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BLADDER CANCER UPDATE:
ADVANCES IN TREATMENT AND THE ROLE OF EARLY DIAGNOSIS

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Dr. Elizabeth Albert: Hello, my name is Dr. Elizabeth Albert. On behalf of Optum Health Education, I would like to welcome you to today's activity, "Bladder Cancer Update: Advances in Treatment and the Role of Early Diagnosis."

I would like to welcome Dr. Matthew Galsky. Dr. Galsky is Professor of Medicine, Hematology and Medical Oncology, Director of Genitourinary Medical Oncology, Co-Director of the Center of Excellence for Bladder Cancer at the Tisch Cancer Institute, and Associate Director for Translational Research at the Tisch Cancer Institute.

Dr. Galsky specializes in the care of patients with genitourinary malignancies, bladder, prostate, kidney, and testicular cancers. His research centers on team science-based approaches to dissecting the mechanistic underpinnings of response and resistance to novel bladder cancer therapies, with a particular focus on immunotherapeutic approaches. It is with pleasure that I welcome you here today, Dr. Galsky.

Matthew D. Galsky, MD, FASCO: Thank you, hi everyone. Thanks for joining today. So, I'm going to provide an update on treatment in muscle-invasive and metastatic bladder cancer today; and there's actually been a lot of developments in the field over the past few years in particular and even in the last six months. So lots to talk about.

Here are my disclosures, and here are the learning objectives. Today, really, we're going to talk about bladder cancer initially at a little bit of a high-level talk about the demographics of the disease, then talk about some of the new therapies that have been developed over the past years and how to integrate those therapies into current practice.

So bladder cancer in the medical oncology world is sometimes considered a less common malignancy, and that's, in particular, because of the most common stage at presentation. And we're going to talk about that a little bit. But it's really not an uncommon malignancy; and, in fact, there's about 82,000 new cases diagnosed each year in the United States. And worldwide, approximately 429,000 individuals are diagnosed with bladder cancer.

So, it's actually a relatively common malignancy. There is male to female predominance of the disease, and there's multiple reasons why that might be. In some exciting data just over the past year regarding the molecular mechanisms that might, in part, explain that, in addition to some differences in risk factors.

It's been difficult to develop new treatments for bladder cancer historically, and that's for multiple reasons. But about a 30-year period of time went by, and you can see that on the slide, where there was very little in the way of new drug approvals; and then things really started to change around 2016, and we're going to talk about some of the treatments that were initially approved around that time, which really led to this increase and interest in research, it's an interest maybe, of therapeutics development in bladder cancer and really this tidal wave of new drugs and new mechanisms that have entered the clinic for this disease.

One of the reasons that it's been difficult to develop new treatments potentially is the demographics of the disease. And bladder cancer is a disease of older individuals. Most commonly patients are diagnosed in their 70s to 80s. The median age of diagnosis in the United States is in the mid-70s. And as a result, there is some disconnect in terms of the

demographics of the disease and what is sometimes eligibility for clinical trials that restrict individuals who have physiologic changes or comorbidities that might, in part, be age-related. And so that has resulted in some difficulties over time, but over the past several years, this seems to have normalized a little bit with both relaxation of ineligibility criteria for clinical trials and the understanding that we need to bridge this disconnect between efficacy and effectiveness. That is we need to develop treatments in the clinical trial setting that can be applied to the real-world setting maybe in a more seamless way.

Hey, I was alluding to this earlier, but most commonly patients with bladder cancer are diagnosed with nonmuscle-invasive disease. That accounts for the vast majority of initial diagnoses of bladder cancer; and, luckily, nonmuscle-invasive disease for many, many patients can be cured with endoscopic treatment. That is with a urologist resecting the tumor and/or maybe instilling treatment into the bladder. And so this really speaks to the fact that early recognition or early diagnosis of bladder cancer is quite important to enable the detection of disease when it is potentially nonmuscle-invasive and can be eradicated with these less-intensive treatments, with these treatments that can potentially impact quality of life in a less significant way.

Unfortunately, despite this recognition, it's been difficult to develop widespread screening strategies for bladder cancer because the presentation of bladder cancer can sometimes be a bit insidious. But we do know that many patients with bladder cancer present with hematuria, with blood in the urine. And so there have been efforts to try and identify patients who are particularly high risk for potential targeted screening.

And, of course, one of the major risk factors for bladder cancer is smoking. This is often underrecognized or unrecognized because we often think about smoking as a risk factor for aerodigestive disease; but, of course, the toxins in cigarette smoke are ultimately filtered

through the urine, and then the urine sits there in the bladder in between periods of time of urination and potentially bathes the urothelium.

And so, certainly, in patients with a history of smoking with hematuria, that needs to be taken quite seriously. In fact, there's the old rule that any patient over 50 with gross hematuria, that's a malignancy until proven otherwise. So blood in the urine requires, gross blood in the urine requires a workup and exclusion of cancer until proven otherwise.

We spoke a little bit about this, but early recognition of these types of symptoms, in particular hematuria, but also lower urinary tract symptoms that really can't be explained in any other ways warrant an evaluation with a urologist just to make sure that there is no underlying malignancy.

So, I spoke a little bit about nonmuscle-invasive bladder cancer and the fact that it accounts for the most prevalent presentation of the disease and can often be managed with endoscopic resection. But really the purpose of today's talk is to focus on these other clinical disease states of bladder cancer, that is the muscle-invasive setting and the metastatic setting.

