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COMMENTARY

The Evolving Role of PD-(L)1 Inhibition in Optimizing Outcomes for High-Risk Non-Muscle-Invasive Bladder Cancer (NMIBC): A Podcast

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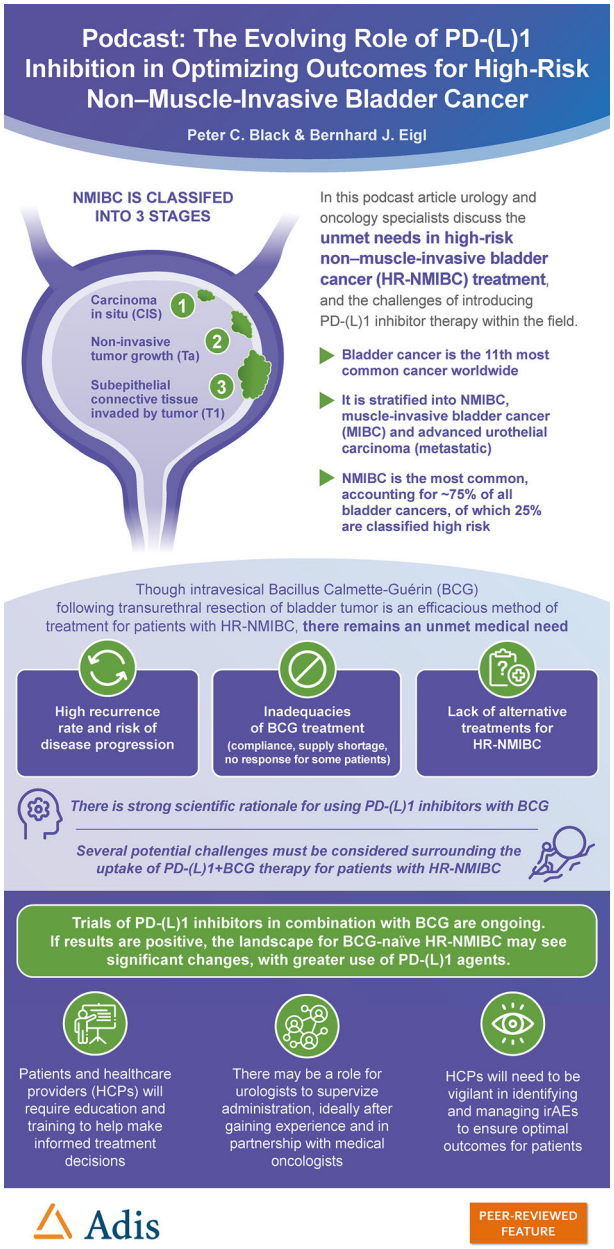
Infographic



Key Summary Points

This solution-orientated podcast involving a discussion between Urology and Oncology specialists focuses on understanding the current non-muscle-invasive bladder cancer (NMIBC) landscape. We explore potential treatment challenges, and the rationale for the introduction of programmed cell death ligand 1 (PD-(L)1) inhibitors within this field for optimizing patient outcomes. We also discuss the patient journey and how the greater use of PD(L)-1 inhibition in the treatment regimen for NMIBC will impact patients and healthcare professionals (HCPs).

Although intravesical Bacillus Calmette-Guérin (BCG) immunotherapy following transurethral resection of bladder tumor (TURBT) can be an efficacious treatment method for patients with NMIBC, there is an unmet need for additional treatment options. There are inadequacies in BCG treatment, such as compliance to treatment, supply shortage, and non-response in some patients. In addition, the risk of disease recurrence and progression is high.

There is a robust preclinical rationale for using PD-(L)1 inhibitors to treat NMIBC, and PD-(L)1 inhibitor monotherapy shows efficacy in BCG-unresponsive patients. However, there are challenges with the uptake of PD-(L)1 inhibitors for high-risk NMIBC, including patient identification/referral, multidisciplinary team collaboration, modest efficacy, systemic toxicity, and higher costs compared with intravesical therapies. Barriers to patient access due to financial constraints and lack of education also hinder uptake.

The landscape for BCG-naïve high-risk NMIBC may see significant changes with the greater use of PD-(L)1 agents if ongoing trials of PD-(L)1 + BCG demonstrate positive results. These changes may include potentially less invasive treatment methods, further education, and training for both patients and HCPs to improve disease management. Increased HCP vigilance in identifying and managing immune-related adverse events will also play an important role.

