Improving Outcomes for Patients With Advanced Urothelial Carcinoma of the Bladder

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INTRODUCER Good evening. Welcome to this certified dinner symposium. My name is Gary Shelton. Anyone know me? Good. Our focus tonight is Improving Outcomes for Patients With Advanced Urothelial Carcinoma of the Bladder. As an aside, well, before my aside, I am scripted, which I often am in life just to stay on focus because I am tangential and I'll go somewhere and never come back, but one quick tangent: GU is very close in my heart and some of my first working relationships were with GU oncology. We did the docetaxel studies at Columbia in the '90s. We did the Viagra studies with prostate cancer in the '90s. And then it seemed like every other Tuesday a new drug would come out for renal cell carcinoma. We did the sunitinib and the sorafenib studies. Bladder was already sort of, you know, you've got your platinum doublets and whatever and that's about it, maybe some BCG, and it never really seemed to be as exciting for the poor folks with bladder cancer. That has changed. Tonight, you are going to – you all may know more, but I haven't been in GU for a while, so this is very interesting to me. I'm learning a lot just by looking at the slides. Welcome this evening.

Allow me to introduce your speakers for this evening for a fabulous program, I might add, again because of my interest in bladder cancer: Dr. Petros

Grivas and Ms. Jeannette Hammond. Dr. Grivas is a board-certified medical oncologist with expertise in genitourinary cancers, working as an associate professor in the Department of Medicine, Division of Oncology, Clinical Director of the GU Cancer Programs at the University of Washington. Ms. Hammond is a teaching associate at the University of Washington in the Division of Medical Oncology, and the APP Professional Development Manager at Seattle Cancer Center Alliance. In this role, she has set up a mentoring program for new APPs and provides opportunities and support for APPs to build skills and expand expertise in research and education. I love you. Please join me in welcoming both of them.

DR. GRIVAS Hello everybody. I realize we have the microphones here. It will be easy to go back and forth. We are very honored to be here. I am Petros Grivas, and as mentioned, I am working here at the Seattle Cancer Care Alliance, University of Washington, and Fred Hutchinson Cancer Center. I always take a few minutes to say my titles, as you can see, with three institutions. We are very honored to be here, and I am very excited because I will give a talk together with Jeannette. We work as a team in the clinic and we work as a team here. It is very exciting to be here with Jeanette. I will give her the stage to start.

MS. HAMMOND Thank you. And thanks, Gary, for the introduction. You are right, we had very little in the way of treatments outside of the platinum doublets, so it is an exciting time. We will be excited to share all that information with you. I think we have to go through some questions first.

You can see the financial disclosures there. We will be discussing some agents that aren't FDA approved at this time and in study, so be mindful of that. Our learning objectives: We are going to look at data regarding mechanistic activity; efficacy and safety of approved and emerging treatment in advanced or metastatic urothelial carcinoma; planned strategies for managing adverse events associated with these drugs; select appropriate lines of therapy for treatment with evidence-based best practices.

Before I get started, I have a couple of take-home messages that I would like to share with everyone. I know I am already going off script. I hope I am not worrying Petros too much. There are a couple of things I think outside of the learning objectives that are really exciting and important. Working in urothelial cancer, there has been this tremendous effort both with the scientific community, the medical community, patients, advocacy groups, to move the research forward so that we have more options for patients. It's this huge coordinated effort. Big systems. It makes a difference for patients. Options are empowering. First take-home message.

The second one is on a much smaller scale, but it's equally important. It's what all of us do every day. It's being in the clinic and making connections with patients and family and making them feel comfortable so that they can share what's going on with you. They can tell you what they are hoping for, what they are struggling with, and then you can take that information and do something with it. Provide the support they need. Manage their side effects better and improve their quality of life. I think in those moments where – it's sort of a gift of being

seen and being heard is the best gift that we have as human beings. That's the magic that you guys are doing every day. Thanks for doing that work.

Urothelial carcinoma is the sixth most common cancer. In 2019, it is estimated over 80,000 new cases in the United States with 17,000 deaths from the disease. Average age at diagnosis is 73. That means a lot of our patients can come with other conditions that we have to cope with as we are deciding treatment regimens. It's a little bit of a misnomer. Urothelial is really the histological type and bladder is the location. Most urothelial carcinomas do originate in the bladder, but they can involve anything along the tract: the urethra, proximal part of the urethra, bladder, ureters, and into the renal pelvis. Urothelial carcinoma is the most common histology, but there are some other smaller subtypes.

Lifetime risk. It's more common in men than in women, so 1 in 26 for men and 1 in 90 for women. In 2016, there were nearly 700,000 people in the US living with urothelial carcinoma.

What are some risk factors? How do patients present? The most widely recognized risk factor is tobacco use, cigarette smoking. There have been some other industrial chemicals that have been implicated, like in printing materials or hair dyes. There are some genetic components to it. Family history of bladder and other cancers. Some association with Lynch syndrome. Some chemotherapies or radiation treatment. It's rare, but we do see it in the clinics. Patients who have been previously treated for prostate cancer who had pelvic radiation can develop bladder cancer decades down the road. There is also a

parasite link to squamous histology in endemic areas. The most common presenting sign or symptom is microscopic or gross hematuria. Very few people will ignore gross hematuria. They will get a workup.

One of the branching decision-making points with urothelial carcinoma is where is it? How deeply into the bladder wall has it gotten? The delineation really is between non–muscle invasive and muscle invasive. So, when you have these more superficial tumors like CIS, which is really kind of a spreading on the surface, or a Ta, which just goes into the mucosa, or even T1, those are all before they get into the muscle. Those are treated more like a local problem. Whereas, when it penetrates into the muscularis layer, there is an increased risk with it getting involved with the lymph system and spreading outside of there. Our treatments then have to be more aggressive. When we look at the disease treatment continuum, we start with the non–muscle-invasive bladder cancers and those are treated more locally; muscle invasive we have to get more aggressive, and the metastatic more systemic. We will go through each of those sections as we go.

Non–muscle-invasive bladder cancer – so it stayed at the surface, or it's just in the mucosa. This is the majority of new bladder cancer patients. It's important to know that in the pathology specimen, it's important that they said that they could see the muscularis propria, but it wasn't involved. Sometimes that even requires re-resection. There is a risk of under-staging. I know this is a huge range, but 30% to 80% of patients will recur in 5 years. The majority are confined to the mucosa, and there are these papillary tumors, so like fingerlike projections

rather than the flat kind of tumor. These are typically managed by our urology colleagues. They will do a TURBT and then provide intravesical therapy. BCG is the main intravesical therapy that's used, but there is evidence that immediate postoperative intravesical gemcitabine or mitomycin decreases the risk of recurrence in certain cases.

BCG is an inactivated tuberculosis bacteria. It essentially irritates the bladder lining, which recruits the immune cells to come and take action against the cancer cells. There is induction therapy, which is typically given weekly x6 and then maintenance, therapy which can be every 3 weeks for up to 1 to 3 years. I kind of smile, flu-like symptoms and local side effects, but it's not comfortable, right? They are urinating more frequently, urgency, it's painful when the urinate, so it's not a complete easy treatment. Then on a side note, there is a manufacturing shortage of BCG. This is a huge problem requiring lots of different people to come together to try and figure that out. The AUA has guidelines about how to prioritize patients and how to deal with that shortage right now, but it's an ongoing problem. I'll turn it over to Dr. Grivas now.

DR. GRIVAS Thank you, Jeanette. It's really exciting and to be honest with you, when we were preparing the slides together with Jeanette, I was so excited to see the progress that has been made in urothelial carcinoma in the last 6 or 7 years. It is really exciting to see this explosion of data and just trying to be a part of that evolution is really remarkable. So, in that context of progress and new data coming in, Jeanette did a great job showing the data with BCG as the standard of care in patients with non–muscle-invasive bladder cancer, high

risk, and it is well known that patients respond to BCG, most of them, but it is very frequent that these patients may have recurrence of the non–muscle-invasive bladder cancer or progression to a deeper stage of invasion. As Jeanette showed you, you may have a Ta or T1 or carcinoma in situ, all these three categories are non–muscle-invasive disease, but the cancer might actually invade deeper to the muscle layer, causing a T2 or even beyond a deeper stage. So, what happens when these patients have what we call BCG-unresponsive disease, meaning, the cancer is not responding to BCG and in that context the standard-of-care treatment is radical cystectomy. If patients have the criteria defining what we call adequate BCG therapy, it has to be adequate treatment of BCG, but if someone, despite adequate treatment, still has recurrence or progression, and they are deemed BCR responsive, then the standard treatment is radical cystectomy. There are two problems though. Some patients are not fit enough for radical cystectomy because of medical comorbidities, poor performance status, or some patients may refuse cystectomy. There may be reasons why someone cannot get a cystectomy – medical, not fitness or refusal.

