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COMMENTARY

Patient and Healthcare Professional Perspectives from ESMO 2022 on Bladder and Kidney Cancer: A Podcast

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ABSTRACT

In this plain language podcast, highlights from the European Society for Medical Oncology (ESMO) Congress are discussed for a second year in a row, from the perspective of both a patient advocate and a healthcare professional. The patient advocacy track at the congress included two patient-focused sessions each day on a variety of topics. Here, the authors discuss the importance of involving patients in the design of clinical trials, as well as strategies to improve dialogue and connections between clinicians, researchers and patients. Patient advocacy organisations provide essential services to patients with cancer and their caregivers, and patient advocates play a critical role in helping to inform patients and caregivers in making clinical decisions. Congresses such as ESMO provide an important platform for patient advocates to connect with each other and with physicians and researchers to ensure that patients are placed at the centre of the conversation and are up to date on the latest findings that affect them. The authors also discuss the latest research on genitourinary cancers, focusing on bladder and kidney cancer. Promising results are emerging for combination antibody–drug conjugates and immunotherapy for patients with hard-to-treat, locally advanced or metastatic bladder cancer who are ineligible for platinum-based chemotherapy. In the management of kidney cancer, we may be reaching an end for immune checkpoint inhibitors on their own; the path ahead will be to find new targets and combinations.

Keywords: Bladder cancer; Clinical research; ESMO Congress; Kidney cancer; Patient involvement

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Key Summary Points

Scientific congresses, such as the European Society for Medical Oncology (ESMO), provide important platforms for healthcare professionals, researchers and patient advocates to connect and learn from each other.

Patient advocates play a really valuable role in helping share the latest scientific research with patients and inform their healthcare decisions.

Patient advocates also bring knowledge and expertise that can help inform clinical research design, including how research can help answer unmet needs and not overly burden patients and their families.

At ESMO 2022, promising results were presented for the management of bladder cancer; in 2023, it will be very exciting to follow studies that are ongoing to learn more about if these therapies improve patient survival.

There have not been many positive results related to the management of kidney cancer in recent years; the goal going forward will be to find new biomarkers and biomarker combinations to target.

DIGITAL FEATURES

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PODCAST TRANSCRIPT

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TP: Hi everybody. I'm Tom Powles. I'm a professor of urology at the Bart's Cancer Institute in London. I'm here joined by Alex. Alex, do you want to introduce yourself?

AF: Yeah, absolutely. Hi, Tom. My name is Alex Filicevas. I'm the Executive Director of the World Bladder Cancer Patient Coalition. It is an international umbrella bladder cancer patient organisation, uniting bladder cancer patient groups all around the world. We are currently in our fourth year as an organisation and have amongst our coalition 14 organisations in 10 countries providing support and information for people affected by bladder cancer.

TP: I like that, super cool! Today's podcast is sponsored by Pfizer, and it's going to focus on ESMO 2022 specifically. It has important information on physician and research engagement with patients and advocacy groups, as well as the latest research in GU [genitourinary] cancer. In the podcast, we will focus mainly on bladder and kidney cancer. We're not going to talk much about prostate or testicular cancer today.

The discussion is going to be in plain language; we will try to avoid technical jargon if we can. Although I'm told I'm really poor at that, so I'll do my best. But Alex, I know you're going to be fantastic at it. So, should we kick off? Where would you like to start, Alex? What's going on from a patient engagement perspective and what are the patient advocacy groups, what's their role in these meetings, and how has it changed over the last few years?

AF: Thanks, Tom! This is a really great way to start the conversation today. And ESMO is a huge congress, right? So, we are all running around there and catching up with the latest research and with everybody. And I think it was really great to see this year for a second year having this hybrid format. But, really what was the most valuable, I think for me, and I think for the whole patient community who was able to participate, it's really coming there together in person for the very first time in quite a few years after the pandemic, where we didn't have a chance to talk to each other in person. We had a patient advocacy track that's been ongoing

since 2016 or so, and it's been integrated into the ESMO programme altogether and we had quite a few sessions this year. This was in person and online, and patient advocates play a really critical role in supporting and informing patients, right, and caregivers and their healthcare decision-making processes. So, it's really important that we provide this platform for patient advocates to come and join scientific congresses like ESMO where they can talk and connect, with each other of course, but also with physicians and researchers to better understand their perspectives and their expertise, and also share the ones that they bring from their own communities.

