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Optimizing the Use of Immunotherapy in the First-Line Maintenance Setting for Metastatic Urothelial Carcinoma

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Optimizing the Use of Immunotherapy in the First-Line Maintenance Setting for Metastatic Urothelial Carcinoma” is provided by AGILE.

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[Chapter 1]

Dr. Powles:
Survival for metastatic urothelial cancer has increased with the approval of immune therapy, antibody-drug conjugates, and targeted agents. In the maintenance setting, avelumab has become the global standard of care. Do you know how to evaluate and effectively implement immune therapy in the maintenance setting in your practice?

This is CME on ReachMD. And I'm Professor Tom Powles. I'm here today with my great friend Petros Grivas. Petros, would you like to introduce yourself?

Dr. Grivas:
Hello, Tom, great to be with you and discuss this very important data, always a great pleasure to discuss together. Thank you.

Dr. Powles:
Let's get started. And to set the stage on this chapterized course, there's going to be various chapters in this course, I'm going to start by discussing data on the use of immune therapy in first-line maintenance and metastatic urothelial cancer and the management of adverse events, which I’m going to ask Petros about.

To summarize the trial, the JAVELIN 100 trial is a randomized phase 3 study. It includes patients with advanced urothelial cancer. They've completed 4 to 6 cycles of chemotherapy, they've not had progression of disease in their cancer during that period of time on CT imaging, and they're starting maintenance avelumab, 2 weekly, or best supportive care until progression of disease. Overall survival is the primary endpoint of the trial. There were other endpoints, such as progression-free survival [PFS] and outcomes in PD-L1-positive patients. The initial results of the trial and the updated results of the trial have been consistent with one another. They've shown a 25% reduction in the risk of death. They've also shown a significant progression-free survival advantage. And indeed, this advantage has been irrespective of the type of chemotherapy, GemCis [gemcitabine cisplatin] or GemCarbo [gemcitabine, carboplatin]; the sites of disease, visceral metastasis, nodal metastasis; the PD-L1 biomarker; the number of cycles of chemotherapy. These have all shown benefit in the avelumab arm. I think it's fair to say the reason why this is the case is because we showed that giving second-line immune therapy such as pembrolizumab, many patients never got there. And in the frontline setting, immune therapy wasn't as good as chemotherapy at getting initial control. And indeed, the combination of chemotherapy and immune therapy were antagonistic together. And so therefore, giving maintenance avelumab, sequencing immune therapy directly after chemotherapy gets control of disease and maintains that control, which is important.

Within the trial, we showed 1 or 2 important other issues. We showed the vast majority of patients who progress, particularly on the best supportive care arm, got immune therapy as the next therapy. Indeed, over 70% of patients who progressed, got subsequent therapy. And we also showed the drug was broadly safe with only 10% of patients discontinuing therapy or requiring steroids.

Petros, do you want to talk a little bit about some of the long-term safety data, what you've shown? And then what I might do is talk about quality of life and TWiST analysis.

Dr. Grivas:
Thank you, Tom. What a great summary. And I think that the data about toxicity are relevant to our patients. Overall, I would say as a general statement, the data with avelumab as switch maintenance immunotherapy in patients with disease control on chemotherapy is in line with the data we see with checkpoint inhibitors as single agents in advanced solid tumors. But we do not see any major safety signals or concerns. Overall, if I give a snapshot, if we look at from the beginning of the trial, the a proportion of patients with any grade treatment-related adverse event that happened during the trial with avelumab was about three-quarters of the patients. But if we focus specifically on grade 3 or higher treatment-related adverse events, only about 20% of patients, 1 out of 5, had a grade 3 or higher treatment-related adverse event.

Now if we look at serious treatment-related adverse events with avelumab, at any point of time, it's about 10%. So 1 out of 10 patients. And if we focus our attention to the treatment-related adverse events leading to discontinuation of treatment, it's about 11%. So again, about 1 out of 9 patients.