What are the options for those patients right now? We have limited options. Patients cannot get cystectomy, some of them may get intravesical bladder chemotherapy with drugs like gemcitabine or mitomycin-C or valrubicin, so intravesical chemotherapy is an option, but the results are modest. We have to improve upon them and create more options for those patients who cannot get a cystectomy if they have BCG-unresponsive high-risk non–muscle-invasive bladder cancer. In the context of pursuing new treatment options for those

patients, there have been a few trials looking at immunotherapy, immune oncology therapy, specifically this trial that I am showing you on this slide, this KEYNOTE-057 trial, is using one of those immune checkpoint inhibitors, specifically pembrolizumab in patients who have, again, BCG-unresponsive high-risk non–muscle-invasive bladder cancer, they are either not good candidates, not fit enough for cystectomy, or they refuse it. There were two cohorts in that study: Cohort A and Cohort B. The results that I will show you here today are specifically for Cohort A, which is patients who have carcinoma in situ. And carcinoma in situ, you may argue, is not invasive cancer; however, the biology of this carcinoma in situ, specifically the bladder is very aggressive, and it is very likely for this carcinoma in situ scenario to either recur or invade deeper to a muscle-invasive stage. It is very important to treat these patients with carcinoma in situ.

In that study, patients got pembrolizumab as a standard dose 200 mg every 3 weeks, and they were getting evaluated with urine cytology, cystoscopy, and CT scans to make sure there is no progression or metastasis in this context. In this table and slide, you see the baseline characteristics of those patients. I would like to focus your attention on the red box. These are patients who have carcinoma in situ as I mentioned, and the majority of them had carcinoma in situ alone; a small portion had carcinoma in situ with what we call papillary tumors, fingerlike projections inside the lumen of the bladder. Either Ta, which is very superficial, not invading the lamina propria, or T1, which means the tumor invades the lamina propria, but, again, not yet the muscularis propria.

In this line, you see that at 3 months, we tried to measure the clinical complete response rate, meaning, if you do urine cytology, cystoscopy, and CT scans, you see no evidence of malignancy, at least none you can detect. Because there is always a chance that microscopic cells may not be detected. So, this is a clinical complete response rate, not pathologic complete response rate, because the bladder is still in place. It is not remote. So, at 3 months, about 40% clinical complete response rate, meaning four out of 10 patients with pembrolizumab, they have no evidence of malignancy at about 3 months. The question is, how durable is our response and how common it is for the cancer to show up again in a subsequent time point after this 3-month time point? This is, again, the clinical complete response rate.

And as you see that we call swimmers plot, you have most of the patients have achieved complete response early on, about 3 months or so, and interestingly this is medium follow-up for 14 months. The patients were still on treatment, there was no patient developing deeper invasion, muscle-invasive disease, or metastatic disease, suggesting some promise here that you may potentially have an option to offer to those patients. As you see, one-quarter of those patients still have recurrence over non–muscle-invasive disease. This response rate of 40% in 3 months, some of those responses are durable, longer lasting, some of them are not. As you see, three-quarters of those patients have an ongoing response at the time that the data cut took place. I think the interesting point here, we have now longer follow-up with this data, and I think the FDA is actively looking at that data, and the question will become whether

this complete response rate, which ends up being about 20% in 1 year, whether it will meet or not the threshold that the FDA has for regulatory approval. We don't know yet whether this will be enough for approval, but definitely shows some promise about checkpoint inhibitors and non–muscle-invasive disease. There is another clinical trial with a different checkpoint inhibitor called atezolizumab and the PD-L1 study showed no finished accrual, so we will have to see again what will happen with those checkpoint inhibitors. These agents are not in practice as I mentioned, but again the regulatory agency FDA is looking at the data, so it remains to be seen whether pembro will make it or not in that particular setting.

The safety profile was consistent with what we show in metastatic disease. In this slide that Jeanette showed you already, we have tried to delineate the different treatment settings of bladder cancer. We covered already the non–muscle-invasive bladder cancer and now we are going to move to muscle-invasive bladder cancer and will show you the data regarding the role of cisplatin-based neoadjuvant chemotherapy followed cystectomy, the role of chemoradiation and bladder preservation, adjuvant therapies, and then we will move on to metastatic disease. This is kind of an overview of what we are going to show you. I will turn it back to Jeanette. She will take you through the muscle-invasive disease category.

MS. HAMMOND About 25% of cases are muscle invasive at the time of presentation. This means we have to be more aggressive about our treatment. More aggressive local therapy with the addition of systemic therapy as well.

There are several decision-making points. First, imaging can be very helpful. Is it locally advanced and unresectable? Or is there evidence of metastatic disease? Is this patient a reasonable candidate for a radical surgery? This is really a big morbid procedure, so are they fit enough for a surgery? Is bladder preservation an option? There are some pretty nice criteria for what makes the best candidate for someone to undergo bladder preservation. Then, are they eligible for cisplatin-based chemotherapy? Cisplatin has been the backbone of treatment for bladder cancer for a long time and there are lots of reasons why patients might not be eligible, depending on the location of their primary tumor. Then, are there clinical trials that are relevant and available for this population?

The rationale for introducing chemotherapy before surgery. We are trying to get rid of any of those cells that have already escaped, that we can't see, that we can't measure, but we know will impact patients' overall outcome. We also hope to downstage the bladder tumor, so you have a higher pathological complete response rate and better outcomes for patients. Then, rather than waiting until after surgery, there is no waiting for recovery after surgery. You do the chemotherapy up front and then you can move forward with the surgery. It's also an opportunity to see how the tumor responds to chemotherapy in real time. We can look at biomarkers, tumor tissue, blood, urine, or stool for research. There is level 1 evidence supporting the use of neoadjuvant chemotherapy in this setting. As I said, cisplatin is one of the most common and standard-of-care options that we have, cisplatin-based chemotherapy. There was some eligibility laid out by Galsky and it's based on function and current symptoms that we might

exacerbate using the cisplatin. Their ECOG performance status has to be 0 to 1. They can't already have hearing loss or peripheral neuropathy that is grade 2 or greater. They have to have good cardiac function, and their kidneys have to be functioning well enough to tolerate the cisplatin. And again, as I said, this could be an issue because some patients can present with obstruction and hydronephrosis and poor kidney function, or outside of their disease state, their average age is 73, so there may be other comorbid conditions, even outside of the bladder cancer.

There are a couple of different regimens that we would typically use in the neoadjuvant and in the metastatic setting. Gemcitabine and cisplatin are a really common regimen that we use. It's given on day 1 and 8 of a 21-day cycle. Typical side effects from that are what you would mostly expect from the cisplatin. Gemcitabine can give you some fevers, but the cisplatin can impact the kidney function. There can be nausea, vomiting, peripheral neuropathy, tinnitus, hearing loss. The other regimen we use is a dose-dense or accelerated MVAC, so methotrexate then blasting doxorubicin and cisplatin. We more often than not give the dose-dense version where all the drugs are given on day 1 and given every 2 weeks with GCSF support.

DR. GRIVAS Thank you, Jeanette. So, we pretty much make the emphasis here that we have level 1 evidence of giving neoadjuvant cisplatin-based chemotherapy in patients with muscle-invasive disease if they're destined to go for radical cystectomy lymph node dissection. That's very important because myself and others have tried to use non-cisplatin regimens in the clinical

trials in the neoadjuvant setting, but the reality is we never rose to the level of evidence that we can use something different than cisplatin. So, the take-home message here is, if someone cannot get cisplatin in the neoadjuvant setting for whatever reason, these patients have three options. Either go on a clinical trial, and we will show you some options today here, some examples of clinical trials, or they go straight to cystectomy or if they are good candidates that can go for bladder preservation approaches with concurrent chemotherapy and radiation. The point here is, if someone cannot get cisplatin, do not give carboplatin as a substitution. This drug is inferior to cisplatin and we don't use it outside of clinical trials in the neoadjuvant or adjuvant setting. We can still use carboplatin for metastatic disease if we cannot give cisplatin, but we do not give carboplatin neoadjuvantly or adjuvantly.

