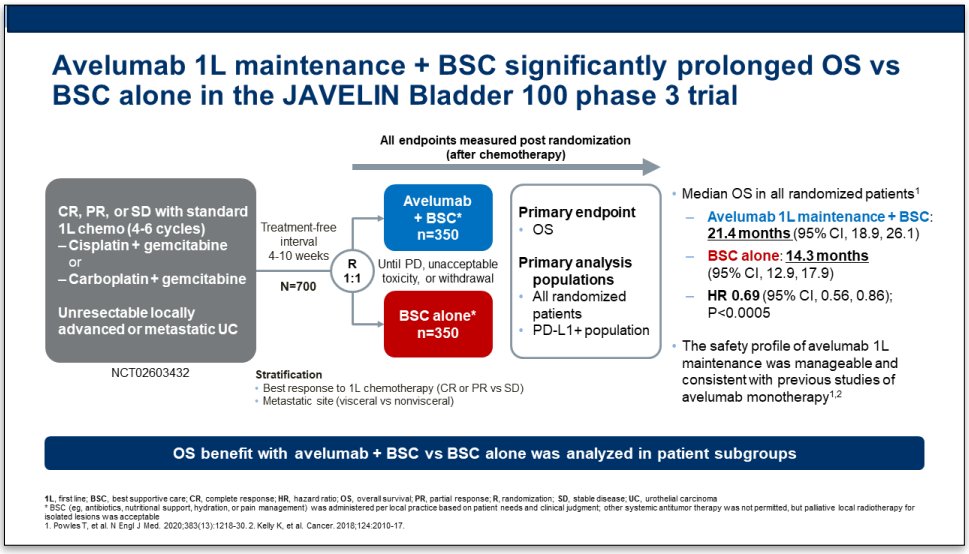
Maintenance for MIBC

Dr. Petros Grivas: Dr. Wright did a fantastic job talking about maintenance therapy in the non-muscle invasive bladder cancer setting, and I'm going to switch gears a little bit and talk about the concept, the idea of maintenance therapy with some examples in what we call more advanced disease. Advanced disease meaning in patients who have bladder cancer that has spread to other organs, we call this metastatic bladder cancer. I know there are some questions about what to do after cystectomy, so we'll touch upon those questions within my talk.

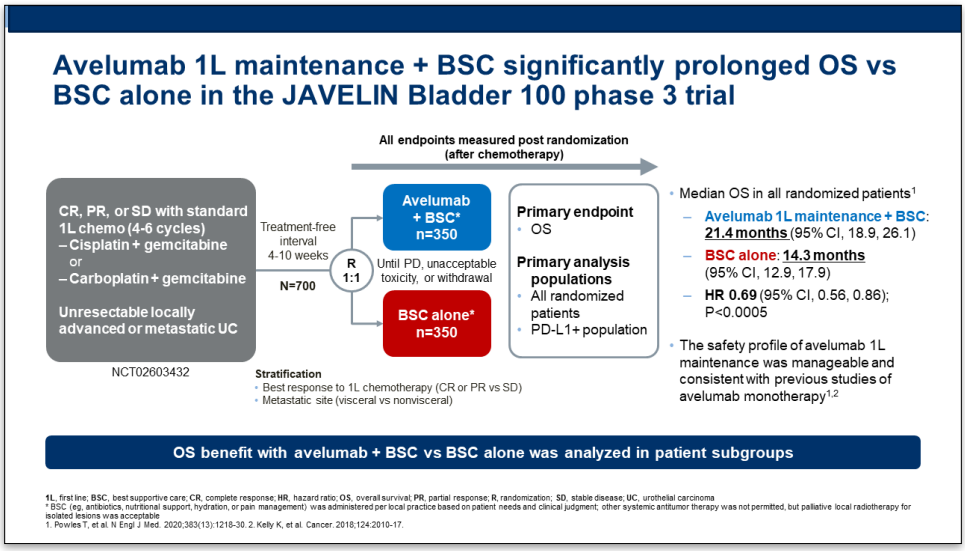
I will start my talk just giving an example of the concept with maintenance therapy based on the practice change in clinical trial that we're able to present along with my colleagues, Professor Powles from UK and others in 2020. This actually resulted in a change in the national guidelines and NCCN guidelines that Dr. Wright mentioned, as well as European guidelines, and changed the practice of how we treat this cancer in some of our patients when the bladder cancer or upper tract urothelial cancer has spread.