And I'm going to start by talking about the metastatic setting because drug development often happens initially in patients with more advanced malignancies. And then once drugs are shown to be safe and effective, then moved earlier in the course of disease.

For several decades, cisplatin-based chemotherapy has been the standard first-line treatment for metastatic urothelial cancer. And this is a landmark study shown here which compared a two-drug regimen to a four-drug regimen so that the four-drug regimen, MVAC, was standard of care for a while. And then the two-drug regimen, gemcitabine plus cisplatin was developed. And as you can see here, the major advance in the field over a period of decades was not necessarily developing a regimen that was better but developing a regimen that had similar activity but seemed to be safer than the four-drug regimen.

So gemcitabine and cisplatin became a pretty standard regimen used for patients with metastatic disease. And you can see here that the progression-free survival data with this regimen, the context of metastatic urothelial cancer is a bit sobering, of course. But what you can also see on this slide, which doesn't happen in every solid tumor, across metastatic solid tumors, is that there does seem to be some plateau on this curve, even with this long-term follow-up that's seen here.

And so there are a subset of patients, and depending on the clinical trial, the data set that you look at, probably ranges between 10 and 20% who do achieve durable disease control even in the metastatic setting with cisplatin-based chemotherapy. And that's one of the reasons why it's been hard to displace chemotherapy, even with some of the newer treatments that I'll be talking about.

In 2016, after a period of several decades without new drugs being approved, there was a series of approvals for the treatment of metastatic urothelial cancer for PD-1 and PD-L1 inhibitors, immune checkpoint inhibitors. And I should mention that I'm using the term urothelial cancer and bladder cancer a little bit synonymously. I talk about urothelial cancer in the metastatic setting because urothelial cancer most commonly arises in the bladder but can arise in the upper urinary tract as well. That is the ureter, the renal pelvis. When those cancers have metastasized, we don't treat them any differently. Under the microscope, they look the same. They're urothelial cancer, and that's why I'm using the term urothelial cancer most commonly when I talk about metastatic disease.

So, a series of PD-1 and PD-L1 inhibitors were approved, starting in 2016. These drugs were first approved in the post-platinum setting, meaning patients had received chemotherapy, their cancer had subsequently progressed, and then they enrolled on trials with immune checkpoint blockade.

Most of these approvals occurred based on single-arm Phase 2 studies and with response rate endpoints. And the reason that these drugs were approved is really the same reason that they were approved in other malignancies, which is that in a subset of patients there is long-term control of metastatic disease with immune checkpoint blockade. So these drugs don't work in everyone by any means. They don't work in the majority of patients. But when they work, they really work quite well.

And so that led to the approval in these settings, and the next most logical place to assess immune checkpoint inhibitors was in the frontline treatment of patients with metastatic disease in an unmet need population that we termed cisplatin-ineligible patients. I told you that cisplatin-based chemotherapy has been standard treatment for many decades. But we know that up to half of our patients or even more can't receive cisplatin because of age-related comorbidities, because of smoking-related comorbidities, things like poor performance status, poor renal function, heart disease, history of neuropathy, etc.

And so in this patient population, gemcitabine and carboplatin have traditionally been used, although we've always felt that carboplatin-based chemotherapy in this disease might not work as well with cisplatin. And because these patients have these other comorbidities, there had been the desire to develop treatments that worked well but were also better tolerated.

And so this became a logical place to next develop immune checkpoint inhibitors, and there were two immune checkpoint inhibitors approved for the frontline treatment of patients with metastatic disease who are cisplatin-ineligible. Atezolizumab and pembrolizumab, both of those drugs were approved based on single-arm Phase 2 studies with response rate endpoints with, through the accelerated approval pathway through the FDA. And what many of you probably know is that the labels for those indications changed dramatically over the years based on subsequent Phase 3 data to read out, which I'm going to touch on a little bit. And ultimately, the

approval for atezolizumab was withdrawn, and the approval for pembrolizumab changed gradually over time from all patients with metastatic urothelial cancer or cisplatin-ineligible to patients with PD-L1 high-expressing tumors to most recently what's called platinum-ineligible patients, that is patients who are not felt to be good candidates for any chemotherapy, even carboplatin-based chemotherapy.

So why did those labels change and what else have we learned since those initial approvals? Well, there was a series of questions that arose once immune checkpoint inhibitors as single agents were shown to have activity and were approved for certain indications in the treatment of metastatic urothelial cancer. And those questions were questions that were being asked in other solid tumors at the time as well, such as is there a role for giving chemotherapy and immunotherapy together? Is there a role for immune checkpoint blockade as upfront treatment for all patients, not just cisplatin-ineligible patients? If there is a role, should we be using PD-L1 testing as a biomarker to select patients? Should we be using immune checkpoint blockade doublet therapy? All of those questions were assessed in a series of Phase 3 studies that were designed around a similar time. We've now seen the readouts from the vast majority of these studies, although not all of them. And these have really informed practice in a significant way.

The set of studies or the study, rather, that really changed practice first among all of these studies was the "switch maintenance" approach. And this involves the fact that when we give platinum-based chemotherapy in urothelial cancer, we generally give a fixed number of cycles. So generally, six cycles of treatment in the absence of prohibitive toxicity or disease progression, and then we stop and we wait.