What is the evidence behind the use of cisplatin in the neoadjuvant or adjuvant setting? Specifically, for neoadjuvant, there was a metanalysis of 10 randomized clinical trials, about 2700 patients that compared cisplatin-based combination chemotherapy plus local definitive therapy, usually radical cystectomy, versus local therapy alone, and so there was statistically clinically significant longer overall survival with the use of cisplatin-based neoadjuvant chemotherapy. The data you can quote to the patient in the clinic based on the study was about 5% improvement in overall survival at 5 years with a clinically significant hazard ratio and interval. I would argue that the benefit is probably more than that, because if you put all the data together, these 10 trials, some of them had some flaws, they did not use optimal regimens, they did not have

enough follow-up, so I think overall I would say that the benefit with neoadjuvant chemotherapy is probably underestimated based on this analysis, probably a bit more. If you look specifically at the large randomized trials, there was a much larger discernable benefit of neoadjuvant chemotherapy. There was also lower risk of recurrence. If you give cisplatin-based chemotherapy, you have a lower chance to have a recurrence of disease. So, longer disease-free survival and longer overall survival. So, I think it is clear that we have to use neoadjuvant cisplatin-based chemotherapy. The problem is it is significantly underutilized, especially in the community practices. It is common for patients to go straight to cystectomy, and it took time. It took, I would say, a couple of decades or so to try to disseminate the data out there and now we have more and more utilization of the level 1 evidence with cisplatin-based chemotherapy in the neoadjuvant setting. As I mentioned before, do not substitute for carboplatin. I think it is important to stick with your best drug if you can safely, and as Jeanette mentioned before, we now have data with accelerator dose-dense MVAC or gemcitabine and cisplatin, either or, but we do not use any more of the older conventional classic MVAC that was used back in the day because this had more toxicity and more challenge to get it through, especially in the neoadjuvant setting.

There are multiple data sets that look introspectively and try to compare the two regimens Jeanette showed you—gemcitabine and cisplatin and MVAC—and this showed very comparable pathologic complete response rates, meaning, if you take bell out and you look at how many patients had no cancer left in the

bladder after the cystectomy, this percentage portion of patients was very comparable between gemcitabine and cisplatin and MVAC regimen.

Now we have this recent data from this trial called SWOG 1314. This trial had a randomization between these regimens: gemcitabine and cisplatin and dose-dense MVAC. This trial presented at ASCO a couple of months ago and showed very similar, almost comparable, complete pathological response rates, about 30% to 35% with either regimen. You may argue that trial was not powered to detect differences between the two regimens, but there was enough indirect evidence that either regimen—dose-dense MVAC or gemcitabine and cisplatin—is reasonable to be given in the neoadjuvant setting. We can discuss if you want in the question-and-answer session if we have some preferences. I tend to use if I can the dose-dense MVAC as my first option, but I am perfectly comfortable with gemcitabine and cisplatin in patients who are not feeling 100% with dose-dense MVAC. I think the point here is we have a lot of clinical trials that we are trying to utilize immunotherapy and start to use biomarkers in the future to try to select which patients have a higher chance to benefit from therapy A or therapy B. I think there is more work to be done about biomarkers. We don't have one right now in clinical practice, but we have clinical trials that are testing biomarkers and hopefully we are going to utilize them in the future upon development of more data.

This is the study that I mentioned before. This is SWOG trial, SWOG 8710. It was part of this last metanalysis that I showed you with 10 trials. There were two large trials there. This was done in the United States. Three cycles of

the older, the classic conventional MVAC, followed by cystectomy, versus cystectomy alone, showed about a 2.6-year median overall survival benefit with the use of neoadjuvant cisplatin-based chemotherapy. Again, this is overall survival and it is hard to argue with overall survival benefit. Now the question is, having this data that I showed you with cisplatin-based chemotherapy, can we build upon that and use immunotherapy, add it to chemotherapy as a combination in the neoadjuvant setting? We are not there yet, but we are doing trials and we are going to open a trial at our institution very soon, looking at a combination of gemcitabine and cisplatin plus pembrolizumab, the three drugs together, compared to gemcitabine/cisplatin alone to see whether the addition of checkpoint inhibitors makes a difference. I think it is still research, but I think it is very important to accrue in those trials. This trial I just told you about was based on this phase 2 trial one of my friends from my days in Cleveland presented at ESMO a months ago, showing that the combination of chemotherapy plus pembrolizumab is promising. There was about 60% downstaging to non–muscle-invasive bladder cancer after neoadjuvant chemotherapy at the time of cystectomy. Again, this is supporting the conduction of this phase 3 trial that I just told you about that we are going to open soon, comparing this triplet versus standard of care, which is gemcitabine and cisplatin alone.

As I mentioned before, there are many patients who are not fit for cisplatin for whatever reason. Jeanette showed you the different factors that we take into account. Some of them are very strict, for example, performance status, it has to be 0-1. The hearing factor is interesting. As mentioned, if you have grade 2 or

more, many of us are a little uncomfortable, but many patients with grade 2 hearing loss say, you know what? I want to go for it. I want to get the best possible treatment and in discussion with the patient, and informed decision, whether grade 2 hearing loss is okay or not. Some people accept that it is and say, I may lose a little bit of high frequency sound, but I want to get the best possible treatment. It's a discussion with the patient, but it's clear, as again Jeanette mentioned to you, we have criteria we use. Kidney function is one of them, performance status, hearing function, uropathy, and heart function. If someone is not fit for cisplatin, which is about 50% of the patients, about half of the patients are not fit for cisplatin. This questions how do we care for the patients. What do we do with them in the clinic? We have many clinical trials that we try to utilize in order to see whether, for example immunotherapy, can play a role in the cisplatin-unfit patients. About 50% of those are not able to get cisplatin.

This is an example of a trial that I wrote about 3 years ago, and now we have the joy and pleasure to have it open at our center. I know Jeanette has seen many patients with me in that study. This is trying to evaluate whether immunotherapy has a role in those who cannot get cisplatin. This particular trial is an example. There are many of them out there looking at nivolumab, an anti-PD1 agent, either by itself as single agent, or combined with a different checkpoint inhibitor called lirilumab is interesting because it is activating natural killer cells, NK cells. So, what we try to do here is engage the adoptive immune system, the T cells, by inhibiting the PD1 and the negative immune system, the

natural killer cells. And where the T cells and NK cells come together, infiltrate the tumor microenvironment, and hopefully kill cancer cells, and therefore receive a high complete pathological response. This trial is ongoing. We have about 15 patients accrued, so we are almost halfway done, so we are very excited. As I mentioned, there are many trials out there. This is just an example, but immunotherapy has no standard role yet in the neoadjuvant setting, but many trials are ongoing either with immunotherapy alone or in combination with chemotherapy. So, stay tuned for those data to come up.

MS. HAMMOND We will kind of pause for a minute between neoadjuvant chemotherapy to cystectomy, and before we get to bladder preservation and chemoradiation. Just a side note about how we deal with obstruction and what we have learned from how we deal with obstruction. They actually looked at 114 patients that had obstruction by the tumor at the outset; 53 were treated with ureteral stents, and 61 with nephrostomy tubes. What they saw is that 13% of treatments with ureteral stents had upper tract recurrence and none of the patients with nephrostomy tubes did. Stenting prior to cystectomy is an independent risk factor for upper urinary tract recurrence, so our general practice is to use nephrostomy tubes.

Moving forward to who are the best candidates for bladder preservation. These are patients who have small tumors, usually unifocal, location away from the UV junction, so there is less risk of an obstruction or long-term toxicity from the radiation. Maximal and optimal resection obtained. Node negative. No extensive CIS. So, they are more the surface tumors. No evidence of

hydronephrosis. They need to already have good bladder function because that is such a quality of life issue for patients. Then, we don't know if they have histologies outside of urothelial cancers. We don't know as much about whether or not they would be a good candidate for bladder preservation or not. Chemoradiation is used in that setting and we typically would give cisplatin as our main go to drug for that. Usually 35 mg/m^2 to 40 mg/m^2 every week. You could alternatively use mitomycin-C, 5-FU, or gemcitabine as radiosensitizers. There is evidence that the radiation is inferior to the combination of chemoradiation. Most of the toxicities – we have talked about the toxicities from cisplatin, but the toxicities from the radiation are all local, so urinary symptoms: urgency, frequency, dysuria. There is a new study at UW called the TraceIT study, which Dr. Grivas will talk about in a minute, but patient selection is really key. There are patients who can be ideal chemo RT candidates, which is not the same as just being a poor surgical candidate and having that be the default treatment method.