There is a proportion of patients when the cancer has spread, again either bladder or in the upper part of urinary tract, and when this happens goals we have is, number one, to prolong the life of our patients, extend the life as long as we can. Number two, to shrink the tumor, what we call response, response

meaning trying to make the scans look normal again, there would be a complete response, or at least shrink the cancer burden, we call this partial response, or at least the third best is what we call stable disease, so keep the cancer stable, not growing. The fourth scenario, which we do not want, is the cancer to grow, we call this progression.

There is of course a discussion with our patients, what we call this frontline setting. Frontline setting is when someone has not had previous therapy for spread or metastatic urothelial cancer, urinary tract cancer, bladder or upper tract, and this decision involves the option of clinical trials, which is a very important, I think, concept. I want to give a shoutout to the BCAN clinical trial dashboard that's available in the website, and gives you ideas of what clinical trials are available in different cancer centers. This clinical trial is an important point, and decision point for our discussion. The other two options will be chemotherapy and immunotherapy. This is an individual discussion with a patient and the provider about which option to go first, do you use chemotherapy or you use immunotherapy? I want to focus this discussion here in the proportion of patients or the examples of patients who get chemotherapy first as the initial, let's say attempt to tackle the metastatic spread cancer.



So far, let's focus your attention on the gray box on the left part of the slide. You see the patients tend to get the two most common chemotherapy regimens, is what we call gemcitabine and Cisplatin, and another regimen, gemcitabine and Carboplatin. As you see the one drug is the same, the difference is between Cisplatin and Carboplatin, the short point here is that if someone, depending on the individual characteristics, Cisplatin is the preferred chemotherapy drug, but if we have concerns about the safety and the ability of someone to tolerate the side effects of Cisplatin, then our second best choice is Carboplatin and gemcitabine. Again, if we are about to select chemotherapy as our fresh tool to tackle or attack this cancer.

What has been happening until 2020 was chemotherapy was given, and then ... we cannot give chemotherapy forever because of the potential of side effects that can accumulate over time. Fatigue, weakness can happen, nausea, irritation of the nerve endings, we call this neuropathy like numbness and tingling, or hearing changes can happen. It's just very hard to keep giving chemotherapy for a long time. We usually do CAT scans after what we call three cycles of cancer, and then we see, "Is the patient benefiting from the chemotherapy? Is the cancer shrinking?" Going back to our goals before with achieving good quality of life, or we have significant side effects, and based on this decision of the benefits and risk ratio we define the duration, how long we give chemotherapy. We give four, five or six cycles, that's usually the range, sometimes we may stop earlier, but rarely we go beyond six cycles, but usually that's a range we use for five or six cycles of chemotherapy.

Then going back to our different scenarios, we may have a complete response, the scans look great, partial response, the cancer looks smaller, stable disease, the cancer is stable, it did not get worse, not get better, or wait, the cancer gets worse. If we take out this discussion, we'll come back to that when the cancer is progressing, is getting worse, and we have to switch gears to something else. We have this three scenarios, complete response, partial response, or stable disease, that means that we had some benefit from the chemotherapy, the cancer did not get worse, did not progress.