We had quite an extensive programme this year at ESMO. Every day there were two patient-focused sessions with various topics and very much focused on patient involvement in clinical research, for example, so really placing the patient at the centre. And, in that session we had presentations and examples of the value that patient engagement really brings to research.

TP: What are the strategies we can use to improve the dialogue between patients and healthcare providers?

AF: We are already doing a great job having these conversations with you, Tom, second year in a row.

TP: It is the second year in a row. It is, yeah.

AF: Yeah, exactly. So, I think that having platforms for exchange, both sort of publicly but also in private settings, I think it's really, really helpful. The scientific congresses, like ESMO, the EAU [European Association of Urology], and others that are now finally happening in person provide a great platform and a great starting point to drive that change in thinking, I suppose, as well. Speakers coming from different backgrounds in these congresses, from different regions of the world, bring very different perspectives and solutions to some of these challenges that we have in creating this dialogue between our patient community and the healthcare professional community.

I would say from the research side, there is a real need to close the gap between patient representatives and the scientists, on how we access the scientific research. So, for example, if we have these presentations at scientific congresses or publications, how do we ensure that these reach patients as soon as possible? And I think patient organisations are very good vehicles to drive that translation and access to patients, to ensure that we don't end up in a situation where patients are the last to know about the research that very much impacts their own health and their own lives. As well, when we're looking at patient organisation engagement in research development, this shouldn't take place at an informed consent level only. I think patients and patient advocates have a really valuable input into clinical research design – how our research answers the unmet needs, but also doesn't overly burden the patient. And I think that's something that can really come from the patient community. And then lastly, I would say, you know, it's an evolving area where we need greater agreement and understanding between everyone on how do we collect and interpret data on patient experiences, especially as we move ahead and this becomes a very critical part of the research.

TP: Alex, what was your favourite thing at the meeting?

AF: I would say my favourite thing at ESMO was definitely connecting with fellow patient advocates and healthcare professionals. I think in some disease areas it's a little bit more advanced than in others, but this is where we're learning from each other and so that has been definitely one of my favourite things – to be able to connect with each other and to learn.

TP: There was some terrific bladder cancer data there [at ESMO]. There was enfortumab vedotin, which is the Nectin-4 antibody–drug conjugate, and that drug is licensed in urothelial cancer and used in patients with cancers refractory to platinum-based chemotherapy and immune therapy. It's essentially a second- or a third-line therapy now, with chemotherapy followed by maintenance with avelumab as the standard, and then enfortumab vedotin is currently the global standard of care. There are other treatments. There's debate around that a little bit, but it's the only one [antibody–drug conjugate] with randomised phase 3 positive data and we saw some data at ESMO this year (ESMO 22), which combined enfortumab

vedotin with pembrolizumab. Now we've seen data before in the frontline setting with that combination with response rates of about 70% [1], and now we saw a randomised phase 2 trial of a single agent, enfortumab vedotin, versus the combination of enfortumab vedotin plus pembrolizumab – randomised phase 2 trial getting cisplatin-ineligible patients – and we showed a 65% response rate versus 45% for the monotherapy [2]. Benchmark controls [were] somewhere between 40% and 50% for GemCis [chemotherapy] and GemCarbo [chemotherapy] in frontline metastatic disease.

And then of course the progression-free survival and the durability, particularly the durability of the responses. It looked like those patients responded for about 12 months, and that's much longer than we're used to. You know, we grew up with platinum-based chemotherapy where many patients progress or many patients' cancers progress while we're giving the therapy. This is a bit of a transformation, I thought. I was really impressed with these data.

