Advances in the Management of Patients with Urothelial Carcinomas of the Bladder

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MR. CAMPEN Welcome back from lunch, everyone. My name is Christopher Campen, clinical pharmacist at the Greenville Health System in Greenville, South Carolina. As a gentle reminder after the break, please silence your cell phones. Our first lecture is on the "Advances in the Management of Patients with Urothelial Carcinomas of the Bladder." It is my pleasure to welcome our speakers, Dr. Emily Lemke and Dr. Amishi Shah, both of The University of Texas MD Anderson.

DR. LEMKE Thank you so much for having us today. We are very excited to be here. Amishi and I spend probably the majority of our waking hours during the week with each other, and about half of that time is talking about bladder cancer, so we're really excited to share this talk with you.

These are the learning objectives, which I'm sure you have. Financial disclosures. Bladder cancer is the sixth most common malignancy in the United States, and I think that it's a little underrepresented in a lot of forums, so we are obviously happy to have the opportunity to share the advances with you. Most common signs and symptoms are going to be hematuria. I would say the standard picture that we see in our clinic is patients who have painless hematuria, maybe some other lower urinary tract symptoms, and they're treated for a UTI a couple times, and when that doesn't help resolve these symptoms, they get a better staging workup and ultimately are found to have a bladder

mass. Most common risk factor is going to be smoking. Smoking, smoking, smoking. This is the biggest one and of course, with other malignancies, advancing age, and then there is a component with urothelial carcinomas that chemical exposures do put you at higher risk.

This is just a nice pictorial view of the different stages of bladder cancer. As you probably know, a big differentiating factor is whether or not the cancer is invasive into the muscle. This just provides a nice example of the different layers of the bladder. This is a picture that Amishi and I draw for all of our new patients who come in with bladder cancer because I think it really helps clarify the how's and the why's of the treatment we give. And so T2, this is going to be the muscle-invasive disease, and so anything T3 and above is going to be what her and I see in clinic. Pretty much T1, Ta is going to be managed by Urology. The focus of this talk is really going to be on T2 and beyond.

Staging workup: you're found to have a hematuria that's not resolving so you start with a CT usually of your abdomen and pelvis, maybe chest if you're pretty suspicious from the get-go. That'll show a bladder tumor or just some thickening of the bladder wall. This then usually leads to cystoscopy and these are what urologists do; we're not doing cystos in clinic. And so once a bladder mass is identified on cystoscopy, the next piece is going to be to resect that with a transurethral resection of a bladder tumor or TURBT. This is where we're going to get tissue. Something that we do at Anderson that isn't done across other institutions is, at this point our urologists do what's called an examination under anesthesia—abbreviation is EUA, that we'll use throughout the rest of the

presentation—and what they do during the TURBT is they actually feel the back of the bladder wall through the rectum with their hand, and in these cases, if they can feel a 3D mass, we consider that clinical T3 disease and that'll become important when we're determining whether or not they meet the qualifications for neoadjuvant therapy.

If any neurological symptoms are present at baseline, we'll also do a brain MRI, and then anybody with small cell histology, we're going to get a brain MRI as well. And then a bone scan if we're suspicious of bone symptoms. So as I said, Ta and T1 disease is something that's primarily managed by urologists. This is a summary of that therapy usually. At first it's a transurethral resection of bladder tumor followed by intravesical therapy, and whether or not its low risk, intermediate risk, or high risk is going to dictate what that type of intravesical therapy is. And then also some people might need an up-front cystectomy if they have more advanced T1 disease or if they recur following intravesical therapy.

DR. SHAH I'll take over to discuss muscle-invasive disease. As Emily mentioned, the initial staging workup is so critical because it really helps define which path a patient goes down. T2 disease is what gets into the muscle of the bladder. T3 disease is what approaches that perivesical fat layer, so the thin layer of fat that surrounds the bladder. And finally, T4 disease is anything that goes beyond the bladder towards adjacent organs. So, board answer standard of care for anybody with T2 or greater disease, they need neoadjuvant chemotherapy followed by surgical consolidation, and we'll go into some of the nuances in a moment here, but the gold standard for neoadjuvant chemotherapy

for these patients is either the regimen of dose-dense MVAC or gemcitabine/cisplatin. The initial work that was done in neoadjuvant chemotherapy, there were a couple pivotal papers, many of you many be familiar with the regimen of MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin. The initial work was actually done with just the CMV part and not the doxorubicin part, and in that work, there was a suggestion that patients who had chemotherapy up front actually had higher rates of pathCRs at the time of surgery, and there was some suggestion that that translated directly to an overall survival benefit.