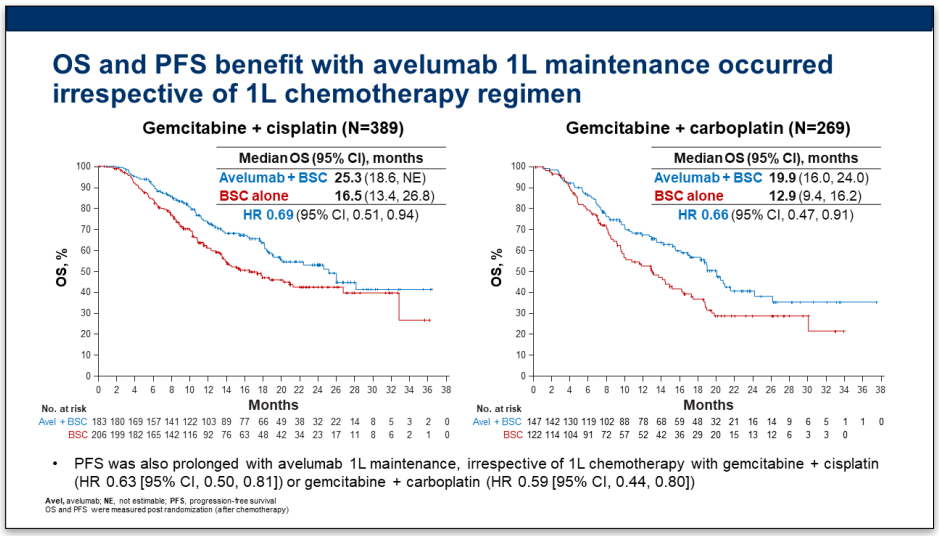
Until 2020, June 2020, we tended to wait and see what happens, and invariably in the majority of our patients the cancer did worsen later, we call this ... There was a medial average time, and it took about seven to eight months from the beginning of chemotherapy for the cancer to ... the effect of chemotherapy even if it controlled the cancer were not long-lasting for the majority of patients. Some of them, about 10% had a long-lasting response which is great, but most of the patients did not have a long-lasting response to chemotherapy, even if they had initial response, did not last for as long as we wanted. So the idea of a maintenance therapy came about, and we said, "Okay, we finish chemotherapy, we achieved some control of the disease, of the cancer, response for stable disease, can we do something else to maintain, sustain or keep the cancer from worsening again? Can we maintain the benefit that we achieved from the chemotherapy that we gave?" Through that idea we designed this clinical trial that you see in the slide. I gave you all the background which is called JAVELIN Bladder 100 Trial.

We actually published this at the New England Journal of Medicine on September 2020. What we did was half of the patients did what we called best supportive care a lot, which is what we knew for decades. Meaning we're watching this patient to see is the cancer going to come back or not, and we're doing this observation or active surveillance at that point. The other half of the patients received this immunotherapy called Avelumab. There are different immune checkpoint inhibitors, it used to be five, now we have four that are approved, and in the market for metastatic bladder cancer or urothelial cancer, and Avelumab is one of them, but the approval was only if the cancer had worsened, had progression after chemotherapy. So the question was, "If you give it that time window just after chemotherapy, but before the cancer gets worse again, starts growing again, can you maintain or sustain, or keep the benefit that was achieved by the chemotherapy as a stable disease or response?"

