Again, pretreatment counseling, we do a baseline assessment for existing neuropathy. On treatment, we ask about it, because it's something that can be very subtle, and sometimes patients actually minimize it because the treatment is working well and they don't want to come off it. So you really sometimes have to ask, can you button buttons? Can you still put on your earrings? Those kinds of things. Managing neuropathy is tricky. Once you hit it, you sort of have to hold the dose, dose reduce, extend the schedule. We are starting to stop the EV if they've had a beautiful response and are starting to have neuropathy. We're doing that in a trial I'll show you on the next slide. And then if you really get into the neuropathy, and this did happen a lot on the studies, there are some adjunctive things that work a little, not great, but gabapentin, pregabalin, and duloxetine are all treatments for neuropathy.

So can we prevent neuropathy? Right? How can we use this regimen to just maximize, squeeze every ounce of efficacy out of it, but try not to get to neuropathy? And I think we probably can. So these data here is EV-301. It's an early cohort of EV/P. The phase 3 trials based on these exciting data. And you can see here that out at the 2-year mark, and that's where the red box is. By then, almost everyone – these are all just responders by the way, everyone had to stop. The gray bar is on treatment. So the treatment kind of stops, but the response does not. So this kind of shows us that everyone has to stop at some point. Nobody is out at 5 years still getting EV. So what is that optimal point? And how can we, sort of , again, squeeze out everything we can? So we're doing this little pilot study at Fox Chase. Maybe it'll be a bigger study once we get some preliminary data, but we're looking at sort of taking EV/P as a standard schedule, getting to a response, and then at 18 weeks, if they have a good response, stopping and monitoring. You can always re-challenge with EV afterwards. We do continue the pembro for 2 years. So patients love this. It's accruing really quickly. We're about halfway, so we'll have some early data to report on that soon. I hope it works. It'd be great.

Okay, moving on to trastuzumab deruxtecan. So the toxicity profile here you can see, obviously, you can't really read, it's too small, but you can see it's all the things we know about with chemotherapy, all the familiar things. So nausea, vomiting, neutropenia, infusion reaction, alopecia, fatigue. The one that's different is really the ILD/pneumonitis. And this is, I think, a black box warning on trastuzumab deruxtecan, and it is a little difficult to manage. So the picture on the left is sort of what it looks like. We're scanning people often with cancer, so we do sometimes pick this up on our patients when it's asymptomatic, but once the symptoms start to hit, hypoxia, cough, and dyspnea, you really kind of have to be careful. So above in the top box, is if you have no symptoms, you hold and just kind of recheck in 28 days. If they have symptoms, you use steroids and discontinue permanently.

And this can actually overlap. So this is trastuzumab deruxtecan, but I'm going to sort of use this to layer in guidance for other ways to get pneumonitis, because EV can cause it, pembro can cause it, and EV/pembro can cause pneumonitis. And so there you'd probably consider holding both drugs. Mild symptoms, you definitely hold them. Use steroids to reverse the pembro. And then sometimes I have given an EV rechallenge, because pneumonitis is more likely from the IO than the EV, especially in a patient who seems to still need it, we can't stop it, and for whom it's working. But certainly for severe symptoms, if you're admitting to the hospital for oxygen, you would discontinue both and reverse it with steroids.

Okay, erdafitinib. The toxicity is a challenge. Here we have CSR, which is central serous retinopathy. It's an ocular toxicity I'll talk about, diarrhea, skin events, hypophosphatemia, stomatitis, and nail events. And you can see those all sort of happen in the beginning. They do come on quickly. And then you can see they diminish, probably because they're managed with dose reduction and holds, is my guess, not because they magically go away. But it is reassuring, unlike IO toxicity, which can happen sort of any time, most likely in the first 6 months, you kind of see these right away, so what you're dealing with.