Following that work, this was really the seminal work that led to the approval of neoadjuvant chemotherapy for T2 and more advanced localized urothelial cancer. This study had two arms; patients received either neoadjuvant MVAC or they went straight to cystectomy. In the patients that had chemotherapy followed by cystectomy, they had a better overall survival, and that survival improved from 46 months to 77 months and leading to the gold standard of neoadjuvant chemotherapy. Of note, with this particular MVAC regimen almost 40%, 38% of patients had a pathCR, meaning no viable tumor left at the time of surgery.

So I wanted to take a moment here to deviate to talk about times that we actually potentially spare patients that chemotherapy. There are particular risk factors that we think are riskier features, and so in patients that have suggestion of variant histology, which essentially means doesn't look urothelial or papillary under the microscope if they have variant histology of micropapillary,

sarcomatoid, plasmacytoid, these are things that make us think, okay, this is a more aggressively behaving tumor, chemotherapy is going to be more helpful here. If they have hydronephrosis, if they have lymphovascular invasion, or they have that palpable mass in the examination under anesthesia, those are all things that say, okay, this is perhaps a more aggressive behaving tumor and neoadjuvant chemotherapy truly is key.

In a patient who doesn't have these risk factors, there's about 70% of them that can be cured with surgery alone. So in those patients, if they have none of these risk factors, we will often let them proceed to an up-front cystectomy, if there are any surprises on path., certainly we want to offer adjuvant chemotherapy, but if you see these risk factors, it really hammers in the fact that they should be offered chemotherapy up front.

Let's talk a little bit about the standard of care regimens. Both of these regimens are cisplatin based, and that is the drug with the most data in urothelial cancer. The original trial done with neoadjuvant chemotherapy was actually done with an older regimen that was not dose-dense scheduling, it was just plain MVAC, and that was a very difficult to tolerate regimen. Patients had severe mucositis; it was really tough to get them through. However, with the advent of this dose-dense scheduling, it has become a much more easily tolerated regimen, and so we used this actually on a daily basis in our clinic. Dose-dense MVAC is scheduled every 2 weeks. Typically patients get chemotherapy on day 1 of that 2-week cycle. If they have a slight reduction in their GFR, we may split that cisplatin on day 1 and day 2 in that 2-week cycle. But what we have found is

that the advantage of dose-dense MVAC is it's 8 weeks total of chemotherapy leading up to surgery rather than 12 weeks, which is what the gemcitabine/cisplatin plan has, and so it's a 3-week cycle. So it's a shorter time to surgery and the rates of pathCR are much higher with dose-dense MVAC.

Gemcitabine/cisplatin is the other gold standard. There was a study done comparing gemcitabine/cisplatin to the traditional MVAC. It was a noninferiority study, and gemcitabine/cisplatin was found to be noninferior to MVAC, meaning equal in terms of that survival curve in that study. But like I mentioned, it is a 3-week dosing schedule, so it is slightly longer time to that surgical consolidation. In all of the reports with gem/cis, the pathCR rate is about 26 to 28% tops, so a little bit lower than the dose-dense MVAC; however, of course with the MVAC because you have that doxorubicin component, you have to make sure your patient doesn't have any major cardiac comorbidities, has a healthy ejection fraction, and so we do tailor that regimen based on people's underlying comorbidities.

DR. LEMKE In our practice, we really don't feel limited to just using gem/cis or MVAC if patients don't meet qualification for those. Cisplatin ineligible is technically defined by a creatinine clearance of less than 60, and we really can push that a little bit with some different regimens and with some supportive care. So in the case that we're not able to use either dose-dense MVAC or gem/cis, this is the menu we turn to. For somebody who's truly cisplatin ineligible, somebody's whose creatinine clearance is less than 40, somebody who has significant neuropathy or hearing problems, the regimen we would use is this:

gemcitabine, paclitaxel, doxorubicin, or GTA as we call it. And this is a regimen that's dosed every 2 weeks where you give it outpatient, and for the most part patients tolerate it exceptionally well, and we've had some really good luck with this regimen. So we don't jump to no chemotherapy or immunotherapy in that situation. For anybody with small cell histology, which is of course a much more aggressive variant of bladder cancer, the standard of care would be etoposide/cisplatin for four cycles, but there's been some papers put out by our clinical faculty looking at this doublet of ifosfamide, doxorubicin, and etoposide, cisplatin, so typically they start out and get IA one cycle, and then next cycle they get EP for a total of four to six cycles, and this has been pretty efficacious for these small cell patients.