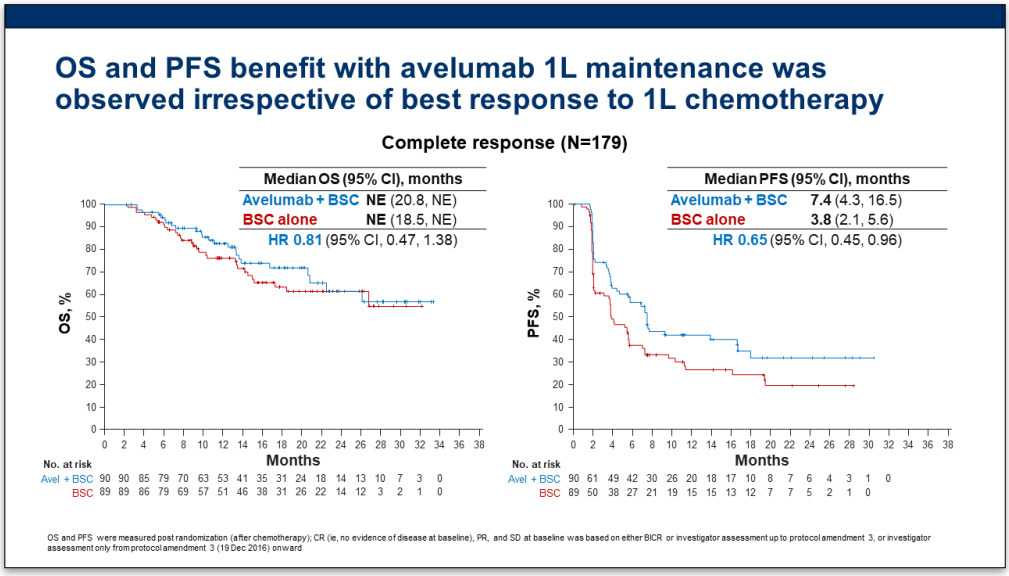
We'd try to compare and see which of the two groups live longer, we call this overall survival was our primary endpoint, to look at this and say, "Okay, let's see if we switch from chemotherapy to immunotherapy, and do this switch maintenance therapy before the cancer grows again, before the cancer has progression, can we benefit our patients more, or is this not working?" Actually after about six years of intense research, and this was a large randomized clinical trial, and it took about 700 patients from different parts of the world, multiple countries. I think there were dozens of countries involved, and multiple investigators, and of course with the amazing support from patients and families we got this trial done. We saw the results, and we presented this results in our national meeting, the American Society of Clinical Oncology. This is a huge meeting with 40,000 attendees worldwide, and it's a five-day meeting, and this was selected as one of the four most impactful research projects.

Professor Powles from England, he presented the results, and I was honored to be one of the two major principal investigators, I would call them. We saw that this switch maintenance immunotherapy result in longer life compared to waiting until the cancer grows again. So the blue box versus red box in that slide you see, at the blue box these patients lived longer. We did the statistical analysis and we saw what we call a statistically, and a clinically significant difference favoring the use of this immunotherapy, this Avelumab drug just after the end of chemotherapy.

As you see in that slide, there was a treatment-free interval between four and 10 weeks, after the end of chemo, until immunotherapy started, and this is just the kind of average of what happens in clinical practice, just to allow for the patients to recover for any potential side effects that may occur at that time. Usually that's the time window we use in clinical practice, but if you ask me, "Do you have a preference? Sooner or later?" I would discuss with the patient if they have any particular scheduling concerns or planned trips, or something like that, and I tend to start the immunotherapy relatively sooner than later, after the end of chemotherapy.