So hyperphosphatemia. There's very clear guidance in the package insert. It actually changed; it's a little more liberal. But that's a sign the drug is doing something, maybe working on the cancer, but certainly causing this high phos. When it goes up, we usually hold and then continue to watch it. Typically, when the phos goes up, all the other side effects we'll talk about in a minute, also kind of come on. So it's never something that I've had to manage in isolation, but there are clear guidance on how to dose reduce from 8 to 6 and beyond.

Okay, erdafitinib GI, skin, and nail toxicities. So stomatitis, nail events where the nails get inflamed at the edges, they can fall off. Skin events, dry skin, PPE, like the kind you get with TKIs that you get for renal cell, and 55% diarrhea. So these are high numbers, right? Of toxicities that actually aren't life threatening but definitely affect quality of life. And so these are all the different tools we have to really just supportive care, manage them, or we've dose reduced as well.

Here is what central serous retinopathy looks like. So this is interesting. This is why you should get monthly retina exams for patients on erdafitinib. But in the guidelines, really, if acuity is preserved, you can usually continue and they'll monitor it. You just don't want to give this drug without the care of an ophthalmologist or someone who can do a retina exam.

So key points. Management of toxicities in an interprofessional environment. So we just talked about endocrinologists, eye doctors, GI doctors, pulmonologists. I said dermatologists already. So you need your team, I think, to really take care of all of these. And you really, I think dose delays and reductions should be used as needed to keep people continuing, if they can.

Chapter 5
Dr. Yu:

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All right, I'm going to talk about some new stuff and some stuff that's relevant to the urology space. I think we all know that when you have non-muscle-invasive bladder cancer, that BCG is the way to go. And it's been around since, what, the 1950s. We still don't know exactly how it works, but it probably induces an immune response there. But we also know that there's this massive worldwide shortage of BCG, and it's hard to access.

One unmet need is for the BCG-unresponsive patient population, and usually we talk about cystectomy for those patients, if they're willing to do it and they're able to undergo it. But there are other agents that are FDA-approved and that can be used in this setting that are more hopefully bladder sparing. And so I put up this slide first because I want to give the historical viewpoint of intravesical valrubicin for non-muscle-invasive bladder cancer after BCG. This was FDA-approved for lack of having anything really better for this very tough-to-treat patient population that didn't want to undergo radical cystectomy. And you can see the data there, 35% complete response rates at 3 months. But that's not really durable. One year in the 8% range. Two years in the 4% range. And 1/4 of the patients eventually underwent radical cystectomy. But this was the bar, and this led to an approval for valrubicin at that time.

Now, I do want to bring this up, because this is what a lot of people use now, is gemcitabine and docetaxel. And it's quite effective, and it's a low-cost agent, and certainly when you're resource constrained and you might not have access to BCG, I don't think it's crazy to use this even in an earlier setting, potentially. But in a salvage setting, here you can see the 1-year disease-free survival rates at 60%, 2 years at 46%, 15% underwent radical cystectomy here, but it is a viable option to consider intravesical gemcitabine and docetaxel.

Now into the newer stuff was the KEYNOTE-057 study, which used pembrolizumab, and they had 2 cohorts. They had a cohort of CIS-positive with or without Ta and T1 papillary lesions, and then they had just a papillary lesion cohort. And DFS was the primary endpoint, and this was with pembrolizumab standard dosing up to 2 years or until recurrence. And what you saw here, with 101 patients in cohort A, which was the carcinoma in situ cohort, was a nice CR rate at 3 months there 41%. But you did get some treatment-related AEs as you can get when you're giving systemic therapy. And I think that's something unique, is that, traditionally, all the other therapies, and all the other future therapies I'm going to talk about are really intravesical. This is the one that was really, really given systemic. But there's immune-related adverse events, as one might expect as well. And I'll also point out, even though it's not on a slide, really, if you look about a year out, what you saw is about 20% who still were at pT0 or complete response.