It is a tough regimen though, and so these patients need to be fit, they need to have a good ejection fraction to get that IA. And the IA is something that we do give in the inpatient setting. For people who are at the borderline creatinine, in that 40 to 60 range of maybe a little bit of tinnitus or a little bit of neuropathy, we still want to try and get them cisplatin; we will do this regimen called CGI, and its cisplatin, gemcitabine, ifosfamide. This is dosed every 2 weeks, and the cisplatin dose is 50 mg per meter squared as opposed to MVAC and gem/cis, which have the 70 mg per meter squared dosing. And similar to the GTA, patients do pretty well with this, and we do it both inpatient and outpatient. If somebody's got a creatinine closer to the 40 or 50 range, we might do it inpatient and just give them a lot more post cisplatin hydration for 15 hours following therapy as opposed to in the outpatient setting where you are obviously

limited by the time of the infusion. So we play with this and we can also give it over 2 days, which as Amishi mentioned, and we do do it with MVAC and gem/cis as well splitting that cisplatin dose.

But if a patient can get cisplatin at all, we really try to do that in the neoadjuvant curative setting. Then this last one, ifosfamide, doxorubicin, gemcitabine, IAGem, this is kind of the big guns. If we have a really fit patient, they're young, typically the unofficial rule is kind of around 50 or younger and really few comorbidities, we will hit them with IAGem, and a lot of times we save this for people who have variant histology or who have not responded maybe to MVAC or gem/cis at first. So when they get IAGem, we usually do three cycles, and if they haven't seen cisplatin, we'll follow that by three cycles of MVAC. This is dosed every 3 weeks, and it is also an inpatient administration primarily because of the ifosfamide dose, the risk of neurotoxicity. They need to be frequently monitored by the nursing staff and inpatient staff to make sure they are not having any hallucinations or other neurotoxicity symptoms; we can sometimes see with those higher doses of ifos.

Monitoring with cisplatin chemotherapy: obviously the creatinine clearance is going to be something that we're constantly looking at and we always calculate the Cockcroft-Gault creatinine clearance; we are not using the eGFRs that are pushed out in the CMP. Electrolytes with cisplatin, we can see a lot of hypomagnesia, hypokalemia, and so I would say for the majority of our patients we are having to do some supplementation of magnesium almost in everybody. Obviously you're going to be asking about hearing, neuropathy; anybody on

cisplatin-based chemotherapy and if anybody is getting the anthracycline, you know we are monitoring. Echos at the beginning of therapy and then typically about every three to four cycles. And then of course with any chemotherapy, cytopenias are going to be something we keep an eye on. In the ideal situation, we like to see our patients in between cycles for a toxicity check, and we use this as an opportunity to boost them up so that we can keep them on schedule. So if their creatinine is taking a hit in between, we might give them some more IV fluids, we might give them some electrolyte repletion; nausea, vomiting is something with the cisplatin regimen that can be problematic. All of our patients who get cisplatin actually will get 3 days of dexamethasone 4 mg BID for 3 days following chemotherapy, and we find that does a pretty good job of nipping the nausea and vomiting in the bud. We usually send them home with Zofran and Reglan prescriptions as well, but when the nausea and vomiting is refractory to that, we've had some really good success with olanzapine, the 10-mg dose. And then of course we need to give blood occasionally, and anybody getting neoadjuvant therapy, we are going to be doing pegfilgrastim as well.

Moving on to a case study. This is a gentleman we both saw at clinic. He was 49 years old, a never-smoker; his presenting symptom was gross hematuria. His up-front imaging revealed a left lateral urinary bladder wall thickening, no hydronephrosis, no suspicious lymph nodes. So he went on to have a TURBT, and it revealed muscle-invasive bladder cancer with focal micropapillary features also suspicious for LVI. His examination under anesthesia was negative. No comorbidities, he had an excellent creatinine clearance, so world was our oyster

as far as what kind of chemotherapy we could give him. EF was 62%. So do you think that he should get neoadjuvant therapy, and what regimen do you think he should get? I'll give you the answer on the next slide. So definitely needs chemotherapy. Why? Because he's got muscle-invasive disease, he's got micropapillary, which is aggressive variant histology and the suspicious LVI. And what chemotherapy did we give him? Dose-dense MVAC. He had a high chance of pathCR with that regimen and a quicker time to surgery.