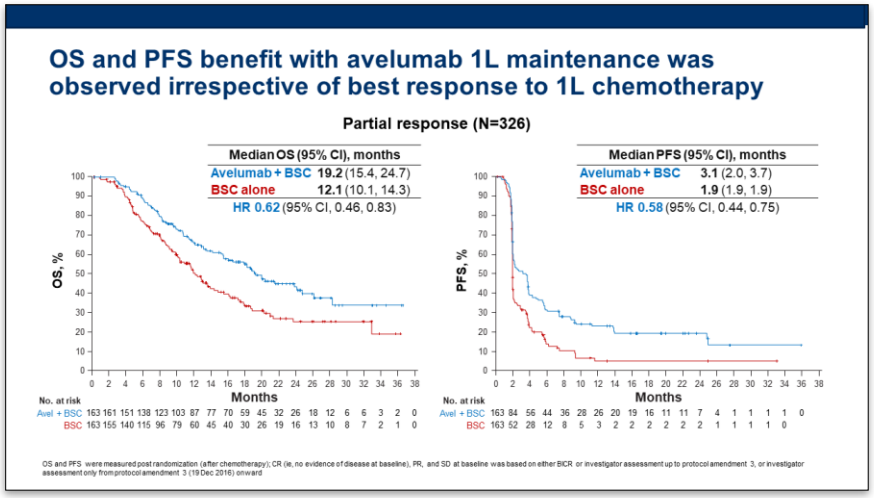


I want to just to point out here, it's also important to talk about what chemotherapy patients get upfront, and as I mentioned before my preference, our preference is to give Cisplatin if we think it can safely be administered for our patients, and would default to Carboplatin for those who have a little bit concerns about the ability to handle chemotherapy. We did an analysis, we said, "Okay, regardless of what chemotherapy the patient received in the frontline early on, does Avelumab maintenance therapy benefit both of those categories of patients?" So we looked at Cisplatin chemotherapy, and Carboplatin chemotherapy, and what we saw was that this benefit in terms of longer life, overall survival, and also progression-free survival, meaning the time until the cancer grows again, or the time of passing was also prolonged in both of those scenarios, regardless of which chemotherapy was used in the frontline. Still though, we tend to prefer Cisplatin if we can safely do it in the frontline setting.

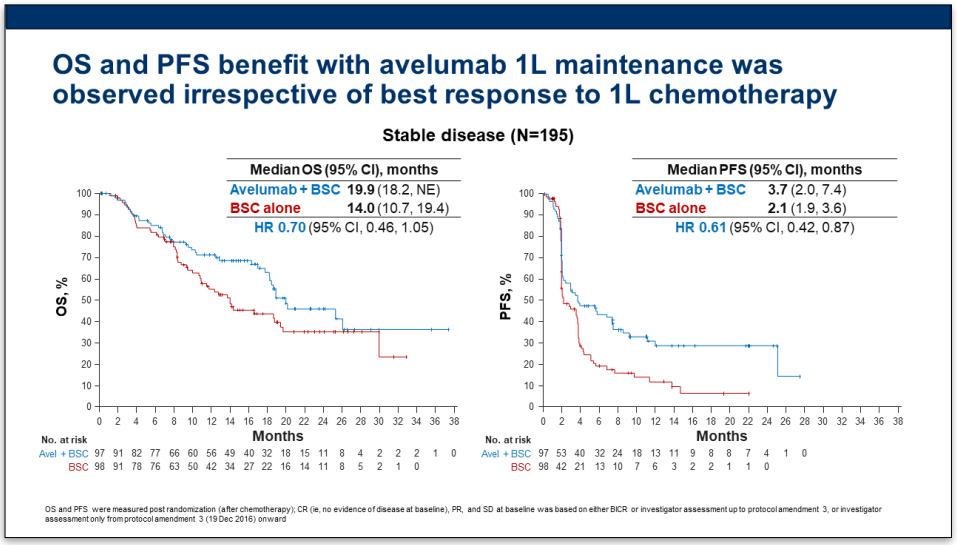


Next slide. Then you may ask, "Okay, if I get complete response in my chemotherapy, do I still need to do immunotherapy to maintain my benefit? Is that the case?" We try to sort this question out by looking at a patient who achieved what we call complete response to the induction initial chemotherapy, and we saw that there seems to be a benefit with Avelumab immunotherapy in those patients. My practice has been, even if those who have achieved a great result,

what we call a complete response, we tend to continue, to at least switch to immunotherapy afterwards, to try to maintain this response. One of the reasons is there is a significant attrition if you look at other data, many patients may not make it to second line because the cancer grows quickly, and may not have the time window to get with second line therapy, so we tend to use this immunotherapy in those patients even if they achieved complete response.