DIGITAL FEATURES

This article is published with digital features, including podcast audio and an infographic, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24632169

TRANSCRIPT

Peter Black: Hi, everyone, I am Peter Black, I am a urologic oncologist at the University of British Columbia, in Vancouver. And welcome to this webinar on high-risk, non-muscle-invasive bladder cancer (NMIBC). Bernie, would you like to introduce yourself?

Bernie Eigl: Hi, I'm Bernie Eigl, I'm a medical oncologist specializing in bladder cancer at the Vancouver Cancer Center in British Columbia, Canada.

Peter Black: It is our pleasure to welcome you today to this podcast. I'd like to acknowledge that the podcast was supported by Pfizer, and we have had editorial support from Haniya Javaid of Envision Pharma, and it was funded by Pfizer.

Bernie Eigl: The goal of this podcast is to provide an overview of the NMIBC landscape with a focus on high-risk NMIBC and this includes understanding the diagnosis and current treatment approaches with a focus on the medical needs and high-risk NMIBC treatment, highlighting the potential challenges associated with the introduction of programmed cell death ligand 1 (PD-(L)1) therapies in NMIBC. And then to provide insights into the patient journey within the institution and its translation into practical settings. Finally, we'll explore future outlooks and directions for PD-(L)1 use in NMIBC treatment.

THE NMIBC LANDSCAPE

Bernie Eigl: Peter, maybe I'll start off with a question to you. How is NMIBC defined? And what are the underlying pathophysiological factors and oncogenic pathways involved in the development and progression of high-risk NMIBC?

Peter Black: Yeah, lots to say on that question, Bernie. I think, you know, one thing I always like to highlight to patients is how common bladder cancer actually is because many patients are surprised that they have it and have never really heard of it. But it is the eleventh most common cancer worldwide, and for us in Canada and also in the USA, it is the sixth most common cancer, so it is a very common disease [1, 2].

We distinguish non-muscle-invasive from muscle-invasive bladder cancer (MIBC). About three-quarters of cases are non-muscle invasive, meaning it has not invaded into the detrusor muscle of the bladder wall, and typically with NMIBC, we're trying to preserve the bladder, whereas MIBC is treated more aggressively with surgery and/or radiation [2, 3]. Within NMIBC, we define three different stages. There is carcinoma in situ (CIS), which are flat lesions just in the urothelial lining, and there's no real tumor formation. There are the papillary Ta tumors, which are non-invasive, but they form like polyps growing into the lumen of the bladder. And then there are T1 tumors, which are sort of the transition stage toward MIBC because they actually show invasion into the subepithelial layer below the mucosa [3–5]. Within these stages, CIS is always considered high grade, so it is aggressive, with cytologic features under the microscope. But the Ta and T1 tumors can be

further divided into high grade or low grade, with most Tas being low grade and most T1s being high grade [4–6]. Sometimes we'll still see the older classification system, the 1973 World Health Organization (WHO) classification system, which will classify NMIBC as Grade 1, Grade, 2, or Grade 3; and, of course, Grade 2s are always the problematic ones because we don't know whether we call them high or low grade, which influences how we treat the tumors [5]. So, beyond the stage, you know, Ta, T1, CIS, and the grade, we also have a risk stratification. So, we put it all together and include some other risk factors; for example, age has come up as a risk factor in the European classification, with age greater than 70 years being an adverse factor [5, 6]. But there are different risk stratification systems to classify patients as low risk, intermediate risk, or high risk. And we're talking about risk of recurrence, but especially risk of progression, so high-risk tumors have a high risk of progression to MIBC and need to be treated aggressively; low-risk tumors will almost never progress and, of course, intermediate-risk tumors are in between the first two. They all tend to recur, so recurrence is a little bit different [2, 5, 6]. One of the main points of difference within the classification systems is: what do we do with the high-grade Ta tumors? We've considered them to be high risk in the past, and most clinical trials have considered them to be high risk. Yet they are often all classified as intermediate risk. So, it is still up to the individual urologists to decide how they are going to deal with those patients [6].