This was his CT before he started therapy, and you can just see some kind of bladder wall thickening right there and then it improves a decent amount after he's gotten the four cycles of MVAC. So this is the gold we are looking for every time is this guy had a pathologic CR, so this is a real success of a patient with a very aggressive cancer who we were able to give the highest chance of cure in a setting with micropapillary bladder cancer.

Another case study. This guy was 73, he again had painless hematuria and this is his TUR path. He had papillary urothelial carcinoma, high-grade, noninvasive, and the muscle propria was present. Now this is a point that Amishi likes to make with all the fellows that come through our clinic that the board answer is if you don't see muscle propria present on the TUR specimen, the answer is you need to repeat TUR to obtain muscle specimen because we absolutely need to know if the bladder cancer is in the muscle or not.

This was—he had a nice clear tumor in the bladder right there. Does this patient need neoadjuvant therapy? I gave you the answer right there. No. Why? Because it was not muscle-invasive and he didn't have any high-risk features, so

this guy went back to Urology and he has had a TURBT followed by some intravesical therapy.

DR. SHAH Let's switch gears here for a moment and talk a little bit about upper tract urothelial carcinoma. The upper tract actually refers to the ureters bilaterally as well as the renal pelvis and the ureters and renal pelvis are both lined by urothelial cells, so biologically the upper tract behaves very similar to bladder cancer even though it is much higher up and has traditionally been its own entity. Biologically it follows some of the same patterns as run of the mill bladder cancer with a couple important things to note. So upper tract makes up only 5% of urothelial carcinomas; it is more rare. The times that we have seen it, automatically Lynch syndrome should be on your radar. So many of you are very familiar with Lynch syndrome. The most common hereditary cancer that forms in patients with Lynch syndrome is colorectal cancer, that's followed by endometrial cancer, but it is becoming a much more clearly recognized entity that upper tract urothelial cancers also fall within that spectrum. So any patient that comes through our clinic, whether it's localized or metastatic upper tract urothelial cancer, we do send microsatellite instability testing to screen that patient for Lynch syndrome. Unfortunately because the entity of upper tract urothelial cancer is more rare, there's not great guidelines on when to do neoadjuvant and adjuvant therapy, and so we see a lot of patients that are referred to us from elsewhere that actually undergo up-front surgery. And if we are seeing the patient ourselves at the beginning, we actually really take much more of a stance like we do for bladder cancer where if there's any high-risk feature that we're

concerned about, we highly recommend neoadjuvant chemotherapy for them before they go onto a consolidative surgery, which for upper tract disease, the consolidative surgery rather than a cystectomy is a nephroureterectomy.

Extrapolating from bladder cancer the risk features we look for is if it's high grade under the microscope at the time of path review or if there's evidence of sessile polyps on direct visualization by the urologist, those are reasons that we will give those patients neoadjuvant chemotherapy. We use the same regimens that we use in bladder cancer, so again, cisplatin-based chemotherapy is the gold standard, but the other regimens Emily mentioned if their GFR is compromised are also fair game here. The other thing that's really interesting with urothelial cancer in the upper tract especially if it's got evidence of microsatellite instability just like in other tumor types that are MSI high, there's a really nice role for immune checkpoint inhibitors here. So we have a couple patients in our clinic with Lynch syndrome, and for example, one of our patients has a GFR of 40. We put him directly on pembrolizumab first line instead of committing him to chemotherapy, and he's had a beautiful response. The success rate of immunotherapies in microsatellite instability–high setting is quite high, approaching 90% in some retrospective reviews. So keep that in mind if you see a patient with upper tract that should be something that should be worked up. Going on a little bit longer about the benefits of neoadjuvant chemotherapy and upper tract, it's much easier for patients to receive chemotherapy prior to their nephrou. Their GFR is going to be better, and then the same concepts apply as with the bladder cancer. We want to eradicate any

microscopic disease that might have escaped that area. It does often help the surgeons with the downsizing, and the time of surgery is a lot easier for them to consolidate. We know there is a reduced risk of recurrence and patients are much more fit before surgery. After surgery, they are healing up from a huge wound, their GFR has declined, they are more deconditioned, it's hard to get them through four cycles of chemotherapy on the backend, so when in doubt, we go ahead and give it neoadjuvantly.