There is a toxicity profile, including skin toxicity, particularly in the first couple of weeks that requires attention. There is also peripheral neuropathy and immune-related adverse events from immune therapy. All that requires attention. So, it's not an easier combination to give [but neither is standard chemotherapy]. I suspect it's about the same as giving GemCis [chemotherapy] or GemCarbo [chemotherapy], but when you look overall in this randomised phase 2 [trial], I think we see something for the first time, which is a combination that clearly looks more active than traditional chemotherapy. All of these trials previously have all honestly been pretty grey; they've been negative as a rule, and they haven't shown a survival advantage. I think EV [enfortumab vedotin] plus pembrolizumab has got a really good chance of showing survival advantage. I think it's got a tolerability profile which is acceptable. And I think there's a really, really good chance in the not-too-distant future that we're going to change practice. I suspect we're going to see more data from that cohort of EV [enfortumab vedotin] plus pembrolizumab at upcoming meetings. I don't know that, I'm not involved in the trial, but there's so much more follow-up that we need to see from that cohort. The overall survival of GemCis [chemotherapy] and GemCarbo [chemotherapy] are both about between 12 and 14 months, and wouldn't it be fantastic when you get results that are longer than that? Now don't get me wrong, maintenance with avelumab has got an important role to play and it will be important to look at the indirect comparisons, because clearly maintenance with avelumab is going to make GemCis [chemotherapy] and GemCarbo [chemotherapy] better. It'll be interesting to see how many patients in the pivotal randomised phase 3 EV [enfortumab vedotin] plus pembrolizumab trial get maintenance avelumab, and that's going to be an important issue, but I can see a seismic change happening in urothelial cancer in the short term.

AF: And so that's a really fantastic direction to hear, especially from the patient community where the research is headed, and I think we're equally excited to follow these. And so that's where I think ESMO Congresses and conversations like this [help] that we can bring that rather complex research into a little bit more understandable terms for [more of] us. And just one more thing from what you've mentioned about enfortumab vedotin, so it's an antibody–drug conjugate. Perhaps you could just briefly explain what that means exactly for those maybe who are not too familiar with it.

TP: So I think we've got sort of three or four classes of drugs in urothelial cancer. The first is chemotherapy and basically, they're just drugs that you put into the system. They tend to be from plants and some of them are synthetic, and they're given and they work in different ways. But usually they work by disrupting DNA, DNA turnover, either by changing the metabolism or binding directly; cisplatin, for example, binds directly to the DNA and that causes apoptosis that way. But it binds to all DNA potentially in the body and it's not super-sophisticated for that reason.

More recently, there's been immune therapy (PD, PD-L1) inhibitors, immune checkpoint inhibitors like pembrolizumab, atezolizumab and of course avelumab, which is standard care currently in the frontline setting (maintenance

avelumab after chemotherapy). And the way these drugs work essentially is [that] cancers have developed a sort of a clever way of evading the immune system that enables them to grow without being detected by T cells, and one of the really effective ways of evading the immune system is by having an immune-protected coat that protects itself from T-cell recognition, and PD-L1 is a protein which essentially achieves that goal by turning off activating T cells. And so, it's a negative signal, and therefore PD and PD-L1 inhibition sort of inhibits that inhibitory access pathway, which in turn results in activation of the body's ability to fight the cancer. So that's how immune therapy works.

There's a third group of drugs, the targeted therapies and the FGF inhibitor erdafitinib is an example of that. Essentially, we know that bladder cancers have lots of mutations and one of those mutations, quite common in about 20% of patients, is to the FGF family. This is a protein family, and mutations to that receptor seem to be associated with growth of urothelial cancer and we can develop drugs which block that receptor and turn that growth pathway off (it's [erdafitinib] been licensed in the United States) [3].

And then the last and perhaps currently most exciting group of drugs are the antibody–drug conjugates that you just talked about. And that's essentially an antibody which targets a protein which is commonly expressed in urothelial cancer; Nectin-4 is [an] example of that, TROP2 is another one. Nectin-4 is overexpressed in about 95% of urothelial cancers. So, when you give Nectin-4, it attaches itself to urothelial cancer. Now that's not a big deal in its own right. But actually, what enfortumab vedotin does is it attaches that antibody essentially to a chemotherapy-type molecular payload, and so it's essentially a targeted form of delivery of a payload chemotherapy. That means you can get much higher concentrations into the target and [fewer] side effects in the rest of the body and that's why antibody–drug conjugates are exciting.

AF: Thank you Tom! And that's such a great summary of what we have currently available as part of the research. And so, there was a promising exploratory study looking at the new biological markers, right, that can help us better understand why certain therapies work in some patients.