But even newer, what we've seen is an approval for nadofaragene, and this is also for the BCG-unresponsive population. And so this is a replication-deficient recombinant adenovirus gene transfer vector. It's an interferon alpha based. And so again, it's infused into the bladder. It's given, really, every 3 months times 4. And so obviously, for the urologist providers, this is something that would be preferable for something that they can use there and not have to give any systemic therapy. So you can see, for the carcinoma in situ population, the 1-year complete response rate is 24%; for the high-grade Ta or T1 population, the 1-year complete response rate is 44%. So comparable to what we've seen here.

And then this is nogapendekin alfa inbakicept.

But this is an interesting, interesting IL-15 super agonist. Okay. Now, the one challenge here is, is this is BCG unresponsive, and they saw the best results when they give it with BCG. So again, this is the one challenge, is that you still have to give this with BCG. And what you see here is about 71% of patients get a complete response. And a year down the road, I think about 2/3 of those patients, or a little bit less than 2/3 of those patients, are still in complete response there as well. But you can see pretty impressive data. But the key thing is you have to have the BCG there as well.

Now, I'm blasting through all this because there's actually a lot of stuff in this area. I think it's a fruitful area and an unmet need. So this is TAR-200 and this is interesting. The urologists love this. It's called a pretzel. So you basically put it in through a cystoscope, and then you let it release, and it kind of winds into a pretzel shape. And there's different things you can place into the pretzel that are slow release. Now, TAR-200 is gemcitabine, and so they did this study of intravesical TAR-200 with or without cetrelimab, another IO agent. And interestingly, you see here 68% for TAR-200 plus cetrelimab, as far as CR rate. But with monotherapy, 83.5% and with cetrelimab monotherapy in cohort 3 was 46%. You look a year down the road and you're still over 50% for the TAR-200 arms. It's pretty similar between TAR-200 plus cetrelimab or TAR-200 monotherapy, whereas you're down to 22% with cetrelimab, which is kind of what you would expect, because it's, again, IO similar to like pembrolizumab. So this is kind of in the ballpark. But this intravesical gemcitabine, and we know gemcitabine has activity, this is pretty exciting as well.

Now, I'm not going to go through this whole graphic of all the different studies that are ongoing. I put this there because you get a handout. You can take it home and look at it there. But I do just want to point out some of the ongoing studies at the bottom there. This TAR-200 is being studied for BCG-naive patients, TAR-200 with or without cetrelimab. And then for the recurrent high-risk, this kind of population, or BCG-unresponsive population, it is monotherapy TAR-200 versus intravesical chemotherapy. So these are all ongoing things to keep an eye out for.

Chapter 6

Dr. Yu:

I want to talk about neoadjuvant therapy. I think the latest and greatest newest thing is the NIAGARA study, which is sandwich therapy of gemcitabine, cisplatin, with or without durvalumab. And when you gave durvalumab neoadjuvant for 4 cycles, it was followed after

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cystectomy with adjuvant therapy durvalumab. And the dual primary endpoints were EFS and path CR. And you can see here, with the path CR, a focus on the reanalysis on the right there is about a 10% difference in path CR there. The numbers look a little bit smaller than some of the studies, but the thing I'll point out there is their denominator to calculate this excluded the patients who did not go to cystectomy. So it was truly the intention to treat population. Some of those patients didn't go to cystectomy because they progressed through but that was probably a small number of patients. Oftentimes, patients choose not to undergo cystectomy if, let's say, they're doing really well. Maybe somebody does a scope and they say, hey, it looks really good. The patient says, I'm taking myself off. So we know traditionally, it's about a 15%-20% drop-off rate for that.

Now here's the event-free survival, very statistically significant. Nice hazard ratio, 0.68. And then next is overall survival. So here's the money slide here, also statistically significant here with a hazard ratio of 0.75. We just saw updated data today, but it was really more of an update focused on outcomes by path CR. And whether you got a path CR or didn't get a path CR, the benefit held true in favor of adding durvalumab to gem/cis in the neoadjuvant fashion and then following with the adjuvant durvalumab there.