Why do we do that? We know that if we keep giving the same chemotherapy, beyond that, you tend to see a plateau in effectiveness; but you see cumulative side effects. And so that's been the historical strategy in this disease. That's the strategy in some other diseases as well. In

some solid tumors, you give chemotherapy until progression and so various strategies among solid tumors. But that's what's been done in urothelial cancer historically.

And so the logical question arose, well, if these drugs are approved in the post-platinum setting, that is in patients who receive chemotherapy and then progress, why don't we move them earlier and give them right away after patients finish chemotherapy? And that's called switch maintenance treatment.

That was assessed in two randomized studies, a smaller randomized Phase 2 and a larger randomized Phase 3. The Phase 3 study was with avelumab versus best supportive care, and that had an overall survival primary endpoint. You see the Kaplan-Meier curve here. There was a significant improvement in survival with that approach, leading to the approval of switch maintenance avelumab, and that really became a standard of care.

What about giving chemotherapy and immunotherapy concurrently as is done in multiple other solid tumors now, such as lung cancer? So, there were two Phase 3 studies designed to assess this question; and these studies integrated a third arm, which was immune checkpoint blockade monotherapy. So really seeking to address the question should we give concurrent chemo with immunotherapy versus chemo alone or should we even give just immunotherapy as a single agent? Is there a role for that?

And so those studies were called IMvigor 130 and Keynote 361, designed in an almost identical fashion. Here's the progression-free survival curves from those studies, and you can see the curves from the two studies look very similar. There might be a slight improvement in progression-free survival when you add immune checkpoint blockade to chemotherapy.

In one of these studies, it met statistical significance. In the other it didn't. The curves look pretty similar, so one could guess that's based on some nuances and the statistical analysis

plan. But certainly the effect size that you see here is not quite as robust as what's been achieved in other solid tumors when you give chemotherapy and immune checkpoint blockade at the same time.

Here's the overall survival curves. This did not reach the prespecified *p* value thresholds for statistical significance. And so even though the curves look similar, you see a little bit of an improvement with atezo checkpoint blockade added to chemotherapy. This has now changed practice. These were not statistically significantly different curves. So unlike other solid tumors, that strategy has not been integrated into standard practice.

What about giving single-agent immune checkpoint blockade versus chemotherapy as upfront treatment? Well, this is the IMvigor 130 study addressing that question. And in the blue curve, you see immune checkpoint blockade. In the red curve, you see platinum-based chemotherapy; so this could have included cisplatin or carboplatin-based chemotherapy, whatever the patient was felt to be appropriate for.

And you can see here that in the initial portion of the curve, about the first 9 months, chemotherapy is beating immune checkpoint blockade; and then the curves cross over a little bit at around 9 to 12 months. And it's for this reason here, that initial detriment with single-agent immune checkpoint blockade versus chemotherapy, that led to the changes in that label that I was talking about with immune checkpoint blockade as upfront treatment for cisplatin-ineligible patients. Now that the randomized data was in, there was a question as to whether or not that was really the right thing to do.

There's the issue of can we use biomarkers to inform this? And what you see on this slide is the IMvigor 130 study. The same curves that I just showed you but now separated based on PD-L1 immunohistochemical testing of the pretreatment tumor with the hypothesis that if there's a higher level of PD-L1 expression, that might identify patients who do better with immunotherapy

than chemotherapy. And you see here in the top curves, that's all-comers; and in the bottom curves restricted to patients who are cisplatin-ineligible.

And now you see there does seem to be some benefit with giving immunotherapy versus chemotherapy in the upfront setting. The problem with this is this was an exploratory analysis, again based on some of the nuances of the statistical analysis plan of the study. And so this has not, even though transiently there was a label for atezolizumab in cisplatin-ineligible patients with high PD-L1 expression, exactly the curve that you see in the lower left on this slide. That label was revoked based on the fact that the overall study was a quote/unquote "negative study."

What about the pending Phase 3 studies that were initiated around the same time? Well, there's been a recent development here; and I don't really have time to go into the details regarding why this might have occurred. But as you recall, those studies that I just showed you with chemotherapy plus immune checkpoint blockade versus chemotherapy all included dealers choice platinum-based chemotherapy. So, those studies included patients who were cisplatin-eligible and those who were cisplatin-ineligible. Patients could get gem-cis or gem-carbo.

There's been some suggestion that perhaps those platinum drugs have different immunomodulatory effects; and maybe cisplatin is a better pair, pares better rather with immune checkpoint blockade. So that was actually assessed in one of the studies, and this is called the CheckMate 901 study. It's a very complicated study, but I'm going to call your attention to arms C and D here, this randomization because this is really two studies in one.

And you see patients who are cisplatin-eligible were randomized to receive chemotherapy plus PD-1 blockade versus chemotherapy alone. And there was a press release in July indicating that this study met its coprimary endpoints. That when you added nivolumab to cisplatin-based chemotherapy, there was an improvement in progression-free survival and overall survival. We

haven't seen the results of this study yet. We haven't seen all of the data. But really this is the first study combining chemotherapy and immune checkpoint blockade concurrently to meet its endpoints, and it does raise this question, is cisplatin different than carboplatin in this regard?