TP: Yeah, so the JAVELIN Bladder 100 study [4], that's maintenance avelumab. So essentially, what happened is patients get GemCis chemotherapy or GemCarbo chemotherapy with advanced disease. And then they were sequenced to get either avelumab or best supportive care. Avelumab was associated with a 30% reduction in the risk of death in the frontline setting, and for that reason it's become a global standard of care [5]. There's been a really dynamic biomarker programme associated with that, and the initial work that was performed showed that both adaptive and innate immunities [were] associated with response, which I think is a bit, it's a bit little bit novel, because historically we've always thought it's to do with an adaptive immunity, but here we've shown [that] NK cells and macrophages have a really important role to play. And then at ESMO this year, we showed some other data which I think is really relevant, and we showed tertiary lymphoid structures associated with response [4]. Tertiary lymphoid structures are complex, essentially, complex activated immune areas, so we sometimes think of the cancer as having equal distribution of immune cells like soldiers surrounding the castle. But actually, that's not the way the immune system works. What actually is happening is you get areas of activated immunity almost like planets in the solar system, and most planets are associated with immune processing because to activate T cells and to get the immune balance right, you need to have different components of the immune system, not just T cells or B cells or adaptive or components of innate immunity, you need kind of all of them there. You also need activating cells and inhibitory cells, so at any one time there are activating inhibitory cells working in us. So, it's actually a really complex process, almost like a city, with all the different components working, and these tertiary lymphoid structures appear to correlate strongly with response to immune checkpoint inhibition, and that makes a lot of sense. We haven't shown it in a randomised trial in urothelial cancer before, but we did show it just

recently [and] I think that's cool. That's the first thing.

And then there was a second piece of research that went on from that which looked at circulating biomarkers. You'll be aware that there's data on circulating tumour DNA and there's a study here, IMvigor 011, that's looking at patients who have circulating tumour DNA that can be identified. So, after a patient had a cystectomy, in 40% of patients you can identify circulating tumour DNA in the blood even if there's nothing on radiology. Radiology is not super-sensitive. Actually, you can find much better ways of identifying minimal residual disease with circulating tumour DNA, and IMvigor 011 tests atezolizumab versus placebo in patients who've had a cystectomy successfully but have minimal residual disease and a[re] ctDNA-positive. And that's a really exciting study for the future, and that was the first sort of big splash of circulating biomarkers in advanced urothelial cancer. And then what's happened now is this JAVELIN group have looked at chromatin structure and chromatin loops in germline DNA. So, in the white cells floating around in your blood you can find your own host DNA, and host DNA you have to package into tiny cells. And the way you do that is use chromatin to do it. And actually, what happens is [that] to result in protein expression from DNA to RNA to protein, loops of this DNA need to be exposed, almost like those sort of sun spots coming out of the sun. Chromatin controls those DNA loops, and I guess it's a bit like getting into a football match or a night club. If you're not expressing that chromatin, you don't have the ID card, you're not going to get your protein made. And so, chromatin's got a really important role in controlling the amount of protein that's made from DNA, and we can now measure those chromatin loops in the germline material to work out which proteins are likely to be more expressed or less expressed. In the JAVELIN [Bladder] 100 trial, we identified a whole series of circulating chromatin loops associated with the response and resistance to maintenance avelumab. And that was really interesting because, firstly, it's not from the cancer material itself. And secondly, it's not even from the circulating cancer material, it's circulating biomarkers from the host.

So what does this tell us? Well, it tells us two or three really interesting things. Personally, not just that we can measure circulating biomarkers and we can build on that ctDNA work and, maybe, we can shift away from tissue-based biomarkers in the future. But the second really relevant thing is that it tells us that host factors, not just tumour factors, are really important in predicting response and resistance to therapy. The cancer cells sit in the tumour microenvironment, and as I said, those tumour cells are not necessarily completely in control of their own destiny. The way the host interacts with those tumour cells, both from an inhibitory point perspective but also from potentially a nourishment perspective and other factors, may be really important in tumour growth. And when we learn more about the micro [environment], the biology of the disease, we now need to take into consideration hosts as well as tumour factors.

AF: Thank you, Tom. So, these are really fascinating developments, and it seems that it will help us better understand the disease and how we can make sure that also the new therapies and new innovations can better respond to the disease. Let's have a look at then quickly, renal cell carcinoma, what did we find out about the latest advances in this area at ESMO 2022?