So overall, the treatment was well tolerated. It's much easier compared to the conventional cytotoxic chemotherapy. And I think overall, if we look at the long-term safety follow-up, so the onset of immune-related adverse events that may happen after a year of treatment, we see that over time, it's become less frequent, less common to have a treatment-related adverse event. The patients who had already at least 1 year of treatment and continued, only about half of them, 50%, had a treatment-related adverse event of any grade, and only about 12% had a treatment-related adverse event grade 3 or higher that started after a year of treatment. So I think it's important to keep an eye on those patients over time. And of course, keep an eye for immune-related adverse events; it can happen anytime. But the chance of that is becoming less over time. And, again, no new safety concerns.

I want to hear, you know, your thoughts about the Q-TWiST analysis we presented at ASCO [American Society of Clinical Oncology] meeting. But I want to briefly mention that our work that was published in *European Urology*, and we looked at the quality of life and patient-reported outcomes. And we showed that the overall survival and PFS benefit with avelumab maintenance was apparent, but there was no significant detriment to the quality of life of those patients. And this is important because patient-reported outcomes matter. And I think, Tom, you saw some very important relevant data from the Q-TWiST analysis at ASCO a few weeks ago.

Dr. Powles:
Q-TWiST is a different way of looking at adverse events. And it looks at the impact of adverse events over time. Essentially, we feel that patients who are progression free who are not experiencing grade 3 or grade 4 adverse events of any description, have the maximum quality of life. And indeed, when you delay progression-free survival, sadly, drugs with side effects will eat into that progression-free survival time. And the way they'll do that is because patients will be living with more toxicity. And therefore, TWiST analysis calculates that key curve where patients are not progressing, but at the same time don't have grade 3 or 4 adverse events. And essentially, it generates an area under the curve. And what we can see with this TWiST analysis is we can see for avelumab that is much longer than with best supportive care because the drug is relatively well tolerated. And so the time with toxicity is only a small amount larger. But also because the progression-free survival is 50% longer, that offsets that increased time with toxicity.

Q-TWiST, the Q on the front estimates the quality of that time. And that can go from 0 to 1; 0, where the toxicity has no effect, and 1, where it has a maximum effect and totally takes away any quality of life. And you can see this Q-TWiST analysis, depending on which model you put in place, reinforces that fact that we can see improved TWiST/Q-TWiST analysis longer progression-free, adverse event-free quality time with avelumab versus best supported care.

Petros, what can you tell us about the clinical guidelines and regulatory approval for immunotherapy in first-line maintenance metastatic disease, as well as the management of adverse events? Perhaps you could start with some of the guidelines, NCCN [National Comprehensive Cancer Network] and ESMO [European Society for Medical Oncology] guidelines.

Dr. Grivas:
Thank you, Tom. I think, you know, it's so difficult to change the paradigm in management of this disease. And, you know, both you and me have been involved in multiple trials over the years, trying to move the needle forward. And I think we're all very excited to see that we can now generate level 1 evidence that translates to clinical practice change and, of course, reform of the guidelines, NCCN, ESMO, and others.

So after your great presentation at ASCO 2020 and the subsequent *New England Journal of Medicine* paper that came afterwards, we see that, you know, this practice has changed globally. On June 30 of 2020, the FDA decided to give regular approval to avelumab as maintenance therapy for patients who have either response or stable disease to induction platinum-based chemotherapy based on the level 1 evidence that was generated on the JAVELIN Bladder 100 trial. And subsequently, other regulatory authorities did the same thing. The European Medicines Agency, EMA in Europe, and of course in other countries have approved avelumab for the same indication as maintenance therapy for patients with no progression of platinum-based chemotherapy in the frontline setting of advanced urothelial cancer. And we see that now across the board with broad utilization of avelumab maintenance in different countries.

I think the important point is that it's hard to generate level 1 evidence, and I think a phase 3 trial with a clear overall survival and PFS signal, I think, justifies this change in the guidelines. And we see uniformity, I would argue, across different guidelines, NCCN, ESMO, and others.