There's one other study in this era that hasn't read out yet, and this was really trying to develop even a more rigorous or maybe a more involved combination regimen. So this involved chemotherapy plus doublet immune checkpoint blockade rather than single-agent immune checkpoint blockade. And the NILE study, we have not seen the results for yet.

Another class of drugs that have really made a major impact on the treatment of urothelial cancer are antibody drug conjugates. Of course, these are antibodies designed to bind to a specific protein that's expressed on cancer cells with a linked cytotoxic drug most commonly. And in this case, there are two antibody drug conjugates that have now been approved by the FDA for the treatment of metastatic urothelial cancer. One of them is called enfortumab vedotin. This is an antibody directed against the protein Nectin-4, which is highly expressed on urothelial cancer cells, and it has the cytotoxic payload MMAE. And sacituzumab govitecan is directed against the protein Trop-2, and this has SN38, the topoisomerase inhibitor as a payload.

So both of these approved. Enfortumab vedotin has full approval, and it has full approval based on this Phase 3 study, which enrolled patients with metastatic urothelial cancer who have received chemotherapy and immune checkpoint blockade had progression of disease were randomized to enfortumab vedotin versus further chemotherapy. And that chemotherapy mostly involved taxane-based chemotherapy. And you can see here that there was an improvement in overall survival and progression-free survival when you gave enfortumab vedotin versus chemotherapy.

In this study, here's the response rates with chemotherapy versus immune checkpoint blockade. And, of course, overall survival data trumps response data. But the reason that I show this is

because the response rate with this molecule has really held up quite remarkably across the Phase 1, 2, and 3 program. And we often see a decrease in the response rate as you move from maybe a select number of centers in smaller Phase 2 studies to large international Phase 3 studies. But that hasn't really been the case here, and you see a fairly high response rate relatively speaking compared to what's been available in the past in patients who have already received platinum-based chemotherapy and immune checkpoint blockade.

So based on these results and the data that was developing in other malignancies showing that combining immune checkpoint blockade with cytotoxic drugs might be beneficial, the logical approach, should we give enfortumab vedotin with immune checkpoint blockade? And that was explored in a single-arm Phase 2 study presented at ESMO several years ago. And when this waterfall plot was shown, showing the responses in individual patients enrolled in this study, this was first-line treatment in patients who were cisplatin-ineligible. This was really quite a remarkable slide compared to regimens that we've had to treat this disease in the past. And you can see here that the vast majority of patients had at least some tumor regression with this regimen with many deep responses at all.

So this raised lots of excitement and led to a randomized study trying to assess the contribution of components. So this study randomized patients who were cisplatin-ineligible with metastatic urothelial cancer who had not received prior treatment to treatment with the combination of enfortumab vedotin plus the PD-1 inhibitor pembrolizumab versus enfortumab vedotin alone.

And you can see here enfortumab vedotin alone response rate of 45%, so a little bit higher than what I showed you in that Phase 3 study in patients who had already received prior treatment. And with enfortumab vedotin plus pembro, response rate of 64.5%. So high response rate, similar to what I showed you in that Cohort A, that smaller study. And really a response rate that is quite competitive with anything that we've seen in the frontline setting in metastatic

urothelial cancer. And based on this study, pembrolizumab plus enfortumab vedotin received accelerated approval for the first-line treatment of patients with metastatic urothelial cancer.

When you look at the toxicity profile with this combination, there's side effects that are quite distinct with immune checkpoint blockade versus enfortumab vedotin. And then there are some overlapping side effects. So the things that we look out for for a regimen like this include rash, because that could incur with either drug; diarrhea, that could occur with potentially either drug, including immune checkpoint blockade-related colitis. And then there are some side effects that are more common with enfortumab vedotin that tend to be cumulative and sometimes impact dosing or schedule, and that includes peripheral neuropathy.

The combination of enfortumab vedotin plus pembrolizumab is now being assessed in a definitive Phase 3 study. And this study enrolls patients with metastatic urothelial cancer, either cisplatin-eligible or ineligible. And patients are randomized to the combination of enfortumab vedotin plus pembro versus platinum-based chemotherapy, again, whichever regimen gem-cis or gem-carbo a patient is felt to be eligible for.

This study has been completed. We haven't seen the results yet and certainly eagerly awaited in the context of the data with this doublet regimen that we've seen so far.

Sacituzumab govitecan is the other antibody drug conjugate approved in metastatic urothelial cancer. It's proceeded along a similar development path as enfortumab vedotin, although the data are a little bit less mature.

So, the approval was based on this TROPHY-U-01 study, and this included a cohort of patients, a large Phase 2 cohort similar to the cohort that led to the approval of enfortumab vedotin patients with metastatic disease who had progressed despite prior platinum-based

chemotherapy and an immune checkpoint inhibitor. And with this antibody drug conjugate, we saw a response rate of 27% in this population, leading to accelerated approval.

And the definitive study, the definitive Phase 3 study, TROPiCS-04 has been completed, but we haven't seen the results yet. And this enrolls a population of patients who had received platinum-based chemotherapy, and immune checkpoint blockade, randomizing patients to either sacituzumab or chemotherapy, which again, largely includes taxane-based chemotherapy.