Now here's what's coming. Let's talk first about the cis-eligible population. We saw great results with EV/pembro in the metastatic disease, why not do it in the neoadjuvant populations, EV/pembro versus gem/cis here? And then this other trial is coming here, also phase 3 that's ongoing. This is for the cis-ineligible population. The difference here is EV/pembro, of course, observation and then the cystectomy versus there's also another arm there with monotherapy, pembrolizumab there. So these will all be interesting to read out, and we'll see if it has potential to change standard of care in the future there as well.

And then back to this TAR-200 theme there. This is neoadjuvant TAR-200 with cetrelimab or cetrelimab monotherapy. Here we see here that SunRISe-4, actually they had some early results there with path CR, and it looks pretty good there with TAR-200 plus cetrelimab path CR of 42% versus cetrelimab monotherapy of 23%. So this is being studied as well in muscle-invasive bladder cancer.

And my last real data slide is super busy. I don't expect you to focus on this, but I wanted all the data to be in there for you in your handouts to look at. It's really a summary of all the adjuvant immunotherapy studies. And I think I'll draw your attention to the fact that atezo was the one negative study there, and they had the observation group do way better than expected there, with a median 16.6 months in the median disease-free survival there, but that was negative. But we saw the updated data with nivolumab from CheckMate 274 today for adjuvant nivolumab, the benefit still holds true. Overall survival looks really good, although technically now it's in a post-hoc analysis, but the hazard ratios don't cross 1. And then, of course, recently, the *New England Journal* paper came out with pembrolizumab also showing benefit in the AMBASSADOR phase 3 study. So nivolumab is the option that we have available right now, certainly potentially pembrolizumab in the future. We'll see.

In summary, I want to say BCG unresponsive has a lot of exciting things happen. There's a lot of intravesical therapies and newer agents that are available. TAR-200 is one of them, and that's basically just a slow-release gemcitabine there. Neoadjuvant chemotherapy, you could still use dose dense MVAC, or if you're going to use gem/cis, certainly consider adding durvalumab there with gem/cis, given the NIAGARA data. And then for adjuvant therapy, there's nivolumab there. It's really for the T3 or greater population that hasn't received neoadjuvant chemo. Or if you've given the adjuvant chemo and you have residual T2 or greater disease, that population does well as well with adjuvant IO.

Chapter 7

Dr. Yu:

This is a 65-year-old gentleman who has 3 weeks of gross hematuria, seen by a urologist, a 5-cm bladder mass identified in-office cysto, confirmed on CT imaging. Then he undergoes transurethral resection of the bladder tumor. It's a 5.6-cm right lateral wall bladder mass. Path shows its muscle-invasive urothelial carcinoma with at least a T3 status and then undergoes imaging. Has these 4- to 5-cm lymph nodes along the right pelvic chain into the upper retroperitoneum, consistent with metastatic disease, no hydronephrosis. Has a past medical history of hypertension, hyperlipidemia, diabetes, chronic kidney disease, creatinine clearance is 39, so it is compromised. He presents to you discuss therapeutic options. You get some somatic next-generation sequencing, nothing actionable that you see, no FGFR3 mutations, no HER2 mutation or amplification, et cetera. So what first-line therapy would you consider for this patient? Anyone want to shout out what you would do?

I think I heard it. Go ahead. A little louder. Yeah. Yes, yes, yes. EV/pembro. That's what I think we would all do here. And so that's what this patient got. Started on in enfortumab 1.25 mg/kg plus pembrolizumab. Two weeks on, one week off, standard scheduling. Tolerated well after 3 cycles, had some restaging scans, demonstrated a partial response. Counts are fine. Glucose wasn't elevated, but he got a little bit of paresthesias early on in his fingertips and the bottom of his feet. So go ahead and dose reduce him from 1.25 to 1 mg/kg. Proceed for 3 more cycles. After cycle 6 of treatment, restaging scans demonstrate a complete response. By this point in time on your study –

Dr. Plimack:

Yeah, you'd come off. You stop the EV.