TP: Well, I think the first place to start is there was a plenary session. Tony Choueiri gave a presentation of COSMIC 313 [6] ipilimumab and nivolumab immune combination therapy, which are CTLA-4 and PD-L1 inhibition – it's a standard of care in advanced disease – and he presented a trial looking at ipilimumab and nivolumab plus a VEGFR-TKI called cabozantinib. So, it's triplet therapy versus doublet therapy; ipilmumab + nivolumab is the control arm. The trial was positive. It showed [approximately] 25% reduction in progression-free survival. So, it kept the cancer under control over 25% longer [than doublet therapy]. It's a positive trial and we haven't yet seen the overall survival signal for this study, but that preliminary data, which are positive, is really encouraging. There were issues around the tolerability

of the triplet, and I think this is an ongoing issue now in renal cancer in that it was harder to give all three drugs (cabozantinib + ipilimumab + nivolumab than just ipilimumab + nivolumab) and that may have dampened the responses and perhaps the complete responses that were not as high as we expected.

So that's the first study, which is in advanced disease, but there were also three really interesting studies in the adjuvant setting. We know that adjuvant (so this is directly after a surgery) pembrolizumab in patients with high-risk, clear cell renal cancer is associated with a reduction in progression and a trend towards overall survival [7]. So relapse rate reduction by a third, a trend to OS [overall survival] and in fact adjuvant pembrolizumab is widely used. We then saw data for atezolizumab in the same setting and that didn't show the same benefit [8], and we also showed data on ipilimumab and nivolumab in that setting (Checkmate-914) and again, that didn't show the same benefit that we saw with pembrolizumab [9]. Why? Why is that happening? And there isn't a clear explanation why pembrolizumab should be positive and atezolizumab negative. And ipilimumab + nivolumab negative. It's not by luck alone. The pembrolizumab study was a phase 3, 1000-patient study that was very robust in that respect, and the probability of the pembrolizumab trial being positive by chance alone is 1 in 10,000. So, guessing someone's birthday correctly is [a] 1 in 350 chance. And so, you've got to do that and then guess the day they were born on as well and that's still not 1 in 10,000. So, it's very unlikely the pembrolizumab study was not a real finding.

So, why was the atezolizumab study negative? Well, there's been this issue around PD-L1 versus PD-1 inhibition and that requires consideration, and perhaps the PD-L1 inhibitors are not quite as active as the PD-1 inhibitors. We don't know that but that's speculation because the trial was conducted properly, but if that was the case, you'd expect the ipilimumab and nivolumab trial to be positive. We didn't see that, and it may be actually that it was difficult to give the ipilimumab and nivolumab and that's worthwhile thinking about.

So, when I pull this together, how do we explain where we are and what do we tell patients? I think we have to tell patients that pembrolizumab is associated with a reduction in the risk of [cancer] progression. Patients should be counselled for adverse events, but at the same time prevention of relapse of disease is a really important goal for our patients. Patients should be aware that other trials have taken place and haven't shown the same findings, because it would be unfair to only talk about the positive results. My experience with the patients I've talked to is many of them find this appealing because they say, well, there's a trend towards overall survival. There's a clear PFS and DFS advantage and I think I'd like to do this at the moment, but let's wait for the survival data in the future. It would also be really nice to see if we could pick those patients who are most likely to benefit from therapy.

AF: And, perhaps briefly, were there any particularly notable studies in prostate cancer as well, that you would like to call out from ESMO?

TP: I think the first is the issue around PARP inhibition. You'll be aware that there's some data looking at abiraterone plus olaparib versus abiraterone alone in CRPC [10], and now there are other trials with similar PARP inhibitors in that same early CRPC setting. And there's a question about whether this works in all comers, or if it works in patients with DNA alterations to essentially the targets of PARP inhibitors, and that debate is a really hotly contested issue.

AF: So thank you so much for presenting the summary, and a refresher as well for my side. I think for me from all the research that we have seen, I think the EV103 cohort study was probably one of the most exciting ones, and I think when we talk with our patient community as well, we look at the data that have been presented there, we are looking to quite significant survival, right? So that has been probably the most exciting one for me to follow and [the] JAVELIN Bladder 100 trial as well.

And as you said, it's really great to see that we have an increasing number of options available for patients with bladder cancer which have seen decades of sort of stagnation in the

research field. Additional studies that are ongoing and we are expecting to see some hopefully positive results and it's an exciting time for our patient community. So, we're following these studies specifically with great excitement. So, when might we potentially see this coming into practice?