DR. GRIVAS For to try to keep the bladder in place, the bladder preservation, we have concurrent chemotherapy and radiation, and that's the standard approach. The question is can we improve upon the outcomes of those patients? At the University of Washington, our colleagues in radiation oncology were great. They came up with this study called TraceIT and what they do there is, when someone is getting chemoradiation, bladder preservation, we always try to do an optimal or maximal TURBT: transurethral bladder tumor resection to maximize removal of the tumor before chemoradiation starts. The urologist, the

urological oncologist, goes into the bladder through the urethra and resects the tumor. At that same time, they can actually inject this biocompatible hydrogel, and the purpose of that injection is to help the radiation oncologist target with external beam radiation the area where the tumor was, because when we removed the tumor and you try to simulate through a CT scan the radiation beam, the tumor is gone through the resection. You may not be able to see it well. If you have this tracer there, this fiducial, you can actually help the radiation oncologist direct the radiation field, exactly where the tumor was. It's exactly in the periphery of the tumor bed. This study we are doing is going very well. We finished accrual recently and seems this fiducial, this tracer, seems to be well tolerated, no significant toxicity, again it seems to be easy to be done when at the time of the maximal TURBT and then when we go through chemotherapy and radiation – actually, in the middle of the chemoradiation we can pause for a couple of weeks, do a mid-treatment evaluation and make sure the tumor is not growing, and at that time we can potentially repeat the injection of the tracer. Again, this is a way to make the radiation more directed, more specific, to know where exactly it will go. It seems to be safe and feasible. We are going to see in the future whether it has any impact on the clinical outcomes. We don't know that yet. This was kind of an interesting study we are doing at our institution.

In an effort to improve upon the chemoradiation alone, I sought out this clinical trial that will actually put together all the research cooperative groups. So, we have SWOG, ECOG, ACRIN, Alliance, NRG, multiple different research cooperative groups, and we tried to come together to design a clinical trial that

potentially can be practice changing. This study, led by my friend, Dr. Singh, who is in the Mayo Clinic in Arizona, and many of us tried to help design it, is getting patients who are not going for cystectomy, either refused cystectomy or just opting for bladder preservation or are not fit for cystectomy and we say, okay these patients are going for bladder preservation approach, and the standard of care is chemoradiation, does it make sense to add atezolizumab, an anti–PD-L1 agent, to the backbone of chemoradiation. It is a phase 3 trial comparing the standard of care, which is chemotherapy and radiation, or chemotherapy, radiation, plus immunotherapy. Again, this idea of standard of care, as a backbone and addition of the new immunotherapy. Patients get randomized and the primary endpoint is bladder-intact event-free survival, which, as you see in the left lower part of the slide, consists of different sub-endpoints. And we have of course long follow-up, we are going to look at overall survival as well as biomarkers, quality of life, patient report outcome. A very important study. It is going to open in multiple centers, probably going to open at your center, so keep it in mind. It's called SWOG/NRG 1806, chemoradiation alone plus/minus atezolizumab. This the chemotherapy we are using in the study: either cisplatin weekly or the combination 5-FU/mitomycin-C or gemcitabine; three options, one of those three options as the radiosensitizer for the chemotherapy part of the chemoradiation.

We talked about neoadjuvant chemotherapy before. We talked about chemotherapy and radiation as separate, bladder preservation approach. What happens if a patient never received neoadjuvant chemotherapy and they get into

our office and our clinic and they try to ask us, “You know what? I never got neoadjuvant chemotherapy; what is the data regarding adjuvant chemotherapy in that setting?” We have a plethora of studies that actually look to that question of adjuvant chemotherapy, and I think the take-home point here is the totality of the data tells us there is probably benefit in the adjuvant chemotherapy with cisplatin-based regimens, but no trial so far has reached individually the level of significance to conclusively say adjuvant chemotherapy prolongs life. The problem is, many of those trials did not have enough patients. They had low accrual, so not enough statistical power to show definitively that adjuvant chemotherapy prolongs life. However, as you see on that slide, if you put all the trials together in this metanalysis, we have a marginal overall survival benefit without adjuvant cisplatin-based chemotherapy and clear disease-free survival benefit as well. There is an example, a European trial called EORTC 30994, which aimed to accrue 660 patients, but accrued less than half the target. So, less number of patients accrued, not enough statistical power to show benefit. Indeed it showed significant disease-free survival benefit with chemotherapy, specifically gemcitabine and cisplatin or MVAC, versus waiting until metastasis occurs; however, there was no statistical significant overall survival benefit, and as I mentioned, as an example of the different flaws and under-accruals we had in the adjuvant chemotherapy trials. However, again, if you put the data together, I think it is interesting and is important to mention, if you pool the data together, there seems to be an overall survival benefit with adjuvant chemotherapy, and because you have this void in the prospective evidence because of under-

accrual in clinical trials, my good friend Dr. Pal in City of Hope, and I think Kathy is here who is working with him is here in the audience, Dr. Agarwal and Dr. Choueiri wrote an editorial at *Journal of Clinical Oncology* underlining this challenge that we have no definitive level 1 evidence; however, if someone walks into our clinic and has no prior neoadjuvant chemotherapy and they are fit for cisplatin and they have pathologic T3 or T4 or node-positive disease, it is reasonable to offer them adjuvant chemotherapy. That's the take-home message. Either regimen, gemcitabine and cisplatin or dose-dense MVAC for four cycles for those with pathologic T3, T4, or node-positive disease who are fit for cisplatin and did not receive neoadjuvant chemotherapy. If they received neoadjuvant chemotherapy, there is no point, there is no high-level evidence of giving more in the future. So, it's either neoadjuvant or adjuvant, but I would not do both. So, it is only for those patients who did not get neoadjuvant chemotherapy.

Think about again the new data. Some patients cannot get cisplatin-based chemotherapy, either neoadjuvant or adjuvant, and of course we capture the momentum with immunotherapy, so what about adjuvant immunotherapy? We have three important clinical trials, one of them is here on that slide, it is led by Dr. Apollo in the NCI. It is evaluating the role of adjuvant checkpoint inhibitor, pembrolizumab and anti-PD1 in patients who had already cystectomy or nephroureterectomy for upper tract urothelial cancer. They got surgery and they have pathologic T3 or T4 disease, or if they already had neoadjuvant chemotherapy, which is allowed, they have pathologic T2 or higher stage and

then get randomized to either pembrolizumab or observation in the adjuvant setting, meaning, after surgery in the postoperative setting. The primary endpoint here is overall survival or disease-free survival, and the question is whether immunotherapy in the adjuvant setting makes a difference.

There is another trial with atezolizumab, versus observation, and there is also a third trial with nivolumab versus placebo. So, we have three trials with checkpoint inhibitors in the adjuvant setting and we have to wait and see how these patients do. The trial is open, and we actually see patients in the clinic in the AMBASSADOR trial. Hopefully in the next few years we will have data from those clinical studies.

In terms of the clinical pearls here, as we put together with Jeanette, cisplatin-based chemotherapy standard of care, again ideally neoadjuvant, if was not given neoadjuvantly, some patients might get adjuvantly. We talked about the criteria that can help us select patients for cisplatin. There is no high level of evidence in the neoadjuvant or adjuvant setting with carboplatin, so don’t use that. Go for a trial or bladder preservation or cystectomy. It is very important to have a multidisciplinary approach, and at the University of Washington we have actually a fantastic clinic. I am very excited about it. With a urologic oncologist, urologic surgeon, medical oncologist like myself, radiation oncologist, pathologist, radiologist, nurses, coordinators, in the same room, it's like a tumor board and we treat patients with localized muscle-invasive bladder cancer and try to make the best decision with the data we have. We do radiology review of the scan, pathology review, and come up with an individualized plan for a particular patient,

either through a clinical trial or a standard-of-care approach. It is very important to have a multispecialty approach in those patients. Jeanette mentions nephrostomy tubes are preferred over stents in patients who are starting their journey and they have urinary obstruction. Sometimes we will put in nephrostomy tubes creating clearance, kidney function improves, which can actually allow us to give cisplatin in some patients. We may do a 24-hour collection to have a more accurate estimation of creatinine clearance in borderline cases. And as I mentioned, there is promise in the future in ongoing clinical trials with immunotherapy, either alone or combination with chemotherapy in that particular setting.

Now, we are moving along to metastatic disease, and there is a lot of excitement with new data and new approvals recently by the FDA. I will let Jeanette start the metastatic urothelial cancer management journey.

MS. HAMMOND Just a small proportion of patients present in the metastatic setting with metastatic disease, but you have to remember that half of all patients relapse after cystectomy, depending on their initial stage. They can have distant metastasis or local regional recurrence, and if we think about our platinum-based chemotherapies, the median overall survival with those combination chemotherapies is 9 to 15 months. This goes over some of the data looking at gemcitabine and cisplatin and the classic MVAC, which is not something we are typically using now, but what you can see is that essentially, they are pretty equivalent. The progression-free survival is similar: 7.7 versus 8.3 months. The overall survival 14 to 15 months, and similar overall survival 5-year

rates 13% to 15%. We do see less grade 3/grade 4 adverse events with gemcitabine and cisplatin, particularly neutropenia less, and a lot less mucositis with that regimen rather than the dose-dense MVAC or regular MVAC. In our clinic, I think most patients tend to get gemcitabine and cisplatin, but it's really clinician choice depending on how fit the patients are. How we think they are going to be able to tolerate those medications. Now we have, also in the first line, for patients that are cisplatin ineligible, we have immune checkpoint inhibitors that are approved for this space, particularly atezolizumab and pembrolizumab. Both were approved in this space from two phase 2 studies. So, in the atezolizumab study, they looked at 119 patients, the patients received atezolizumab 1200 mg IV every 3 weeks. They saw response rates around 23%. That sort of sweet spot of ongoing responses is something that we are looking at, so 70% of responses were ongoing at the 17-month mark. Pembrolizumab also – another phase 2 study placed it in this front-line cisplatin-ineligible group of patients. So, it's given 200 mg every 3 weeks, 29% response rate and 82% of the responses were ongoing greater than or equal to 6 months. So that median overall survival had not been reached at that time. The rate of grade 3/grade 4 treatment-related adverse events was pretty similar.