Another risk feature that we have with NMIBC is the histologic subtype. Previously, we talked about variant histology, but some of the T1 tumors that are invasive into lamina propria can have different morphologies, such as, for example, a micropapillary or a sarcomatoid carcinoma, and those really need to be treated more aggressively. They have a higher risk of being under-staged, so, they are actually muscle-invasive and we think they are not; they may have nodal involvement, and typically they need to be treated with cystectomy [7]. There are molecular correlates to all of this, and you know that we could spend another half hour talking about those issues. But we think of NMIBC as evolving along two molecular pathways, which explains a little bit of the differences in risk of progression [8–10]. So, the low-grade tumors, and you know that all low-risk tumors are low grade, and almost all intermediate-risk tumors are low grade, very frequently have mutations in *FGFR3* (fibroblast growth fibroblast growth factor receptor 3 gene) or in *HRAS*, and these are sort of proliferative genes that drive growth, meaning proliferation, but they don't necessarily lead to invasion. These tumors are still at risk for recurrence and that type of thing, but they don't invade. Whereas in the second pathway, which are mostly high-grade tumors in CIS, there are mutations in *p53* (*TP53*) and *RB1* (retinoblastoma gene), which I think we've all heard of, and these alterations lead to a more invasive phenotype that is at risk for progression [9–11]. And I would say, lastly, just with respect to molecular classification, that we can classify based on RNA expression, which has become popular in MIBC but can also be carried over to NMIBC. And most NMIBC if we're thinking of the big luminal versus basal split, are luminal. And then there are newer classification systems that will subdivide that further. Those have not really gotten into clinical practice yet, and are still experimental tools [8, 10].

Bernie Eigl: So many nuances in the diagnosis and approaches to disease. Let me ask you about what it looks like from the patient's point of view? What are the diagnosis and treatment approaches for patients with high-risk NMIBC?

Peter Black: As urologists in practice, we have a couple of tools that we use most frequently for diagnosis. Cystoscopy certainly is the cornerstone—we want to visually see and identify tumors and characterize them [5, 6]. We can use urine markers as an adjunct, and I think cytology is used quite widely because it can reveal things that we might not see. So, you may have high-grade cancer cells in the urine, but you have not seen a tumor, and the tumor has a very high specificity. So, if cytology is positive, there's probably something there. There are various other urine markers that are in development—and there's many that have been abandoned—but there are newer, very

interesting ones that are coming on the market as well. So, we have to see how we implement those [3, 5, 6, 12]. Typically, a patient will have a cystoscopy to diagnose the tumor and then they will have an endoscopic resection—a transurethral resection of bladder tumor (TURBT), and that is where we really confirm the diagnosis by getting tissue to send to the lab, and the pathologist will tell us the stage, the grade, and then any histologic subtype [3, 5]. All that type of thing we can use: past history of tumors, patient age, as I mentioned, those types of things [are used] to then risk stratify, and based on the risk stratification and patient factors, we decide how to treat [3, 5, 6]. We will often use imaging modalities. For high-risk NMIBC, we will typically image the upper tract, kidneys, and ureters. Most often with a computed tomography intravenous pyelogram (CT IVP), but magnetic resonance imaging (MRI) can also be used. It can be important, of course, also, to look at local staging in the bladder, but imaging is primarily for the upper tracts [3, 5, 6, 13].

When it comes to treatment, there are some guidelines, and we have Canadian guidelines, as well as EAU (European Association of Urology) and AUA (American Urological Association) guidelines, of course, to guide treatment [2, 5, 14–16], but the treatment of high-risk disease is actually fairly uniform around the world. After TURBT, if there's T1 disease, patients typically get a second TURBT, to make sure that we have not under-staged the disease. That is very important. It is kind of a peculiarity of NMIBC that we go back and do the same thing again [2]. We may do a radical cystectomy for the highest risk patients. I mentioned, for example, micropapillary and sarcomatoid tumors, T1 tumors, so that is always on the table [2, 17].