So, we await the results of this trial to determine the definitive role of sacituzumab in the treatment of metastatic urothelial cancer. In clinical practice, because these antibody drug conjugates are available, and because they have nonoverlapping therapeutic targets, they have nonoverlapping payloads and nonoverlapping side effects, there is an increase practice of administering these drugs sequentially. We don't have prospective data to fully understand the cross-resistance between these drugs, although there were some patients enrolled in the clinical trials program who had one sequence of these drugs versus another. And we know that at least some patients respond to one of these drugs, having had received the other and vice versa.

Molecularly targeted therapies are now integrated into the treatment of urothelial cancer as well. We've known that mutations in the gene FGFR3 are relatively common in patients with urothelial cancer. They're actually more common in low-grade, non-muscle invasive disease. That's where they're the most common. But even in patients with muscle-invasive disease, FGFR3 mutations are present in about 15 to 20% of patients.

This is a gene that is mutated in the germline as well, and when it's mutated in the germline, it causes the most common form of short-limbed dwarfism, achondroplasia. That probably happens because of inhibition of chondrocyte proliferation at the growth plate. And so the

mutations that we see in FGFR3 in urothelial cancer are slightly different mutations than we see in achondroplasia. But again, one is germline and the other is somatic.

The somatic mutations were identified quite a while ago, in 1999; and it took a while for this to have clinical impact. One of the reasons was because the first generation of drugs targeting FGFR3 were not highly potent or selective. And so we didn't see a lot of activity with those initial drugs. But when more potent and selective FGFR3 inhibitors entered the clinic, it was pretty apparent that targeting this mutant kinase was relevant in terms of driving the disease.

And you can see one example. Here, a patient with lung metastatic disease who has really a major response to treatment just after two months of this more potent and selective FGFR inhibitor are really reminiscent of oncogene addiction that we see in other tumor types.

We do see class effect side effects with FGFR3 inhibition as several of these drugs have now been in clinical trials. And two of the side effects that occur as class effects with these drugs include hyperphosphatemia, which is a little bit unusual for other drugs that we use for the treatment of cancer and hand-foot syndrome as well, which, of course, we do see with some other therapies. This tends to be a little bit more prominent in terms of nail toxicity, although certainly there is skin toxicity as well. And so this, the use of these drugs certainly does require a learning curve.

The initial approval of an FGFR inhibitor in patients with metastatic urothelial cancer was based on the BLC2001 study, and this was a Phase 2 study, single arm that enrolled patients with metastatic urothelial cancer that progressed despite platinum-based chemotherapy. These patients had tumors harboring FGFR mutations or fusion. Fusions are a little bit less common, but those patients can be included as well in these studies. And FGFR inhibition has been shown to have activity in the presence of fusions.

Patients on this study were given one of two different dose levels of erdafitinib, and you can see here that there's single-agent activity with this orally available small molecule with a response rate of 40%. Some of these responses quite long-lasting.

That led to accelerated approval of erdafitinib, and then the Phase 3 THOR study was really the definitive study; and this was really two Phase 3 clinical trials in one. We've seen the results from Cohort 1 now. We haven't seen the results from Cohort 2 yet. This included a similar patient population, although patients could have received a prior immune checkpoint inhibitor or not. In patients who did not receive a prior immune checkpoint inhibitor, they were randomized to erdafitinib versus pembrolizumab. That's Cohort 2. In patients who had received a prior immune checkpoint inhibitor, they were randomized to erdafitinib versus chemotherapy.

And here you see the results of the Cohort 1. You see a response rate of 45.6% with erdafitinib versus 11.5% with chemotherapy. So intravenous chemotherapy versus an orally bioavailable drug targeted against a mutation that's present in these patients' tumors clearly has difference in activity.

And here you see the survival curve favoring erdafitinib versus chemotherapy in Cohort 1 of the THOR study.

So putting all of these results together, this is really the current treatment strategy for metastatic urothelial cancer in 2023. There's still a role for first-line platinum-based chemotherapy with switch maintenance immune checkpoint blockade. However, enfortumab vedotin plus pembrolizumab is approved for the frontline treatment of patients with metastatic urothelial cancer versus cisplatin-ineligible and is certainly recommended in the NCCN guidelines in this context based on the high response rates. We're awaiting the Phase 3 data.

I showed you a press release that gemcitabine-cisplatin plus nivolumab improves survival compared to gem-cis. We haven't seen the full results yet. That's not yet an approved regimen. And then we have two antibody drug conjugates approved in later lines of therapy, in addition to erdafitinib for patients with tumors harboring FGFR alteration.

I'm going to switch gears and talk a little bit about muscle-invasive bladder cancer. So muscle-invasive bladder cancer is exactly what it sounds like, cancer that has invaded the muscularis propria layer of the bladder. We know that surgery alone can be curative for patients with muscle-invasive bladder cancer. This involves removing the entire bladder, a cystectomy. But we also know that despite that operation, unfortunately, a fair subset of patients will develop metastatic recurrence; and so this has really raised the issue that systemic treatment to try and eradicate micrometastatic disease is likely to be an important part of this strategy.

Unfortunately, a series of practical and technical challenges has limited our ability historically to improve outcomes in muscle-invasive bladder cancer. And just in the past few years, some of those challenges, some of those barriers are really starting to be chipped away.

So probably the biggest barrier in the muscle-invasive setting, and this is not specific to bladder cancer, this is common to all clinically localized solid tumors is that we don't really know who needs perioperative systemic therapy and who benefits from such treatment. And those are related, but they're actually distinct considerations.