I just want to give a little shout out to atezolizumab because this was FDA approved only in 2016, so when you think about that, we had cisplatin-based chemotherapy for a long time, and we sort of were waiting for these drugs to come along. That’s only 3 years ago, right? It was the first drug approved in the urothelial cancer space in over 3 decades. It is a PD-L1 inhibitor. It has approval

for first-line therapy in patients with locally advanced unresectable disease or metastatic disease who are cisplatin ineligible, and also salvage therapy in patients who have progressed post-platinum therapy.

In the salvage setting, or second-line setting, these are all of the immune checkpoint inhibitors that we have available to us. I am going to call out to pembrolizumab. It was both pembrolizumab and atezolizumab tested in a phase 3 randomized trial versus chemotherapy of choice. The data for the pembrolizumab actually showed a better overall survival rate compared to the chemotherapy, about 10 months compared to 7 months. It was significant enough that it has category 1 evidence in the salvage setting. Response rates were about 20% for that. Atezolizumab was also evaluated in a phase 3 clinical study. It showed pretty similar overall response rates and overall survival to the chemotherapy. It doesn't have that same level of evidence of use as pembrolizumab, but it did show there was some leaning towards less toxicity and longer duration of response. You will see that as all of these drugs are getting approved in the metastatic setting, then we start backfilling. Can we use them earlier on, as Dr. Grivas has showed in some of the earlier studies?

Thinking about toxicities from these drugs, we all know how these drugs work, right? We have taken the breaks off the immune system, and that may make it active against the cancer, but it also may make it active against our own cells. The types of immune-related adverse events we see are certainly dependent on the type of immune checkpoint inhibitor we use. This kind of shows – I'll just call out the pembrolizumab and the nivolumab. You can see that

pembrolizumab has higher rates of pneumonitis and hypothyroidism, some colitis as well, and so it sort of depends on which one, what the toxicity will be. A lot of them have fatigue or pruritis or rash as part of their toxicity profile. I tend to talk to patients about the more common toxicities and then let them know that these drugs could have rare side effects and how important it is for them to let us know if they have any new or concerning symptom that we can work it out together and figure out if it is one of these outlier immune-related adverse events.

How do we manage these types of toxicities? Steroids remains our standard option for grade 3 and grade 4 adverse events, but we have a lot of resources now. ESMO has a practice guideline, the Society for Immunotherapy of Cancer has toxicity management guidelines, and ASCO also has guidelines. One of the things that we do at our center is we have a tumor board about once a month where people can discuss cases and how patients were managed with all variety and manner of immune-related adverse events, and what is sort of nice, that has developed over time, is we have colleagues in nephrology and dermatology who have taken a special interest in helping the oncology team manage these toxicities for patients. I had a patient recently who had a really significant rash from his first dose of pembrolizumab. I hadn't quite seen a rash like that before. It was full chest and back. He had desquamation over his legs and his arms, and he has very limited treatment options. I thought I was going to have to give him systemic steroids, but I happened to have clinic in the same hallway and the same afternoon as our dermatology colleagues, so really it was great. They just hopped in and we decided that we could manage this patient

with steroid creams and a sauna suit. It all happened in a very collaborative, wonderful way, and the patient's actually responding. The hope is that we can treat it from the outside in, so we don't take away any advantage he might be getting from that drug. Whether we continue to treat him, we will decide in a couple of weeks, right?

DR. GRIVAS It is actually a great point that was just made by Jeanette, that we have this immunotherapy-related adverse event tumor board that we put together as a group at CCA and UW and the reason was to learn together. How to manage these patients with these terrible rashes or other side effects. We are able sometimes to get the patients through and we sometimes have to stop treatment and give steroids or other agents. Sometimes we are able to continue treatment, depending on the case. I think it is important to have a multidisciplinary approach and be able to utilize expertise, not only from oncology, but from other specialties, as it was mentioned, rheumatologists, cardiologists, pulmonologists, so on and so forth. It is very important to have this multispecialty approach.

Moving along here. We talked about immunotherapy data. We have five different checkpoint inhibitors approved for the management of metastatic urothelial cancer in the salvage setting after progression on platinum-based chemotherapy standard of care in the first line, but patients who are fit for cisplatin get cisplatin, but the question is, what else is happening in this first-line setting? We have four important randomized, phase 3, clinical trials that are actually, in my opinion, going to shape the future landscape of how we treat

those patients when they are diagnosed with metastatic disease. One of those trials was recently reported at ESMO just a few weeks ago. I will show you the data today. Fresh, hot off the press. The other three trials are the DANUBE trial, which as you see on that slide is comparing durvalumab, anti–PD-L1, to chemotherapy or the combination of durvalumab and tremelimumab. Tremelimumab is an anti-CTLA4 checkpoint inhibitor. Durvalumab is anti–PD-L1, so the question is here, if you combine anti–PD-L1 with anti-CTLA4, this combination of immunotherapy, can you beat chemotherapy? And we don't know yet; the trial is still ongoing. The trial has finished accrual but has not reported yet. CheckMate 901 is finishing accrual in the near future, is comparing the similar combination of anti-CTLA4 and anti-PD1, ipilimumab, nivolumab, and we have data from this combination in kidney cancer, melanoma, compared to chemotherapy, and now there is a second comparison within the same trial, which is gemcitabine and cisplatin plus nivolumab. This triplet combination compared to gemcitabine and cisplatin alone. It is very interesting to see whether the triplet chemoimmunotherapy versus chemotherapy alone may have a significant difference or not, and again this trial is very interesting. It still has not reported yet.

Moving along here, we have two other trials, KEYNOTE-361 and IMvigor130. Very similar design. These trials are checking chemotherapy compared to checkpoint inhibitors, either atezo or pembro, or the combination. Again, chemotherapy plus either pembo or atezo, similar to what I just told with nivolumab; the gem/cis/nivolumab versus gem/cis alone. Here, we have

opportunity with these four different clinical trials to see whether you have to use chemotherapy or immunotherapy, single agent or combination, or combination with chemotherapy immunotherapy in the first-line setting. We don't have the data from the three trials, but we have the data from the fourth trial I will show you in a second. About a year and a half ago, the FDA showed interim analysis of those two trials, the KEYNOTE-361 and the IMvigor130, and about that point they showed that if patients had tumors with low PD-L1 expression in the tumor tissue, measured by immunohistochemistry, those patients with low PD-L1 expression, they did worse on checkpoint inhibitor alone compared to chemotherapy-based therapy. At that point, the label of the approval changed and they said if you are in the first-line setting and you are not fit to get cisplatin, and you have a low PD-L1 expression, you probably have to get chemotherapy with carboplatin/gemcitabine, but not checkpoint inhibitor alone. That's interesting because the trials were ongoing. We haven't seen the data at that time. So, right now we are slowly going to see the data from those trials and understand better what is the outcome of those patients with low PD-L1 expression. Now the interesting question here is what happens if someone has high PD-L1 expression. Do you use chemotherapy or checkpoint inhibitors? We don't know yet, but I will show you some early data from the IMvigor130 trial.

This study was presented by Dr. Grande from Spain a few weeks ago in Barcelona at ESMO, and this, again, is the fourth trial I showed you in the previous two slides. This trial, again, I repeat, the design is chemotherapy plus atezolizumab or atezolizumab alone or chemotherapy plus placebo. Again, the

question is chemo alone, chemo plus atezolizumab or atezolizumab alone. The primary endpoint was progression-free survival and overall survival and what we call coprimary endpoint, meaning either/or has to be met for the trial to be called positive. So, if you meet progression-free survival benefit, it is a positive study. If you reach overall survival, it is a positive study. There was an interesting hierarchical design, the statistical design of this study, that outlined what was considered a positive trial. You see the factors on the left part of the slide, PD-L1 expression, prognostic markers like the visualized metastatic and performance status, considering the majority of risk factors, if you have visible disease, visible metastasis, liver metastasis, and you have a very poor performance status, you are destined to do worse, so you are going to balance these factors between the arms of the study. And of course, whether the patients got cisplatin or carboplatin was another factor.