TP: Well, I think that unfortunately the enfortumab vedotin pembrolizumab data is in the United States, and I've got no idea about the answer to this question. I'm not involved in the process, but you know, if you got a randomised phase 2 trial that's positive and the FDA might give accelerated approval to that. So, I can see this being available just off that trial. But there's another study (EV302), which has completed its enrolment and that's EV [enfortumab vedotin] plus pembrolizumab versus chemotherapy, in the frontline metastatic setting. So, I would say I would genuinely say that this is in the United States a 12-month issue if they get approval and then in the rest of the world, well, who knows? Not too far behind that. I would hope. So, I actually think that in, you know, in the short term from a drug-development perspective, we're going to see a big change in urothelial cancer, all things being equal.

AF: Great, and I think that's what, you know, from the patient community that we're looking forward to as well. And when we look to other congresses in the future, ESMO 2023 and others, I think would be [looking forward] from my perspective, seeing greater patient-focused content such as what we've seen with the patient advocacy track and bringing those research findings that are being presented at the scientific congresses into the patient community much faster in a more understandable way that you, for example, have presented so well today. So, thank you for that, but also for bringing the other way around and somehow involving patients much more into the main scientific programs as well, and bringing those perspectives that way. Is there anything you know, as my last question to you, is there anything from the studies ongoing that we perhaps are expecting to be presented in 2023 or a little bit beyond that you are most excited about?

TP: I'd love to see a nivolumab survival signal in the adjuvant setting. I'd love to see that data. We've not seen it yet. It's probably the most important dataset out there. We've also got the ipilimumab plus nivolumab trial kicking around, and that's the frontline ipilimumab plus nivolumab bladder cancer trial, and we know that hasn't hit a survival signal. Would like to see that data also. And, I'd like to see, of course, EV-302. There's the THOR trial of erdafitinib versus chemotherapy. I'm really excited about that trial. You know, there's so much I could talk for hours about this. But there is so much in urothelial cancer.

What about kidney cancer? Well, you know, there's the belzutifan randomised trial, which is a HIF-2a inhibitor. I think that's really interesting, but actually there are not that many new drugs in kidney cancer right now. We might be reaching a plateau, which is why I think biomarkers are so important.

AF: Super, thank you. So, I would like to, I suppose, to wrap up and thank everyone for listening to this brief conversation that we had with you, Tom, today, and thank you for helping us to translate all the exciting research.

TP: I want to thank you for doing as you did last year, your amazing job in making this work, and I'm really grateful for the time you spent today.

AF: Thank you. That's it. It's a team effort, right? ESMO as well, I think it's been paving the way for greater patient participation and access to their research system, scientific congresses. And I'm really confident that they will continue in that direction. So, I'm really grateful for ESMO for providing that platform for the patient community to come together to learn from people like you and from people like their colleagues in the patient community. Is there anything, any last thoughts or messages you'd like to share, Tom?

TP: I think I'm done.

AF: Fantastic. So, thank you so much, Tom. It's been a great pleasure.

TP: Thank you. And I'll see you soon.

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APPENDIX

Patient and Healthcare Professional Perspectives from ESMO 2022 on Bladder and Kidney Cancer—Glossary

Term	Definition
Adaptive immunity	Specialised immune cells and antibodies that attack and destroy foreign substances and are able to prevent disease in the future
Adjuvant therapy	Additional cancer treatment given after the initial treatment, such as surgery, to lower the risk that the cancer will come back
Advanced disease	The cancer has spread from where it first started to nearby tissue, lymph nodes or distant parts of the body
Advocate	A person who supports, recommends, defends or pleads a cause or policy