So what I mean by that is that we need to know who harbors micrometastatic disease in order to know who should get perioperative systemic therapy. There are patients who are cured with surgery alone. Anything we give to those patients in the terms of medication beyond surgery by definition can't help them. It can only hurt them. So knowing who needs treatment is critically important. But knowing who needs treatment is not sufficient to know who benefits from treatment.

Of course, you can't benefit from treatment if you don't need treatment. But if we think about the metastatic setting, unfortunately, we know that many patients don't respond to the drugs that we give them, even though we know they have metastatic disease on imaging. And the same thing applies in the micrometastatic setting. A patient might have micrometastatic disease. That does not mean that the systemic therapy that we're administering is going to be effective, and so ideally biomarkers to define both of these are going to be needed to truly enter the era of precision medicine in the perioperative setting.

Biomarkers to define one of these questions I think are coming, and they're coming quite quickly. And I'm going to get to that in a few minutes.

In the absence of such biomarkers, we've used T and N staging as a surrogate as to who might need treatment. And we know that patients with pathological T3 or lymph node-involved bladder cancer certainly have a much higher risk of metastatic recurrence in historically giving systemic therapy after surgery has been reserved for such patients.

There's been difficulties completing chemotherapy or, I should say, perioperative therapy trials in bladder cancer. And so the very simple question should we give adjuvant chemotherapy is sort of a simplistic question that has been addressed in virtually every solid tumor has been difficult to answer definitively in bladder cancer. We think that probably is the case, based on the data that we do have available, but there's been some challenges developing that data.

We do know that if you give chemotherapy prior to surgery, then that leads to an improvement in survival based on two randomized Phase 3 studies. And so neoadjuvant chemotherapy is a standard of care. But like I told you before, we also know that a large subset of our patients can't get cisplatin-based chemotherapy, which is the only chemotherapy that's been shown to be beneficial in the neoadjuvant or adjuvant setting.

So we have this Level 1 evidence, but it can only be applied to a subset of our patients. And, of course, we know that if a patient receives neoadjuvant chemotherapy and has a cystectomy and there's cancer left in the bladder, there's a high risk for recurrence. That's, of course, a surrogate for aggressive tumor biology for resistant cancer cells.

And so this has been a challenge as well. And so if we think about developing the next-generation treatments in this setting, really you'd want to be able to address all of these things. We want to be able to give treatment, regardless of whether or not a patient was cisplatin-eligible or ineligible. We'd want to have a treatment that could be given despite the presence of residual cancer after cystectomy, meaning that a drug that's not cross-resistant with chemotherapy. We'd want to have tools to inform who really needs treatment and ideally who benefits from treatment. And ideally, we could deescalate treatment as well and identify patients who don't need perioperative systemic therapy who were cured with surgery alone.

So there have been three studies designed to assess the role of immune checkpoint blockade in the post-cystectomy setting in the adjuvant setting. All these studies were designed quite similarly with a few nuances. We have the results from two of these studies already. One of them is still pending.

So, all of these studies enrolled patients with very similar eligibility criteria. High-risk muscle-invasive urothelial cancer was defined as the presence of pathological T2 or higher disease despite having received neoadjuvant cisplatin-based chemotherapy or a patient who did not have neoadjuvant chemotherapy, had pathological T3 or higher disease, but were cisplatin-ineligible. And so those patients were randomized to receive adjuvant immune checkpoint blockade versus observation or placebo, depending on the study.

Here's the results from the IMvigor 010 study. Unfortunately, adjuvant atezolizumab did not meet its coprimary endpoints in this study. And that was certainly disappointing, and then we

saw the results from CheckMate 274; and, again, some nuances in terms of the design of this study.

And here we saw that patients who were randomized to receive adjuvant nivolumab had a significant improvement in disease-free survival and hazard ratio of 0.7 in the all-comer population. And then in patients with PD-L1 high-expressing tumors, the effect size was even greater with a hazard ratio of 0.52. And this led to the approval of adjuvant nivolumab for the treatment of patients with muscle-invasive urothelial cancer who are at high risk for recurrence after surgery.

Why do these studies show different results? Of course, that's hard to say. There's some hand-waving reasons, but we don't know definitively. The drugs are not exactly the same. One's a PD-L1 inhibitor and the other is a PD-1 inhibitor. There could be some differences in the biomarker performance in the studies. There could be some differences in the use of observation versus placebo as the control arm. But we don't know definitively.

Even though the IMvigor 010 study did not meet its primary endpoint, this data set has been incredibly important in informing how we think about moving the field forward.

What the investigators did on this study was they retrospectively asked the question if they had a surrogate for microscopic metastatic disease, if they had a test of molecular residual disease, would the results of the study have been different? So, they employed this tumor-informed ctDNA test. This is called Signatera™. It's a commercially available test. I say tumor informed because this involves DNA sequencing of the primary tumor, identifying up to 16 mutations in that tumor, designing a bespoke PCR-based assay to check for those mutations in the plasma, and then checking patients' plasma to see if one could detect those mutations as a surrogate for the presence of residual cancer in the body.

So this testing was done. It was done on Cycle 1, Day 1 of treatment or observation. And then it was done one repeat sample as well.