These are the baseline characteristics in that study. As you see, you try to have a balance as I mentioned between performance status, pathology factors, PD-L1 expression, and these appeared to be relatively balanced between the three different arms. What is interesting to me is if you focus on this red box there, many patients who were deemed not fit enough for cisplatin, not eligible for cisplatin, ended up getting carboplatin, which is reasonable to make sense; however, about 55% of patients as you see here are eligible to get cisplatin. However, even patients who were fit for cisplatin, many of those ended up getting carboplatin. So, you see some overutilization of carboplatin in the community setting. Even the codex of the clinical trial, in the proportion of cisplatin-fit

patients, which is very interesting to me how sometimes the optimal treatment, which is cisplatin, is not being used if you go in the real-world setting. That is an interesting message. So, take-home point here: if someone can get cisplatin, that's our preferred drug, even in metastatic disease. And carboplatin is used only in cisplatin-not fit patients. Here you see the difference in some cisplatin-fit patients still got carboplatin.

This is the baseline characteristic context, and with that, what did the trial show? Well, if you compare arm A, which is chemotherapy plus atezolizumab compared to chemo plus placebo, you see statistically significant progression-free survival benefit favoring the combination chemoimmunotherapy compared to chemotherapy placebo. If you look at the median progression-free survival, it's about 2 months, so about a scan, so it was a scan time difference favoring the chemotherapy atezolizumab combination and this was statistically significant as you see, and this is the *p* value here with a hazard ratio of 0.82, which I would say is barely statistically significant. However, if you look at overall survival, this did not meet, as of now, the statistically significant level; however, there is a trend toward overall survival benefit with a combination of chemoimmunotherapy compared to chemotherapy alone. However, this is an interim analysis and because of the statistical design, this did not yet meet overall survival benefit. We have a situation where progression-free survival benefit was shown, but not overall survival as of yet. The question is whether this will change our practice. In my humble opinion, not yet. I think we have to wait to see what happens with overall survival and whether longer life is shown before we change our practice,

and with longer follow-up we will see what happens with those curves here, and whether we stay apart and whether this will translate or not to overall survival benefit. An important point to make here is about only 20% of patients, one out of five, who are given chemotherapy alone, were able to receive immunotherapy after progression. If you think about that, in the United States, most patients if they don't get immunotherapy first line, they get the second line, so 20% is a low number. The question here is, if you get immunotherapy as second line, this could potentially washout any overall survival benefit. I think this 20% is something to keep in mind. It is a low number of patients who go to immunotherapy second line and could potentially help the combination of chemo showing benefit. We will see what happens with longer follow-up. But definitely very impressive data, no doubt. I would say one of the most important trials. Congratulations for the investigators, but in my humble opinion we have to wait a little bit more to see what happens with the practice changing or not. If this is met, I think this will be practice changing in the future.

If you look at atezolizumab alone compared to the chemotherapy alone arm, to me that's very interesting. Look at this data here. If you look at that, those curves, initially in the first about 10 months or so, the chemotherapy is doing better, right? Which is a significant difference. There was a time when the FDA and EMA saw the preliminary data and they said if you have low PD-L1 you have to get chemotherapy, but now with longer follow-up, you see the curves cross over, right? So, with longer follow-up atezolizumab seems to be doing, if anything, slightly better, or at least not worse. Statistically speaking, not worse

with chemotherapy. As you see the hazard ratio here is 1. You may look at the curves and say, can I get by without chemo? Can I just use atezo alone in this setting? This is a hard question because the study was not powered to show noninferiority of atezolizumab versus chemo, but the question will be whether this data will be provoking enough to pose the question to the FDA whether atezolizumab can be approved. I think we are not there yet. As I mentioned, statistical design of the study plays a role and it was not designed to show noninferiority, but definitely to me is very provoking that you can potentially have comparable outcomes with immunotherapy alone with this trial of atezolizumab compared to chemo alone. We will see what happens. This study has not changed practice yet as I mentioned. This is the breakdown. Look at this PD-L1 low, this difference over here, this gap is when the FDA and EMA said if you have low PD-L1, don't get atezolizumab or pembrolizumab, because at this time point, look at the difference. But now with longer follow-up, the curves cross over, so the question in my mind will be, what will happen when the data matures down the road, will this label change stay or be removed, right? Again, we don't have the answer yet. The question here is, do you use chemotherapy because initially people do better, or you can use checkpoint inhibitors. The answer is not available as of today, we will have to wait for the data to mature, but the take-home point is as of today, if you have low PD-L1 expression, and you are not fit for cisplatin, the FDA and EMA mandates to make sure you get chemotherapy and not checkpoint inhibitor alone for the moment.

If you are not fit enough for any chemo, for even carboplatin, because you are too frail, too sick, and you don't feel comfortable giving your patient even carboplatin, in the US it is fine to give atezolizumab or pembrolizumab in this setting regardless of PD-L1 expression. Pretty much, the FDA said, if you're not fit for any chemo, we will give you an option regardless of what your PD-L1 is. Let's keep that in mind. In Europe, you still have to test for PD-L1 even in those settings.

If you are PD-L1 high, this subset of patients, again atezo alone versus chemo, you see that atezo alone seems to be doing better in this situation compared to chemo; however, this is not significant yet, so we have to wait with longer follow-up to see if in this population of patients atezo alone beats chemotherapy. We are not there yet, but we will have to see what the trial shows in the near future. So, stay tuned about those results with longer follow-up.

Response rate – to me that was interesting. Chemo/atezo combination, chemo alone, very comparable response rates. The addition of atezolizumab did not significantly improve response rates, and that to me was an interesting observation, and atezolizumab alone, this 23%, is exactly what Jeanette showed you before in the phase 2 trial. Atezo alone shows response in about a quarter of patients without the side effects of chemo, but if you add atezo to chemo, the response rate is comparable to chemo alone.

This is the summary of side effects, and as you can see, if you look at the table carefully, there seems to be adequate tolerability. Patients did okay with a combination of chemotherapy and atezolizumab. The side effects are of course

something to keep in mind, and we discussed about immunotherapy adverse events a few minutes ago. So, keep in mind for those, as well as chemotherapy toxicity, but at least based on this data, the combination appeared to be feasible and the toxicity appeared to be manageable overall.

Now, you may argue there is a plethora of other clinical trials looking at additional combinations of checkpoint inhibitor with other mechanisms of action. In this particular example, we have a clinical trial combining atezolizumab with a vaccine called CV301. It is a vaccine against CEA and MUC-1, which are proteins expressed in urothelial cancer cells. The question here is, can you utilize non-chemotherapy combinations in order to improve upon checkpoint inhibitors alone. Atezolizumab is approved, as I mentioned, in the first line and the salvage setting, but the question is, can you improve up the response rates, can you improve upon progression-free survival or overall survival if you combine the checkpoint inhibitors with other factions in this particular trial of vaccines and energize stimulate the immune system? This trial is still ongoing. We have two cohorts in the first and second line, and we combine the vaccine with atezolizumab to see whether we can improve upon the response rates compared with a historical response rate with atezolizumab alone.

Similarly, we have data that suggests, in a very preliminary fashion, that if you use cytokines, we might potentially improve the outcomes of patients getting checkpoint inhibitors. In this particular trial, led by Dr. Yu, who is also at the Seattle Cancer Care Alliance, is comparing atezolizumab plus interleukin-7, compared to atezolizumab alone in a randomized phase 2 design to ask the

same question: Can the addition of a new mechanism of action, in that case not a vaccine, but a cytokine, IL-7, can improve outcomes or not compared to atezolizumab alone? This trial is ongoing. We have it open and we are accruing patients actively. We see some patients in our clinic. Again, stay tuned for those trials.

There is a lot of data about salvage chemotherapy in urothelial cancer. As you see, plenty of trials have done a lot of work; however, they are also very modest with salvage chemotherapy. In the United States, if someone has progression to prior therapies and we don't have other good options or clinical trials which are preferred, we tend to use either docetaxel once every 3 weeks or sometimes weekly paclitaxel, but as you see, overall, the data with salvage chemotherapy, non-platinum chemotherapy, I would say the data is very modest. We have to improve upon this data with new treatments. I will give it back to Jeanette to talk about the very exciting part of developments in urothelial cancer. The first ever targeted therapy that is now FDA approved for patients with urothelial cancer who have particular mutations or fusions.