But the standard of care for most patients with high-risk disease will be intravesical Bacillus Calmette-Guérin (BCG) therapy [6, 17]. This is a type of immunotherapy. BCG is the vaccine used for tuberculosis [18], and BCG treatment involves multiple installations into the bladder over time, both induction and maintenance courses.[1] BCG is relatively effective, but when it does not work, and you know there are patients who don't respond or they experience recurrence afterwards, we don't really have good second-line options, or we have not had good second-line options until recently [2, 5, 6, 15].[2] We have two recent additions to treatment, you know, FDA [US Food and Drug Administration]-approved additions in the USA and those developing elsewhere. One is pembrolizumab, a PD-1 inhibitor, which is given systemically or intravenously, which is a paradigm shift for the treatment of NMIBC. But that can be effective in patients who have BCG-unresponsive high-risk disease [5, 17]. And most recently nadofaragene firadenovec, which is a gene therapy that leads to interferon production in tumors; this treatment is also being approved and is an intravesical therapy, approved but not yet launched, so we don't have experience with it yet [17]. In the absence of those two recently approved drugs, a lot of patients will get the combination chemotherapy gemcitabine and docetaxel as a second-line treatment after BCG, but that is only based on retrospective data. So, there's a bit of a data hole there [17]. And, of course, clinical trials are important for these patients, and so, when possible, we try to get these patients on clinical trials.

Bernie Eigl: That leads to the next natural question, which is, what are the unmet medical needs in high-risk NMIBC treatment?

Peter Black: This year we have celebrated 50 years of BCG therapy, which is quite remarkable for something so simple, but it also tells you, on the one hand, that it works well, and maybe it tells you that we have not made rapid progress in the management of bladder

[1] The induction phase consists of six-weekly intravesical instillations of BCG. This is followed by the maintenance phase which can last up to three years, and often consists of three-weekly instillations at specific intervals (three, six and 12 months; [5, 32]).

[2] Besides BCG-unresponsiveness, BCG toxicity can be a problem for patients being treated. Local toxicity can lead to side effects such as, hematuria, irregular urine frequency, bacterial cystitis, and/or chemical cystitis. These complications are often unserious but common, occurring in 62.8–75.2% of patients overall [32–35]. Systemic toxicity can lead to symptoms such as general malaise, rash, fever, infection and/or sepsis. These complications account for a smaller proportion of intravesical BCG reactions, but can still affect 30–40% of patients overall [32–34, 36].

cancer. But the big issues are that some patients will not respond to BCG—maybe up to one third. Those that do respond are still at risk of recurrence (greater than one half), and overall there's a significant risk of progression, especially [in] patients with T1 and CIS, and that can be in the order of 15–20% after a few years. And progression is what we really worry about [2]. We know that if patients progressed to muscle-invasive disease from non-muscle invasive disease, that they have a much worse outcome, actually a worse outcome than if they were diagnosed with muscle-invasive disease in the first place [5, 19]. So, recurrence and progression are a problem.

BCG shortage has been a huge problem around the world for the last 10 years. We've been lucky in Canada, it has not been as impactful, but it is still leading to treatment shortcomings in the USA, for example [2, 17]. And so, if you don't even have BCG there, there are no good alternatives really for the first-line treatment of high-risk NMIBC, and some people are moving to chemotherapy, which we think is not as good [5, 17]. If we have BCG, there's still an issue of tolerance, so patients will often discontinue because of side effects; compliance is also a problem, and some patients are ineligible [5, 20]. So, for example, we see patients who had kidney transplants and are on immunosuppression therapy [5, 17]. And so, we think there's a higher risk of complications with BCG, and we don't know if it is going to work with immunosuppression; those patients don't have any good options currently. There are a lot of potential limitations [to BCG treatment], and we really need new treatments as an alternative to BCG and for those who can't get it, or if there's no BCG available, and then certainly for second-line therapy. In the second-line therapy, if patients are BCG unresponsive, we will often recommend a cystectomy which is, of course, a huge surgery. Many patients are not fit for it, many patients will decline it, and there's no question that for those who have it, it impacts quality of life [5, 17]. So more effective bladder-preserving therapies would allow us to avoid that life-altering surgery.

PD-(L)1 INTRODUCTION INTO NMIBC TREATMENT

Peter Black: So, Bernie, maybe I can ask you a next question, which is, you know, how does BCG work? What do we know about its mechanism of action? And how might a PD-1 or a PD-(L)1 inhibitor work in addition to, or maybe even synergistically with, BCG, so that we could justify combining the two?

Bernie Eigl: I work with immunotherapies all the time, but truly, BCG is probably the archetypal immunotherapy. After intravesical installation it infects the bladder urothelial cells and induces a local immune activation [2, 21–23]. It works through different elements of both the innate and adaptive immune system to, hopefully, eradicate the bladder cancer cells and prevent recurrence. For example, BCG treatment decreases myeloid-derived suppressor cells and increases activation and infiltration of T cells into tumor tissue via cytokine production [22, 23]. In both preclinical and clinical settings, it has been reported that BCG may upregulate PD-(L)1 expression, which is interesting given the agents we have available now [22, 23].