Here you see the results from just that baseline specimen on the observation arm of the IMvigor 010 study. So no adjuvant immunotherapy here, just observation. You can see the powerful prognostic impact of this single test. If you can detect ctDNA after surgery, then the risk of disease recurrence or death is markedly higher than if you can't. And the investigators then asked the question, "Well, what if we applied this to the treatment versus control arm? Would we see a difference?" And now you see that there is an improvement in disease-free survival and overall survival in patients who receive adjuvant atezolizumab who had detectable ctDNA at baseline but not in patients who didn't.

And so this is a retrospective analysis. We certainly need to establish clinical utility, but very compelling in terms of this issue. Can we identify patients who need treatment? So this bit is being assessed definitively. There's the IMvigor 011 study which is really identical to IMvigor 010 that I just showed you. But instead of randomizing all patients to receive atezolizumab, only patients with detectible ctDNA are randomized. And that study is ongoing.

There's also a study that's being initiated through the US Cooperative Group System known as the MODERN study. And MODERN is asking a slight variation on that question and really seeking to determine if we can escalate treatment in patients with detectable ctDNA using a doublet immunotherapy regimen versus a single-agent immunotherapy. And in patients with undetectable DNA, do they need treatment with adjuvant therapy? And the randomization there is to standard of care adjuvant nivolumab versus initial surveillance with initiation of nivolumab only if there's conversion from undetectable to detectable ctDNA.

So, clearly, immune checkpoint blockade has changed the treatment landscape. Chemotherapy though is still playing a role, and it's really been hard to displace chemotherapy. The

combination of antibody drug conjugates plus immune checkpoint blockade though have really the potential to do this, and we've already seen the approval of enfortumab vedotin plus pembro in the frontline setting in cisplatin-ineligible patients, really starting to displace gemcitabine and carboplatin.

And to move in all of these treatments earlier, we'll certainly shift the landscape further as in patients who have disease recurrence despite getting these therapies in the clinically localized setting. There will be a knowledge gap in terms of what to do next.

So thanks for your attention, and I'm going to stop there.

Questions?

Dr. Albert: Thank you, so much, Dr. Galsky for this excellent presentation. At this time, we would like to take questions from the audience. Questions may be asked via the Type Your Question Here field to the right of the webcast. As this session will end at the top of the hour, Dr. Galsky has agreed to answer any remaining questions that are not addressed; and the answers will be posted to the activity website by this Wednesday, September 21.

So, Dr. Galsky, we have received a few questions here; and I'm going through them, and I'm going to ask a few. One person asked, "For local disease that's not invasive to muscles, that recurs, is there any oral immunotherapy to reduce recurrence?"

Dr. Galsky: So, for nonmuscle-invasive bladder cancer, the nonmuscle-invasive bladder cancer comes in many different flavors. And there's what's called low-grade papillary disease or Ta tumors. There's carcinoma in situ which are high-grade under the microscope but not invading, sort of carpeting the lining of the bladder, of the urothelium. And then there's T1 tumors which are tumors that actually invade the first layer of the bladder, the lamina propria. The treatment

of each of those is slightly different and depends- So the details in terms of recurrence make it even more complicated because it depends on prior treatment timing, etc., etc.

Long story short, there's no oral therapy for the treatment of any of those. But there is clinical trial data that suggests that potentially the use of FGFR3 inhibitors could have a role because we know that in patients with low-grade papillary tumors, the likelihood of having FGFR3 mutations is really quite high as I was alluding to earlier in the talk. And so even though FGFR3 inhibition is approved for the treatment of metastatic urothelial cancer first, those mutations are actually much more common in low-grade papillary disease and certainly that speaks to a potential role of that target in nonmuscle-invasive bladder cancer. But the right strategy in that patient population has yet to be fully defined.

Dr. Albert: Thank you. Another person asks with platinums considered as the first-line therapy for metastatic urothelial disease, were there any modifications you've had to make in your practice in the past few months with the drug shortages affecting the supply of both cisplatin and carboplatin? And if so, did that lead to an increase in usage of pembro and/or EV plus pembrolizumab?

Dr. Galsky: So, we've been pretty lucky in terms of the shortage being transient. There was internal discussion about prioritization of patients for cisplatin in terms of the disease indication. But we really didn't have to enact those recommendations in a rigorous way because of the transient nature of the impact locally. But I've certainly heard nationally from my colleagues in places where the impact has been more significant; and, indeed, this discussion about using enfortumab vedotin plus pembro in a much more relaxed way given the inability to give cisplatin-based chemotherapy.

Dr. Albert: Thank you so much. Another person asks about lower-grade bladder cancer, your opinion on the treatment options for those who have low-grade bladder cancer if they have failed BCG treatments with tumor recurrence and mitomycin.

Dr. Galsky: So most of the time for low-grade bladder cancer, with some less common exceptions, those treatments wouldn't be a major part of the treatment strategy. And so we need to distinguish nonmuscle-invasive disease from low-grade disease because low-grade disease occurs in the nonmuscle-invasive setting, but definitely not all nonmuscle-invasive disease is low-grade disease.

For nonmuscle-invasive bladder cancer, with that situation that's being described, most commonly that occurs in the setting of high-grade disease carcinoma in situ or T1 disease. And the appropriate strategy in that setting really depends a bit on if it's carcinoma in situ versus T1 disease and the timing of when the recurrences happen and the response to the prior treatments.