Going to the metastatic setting, again, the same regimens are really key in the first-line setting. So in the first-line setting, we do rely upon that cisplatin-based chemotherapy. In the second-line setting, this is where many approvals for the immunotherapy realm have come into play; however, please do take note that if a patient is cisplatin ineligible, immunotherapy is approved and indicated in the first-line setting. As Emily mentioned, technically the definition of cisplatin ineligible is a creatinine clearance of less than 60, severe underlying neuropathy, issues with hearing loss; however, we do push the envelope and if a patient has a creatinine clearance of 50, we don't necessarily deem them cisplatin ineligible off the bat, we might use an alternate regimen. So immunotherapy in urothelial cancer has been kind of an interesting story. Five drugs that all behave pretty similarly were approved back to back to back in bladder cancer over the course of the last year plus, and these drugs include atezolizumab, nivolumab, pembrolizumab, durvalumab, and avelumab. Of those there are two, nivolumab and pembrolizumab, are PD-1 inhibitors, the others are PD-L1 inhibitors. And the big question we often get is how do you decide which one to use? What are the

pros and cons? So I'm going to talk a little bit about the data behind each of them, but keep in mind that they do have very similar mechanisms of action.

Atezolizumab was the first immunotherapy agent approved in urothelial cancer, and the approval of atezolizumab was based on the results of this phase II trial that was published in *Lancet Oncology* last year. This was a trial where all patients, it was a single-arm trial, and all patients got atezolizumab after they had progressed from previous platinum-based therapy. So this was in the second-line setting. And the patients that received atezolizumab, all of them, had an overall response rate of upwards of 20%. That was a very clear improvement of the 10 to 15% that we had typically seen with second-line traditional cytotoxic chemotherapy. Based on that objective response rate, the overall response rate, the FDA led to the approval of atezolizumab. There's a couple of interesting things to note from this data. In urothelial cancer, immunotherapies are approved agnostic of PD-L1 status. We do not really check or determine if PD-L1 expression is high, they should get it, if it's low they shouldn't; that is not an entity in urothelial cancer. It is approved across the board regardless of PD-L1 status. That being said, the PD-L1 story has really played out in different ways. It's been a little bit messy of a story in urothelial cancer.

So you can see in the atezolizumab data, the patients who had high PD-L1 expression, which is represented by the blue line on the Kaplan-Meier curve did seem to have a better response, but all comers actually had a better response compared to traditional therapies, so it's still approved across the board. A quick update here—and this data is still pending, we don't have the full

paper so we don't know the exact details—but atezolizumab actually was evaluated in a phase III study, so it was taken head to head compared with cytotoxic chemotherapy in the second-line setting. Physicians were allowed to choose their choice of cytotoxic chemotherapy in the taxane family versus atezolizumab. It was a randomized study, and all we have right now is a press release saying that this study did not meet its overall survival endpoint, so based on that we don't know whether it was the patients that were chosen, we don't know if there was crossover, we don't know truly what this means if it really didn't improve survival, but just know that in the phase III setting, atezo did not improve overall survival and that will come into play again in a moment.

Nivolumab was the next agent approved in urothelial cancer. Again, this was a phase II setting, and again, approval was based on the fact that the objective response rate was improved compared to normal cytotoxic chemotherapies in the second-line setting. And again, you see this representation that perhaps the patients with higher PD-L1 expression did better, but all comers still had a better response rate compared to chemotherapies.

Pembrolizumab I want to spend a little bit longer on because this is the category 1 evidence of NCCN. This is what we use daily in urothelial cancer in our clinic. The first approval for pembrolizumab came in the second-line therapy just like for atezo and nivo that we discussed, again based on objective response rate. However, that was followed by this study, which was a phase III study comparing head to head pembrolizumab versus dealer's choice chemotherapy in the metastatic second-line setting for urothelial. And here, pembrolizumab did

achieve an overall survival improvement, so there was a definite higher response rate as well as improved overall survival leading to the approval of pembrolizumab in this setting. If you see on NCCN while all of these are listed, this is the highest, strongest data and so the one that's utilized more frequently. So again, it is after that on the tails of this paper came that its approval in the platinum-illegible setting. Pembrolizumab is dosed every 3 weeks. Depending on which agent you use, some of them are dosed every 2 weeks and some are dosed every 3 weeks, so that's something to keep in mind when you are thinking about patient convenience and such.