MS. HAMMOND Erdafitinib is a new drug that has been approved in urothelial cancer. Urothelial cancer is a very mutation-rich cancer and erdafitinib targets the FGF receptor, or mutations in that receptor, whether they be fusions or activating mutations, so it's a tyrosine kinase inhibitor that was recently approved for urothelial cancer that shows this type of mutation. The overall response rates are around 40% and it's an oral drug. You typically start off at 8 mg daily. It can escalate depending on tolerance. It received accelerated

approval. It was approved in April of this year. There are some interesting different types of toxicities from this, primarily you can get elevated phosphate levels, so patients are put on a low phosphate diet and sometimes require phosphate binders. The other interesting toxicity is there is some ocular toxicity with this drug, so keratitis, dry eyes, field deficits, field cuts. These patients are typically seen by ophthalmology at least once a month for the first four months while they are on the drug, and then various electrolyte abnormalities that need to be monitored pretty closely. The most common reason for patients to come off study was because of ocular toxicity. It's also being looked at in a phase 3 clinical trial where they are comparing erdafitinib to your chemotherapy of choice.

DR. GRIVAS Erdafitinib is the first target therapy approved in advanced urothelial cancer, so I think it is very exciting to have after so many trials that did not meet the primary endpoints, now we can test for a target receptor 2 or 3, activating mutations or fusions, and I would like to make the point there is a comparing diagnostic you can use called QIAGEN RT-PCR test or, in our practice, we see patients coming through already with genomic sequencing being done, so I think it is a very important point to test our patients with metastatic urothelial carcinoma early on to see if they have a mutation or a fusion for this drug or for other clinical trials. Because other clinical trials might require some other alteration. I think it is important, the take-home message is, genomic sequencing in tumor tissue for sure, and sometimes in the blood, I think, can be very important, and my practice has been to test those patients at the time they have urothelial cancer. There is about 10- to 14-day turnaround time when you

send the test out, so I think it is important to have the test ready if someone is getting platinum-based chemotherapy and has progression, to have it ready and not scramble around at the last minute to get the test done. Think about genomic sequencing, not only for this drug, but overall for the management of those patients.

This is a slide I made for ASCO last year just to illustrate the wave of new emerging agents being tested in clinical trials. We talked about FGFR checkpoint inhibitors already and there are many others. Erdafitinib is approved, but we have others in multiple clinical trials. In your site, you may have other trials, so keep that in mind. Here family inhibitors, PARP inhibitors, antiangiogenesis inhibitors are being tested in clinical trials. I talked about cytokines, we talked about vaccines, I talked of distal therapy, and we are going to show you some data with antibody-drug conjugates, which I think are coming as a next wave of agents that might be approved in the near future of urothelial cancer, so a lot of activity, a lot of enthusiasm, with multiple different mechanism of actions. Of course, the take-home point here is when it targets and biomarkers but have clinical utility and that's where we suffer. We don't have good biomarkers with clinical utility in urothelial cancer. This comes through clinical trials, but definitely it is very important to do this tumor genomic sequencing for those patients, get the report back, and see carefully if there is any particular mutation or fusion or amplification that may be relevant for clinical trials, or as I mentioned, for erdafitinib.

This is an algorithm I put together for ASCO a few months ago. How we treated urothelial cancer in the clinic. We can discuss about that in the Q and A session, but if someone is fit for cisplatin, I would argue cisplatin-based chemotherapy as standard of care. This has not changed after the IMvigor130 as of today, but we will see whether with longer follow-up it will change. If a patient cannot get cisplatin, we can use carboplatin/gemcitabine combination, or if they have PD-L1 high or are not fit for carboplatin, we can use pembrolizumab or atezolizumab. In the platinum-refractory setting, the question remains, do you use erdafitinib if they have the mutation or fusion, or do you use pembrolizumab or any of the other checkpoint inhibitors? I think there is a phase 3 trial Jeanette mentioned to you comparing pembrolizumab with erdafitinib, so we will have the answer in the near future and the patients will have progression already to all those agents, either docetaxel in the US or vinflunine, which is approved in Europe, can be an option. But I think the right answer is clinical trials. That is the take-home message. That is what we try to do every day: put patients in clinical trials so we can increase the number of options we have for our patients. Jeanette will talk to you about one of the two antibody-drug conjugates, enfortumab vedotin, and then I will take over for the closing.

MS. HAMMOND This drug represents a new mechanism for us to exploit for drugs for urothelial cancer. It's an antibody-drug conjugate that targets Nectin-4 on urothelial cancer cells. It's linked to a drug that is a microtubule disruptor. It gets taken into the cells, disrupts the cell cycle, and prevents the cell from processing through and growing. The cohort 1 data is really what we are

going to be looking at. It's previously treated locally advanced or metastatic urothelial carcinoma. Cohort 1 patients were previously treated with PD-L1 inhibitors and platinum-based therapy. The enfortumab vedotin is given as an IV infusion on days 1, 8, and 15 of every 28-day cycle, so primary endpoints were overall response rates. The data was promising. The overall response rate was 44%, and they saw good responses in patients who didn't respond to checkpoint inhibitors and also patients who had liver-predominant disease, which traditionally is a little bit harder to treat. The most common adverse events were fatigue, alopecia, but there were a few that I want to point out that have some significance. Peripheral neuropathy: 50% of patients had peripheral neuropathy on this drug. Now remember, they also had prior platinum therapy too, so this is a group of patients we want to protect their quality of life and their ability to do the things they want to do. That is significant. There was a lower fraction. Only 3% had greater than grade 3 toxicity; 48% of patients developed a rash. Most of them resolved or improved at their last follow-up. Then, hyperglycemia was also seen, 11% any grade and 6% grade 3 or greater.

This was presented at ESMO. It is a new study looking at enfortumab in combination with pembrolizumab in these patients that are locally advanced or metastatic starting with a dose-escalation phase where it could be in either the first- or second-line setting, and then dose expansion, where it was just in the newly diagnosed setting. I will just quickly go through this. It's a small study, right? It's only 45 patients, but if you look at these response rates, we get excited about it anyway. It's a 71% response rate. If you look at the proportion of patients

who also had stable disease, you are getting about a 93% clinical benefit. So, granted, really small study, but exciting to think about that combination.

The toxicities were what you would expect from each individual drug. There wasn't a synergistic or increased toxicity. It's what you would expect from each one. They are also looking at a phase 3 study with enfortumab. Again, comparing it to chemotherapy. Then we have another antibody-drug conjugate that is being studied and Petros will talk to you more about that.

DR. GRIVAS There are many antibody-drug conjugates and the concept here is you have an antibody that can bind to a target, linked to a toxin, a payload, that can be delivered in the cancer cell in a selective way. It is like a smart missile kind of thing that would target your chemotherapy, not in the whole body, but specifically in the cancer cells.

The first antibody-drug conjugate is enfortumab vedotin that Jeanette mentioned to you. The other one is substitution of sacituzumab govitecan. This antibody-drug conjugate has a different target. Instead of Nectin-4, the target for sacituzumab govitecan is Trop-2. Trop-2 is expression of the brain cancer cells. This antibody-drug conjugate has the Trop-2 antibody linked to metabolite of irinotecan, called SN-38. You have an irinotecan metabolite as a chemotherapy payload, you have the link here, and then you have the antibody against Trop-2. This drug looks very promising. The data looks very promising for this antibody-drug conjugate. As you see, I already explained to you the structure of the molecule SN-38 as the metabolite of irinotecan, and the data looks very promising. The phase 1 study showed about a 34% response rate in patients

with multiple prior treatments, which I think is very promising. This prompted phase 2 study that was presented at ESMO just a couple of weeks ago by Dr. Tagawa who is in New York, and this phase 2 study examined the same drug in patients with prior treatment with chemotherapy and checkpoint inhibitor. As you see in the cohort 1, we have 100 patients who have finished treatment with accrual, and the first 35 patients were analyzed for the presentation that was given at ESMO, and this is the breakdown of patients. As you see, about a quarter of those had liver metastasis, and as you see, there was a range of prior therapies, between two, three, four, five, or six prior lines of therapy. That's impressive to begin with because as we see in the clinic with Jeanette, patients who have one or two prior therapies are usually not able to get more treatment, so to be able to give multiple prior therapies for advanced urothelial cancer by itself, is telling us how we are moving forward in this disease. The point here is heavily pretreated patients are getting this regimen. As you see, the toxicity profile is something to keep in mind. You can see neutropenia. A few patients with febrile neutropenia, most of them is asymptomatic neutropenia. Nausea and diarrhea can be an issue. Think about irinotecan and how it can cause diarrhea and neutropenia itself; however, it seems to be much easier than classical chemotherapy. Fatigue can be an issue, skin rash in a few patients, alopecia, low appetite, so keep in mind that toxicity can happen, but overall appears to be manageable in most of our patients with growth factor or dose reduction. Very impressive in my opinion, about 30% overall response rate as you see here. This is again only in 35 patients, so we need longer follow-up for the entire cohort, but