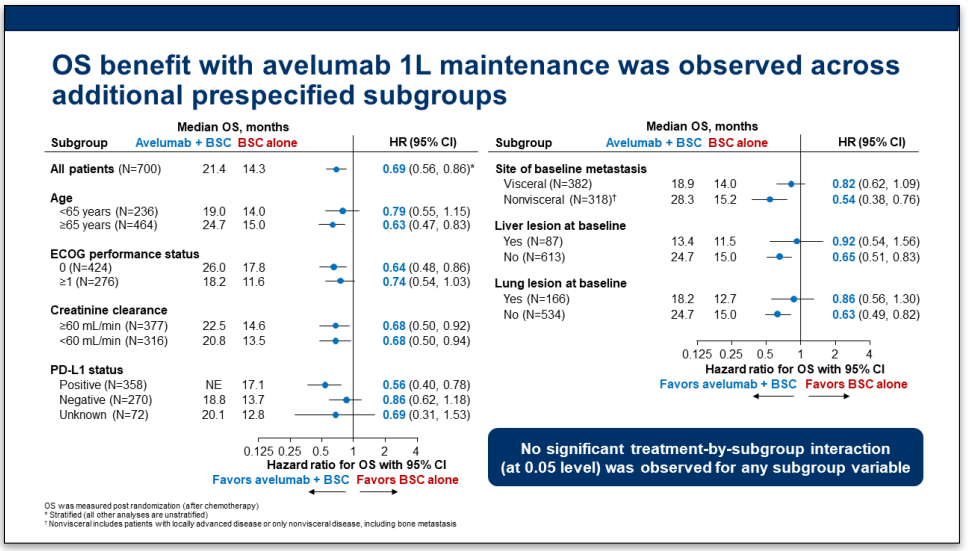


So, if they achieve partial response, so if the cancer shrunk but not completely, they're still a great candidate to switch to this immunotherapy maintenance strategy, and in the next slide you also see the third category, the patient who had stable disease, the cancer stayed kind of the same, stable in the CAT scans, this patient still benefited from this switched immunotherapy at that time point. As long as there's no contraindication to immunotherapy, for example any active autoimmune condition that someone may need to get steroids, and may make us a little bit more worried about immunotherapy. Our practice has been to do the switch maintenance for patients who achieved a response or stable disease to chemotherapy frontline.

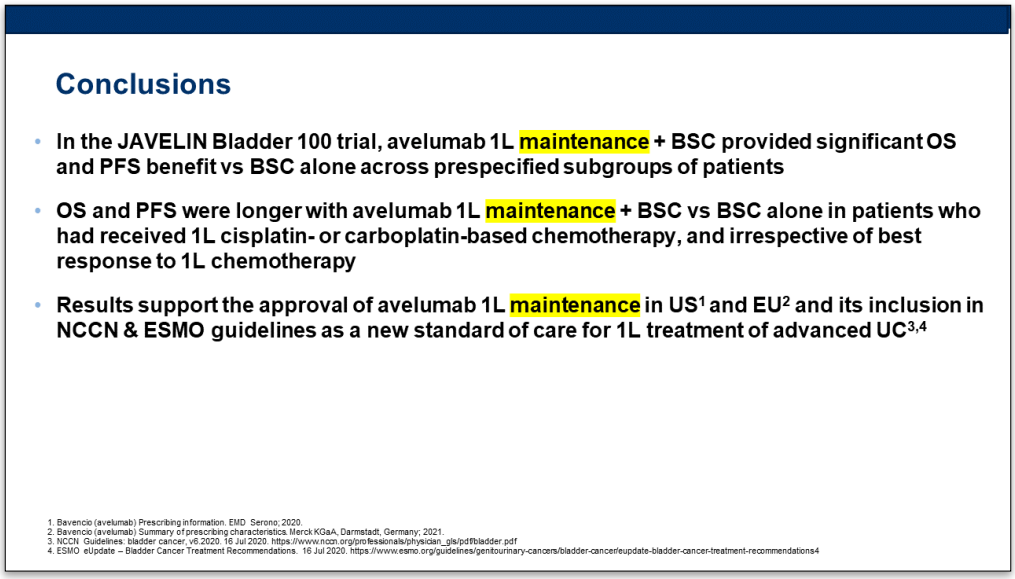


I want to just make the point here that as I mentioned, in regards to the different characteristics of the cancer, metastatic location or the age of the patient, or the functional status, there seems to be a benefit with this approach across the board, across different categories of patients, what we call subsets of different categories of patients.