The other point that you raised is about management of adverse events. Again, we're always trying to maximize that. And in different cancer centers, we may have different multidisciplinary teams looking at the management of immune-related adverse events. As we discussed before, avelumab overall seems to be well tolerated in the vast majority of patients with no significant new safety signals. However, I think all of us should be on the lookout, right, for treatment-related adverse events. We have multidisciplinary approach, we have a team here at our institution looking at, for example, immune-related adverse events, we have a tumor board, we have a Listserv, and we try to involve other disciplines that may be relevant. For example, if a patient develops colitis, to develop, of course, a relationship with gastroenterology to optimize the management of this patient in a timely manner.

The other point I would say is that, you know, the multidisciplinary approach can, you know, definitely lead to early, optimal management of those patients. The other thing that happens is the infusion reactions. So there has been a discussion about that. If we look at the overall incidence from the beginning of the study, about 20% of patients or so, about 1 out of 5, had any-grade infusion reaction. Usually this is mild, and is grade 1, grade 2 and usually mannered with antihistamines and acetaminophen. And I would say only about 3% of patients who have been treated for at least a year developing a new-onset infusion reaction. So something to keep in mind. Be alerted to it, but it's usually, you know, mild and easily manageable.

And as I mentioned before, obviously optimal education of patients and the providers through a multidisciplinary approach can help. And of course, always I tell patients to not underreport, right, just to make sure they tell us if any changes happen in their treatment course.

Dr. Powles:
Petros, what's happened to the frontline approval of atezolizumab and pembrolizumab? Because there have been various changes by the FDA.

Dr. Grivas:
Great question, Tom. So back in 2017, when we were still in the early days of immune checkpoint inhibition development in advanced urothelial cancer, initially, we show an approval by the FDA in the frontline setting in chemotherapy-naïve patients for cisplatin-ineligible, cisplatin unfit patients in the frontline setting. Basically accelerated approval that came because of some promising response rate between 20% to 29% and durable responses and a favorable toxicity profile with checkpoint inhibition based on phase 2 non-randomized trials. For example, the IMvigor210 in Cohort 1 in the first-line setting and the KEYNOTE-052 with atezo and pembro, respectively. The FDA has said accelerated approval is given but we need to see the phase 3 randomized clinical trial data. And that subsequently came after. But during the phase 3 trials, the FDA has changed the indication of the accelerated approval in the label and restricted that in cisplatin-ineligible patients, not all comers, but specifically for PD-L1 high expression. And then or subsequently over time, we saw the results on those phase 3 trials. And you alluded to it. Those phase 3 trials, like IMvigor130, KEYNOTE-361, showed that checkpoint inhibition by itself is not superior to chemotherapy and actually in the beginning, in the first few months, you may lose more patients with immunotherapy.

So I think in patients who can tolerate chemotherapy, cisplatin ideal or carboplatin at least, with those patients start with platinum-based chemotherapy and then maintenance avelumab for those with no progression. But we actually, based on those data in the United States, atezolizumab was withdrawn and has no indication currently in advanced urothelial cancer, but also had to do with a phase 3 trial in platinum-refractory disease, IMvigor211, that did not show the survival benefit atezo versus chemotherapy, so atezo was completely withdrawn. And pembrolizumab in the frontline setting, the indication is only for platinum-ineligible patients, meaning patients who cannot tolerate cisplatin and carboplatin. So about 10% of patients in my practice cannot get any platinum. And this is for pembro first line. But in platinum-refractory disease, pembrolizumab maintains its level 1 evidence for platinum-refractory disease for patients who have progressed on platinum based on the KEYNOTE-045 trial that showed overall survival benefit of pembro versus taxane or vinflunine, but this is platinum refractory.

So a lot of evolution over time. And just so as, you know, sometimes with phase 3 trials, randomized trials, we may get more clarity in

the randomized setting and context.