PD-(L)1 inhibitors, in contrast, disinhibit the immune system. So they really will unmask cancers, hopefully, that are using the PD-1 signaling access to evade the immune system through sending out self-signals. And one can then hypothesize that maybe the combination [therapy] of BCG and PD-(L)1 inhibitors can inhibit tumor growth even further [22, 23]. And we see this in other areas now, where we're using immunotherapies in the advanced bladder cancer setting with antibody–drug conjugates in combination or sequentially with chemotherapy, that there is, likely, a synergism in terms of the immune system being activated and more antigen presented through the other therapy prior to or along with PD-1 therapies [22–24]. PD-1-targeted therapies have proven activity in more advanced forms of urothelial cancer [25]. As I've said, pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab are all PD-1 or PD-(L)1 inhibitors that have

been approved by the FDA for refractory metastatic urothelial cancer.

The rationale of using PD-1 inhibitors along with BCG, specifically to optimize patient outcomes in BCG-naïve high-risk NMIBC, can be summarized as there being really a significant unmet need for improved treatments of high risk-NMIBC because of all the reasons you've already alluded to, Peter. There is a robust preclinical rationale, as I've stated [22, 24], and PD-1 inhibitor monotherapy has been demonstrated to have efficacy in BCG-unresponsive high-risk NMIBC [24, 26].

Peter Black: So, Bernie, what are the potential challenges that we might encounter if we introduce PD-1/PD-(L)1 inhibition into the treatment of high-risk NMIBC, especially if it moves into the first line?

Bernie Eigl: I think there are quite a few challenges, and opportunities as well. Guys like you and me are going to be working more closely together, I think, as time goes on. But really, that is only part of it; the identification/referral of patients most likely to benefit from these therapies [is important]. We don't know exactly who the right patient at the right time is as yet [27]. Currently, pembrolizumab is FDA-approved for BCG-unresponsive high-risk NMIBC, but it is rarely used. It demonstrated modest efficacy compared with previous studies with intravesical chemotherapies. But it carries a higher risk of systemic toxicity than intravesical therapy, and this needs to be managed in a multidisciplinary setting—especially the immune-related adverse events. And of course, it is much, much more costly [17, 27].

So really, improving multidisciplinary care, collaboration, cooperation, and having the right people managing the different therapies is going to be important to improve shared decision-making; and really, when we look at it now, the management of patients with high-risk NMIBC has been almost exclusively in the hands of urologists who really are doing all the work that is involved in diagnosing and managing this disease. But the introduction of PD-1 inhibitors is going to represent systemic treatment that, up to this point, really has been in the realm of the medical oncologists, and for good reason [28, 29]. Monitoring and managing the immune-related adverse events of these agents require close follow-up and teamwork with other medical specialties in managing the specific types of adverse events they are, whether they are respiratory, GI [gastrointestinal], rheumatologic and so forth [28, 30, 31].

And financial constraints, especially in Canada, are going to create potential barriers to patient access. And, of course, patient and physician education are going to be very important [15].

Peter Black: I think it is funny if you think of other disease states where we share patients between medical oncology and urology that there's really significant overlap. But here, there's almost no overlap, currently. I mean, medical oncologists generally don't see NMIBC; there are some places where the medical oncologists are doing intravesical therapy, and urologists simply do not do immune checkpoint therapy. And now we're going to have to really merge and do it together. I see one of the biggest challenges being just getting the urologists to refer the patients, to recognize that this is a new treatment and that, if it is shown to be efficacious, it *is* efficacious, and that patients need to see medical oncologists, which is not the norm up to now. And these paradigm shifts are often challenging.

Bernie Eigl: I think it really is very much a team approach, not just for medical oncology and urology but, like I said, for the other specialties also because if immune-related adverse events are picked up early and managed early, then patients can still benefit from further treatment. But if they are not, then you know, in a best-case scenario, the adverse event is dealt with, but patients wouldn't be eligible for further therapy [30, 31].

Peter Black: I think the experience with pembrolizumab in the BCG-unresponsive setting has not really tested the waters because it is really only used in the USA. And even there, the efficacy has been marginal, so that there has not been a lot of buy-in [26]. So, you know, if we had immune checkpoint blockade in the first line for high-risk disease, it would be a much bigger indication, and if the evidence is compelling it really does represent a new challenge.