it's very promising to see patients with liver metastasis if they have responses. Liver metastases are hard to achieve responses at, and both enfortumab vedotin and this antibody-drug conjugate have shown some benefit in those patients. Again, these are promising factors, promising agents, coming down the pike. Are not ready for prime time, but I think enfortumab vedotin is very close to being approved by the FDA based on the phase 2 data and sacituzumab govitecan potentially in the future. This is the swimmers plot that you saw that if you have response, you might potentially maintain that response for a while, and then medium duration of response was about 7 months or so in the study. So, three-fourths of patients had reduction in the tumor side of the lesions. Again, very promising with this antibody-drug conjugate. I think if you put the whole thing together, platinum-based chemotherapy as I mentioned is the standard of care. I mentioned there are five checkpoint inhibitors, pembrolizumab, atezolizumab, nivolumab, durvalumab, avelumab, five agents in the platinum refractory setting that have been approved. There are many clinical trials trying to utilize these checkpoint inhibitors. There is another trial combining nivolumab, this anti-PD1 agent with one of the other antibody-drug conjugates against *HER2*. Interesting concept of combining an anti-HER2 antibody-drug conjugate with nivolumab. an anti-PD1 agent, which is approved as I mentioned. Whether these combinations will move the needle forward remains to be seen. Of course, clinical vigilance and education are very important for us, the nursing team, the patients. We talked about erdafitinib and the antibody-drug conjugates, and I think it is important to always keep in mind we are a team and we have to utilize the

expertise of each other. Blood clots and thrombosis is a very common problem in patients with advanced urothelial cancer and other malignancies. We have many patients we treat with Jeanette in the clinic and they have blood clots always and constipation, to walk around ambulate always to avoid blood clots as much as we can. But if we do have blood clots, we frequently discuss about use of enoxaparin or other oral anticoagulants, and I think it is important to keep in mind to balance the risks of bleeding and clotting in those patients and discuss with the experts if need be to select the proper anticoagulant in particular patients. Usually we use enoxaparin in patients with active cancer, but now we have emerging data in the future with oral anticoagulants.

I think we have a lot of excitement in this disease and all of us are looking forward to the results of the studies that I showed you, and I will go through the next few slides very quickly just to pass the message that we have a lot of biology being understood right now in urothelial cancer. Through the understanding of biology, we identify more targets. We talked about FGF receptor, but there are many other targets we can identify and utilize in clinical trials. I think that is an important point. Biology and lab work are actually enabling us to use and design more clinical trials in the clinic. We have many alterations in DNA repair genes in urothelial cancer. *BRCA1/BRCA2* is not only present breast and ovarian cancer. We have prostate cancer and even urothelial cancer that may have mutations. This can be somatic, only the tumor, or it can be germline in the hereditary fashion and that can have implications, not only for the patient's treatment, but in the broader family. So, think about germline mutations and

somatic mutations in urothelial cancers. Some of those mutations in DNA repair genes may have a negative prognostic role. *ATM* mutations appear to have a negative prognostic role, and these patients usually don't do that well. We are trying to find out what is the mechanism, why these mutations are driving a negative outcome in these patients. This is what we try to do in the laboratory. Going back to germline mutations, as I mentioned, we frequently forget in the clinic to ask about family history. It's one of my pet peeves. I always take a very detailed family history. I talk with the fellows to make sure we don't forget that because you may have germline mutations, even in urothelial cancer. They are not common but can happen, and I think it is important to think about Lynch syndrome, especially with upper tract urothelial cancer. You can pick up those patients, especially if they have family history. The question is how often do we need to send this patient for germline testing? I think it depends on the age at diagnosis, the family history, and what other cancers the patient may have.

This is just incidents of germline mutations in different studies can be very high, so keep that in mind as I mentioned and think about sending these patients for genetic counseling. I would say in the upper tract disease, most of the patients are being referred for genetic counseling. With bladder cancer again, think about age, younger age of diagnosis, or relevant family history or personal history of cancer. Maybe a younger patient without history of smoking, why did they get bladder cancer. Think about genetic testing in that context. Now we are actually hiring more genetic counselors to have more capacity and the

implications are for the patient, but also in the broader family, close and distant family, there is some germline mutations.

To conclude, we have clinical trials as our favorite two words. If you can take two words out of this talk, it is clinical trials. FDA approval, we talked about the different checkpoint inhibitors, we talked about erdafitinib and other FGFR checkpoint inhibitors being tested in clinical trials and very promising agents. Antibody-drug conjugates are very promising, we talked about two of them. I think in the future with combination clinical trials and sequential trials, we are going to find out the best sequencing of the treatment in patients who have advanced urothelial cancer, and whether we should or not combine chemotherapy with immunotherapy. Should we combine them or do one after the other? The answer will come with the trials that I showed you. Of course, we need to do a better job aligning our biomarkers and clinical trials. When we have a clinical trial at City of Hope and here, try to align our other centers of course in the country, there are many of them around the country, can we align biomarkers and try to measure the same thing to have a validation and use biomarkers to select patients in the future.?

I would like to thank you so much, on behalf of Jeanette and myself for coming here today and staying with us till the end We left limited time for questions and answers, but feel free to ask questions. We are going to stay around here if you want also, if people want.

QUESTIONER: (indecipherable)

DR. GRIVAS The question is whether the atezolizumab plus CV301, this trial I showed you, has interim analysis. The answer is not yet. But this study had two arms, the first line and second line, two cohorts. Both cohorts are now on hold because we finished accruing the first stage, and we have to meet a certain number of responses to move on to the second stage. So, for now we are in this pause. We have finished the stage 1 accrual for both cohorts. We have to wait to see whether we will move forward or not.

QUESTIONER: You mentioned in the chemoradiation to try to give the cisplatin on Mondays. Is this for efficacy or so you can monitor?

MS. HAMMOND: It is both actually. You want to get the best synergy with the chemo and the radiation, so if you get it up front earlier in the week and then you can monitor them, particularly their counts throughout the week. We sometimes have patients who have issues with myelosuppression and it's nice to sort of be able to check in with them later in the week too so that they are not hitting issues over the weekend. I am curious what your practice is?

QUESTIONER: Some of the doctors think this matters, and some of the doctors say it doesn't matter. For years I was taught it did matter, but I have some doctors who think it does and some who think it doesn't.

MS. HAMMOND: We typically – Monday or Tuesday is usually how we do it.

DR. GRIVAS I agree with Jeanette. I think it is ideal Monday or Tuesday and we try to, in addition to what Jeanette said, is also we try to have the maximum overlap between cisplatin and radiation for efficacy. Now, there are

practical issues. Sometimes you may not have a slot in the infusion clinic, but it's ideal if possible, but pragmatic scenarios may not be ideal sometimes.

QUESTIONER: Doctor, could you define that low PD-L1.

DR. GRIVAS Great question. So, the question is how do we define PD-L1 expression? That is a complicated answer because we have many different assays. I showed you five approved checkpoint inhibitors and each one of them has a different companion assay to go with it. Nivolumab has one, avelumab has another, durvalumab has a different, atezolizumab, pembrolizumab, so the short answer is if you are using the first-line setting, we have two agents approved, cisplatin-unfit patients, pembro and atezo. Pembro is using this assay called 22C3 Dako Agilent assay. It is commercially available, and they used a composite score called CPS and it has to be 10 or more by CPS, 10 or more to be allowing to use pembrolizumab in this first-line setting. If you use atezolizumab, the assay is VENTANA SP142, and in that assay they need 5% or more of tumor-infiltrating cells, inflammatory cells, to express PD-L1, so it is very dependent on the assay. VENTANA SP142 5% or more infiltrating cells, 22C3 Dako assay is actually the measured tumor cells and infiltrating cells together, and has to be a CPS 10 or more for the pembrolizumab assay. It is important not to mix and match the assays. It has to be the right assay for the right drug. It is very confusing.

QUESTIONER: When you see a high expression of PD-L1, what number are you thinking of? Greater than what? When you talk about high expression of PD-L1, I mean obviously 100%. What is high?

DR. GRIVAS I think this is a great question. How do you define high for the purpose of the slides and what I told you? It is exactly the same cut off. I would call it positive, so 5% or more infiltrating cells on the VENTANA SP142 is high and the CPS 10 or more is high. So, it's kind of high and low. It's kind of dichotomous definition. You may argue, if it is within the high subset, how high it is, we don't have clear data with correlation with response. I think we have time for a few more questions. We are good? We can hang out here to answer questions if you want. Thanks again for having us, and again, the take-home point is (indecipherable due to loud noise) we are a team here. Thanks again for having us.

[END]