Dr. Powles:
So Petros, in summary, what we have is we have a standard of care which is now established from a global perspective, which is maintenance avelumab. This is sequenced directly after 4 to 6 cycles of chemotherapy for those patients whose cancer is not progressing. It's associated with a survival advantage. Updated data on quality of life and TWiST and long-term toxicity suggest that it's a well-tolerated regime, it's working across broad subgroups of patients. Other approaches, as it currently stands, haven't superseded that. We're looking forward to data with antibody-drug conjugates and other combinations in the future. But as it currently stands, we have what we think is a relatively well-tolerated and efficacious regime for our patients.

In Chapter 2, we'll be discussing improving the applications and accelerating the adoption of immunotherapy first-line maintenance setting for metastatic urothelial cancer. So stay tuned.

[Chapter 2]

Dr. Powles:
For those just tuning in, you're listening to CME on ReachMD. I'm Professor Tom Powles, and I'm here today with my great friend Petros Grivas. We're discussing the first-line maintenance setting for metastatic urothelial cancer.

Welcome back. We were just talking about improving awareness of immune therapy in first-line maintenance avelumab in metastatic urothelial cancer. We're now turning to accelerating the adoption of immunotherapy in this setting. Petros, how do we apply the current data to the first-line maintenance setting?

Dr. Grivas:
Tom, I think you're absolutely right, that we have level 1 evidence generated by the JAVELIN Bladder 100 trial with maintenance avelumab. And I think the implementation in clinical practice is a very important step. You know, as we say, you know, if there's no access to therapy, we cannot improve outcomes.

So I think the first comment I have is access. And I think based on our prior discussion in Chapter 1, based on regulatory approvals across different countries and subsequent, of course, reimbursement coverage, I think there is an expanding access to avelumab as maintenance therapy after disease control with chemotherapy in the frontline setting. So I think it's a very important point.

Globally, we think about, you know, how to provide more access, you know, in life-prolonging medications, and in that way, to eliminate disparities, you know, across different countries. And I know ASCO is working a lot, you know, working with different countries, different governments, to try to provide resources, again, accessing life-prolonging medications. And I think in that context, avelumab maintenance is a life-prolonging medication.

Another comment that is about how to discuss with the patient, right? And I can say with you, Tom, my practice, when I see a patient with metastatic or locally advanced unresectable urothelial cancer, we discuss, of course, the estimated prognosis, the incurable disease nature, and the goals of treatment. And I discuss with them that patients who are fit enough to get chemotherapy, which the vast majority, probably 90% of my practice, we start with induction-based chemotherapy. And I discuss up front that if we have disease control, meaning response or stable disease, the intent and the goal is to transition them at some point to maintenance avelumab, to switch to maintenance avelumab therapy. And I tend to do 3 cycles of chemotherapy and then do restaging scans. And based on the benefit and risk, right, if the patient has a great response to treatment, tolerates treatment well, I may put up to 6 cycles. If the patient is struggling with the toxicity side effects despite those adjustments and have stable disease, I may stop at 4 cycles of chemo. So we'll discuss those individual customized scenarios and the timing when we may switch to treatment with maintenance avelumab after disease control, and we always do imaging restaging at the end of the chemo. And I think that discussion up front helps the patient plan ahead. I think many patients, you know, want to know ahead of time what the plan of treatment may be, and I think this can help with implementation of this strategy. At the same time, we may discuss doing next-generation sequencing, you know, to profile the tumor for later therapies. But I think in a majority of our practice here, this up-front discussion and, of course, the dialogue with the patient that our goal is to control the disease and then maintain the benefit, I think it resonates with them. And I think the vast majority of patients, they follow along and we have a significant, I would say, proportion of patients follow this paradigm of treatment.

And as I discussed with community oncology colleagues and different practices, they follow the same approach with an up-front discussion of patients and think about the potential options, especially when we have disease control and discuss avelumab maintenance up front.