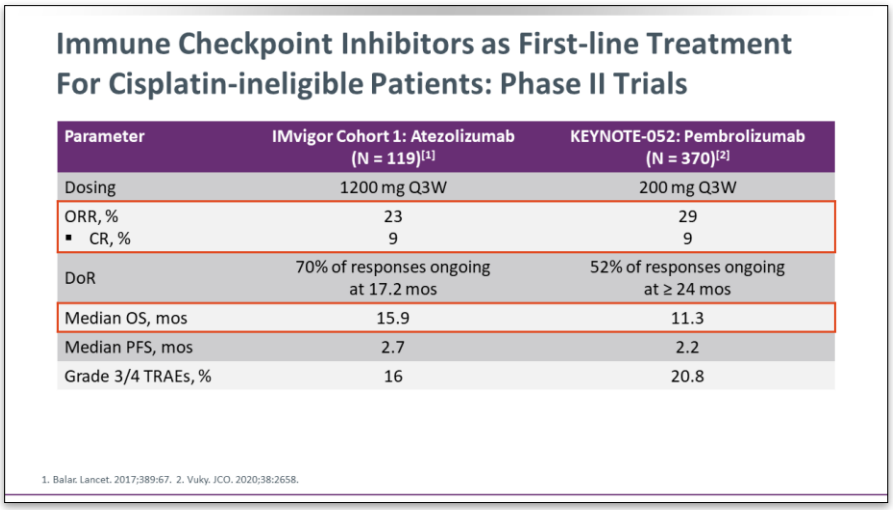
There is different, of course, decrease of benefit, some patients may benefit more than others. There's a significant variability, and we're doing research now to find out can we predict who is going to respond or benefit more from the treatment. That's the research we're doing right now, and we have a lot of work in universal classroom as well, I'm working with Dr. Wright and others, looking at this potential markers trying to predict the future, and we have to do a lot of work in that regard.



So to conclude very briefly, and I have a couple of more slides very quickly, this trial showed that if you do this immunotherapy with the drug Avelumab as a maintenance, plus the best supportive care, we saw that people lived longer compared to waiting until the cancer grows back after chemotherapy. We saw this across the different categories of patients. The overall survival in this progression-free survival were longer regardless of what chemotherapy regimen patients had received, and regardless if they had complete response, partial response, or stable disease. As I mentioned my preference is to give Cisplatin if I can, but if I cannot give Cisplatin, Carboplatin is very reasonable regimen in that case. Based on the drugs on that trial, it's one of the first classical maintenance trials that's ever done, and saw this benefit. The European Guidelines and NCCN Guidelines saying this has become the new standard of care, prolonging the life of our patients in this initial approach of treatment of metastatic spread of urinary tract cancer.



I will take only a couple of more minutes or less of your time, and I will just take the other scenario. I mentioned before, clinical trials, or chemotherapy, or immunotherapy can be used as initial tool to fight metastatic bladder cancer. For patients who receive immunotherapy we have two potential immunotherapy drugs, atezolizumab and pembrolizumab, and both of them have been approved by the FDA for patients who cannot safely get Cisplatin, and they have a high expression of this marker called PD-L1, or for patients who cannot safely get any chemotherapy, Cisplatin or Carboplatin. Now we call this situation with patients who we have concerns about the ability to tolerate either Cisplatin or Carboplatin. We may use either of those two drugs, the atezolizumab and pembrolizumab, both of them are immunotherapy, so like Avelumab, the previous drug I showed you, they activate the immune system, so they take the brake away of the immune system. We call them checkpoint inhibitors because they restore the balance.