Dr. Yu:

This person would come off, right?

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Dr. Plimack:
Keep pembro going, yeah.

Dr. Yu:
So, yeah, I think, that's what we talked about with this patient, and yeah, that's what we do. So I actually take a lot of people off now.

So I'll tell you a story that when in the early days of EV and when I was doing a lot of studies with EV, you had to kind of stick this study protocol. But the study protocol allowed you to kind of do a lot of dose reduction and dose deintensification and dose less frequently, and there was a little bit of flexibility. So I had a lot of patients that they ended up getting EV, like, once every 4 weeks, and then I started going once every 8 weeks. And then at some point we had – I know, I mean, so I didn't want to do it that way, but the patients didn't want to stop, because I had a great response, right? And then one time, we had Jonathan Rosenberg over to give Grand Rounds, and we were out at dinner afterwards, he said, "I don't know why you're doing that." He goes, "Maybe if they do still have residual disease and they're not cured, maybe you're just inducing resistance by giving this kind of low-dose thing, because you just got to stop. Come on." And I'm just like, okay.

Dr. Plimack:
Please stop, yeah.

Dr. Yu:
So I went back and I'm like, I like Jonathan, and I'm like, I trust his advice. So I went back and I stopped all those patients, and I don't think a single one has relapsed. So, I'm like, okay.

Dr. Plimack:
Yeah, I mean, with any stopping, you don't know until you try and you give them the opportunity. And you might be wrong, but if you're right, it's a beautiful thing. Do you continue the pembro when you do that?

Dr. Yu:
So I continue out to 2 years with the pembro. I don't know that I need to do that either, but I have done it, and then I stop. And I always stop everybody. So I tell everybody every visit, if you build it in advance, that's 2 years to stop, then people are fine with it. But if you don't address it till the very end, then people are nervous about it.

Dr. Plimack:
Exactly.

Dr. Petrylak:
Yeah, I have a similar experience with a patient of ours who it took me about a year for me to convince her to come off treatment. She was actually one of the first real responders to EV by itself with metastatic disease to liver, and she's been off treatment now for 3 years with a CR.

But think back to the presentation we did at ASCO last year where you're able to interrupt patients and actually still maintain their responses. And I think that's really, really important. It seems that, at least as a single agent, that the dose intensity within the first 2 cycles is important. As you get out, you can dose reduce and not affect the progression-free survival and potentially improve toxicity. So this may make it more tolerable in the long term. I think again, we have to understand the resistance mechanisms of EV, and how we can incorporate this into our treatment. And I think that, what's the minimal effect of treatment for this drug? Because clearly, the neuropathy is a problem. I have patients on EV-103 who are now 5 years out and the CR with liver disease, who are now beginning to feel their fingertips for the first time. So it's something we have to be conscious of.

Dr. Plimack:
Yeah. Yeah, it's great. It's great to have that experience over time now, right, under our belt. We can say responses might be durable. We have more confidence to stop. We have more stories like the neuropathy improving. And I think all of this is important to keep track of and helps inform how we make the decisions in the beginning of care for patients just starting.

Chapter 8
Dr. Petrylak:
A 63-year-old man who's a smoker develops gross hematuria. Cystoscopy demonstrates a large bladder mass. He has a TURBT, which demonstrates high-grade urothelial cancer with muscle invasion. He gets staged and has a CT scan of his chest, abdomen, and pelvis, which demonstrates a bladder mass in multiple pulmonary nodules. His creatinine clearance is 40. So we decide to treat him with EV/pembro. He has a partial response after 6 cycles. He does develop grade 2 neuropathy after 12 cycles, which necessitates a reduction to 1 mg/kg of enfortumab. He remains on this treatment. Then 5 months afterwards, he has a CT scan which shows he has new liver mets. We biopsied those mets, and he has metastatic urothelial carcinoma, which is 3+ positive for HER2. So what would you

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do in this situation? Would you give him HER2-targeted therapy? Would you give him gem/carbo? Gem/cis?