Dr. Powles:
Petros, I guess, overall survival hasn't been achieved by other regimes in the frontline setting. Overall survival is very important. We've

recently also seen some real-world data from 2 European groups, the French and Italian group, large numbers of patients looking at expanded access programs or real-world data collected with a large number of patients that have pursued this approach. And they've shown very similar results with progression-free survival in the region of 12 months – I'm sorry, in the region of 6 months, and overall survival consistent with a randomized phase 3 tail on that curve, which is really reassuring that we've managed to reproduce those results.

One of the questions which I often get asked is: How do we decide on cisplatin eligibility? And how important is it? My feeling on that at the moment, and some people disagree with me, is that actually there are more similarities than differences between GemCis and GemCarbo, and in the real world, and we showed from these real-world data actually, in the French series, the majority of patients got GemCarbo, the vast majority. And I don't think that's a big issue.

There's also been question around the PD-L1 biomarker. And the reality is that that PD-L1 biomarker has more uncertainty, more inconsistency than consistency. There are many different PD-L1 biomarkers and many different methods of measuring PD-L1 status. And in the end, all of them have had their flaws. And so the maintenance avelumab program is from selected patients. We hope in the future, we can develop better biomarkers.

And then the last issue is, you know, of course, what do we do about those patients who are not eligible? What do we do about those patients who progress on chemotherapy? And that's a challenging group because it doesn't look like salvaging those patients with immune therapy such as second-line pembrolizumab works that well. And I would certainly encourage you to test their FGFR status. Erdafitinib, as you know, the recent THOR trial showed a survival benefit for erdafitinib versus chemotherapy. But also, of course, enfortumab vedotin is a really exciting antibody-drug conjugate.

So to summarize what we've said so far, Petros highlighted some of these real-world issues about how we should be scanning patients, how many cycles we should give. I've talked about some of the practical issues about differences between GemCis and GemCarbo, the importance of the PD-L1 biomarker. And I've also talked about how to look after that very difficult group of patients whose cancers progress on chemotherapy.

In the third chapter, we will be discussing how we incorporate immune therapy into the first-line maintenance setting for metastatic urothelial cancer. So stay tuned for us.

[Chapter 3]

Dr. Powles:
Welcome back, everybody. We spoke about accelerating the adoption of immunotherapy into the first-line maintenance setting. In the first chapter, we went over the data associated with maintenance avelumab. In the previous chapter, we talked about some of the practicalities of selecting patients for therapy, how to give the chemotherapy, and which patients are appropriate for maintenance avelumab. And here today we're going to talk about how we actually give the avelumab in this setting.

So let's start with the first question. Petros, when do you give avelumab? Or how long after completing the chemotherapy do you give the avelumab? And what do you tell your patients before you start the avelumab?

Dr. Grivas:
Tom, these are great practical questions. So let me start by just making the point I made before that I have this discussion up front so the patient is aware. We published the data, as you mentioned, that we look at the treatment-free interval between the end of chemotherapy and initiation of avelumab in the JAVELIN Bladder 100 trial. The treatment-free interval was between 4 and 10 weeks. And in the subsequent exploratory analysis, we saw that the benefit with avelumab maintenance in overall and progression-free survival was regardless of, you know, this specific subinterval 4 to 6, 6 to 8, 8 to 10 weeks, as long as you stay within that time interval, there is significant benefit.

Now in my practice, I tend to start sooner than later, Tom. I'm worried about progression of this disease. We know that the median PFS without treatment is about 2 months. And even with complete response, you know, median PFS is maybe, you know, 4 months or so. So I tend to start about a month. I'll show, if the patient agrees and has no other conflict of schedule, we tend to start about 4 to 5 weeks after finishing chemotherapy.

Dr. Powles:
When do you do your end of treatment chemotherapy plan? Is that done after the final cycle, or is it done a couple of weeks after the final cycle? Because sometimes it can take time to book a slot on the chemotherapy ward, the subsequent immunotherapy. And do you book that slot on the chemotherapy unit immediately, or do you wait until you get the result of the CT scan?