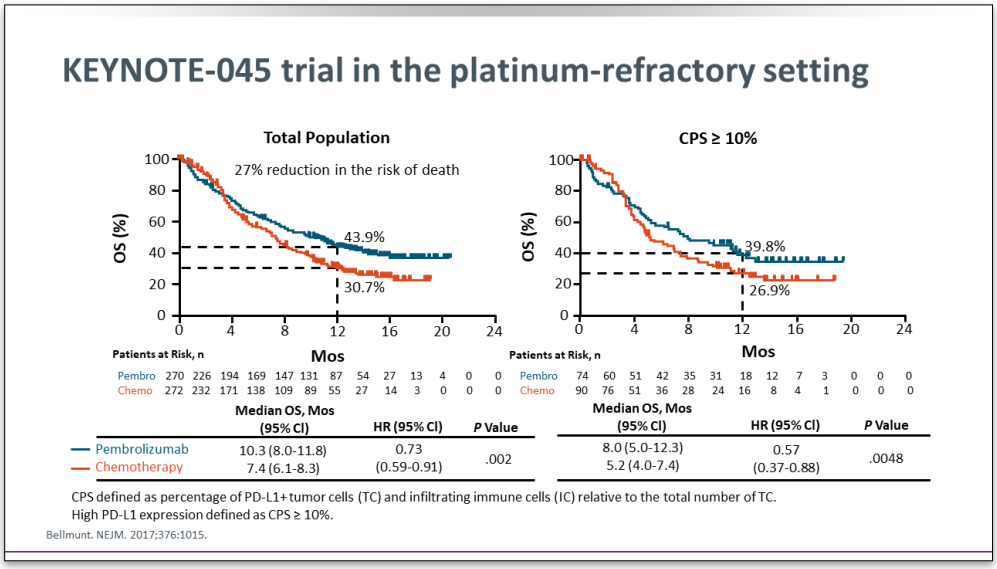
Think about a car, a vehicle, you have the gas pedal and the brake, the cancer is smart and they upregulate the brake of the immune system, so what this drugs do, these two here, and the Avelumab in the previous study, they take one of the major brakes away, they restore the balance, so the immune system, the vehicle, the car in my example, can keep moving along, can go patrol and fight the cancer cells. That's how, in a very simplistic way immunotherapy may work.

So in this particular Phase II studies that we've done, both of those drugs, atezolizumab and pembrolizumab, individual and separate trials saw what we call responses, about a quarter of the patients had a response. Interestingly, about half of the patients had a long-lasting response, and that's great. We want our patients to have a great response, long-lasting, and ideally have no side effects. I want to make the point here that all the immunotherapy drugs I talked about today, those two and the Avelumab, has the potential of side effects, immune-related adverse events, and it's very, very important to discuss with the providers how to educate our patients to recognize early any potential change. Because what may happen is when the immune system gets over-activated, aggravated and try to attack cancer cells, there is a small chance that it may cause some side effects attacking our own body, and we call this an immune system over-activated, or immune system-related adverse event or side effects. We need to be cognizant of that risk, and be very vigilant. If that happen, give some steroids maybe to cool down the immune system.

We know that some patients may have this durable, long-lasting responses, and again we're doing research in our institution, and other cancer centers to find out can we predict features, characteristics that can help us know this patient will have a great benefit from immunotherapy, another one may not. Can we predict a priori, and that's of course again a very hard thing to do, but we're doing research on it, but this trials continued, the immunotherapy for a long time. The atezolizumab did not put a stop, they keep going until a major side effect happened, or if the cancer grew again. The pembrolizumab study stopped at two years, so people finished the trial then they stopped, and there's a frequent question

we're discussing with many of you, what is the optimal duration? How long do you continue? That's a big question, unanswered question still, and we have individual discussion. I think Ms. Dykstra will talk to you about that maybe in a little bit. It's something we try to create guidelines with bladder cancer and others, but we don't have a great answer how long we should give the immunotherapy.

I told you before we give chemotherapy first, if the cancer grows, progresses in those situations we may use immunotherapy as one of the tools we have. This trial saw that if you use immunotherapy versus some other chemotherapy, different, for example docetaxel or paclitaxel, patients live longer. Again, these are patients who had already platinum-based chemotherapy, had cancer progression, and did not have maintenance at the time, and they saw a benefit with immunotherapy. Again, the question remains, how long you give immunotherapy in that setting, and that's an unanswered question we try to tackle.



Definitely the concept of immunotherapy has become more and more common, and obviously we have to balance the benefits and risks, again select the bases properly, discuss about the risks of side effects, and again our goal here is longer life, better life, better quality of life, and delay the cancer progression. I'll stop here.