DR. LEMKE There's still a lot we don't know about immunotherapy. These drugs have still only been around for the last 3 or 4 years, and specifically in the bladder cohort, there's a lot that we don't know. As Amishi touched on, the usefulness of whether or not their tumors express PD-L1 seems to be an inconsistent story across all of the approvals and their respective studies. Whether or not PD-1 is superior to PD-L1 blockade is something we also don't know. Combination with CTLA-4 blockade, which is ipilimumab, is the one we all think about, is something that's coming out as being investigated right now. We don't know if that's going to provide a more robust response than the PD-1 alone. And then combining with cytotoxic chemotherapy in the long data, I know they are looking at pembrolizumab, carboplatin, and pemetrexed, and that's something that is being explored currently in the bladder data as well, so stay tuned to see if combination therapy is going to be the next treatment. And then sequencing of treatment. You know with these up-front approvals in

cisplatin-ineligible patients, is there benefit to having pembro or immunotherapy prior to chemotherapy or vice versa? Amishi and I are kind of in the thought of we still—if we can give chemotherapy to patients, we still like to do that prior to turning to immunotherapy. A lot of times these patients have a lot of symptoms associated with metastatic urothelial carcinoma, and their response rate is just going to be quicker if you can get them on a cytotoxic regimen.

Duration of treatment: how long do you keep these people on these therapies? If you have one of those outliers who is a very long durable response, a lot of times they do not want to stop being on their immunotherapy, and we just don't know if that response is going to remain durable if we take them off. And then of course, moving this up to the curative intent and even the bladder-sparing setting where immunotherapy can be useful. And a big thing that everybody is wondering is how do we predict who's going to respond to these immunotherapies? Of course, we have the data now on the MSI-positive population, but what are the characteristics? We don't have clear-set "this patient is great for immunotherapy;" "this patient isn't," so we are trying it on everybody if they progress after chemotherapy. We had an excellent talk on immunotherapy side effects yesterday, so I will not belabor this point. We are very privileged in our department that we work with some of the leading voices in immunotherapy, and we have a standard set of labs that we check in these patients, so before we get them started on any immunotherapies, these are the baseline labs we check. They are all listed there for you. And then in the case of toxicities, this just outlines what the more common toxicities we see: the endocrinopathies,

diarrhea, pneumonitis, what we are checking. Having those baseline studies is important because some of these markers can be a little bit nonspecific so knowing and checking them initially is going to help you tease out whether or not side effects that are happening are indeed related to the immunotherapy.

Early detection, I would say, is the most important thing when you suspect an immune-related side effect with these patients. I tell everybody at the beginning of therapy, for the most part people tolerate these therapies excellent, but there are about 10% of patients who are going to have some significant side effects. And we don't know what we don't know, so anything is really possible with these, so I of course educate them on the more common side effects, the colitis, the pneumonitis, the things we can objectively talk about, known presenting symptoms. However, what's important is that these patients know throughout the duration of their therapy if anything seems off that they need to tell us because nothing is out of consideration when you're on these therapies. Anybody who you're suspicious for colitis, we do like to get a biopsy to show the lymphocytic infiltrate in those patients. And obviously we all know about the 1 mg per kg steroids as management, but in the cases that patients are steroid refractory with colitis, we also use the mesalamine or infliximab.

This is an example of a patient who is currently on immunotherapy. This guy is a 54 year old, he had metastatic urothelial cancer to his regional lymph nodes and so he was heavily pretreated. He got everything we've got: he got lAGem times four cycles, didn't touch the lymph node. Got dose-dense MVAC, didn't touch it. Same with GTA. Oh and here's the lymph node. So after he

started nivolumab, and this was on trial because this was about 2 and a half years ago that he was started on nivo, you can see that the node has disappeared. This guy would be so thrilled for us to tell you that he's doing excellent; he continues on nivolumab, he will not let us talk about even stopping it because that's one of the things we discuss is should we take him to cystectomy, should we stop the nivolumab, should we spread it out, so these are things that, in his case, he's very opposed to, so he continues on nivolumab. He is thriving at life, he's winning amateur car races, he's in pool competitions out in Vegas, and he would love to know that I shared that with you because he's so proud of that, and he's so excited to be one of our poster children for nivolumab.

DR. SHAH As Emily mentioned previously, there's a lot we just don't know about where things are going to hang. There was nothing in the field of bladder cancer for 30 years. All we had was chemotherapy until all of a sudden the last year we got five immunotherapies, so it's an exciting time because things are going to change and hopefully keep getting better and better. But it's really a big question mark which way things will go. We hope to see in the coming years some expansions on the approvals for immunotherapy. There' s a couple specific arenas where there's a lot of work ongoing. One of those is combinations of immunotherapies. For example, both CTLA-4 and PD-1 or PD-L1 blockade are under investigation. We know there's higher response rates with those combinations; however, there's also increased toxicity. So how do we balance that? How do we manage that? And does it really improve our overall cure fraction down the line?