Dr. Plimack:
Dan, does he still have that neuropathy?

Dr. Petrylak:
He does still have that neuropathy, yes.

Dr. Plimack:
Well, I think I would reach for trastuzumab deruxtecan. One, because I'm eager to try new things, and it's an opportunity to use an agent I don't have a lot of experience with. Two, of course, the data, 3+, it's compelling. It's not 1+ or 2+. And you can always have carbo/gem or just gem for later.

Dr. Petrylak:
Yeah? I mean, I like using the most targeted therapy first.

Dr. Plimack:
Yeah.

Dr. Yu:
Yeah, I think the key thing here is this patient has a little neuropathy. But DXd is a topoisomerase inhibitor with trastuzumab deruxtecan. So that's the nice thing. You don't have to worry about the competing or the adverse events that add on top of each other.

Dr. Petrylak:
And if HER2-targeted therapy doesn't work, it does give them some time to recover. Perhaps you can get some function back. I mean, although it's variable the speed at which it comes back and whether it comes back at all. So think that's reasonable. Okay? Start trastuzumab deruxtecan. On reassessment 3 months after starting treatment, he has a partial response.

Chapter 9
Dr. Plimack:
A young man, 49 years old, came into his diagnosis with baseline grade 2 diabetic sensory neuropathy. I mean, it didn't really affect his ADLs that dramatically, but it was significant. He had muscle-invasive bladder cancer. He got dose-dense MVAC.

We got 2 cycles into him, and he actually asked to stop early because of neuropathic pain that was worse with dose-dense MVAC with the cisplatin. So he went to cystoprostatectomy, and unfortunately, had T3 N2 disease. We did give him adjuvant nivolumab. He started on that, but at cycle 4 had his first scan, really on adjuvant, he developed metastatic recurrence. Significant with new liver and retroperitoneal nodal mets. So we did a fresh biopsy of the lymph nodes for NGS. He was PD-L1 CPS 10, FGFR3, with a pathologic variant. And so after careful discussion about his neuropathy, we did something that might sound crazy, but he really wanted the best response. He sort of said to us, “I already have neuropathy. I've lived with it for years, give me the best thing.” So we started EV with pembro. And his neuropathy actually did not get worse. I was surprised. But we only got 6 months out of EV/pembro. And so remember, we had done his NGS before on a fresh lymph node, because the metastatic presentation was new, and he did have the FGFR3 pathologic variant. What would you guys do?

Dr. Yu:
Yeah, well, he's got this FGFR3 pathogenic variant, I'd give it a shot. I think I'd give it a shot.

Dr. Plimack:
Yeah, we could. Yeah. Yeah. Dan?

Dr. Petrylak:
Yeah, I would agree with that as well, I think. But the one thing also, too, that I think was alluded to in Evan's talk about the combination of EV/pembro, is that you really have to think about this as one drug, not 2 separate because there is some pre-clinical evidence that there may be synergy between the 2, so that may overcome the checkpoint resistance that occurred with the nivolumab.

Dr. Plimack:
So are you supporting my decision to use EV/P in a man with neuropathy who progressed on nivolumab?

Dr. Petrylak:
Having a little bit of neuropathy is certainly better than being dead.

Dr. Plimack:

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That's what he said. That's what he told me.

Dr. Petrylak:
That's the way I look at it. That's the way I would look at it.