There are a few therapies approved in that setting. The first therapy approved in that setting in recent years was actually systemic immune checkpoint blockade, pembrolizumab approved for the treatment of BCG-unresponsive carcinoma in situ. And so that's really the first example of an approval of a systemic therapy for nonmuscle-invasive disease. There's additional intravesical therapies that have been approved, although not widely available yet. And then there is the use, again, assuming high-grade disease, there is the use of other intravesical chemotherapy regimens routinely when some of the other treatments are not available.

Dr. Albert: Thank you so much. At least two people have asked questions regarding specific genetic testing for current blood test availability for bladder cancer mutations and/or biomarkers prior to even having or being diagnosed with an active cancer.

Dr. Galsky: So there's nothing that definitive in terms of a screening test in terms of trying to inform the diagnosis of bladder cancer. In terms of tests that are available for informing treatment, really the only genetic test that's available for informing treatment has to do with germline. I'm sorry, has to do with somatic genomic testing, somatic DNA testing for FGFR3 mutations as mentioned. Those mutations are present on virtually all commercial, panel-based DNA sequencing; and so that is probably the most common strategy that physicians use institutional panel-based next-generation sequencing or commercial-based testing to check for a variety of mutations, including FGFR3, which is the most actionable.

Dr. Albert: Thank you. A few people have asked about the influence or if it has been determined that there is an influence of dietary toxins, a current diet status, and even the role of chlorine and other more general chemical exposures such as that in the causative agents for bladder cancer?

Dr. Galsky: Yes. So, we know that certain occupations are associated with an increased risk for bladder cancer and certain toxins are associated with an increased risk – industrial solvents, traditionally hair dyes have been associated with an increased risk.

There's an increased risk of commercial drivers for bladder cancer, and that's felt to be for a couple of reasons. One, potentially because of exhaust. Two, because of the fact that patients who are, individuals who are commercial drivers probably urinate less frequently and drink less water. And so not only are they exposed to those toxins, but they sort of sit in the bladder, in base urothelial lining.

So, certainly from an epidemiologic standpoint, specific toxins in specific occupations have been linked to a higher risk of bladder cancer for several decades.

In terms of specific diets or specific foods in terms of risk or diets in terms of prevention, nothing that's really been definitive. Based on the potential pathogenesis of toxin exposure in terms of bladder cancer development, one could envision that there could be chemo-preventative strategies; but we're certainly not that advanced in terms of knowing what those strategies should be.

Dr. Albert: Okay. A few people have asked about BCG treatment and the questions address can you provide more information about using BCG in MIBC per the NCCN guidelines? And also, has there been any progress in solving the BCG shortage, to your awareness?

Dr. Galsky: So BCG is an activated bacterium, tuberculin bacterium that creates an immune response within the bladder. It's administered into the bladder weekly for six weeks as an induction cycle and then as a maintenance strategy after that, depending on the response. It's given for patients with high-risk nonmuscle-invasive disease, including T1 disease or carcinoma in situ.

It's not used for muscle-invasive disease that's penetrated deeper into the wall of the bladder. Local treatment into the bladder is not felt to be sufficient treatment for muscle-invasive bladder cancer.

BCG has been a standard treatment since the late 1970s, early 1980s for nonmuscle-invasive bladder cancer, and it's really one of the prime examples of the success of cancer immunotherapy, even though there has been some limited understanding of the immunomodulatory basis in the mechanistic basis for the activity of BCG. There have certainly been advances in that regard in recent years, but historically, somewhat of a limited understanding. But despite that, from a clinical perspective, it's really been a hard treatment to beat.

The BCG shortage, certainly because urologists are the primary prescribers of BCG and, as a medical oncologist, I don't administer that treatment I have less of a day-to-day handle on the shortage. I know that it has impacted certainly our patients over the last several years and that there had been manufacturing facilities that have been in development to try and address that, and I don't know the current status in terms of those facilities.

Dr. Albert: Thank you. Can you speak to information surrounding if a patient were diagnosed with in situ or localized bladder cancer and then in remission for ten years or so, what is the likelihood that they would have a recurrence of bladder cancer as they age?

Dr. Galsky: So, the likelihood that they would have a recurrence per se is low at that time; but I think that we also need to think about what recurrence means in the context of bladder cancer.

And so we know that patients who will have developed one urothelial cancer of the bladder are at risk for other cancers; and that occurs probably for a few different reasons. But the concept of the field cancerization effect is felt to explain at least a large number of those multifocal bladder cancers and that is that whatever insult, whatever toxin was impacting the urothelium probably, as we discussed already, urine is sitting there with toxins bathing the urothelial lining; and there's probably an insult in a multifocal nature to the urothelium, resulting in distinct bladder tumors frequently arising within the bladder.

And so because of that insult to the urothelium, certainly there's the possibility for a second primary cancer within the bladder to develop over time. That's not necessarily recurrence of that initial cancer that was treated successfully. Even that though at ten years in the absence of any cancer detectable in the bladder, that becomes markedly less.

Dr. Albert: Thank you so much. I believe we've come to the top of the hour, and so I just want to say, Dr. Galsky, thank you so much for sharing your expertise and your experience with the participants today. And to all the participants as well, thank you for joining us today.

On behalf of Optum Health Education, I would like to thank Dr. Galsky for his participation. I would also like to thank Seagen and Astellas for their support of this activity. Please contact us at moreinfo@optumhealtheducation.com with any questions. This concludes today's webcast.

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