Other areas that are being investigated with immunotherapy are potential combinations of chemotherapy and immunotherapy that have panned out in other tumor types such as lung cancer. With bladder cancer having a higher mutational burden, exposure to tobacco and other sort of irritants, this is an area of great interest. Can it be moved to the neoadjuvant setting in these curative intent patients? It likely will in the coming years, but there's a lot unknown as of date. Further molecular characterization is key, and I'm going to go into that in just a second. It really helps us to tease out the individual biologies that patients are following in urothelial cancer. So many of you are familiar in breast cancer with the different subtypes: you have *HER2* disease, you have ER/PR-positive disease, you have triple-negative disease, and they behave incredibly differently. You go down different treatment algorithms for each based on this very core feature. In the recent years, there has been very similar work done in urothelial cancer, and we think this is really going to help guide a lot of future treatments because we are finding the same story, that these diseases behave very differently based on their subtype. There's a number of groups that have done this, and some of the terminology is a little bit different, but to summarize, these are the major three subtypes that have come out of urothelial molecular characterization.

Basal subtype is the most aggressive biology, and we see a lot of high proliferative markers on these tumor specimens on pathology. Traditionally they have the poorest outcomes, and these are the patients that often walk into your clinic metastatic at presentation rather than having a recurrence later on down

the line. Interestingly, these are the tumors that are chemotherapy sensitive, and so these are the patients you don't want to miss that opportunity to cytoreduce them with chemotherapy. This, in my mind, similar to the triple-negative story of breast cancer. Again, you want to remember chemotherapy in this type of biology. Luminal tumors often start out very superficial, we have found in bladder cancer, and they have a high predominance of *FGFR* mutations, and so there's a lot of work being done with FGFR inhibitors in bladder cancer both in the metastatic setting as well as the localized setting to see how we can target these alterations. There's also work being done with *FGFR* and immunotherapy combinations. We see the luminal histology sometimes more often in the micropapillary; they're certainly not hand in hand all the time, but it's an interesting predominance there. And then the *p53*-like patients are the ones I think about as the ER/PR-positive breast cancers, the lower proliferation, they have a lot of stromal enrichment, they tend to be pretty chemotherapy resistant, but they do have better outcomes because it just seems to be a more indolent type of biology. We see more bony metastases in these patients, and I think this is going to be a real key principle in bladder cancer in the years to come because as these branch out and we find out more and more of these individual subtypes, it's really going to help us to better guide therapy towards each patient. Right now we hit everybody with one umbrella or the other, but it's going to branch out a lot more in the years to come.

So just a quick plug: we are all used to doing this across different tumor types, but some of the things you may want to consider in your metastatic

urothelial patients—panel molecular testing is always a good thing to send to see if there's any kind of targetable mutations that we can do for that patient. *FGFR,* I just mentioned, because there's a lot of national ongoing interest and trials in this arena. MTAP is another area that's becoming increasingly interesting. Patients that are MTAP deficient, it's just an IHC marker that's checked, seem to be a little bit more sensitive to chemotherapies in the pemetrexed and methotrexate family. Interestingly, when those patients are treated with pemetrexed or methotrexate, they actually have upregulation of PD-L1, so you can potentially nicely follow that with an immune checkpoint inhibitor. So consider testing that again in the setting of it you have access to a clinical trial that's looking at that. And then the microsatellite instability you want to think about definitely with your upper tracts. There was some nice work at ASCO earlier this year that we're maybe under-recognizing it in bladder cancer too, and so certainly consider sending that in the metastatic setting to see if there's any role for immunotherapies for that patient. And with that we're happy to take any questions. Thank you very much for your attention.

FEMALE Thank you. That was really informative. This is probably a novice question, but for the folks that are candidates for radical cystoprostatectomy, who decides whether they get a neobladder or a urostomy? How does that work? And then also for the people who have ureterectomy, what do you do to get the urine down to the bladder?