Dr. Plimack:
Yeah, yeah. Okay, all right. Well, we did give him erdafitinib. We started. He was good, and started with the monthly eye exams, including his baseline. At his very first 1-month visit, we had to dose reduce him from 8 to 6. He did have hyperphosphatemia, but he also had so many other things at that point, dry mouth, PPE, the neuropathy sort of made it so he didn't feel his PPE quite as much, which is good, but then the sores could be exacerbated. Really poor appetite with taste changes so it was hard for him to eat, and fatigue. And that did get better with the dose decrease from 8 to 6. And really, I think his quality of life improved with his first good scan in a really long time, showing a true partial response with regression at all sites of measurable disease, including the lymph nodes and liver. I'll be honest, I had somewhat low expectations having to dose reduce him so early, but that was really nice to see. And he's still on treatment.

Dr. Yu:
That's awesome.

Dr. Plimack:
Yeah.

Dr. Petrylak:
So it's going to be interesting. We just started treatment on an FGFR-positive patient with a brain met.

Dr. Plimack:
Okay.

Dr. Petrylak:
And let's see if that's actually going to work or not.

Dr. Plimack:
Yeah. Yeah. Do you treat the brain met with radiation?

Dr. Petrylak:
It's been radiated already. He actually progressed on EV/pembro in the CNS. He had an initial response.

Dr. Plimack:
I don't know if you want to talk about it. That's fascinating.

Dr. Petrylak:
Yep. Initial response, and now we just started erdafitinib on him. So I'd be very interested to see how this goes the next couple of months.

Chapter 10
Dr. Petrylak:
What are your summary and key takeaways from this evening?

Dr. Plimack:
Yeah. So I think so much excitement. If we think back even just a little bit on where the field was and where we are now and what's coming, so no doubt next year we'll have a lot more new data in this space, I think it's great. Every time the field shifts, like moving EV/P to the frontline, everything else has to adjust. All of our trial designs have to adjust; our control arms have to change. And that's sort of where we are now in both drug development and clinical care. I think beyond EV/P, it is still a data-free zone. It's great that we have these matched biomarkers for which we can personalize therapy for patients. We do still have platinum. I don't think that's – someday that might go away, but not quite yet. And then the side effect management, just the better you are at that, the better your patients will feel, the longer they can stay on these active therapies. And looking at key ways to sort of prevent, for instance, the neuropathy with EV/P, stop treatment early, know when to stop. Switch to a maintenance pembro. I think those are all exciting avenues that we'll see in the future.

Dr. Petrylak:
Evan?

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Dr. Yu:
Yeah, I would say that with all these great new drugs, I mean, we're ecstatic in this field. I just feel lucky to be in this field. But with that being said and done, oftentimes, I hear people say, “Oh, there's all these such great drugs and such great response rates. And people are living so long, it's kind of like we're done. Okay. We can't do anything more. It's statistically impossible. How are we going to do studies anymore?” I think that's the wrong way. I mean, we could do dose deintensification studies. Quality of life is important. When can we stop? There's all kinds of things we can do. And there are newer antibody-drug conjugates being developed. I mean, if you think about the technology, there's so many different components that go into an antibody-drug conjugate. We can keep making them better and better and better. And although enfortumab vedotin is a great drug, it still has toxicities, and I think I will be shocked if we don't make better antibody-drug conjugates moving forward.

Dr. Petrylak:
Well, I only hope that somewhere Alan Yagoda is watching all this, thinking back to his original observations with MVAC in publications, because we've come a long way since that time. But remember, if you look at Jonathan's data from ESMO this year, the 5-year survival is 40%; 60% are not making it. And the question is why, and how can we improve that to 100%? It really seems to be an ambitious goal, but think about where we were 10 years ago and how far we've come at this particular point. And I think the future is incredibly bright. We've got new drugs, new approaches.

And I think what this also emphasizes the fact in managing toxicity, a team approach is necessary. You need a good staff, excellent nursing and nurse practitioners to identify neuropathy, physical therapists for neuropathy as well. And of course, internal medicine docs to help take care of the diabetes, if that does happen. So this is opening up a new era in bladder cancer and multidisciplinary care. And I'm just really excited about the future, and especially for the patients. They deserve it. They deserve the best possible treatment.

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