Dr. Grivas:

Because of the challenge with infusion share and capacity, I try to be proactive, and I tentatively block this infusion time approximately 4 to 5 weeks after the last chemotherapy dose. I get the CAT [computed axial tomography] scans in between, of course, and to make sure there's no progression of chemotherapy. And try to get prior authorization from the insurance company, make sure that we get everything ready to go. And then after the CAT scan result, then we can confirm the plan. You know, in rare scenarios when there is progression, then we can abort that plan and switch gears to something else, antibody-drug conjugate, as you mentioned, erdafitinib or pembro, depending on the case. But I try to be as proactive as possible and plan ahead of the time when the patient finishes the last dose of chemotherapy.

The other thing that you asked which is very important is the frequency of avelumab and the duration of treatment. I would say that the trial design was to give avelumab every 2 weeks. I completely acknowledge that this is a significant commitment from the patient to come every 2 weeks for a long amount of time. Some people may live far away from the cancer center, right? So you ask them to come every 2 weeks, it's a significant therapy burden. However, we do not have good data with longer intervals, so we try as much as possible to stick with that every-2-week interval as much as possible. Obviously, if there is any conflict of schedule, we can potentially adjust. But I think that the rule is and the standard is to maintain this every-2-week schedule.

In terms of duration of therapy, that's a big question in the field of immunotherapy, advanced solid tumors in general. My approach has been to – and I discuss it with the patient up front – to continue avelumab until progression of the cancer or unacceptable toxicity. As I mentioned before, only about 1 out of 10 patients need to stop because of unacceptable toxicity, grade 3 or higher treatment-related adverse event. The majority of patients who end up stopping treatment is because of progression. The patient asked me, "Will I get this treatment forever?" And it's a good discussion to a degree, right? Because we discuss with the patient, "We want you to have no progression," right? So hopefully we'll have, you know, this discussion again and again. But when we reach, you know, a longer-term time point, maybe 2 years, we have a dialogue, and we say we do not have data about stopping. The trial was designed to continue. However, we have this dialogue with the patient, and I ask for their opinion, too, and what they feel about stopping or continuing, you know, after 2 years keeping the trial design into account. And most patients are worried about progression, so most of them decide to continue until progression or an unacceptable toxicity.

Dr. Powles:
Petros, how often do you see the patients yourself? Is it every 2 weeks or every month? And how frequently are you scanning these patients while they're on immune therapy?

Dr. Grivas:
Great question, Tom. I tend to see them, you know, in the beginning of the visit, you know, I review the scans from prior chemotherapy, make sure there's no progression there, and see them for Cycle 1, Day 1 of avelumab. And then we work with advanced practice providers, a PA [physician assistant] or nurse practitioner, and they see these patients in subsequent cycles. But I see them every time there is a CAT scan imaging evaluation. In the beginning, I do imaging every 2 months, so every 4 doses. And if the patient is doing well and there is no progression, after probably 4 to 6 months, I switch to every-3-month interval of scans. So and it depends on the case, if I found something that's concerning, I may keep it every 2 months. If everything looks good, and there is no concern, I may increase the interval to every 3 months down the road. And as we go forward in outlier situations where a patient is more than a year out, we could potentially, you know, extend it to every 4 months. However, I think usually, you know, every 2 to 3 months is a typical timeframe for interval imaging.

Dr. Powles:
So a couple of takeaways from today is that there's this seamless process, ideally a seamless process between cessation of chemotherapy and switching to maintenance avelumab. And while the regime is given every 2 weeks, patients don't necessarily need to have that intensity of regular blood tests every 2 weeks. And things like imaging can be done every 12 weeks. And there needs to be a discussion with patients probably at the outset about how long they want to continue on avelumab for.

That's all we have time for today. I wanted to thank the audience for listening and of course, Petros, thank you for joining me and sharing your really valuable insights. I really enjoyed today. Goodbye and thank you.

Dr. Grivas:
Thank you.

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