DR. LEMKE For the first question, the neobladder versus ileal conduit, that's something that our Urology colleagues make the decision on, along with

the patient. I would say the majority of our surgeons at Anderson are doing about 80% ileal conduit and about 20% neobladders, and there's different qualifying characteristics that the patients need to have specifically with their GFR. So in order to get the neobladder, you have to have, I believe, a GFR greater than 60. And I think it's pros and cons: age of patient, what kind of lifespan do they have left, the self-catheterization that can need to happen with a neobladder might sound like a piece of cake at age 50, but ideally we are curing these people and hopefully they are going to be alive at 85 or 90, and if you've got urinary retention in that setting, it's a little bit of a different game. Then the surgical time on the table I know varies between those. A neobladder I think can be approaching 10 to 12 hours, and I think the ileal conduit is 6 to 7 hours, but this is all information our Urology colleagues have shared with us, so don't quote me on any of that. And your second question was about urinary diversion in a nephro-u?

FEMALE Yes, if they have a ureterectomy then how does—where does the urine go?

DR. LEMKE Since they still have their other kidney and ureter, it diverts through that. Since kidney is removed, they are not having their urine come through there.

DR. SHAH One of the other things that goes in to the decision about ileal conduit or neobladder are patients who will actually go to a specialized clinic where they do all kinds of fittings so they see where does that patient's pants sit, do they wear a belt often, what's their body habitus like, and they're really thoughtful about where to discuss placement as long as it's surgically feasible of

that conduit, so that patients can be a little bit more comfortable. It's a big preoperative part of the plan.

FEMALE Hi, there. I had a question about—you said sometimes you're able to spare folks neoadjuvant chemotherapy for high-grade muscle-invasive bladder cancer. We give a lot of neoadjuvant therapy, so is that an institutional policy where you're basing the risk factors, or do you have data, or how's that work?

DR. SHAH Yeah, so great question. It is right now very much of an institutional practice for us. We've gotten quite a bit of data together with our Urology colleagues over the years. So at our institution, for example, if a patient has T2 disease, so it's just in the muscle and not T3 or beyond, doesn't have any of the high-risk features, our long-term outcome is that 85% of those patients are cured with surgery alone. Based on our internal validation of this data, we feel like a lot of those patients can be spared chemotherapy if up to 85% are cured with surgery. So that's where this risk stratification came about. There is other data that's been published, but I think by and large, the majority of people do practice that any degree of muscle-invasive T2 disease does require neoadjuvant chemotherapy, and we feel the same that if in doubt, err on the side of caution and go ahead and give neoadjuvant. But if a patient just has no high-risk features and a minimal amount of disease, something to consider with the idea of adjuvant on the backend if you need it.

DR. LEMKE It's usually a pretty easy sell to the patient telling them that they don't need chemo, so we don't get a lot of pushback on it at all.

FEMALE And one other question. You mentioned you had a patient that had the microsatellite instability, and let's see, what did I write down? Oh, so you gave them up-front pembro. Was that in the adjuvant setting or metastatic setting?

DR. SHAH He was metastatic actually. He was metastatic and had been diagnosed with Lynch syndrome, had seen a genetics counselor and everything, and part of it was that he just wasn't a good chemotherapy candidate. He had had a lot of issues with previous surgery where his GFR was impaired, and so we did pembrolizumab and he was 45, so he was so nervous: "I feel great on immunotherapy. Are you sure it's doing anything?" you know, "Am I even getting treatment?" So it's a nice option for those patients with Lynch, but especially because in the microsatellite instability population, they just don't have great responses to chemotherapy, but definitely in the metastatic setting, not indicated in the curative intent setting.

FEMALE Thank you.

FEMALE What's the increased risk for the Lynch patient population? I know it varies between which gene mutation they have, but is it 20%, 5% increase over the average population? Do you know?

DR. SHAH Yeah, it's in the 15 to 20% range, and we check the same as colorectal, the IHC includes the *MLH1, MSH2, MSH6, PMS2,* and then we verify that with the PCR assessment.

FEMALE You said you use creatinine clearance Cockcroft-Gault versus eGFR. Is that because eGFR over- or underestimates kidney function?

DR. LEMKE The GFR that your BMP or your CMP spits out is going to be just based on the average weight, average height of patients. So with the Cockcroft-Gault, it's a more personalized measurement of their kidney function because the calculation includes their weight, their creatinine clearance, their age, and their gender and so it's just a cleaner measurement. That being said, if you have somebody who is very morbidly obese, you might look at both and meet somewhere in the middle. But for the most part, it's a better measurement and more specific to that patient.

FEMALE Thank you very much.

DR. SHAH Thank you everybody.

MR. CAMPEN Thank you, Dr. Shah and Dr. Lemke. Just a couple of quick notes to point out. This presentation was part of the Smarty Program, so please be on the lookout for an e-mail this afternoon with questions about the session, we'd appreciate your prompt reply.

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