Appendix continued

Term	Definition
Antibody–drug conjugate	A substance made up of a monoclonal antibody chemically linked to a drug. The monoclonal antibody binds to specific proteins or receptors found on certain types of cells, including cancer cells. The linked drug enters these cells and kills them without harming other cells
Apoptosis	The death of cells
Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease
Chromatin	A mix of DNA and proteins that form the chromosomes found in human cells
Chromatin loops	Occurs when stretches of genomic sequence that lie on the same chromosome are closer to each other than to intervening sequences
Circulating tumour DNA	Small pieces of DNA that are released into a person's blood by tumour cells as they die
Clinical trial	Research studies of treatments, performed in volunteers (participants), which are intended to add to medical knowledge
Cohort	Several individuals who are grouped together for the purposes of a research study
ctDNA positive	Detection of circulating tumour DNA, which suggests there are cancer cells in the body
CTLA-4	A protein found on T cells (a type of immune cell) that helps keep the body's immune responses in check
CRPC	Castration-resistant prostate cancer
Cystectomy	Surgery to remove the bladder
DFS	Disease-free survival (DFS for short) in cancer, the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer
Durability	A long-lasting (generally greater than 1 year) positive reaction to tumour therapy
EAU	European Association of Urology (EAU for short) is a non-profit organisation committed to the representation of urology professionals worldwide
ESMO	The European Society for Medical Oncology (ESMO for short) is professional organisation for healthcare professionals and researchers who care for people with cancer
EV (enfortumab vedotin)	Nectin-4 antibody–drug conjugate
FDA	The US Food and Drug Association (FDA) for short) is a federal agency of the Department of Health and Human Services, responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics and products that emit radiation

Appendix continued

Term	Definition
FGFR	Fibroblast growth factor receptor (FGFR for short) is a protein that is involved in cell growth, bone growth, the formation of new blood vessels, and wound healing
GemCarbo	The shortened name of a chemotherapy combination (gemcitabine and carboplatin)
GemCis	The shortened name of a chemotherapy combination (gemcitabine and cisplatin)
GU (genitourinary)	Relating to the genital and urinary organs or functions
Germline DNA	Tissue that come from reproductive cells (egg or sperm) that become incorporated into the DNA of every cell in the body
HIF-2a inhibitor	Inhibitor of a protein called hypoxia-inducible factor 2-alpha
Immune checkpoint inhibitor	A type of drug that blocks proteins called checkpoints that are made by some types of immune system cells, such as T cells, and some cancer cells
Immune therapy	A type of treatment that uses the body's own immune system to treat certain types of cancer
Maintenance therapy	Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy
Metastatic	The cancer has spread beyond the first organ concerned to other parts of the body
Monotherapy	The use of a single drug to treat a disease

Appendix continued

Term	Definition
NK (natural killer) cell	A type of immune cell that has small particles with enzymes that can kill tumour cells or cells infected with a virus
Nectin-4	A molecule that is highly expressed in urothelial cancer and may contribute to tumour-cell growth and spread
Neuropathy	A nerve problem that causes pain, numbness, tingling, swelling or muscle weakness in different parts of the body
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive
PARP inhibitor	A poly (ADP-ribose) polymerase (PARP for short) inhibitor is a substance that blocks an enzyme in cells called PARP. PARP helps repair DNA when it becomes damaged
PD-1/PD-L1 inhibitors	Groups of immune checkpoint inhibitor drugs that block the activity of two immune checkpoint proteins, called programmed death-1 (PD-1 for short) and programmed death ligand 1 (PD-L1 for short), which are present on the surface of cells
Phase 2 trial	A study that tests the safety and how well a new treatment works compared with standard treatment. This is done in approximately 100–300 participants

Appendix continued

Term	Definition
Phase 3 trial	A study that tests the safety and how well a new treatment works compared with a standard treatment. This is done in a larger group of people compared with the phase 2 trial
Platinum-based chemotherapy	Drugs that fall into a class called alkylating agents. The platinum molecule in platinum-based drugs binds to the DNA of cancer cells, which induces DNA damage and cellular death
PFS	Progression-free survival (PFS for short) is the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse
Randomised study	A research study in which the participants are divided by chance into separate groups that compare different treatments
Refractory cancer	Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant during treatment
Renal cell carcinoma	Cancer that begins in the lining of small tubes in the kidney
Response rate	Measurement of a patient's response to treatment
T cell	A type of white blood cell. T cells are part of the immune system and develop from stem cells in the bone marrow
Tertiary lymphoid structures	Clumps of active immune cells
Toxicity profile	The degree to which a drug or drug combination can cause adverse events
Urology	A medical field which diagnoses and treats diseases of the urinary organs in females and the urinary and reproductive organs in males
Urothelial cancer	Cancer that begins in cells called urothelial cells that line the urethra, bladder, ureters, renal pelvis and some other organs
VEGFR-TKI	Vascular endothelial growth factor receptor–tyrosine kinase inhibitor (VEGFR-TKI for short) is a substance that blocks an enzyme needed to form blood vessels

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