OPTIMIZING PATIENT OUTCOMES FOR NMIBC

Bernie Eigl: So, Peter, at your institution, what does the patient journey look like? Patients who present? What different roles do health professionals play and walk me through the journey?

Peter Black: Patients will usually start with the family doctor. Almost all bladder cancer patients present with gross hematuria, sometimes microhematuria. A smaller percentage will have voiding symptoms, frequency, urgency, that type of thing. But they will end up in primary care, and the primary care doctor will refer the patient to the urologist, recognizing the need to screen for bladder cancer. We will typically, after doing the usual history and physical and that type of thing, move straight to cystoscopy. And if we see a tumor we will take the patient to the operating room for a complete resection, so TURBT. And then, of course, we'll get the report back from the pathologist that tells us what the tumor is, and we can then risk-stratify. And that is when we then sit down with the patient and say, 'Okay, this is what you have, and this is what we would recommend', and together with the patient, we work out a treatment plan, whether that be another TURBT, or BCG, or even cystectomy.

You'll note, of course, that the medical oncologist does not really have a role in any of this up to this point, except in some centers where the medical oncologist does administer the intravesical therapy. I'd say that nurses are perhaps the other important members of the team as they will often be administering the intravesical therapy, and in that context, have a very important counseling role as well. They see the patients a lot and help them through all the side effects of treatment.

During treatment and after treatment, patients will continue to see the urologists frequently for cystoscopy, and we'll often do urine cytology at the same time. Typically, that is every 3 months for 2 years, and every 6 months for 2 years; so, it is quite intensive. And together with the nursing staff, we'll manage any side effects. If there's recurrence or progression, of course we jump in again and manage those.

Peter Black: So, Bernie, if we embark on a new era of immune checkpoint blockade for high-risk NMIBC, what do you think are going to be the keys to make this work effectively, and also the potential pitfalls that we want to avoid as we roll this out.

Bernie Eigl: I think just as MIBC is very much a team-based approach where we have to work very closely together, medical oncology and urology and other specialties. The same is true if and when the PD-(L)1 inhibitors move into the earlier disease setting. And so, teamwork is important, but the teams also have to be well trained to do what they do. And so, clear treatment guidelines and protocols need to be developed, and further refined. Treatment approaches need to be standardized, especially to help HCPs across jurisdictions make informed and consistent decisions for patients. Standard of care needs to be provided, like I said, along with access to the appropriate healthcare specialists. And that is not just, again, to urologists and medical oncologists, but really there needs to be a network in place for the relatively uncommon adverse events that happen with immunotherapies, but also for the ones that really need specialist intervention early. Insufficient communication and coordination or lack of proper care can lead to fragmented care with really not the best outcomes. Patients also need to be educated about immunotherapy, and I spend a lot of time doing this. So they need to be aware of not just the potential benefits, but also the risks and the toxicities that are involved, and ensure that they respond early with reports of any toxicities, so that we can investigate and treat appropriately [14, 15]. I think equally that it is important that medical oncologists are more educated on NMIBC. It is an area that, really, we've had the benefit of ignoring for a very long time. And now we really are becoming practitioners in that area, and so need to be well trained on the diagnosis and management of this disease [28]. Access to PD-(L)1 inhibitors and concerns regarding their affordability will also need to be addressed. Limited access due to reimbursement challenges or high costs, for example, can negatively impact patient outcomes once these are standard treatments.

Peter Black: I think from a urologic perspective that if these [agents] were used much more commonly, and urologists were thinking of prescribing these agents, that the big thing we're lacking, certainly one we are able to learn, is the need for the support system. You need to be able to, you know, have your team that can deal with side effects rapidly, and also need the support to educate the patient and those types of things. I think that might be what many don't see initially, and I think that is a particularly important piece of the puzzle.

I must say, I also look forward to you calling me up and say, 'Hey, I think it's time, for you know the cystoscopy on this patient.'

PROSPECTS IN NMIBC TREATMENT

Bernie Eigl: So, let me ask you a two-part question here. How is the landscape of NMIBC expected to change with the more widespread use of these checkpoint inhibitors, and how will it impact HCPs and patients?

Peter Black: It is interesting to think how bringing this treatment into the first line could impact things; you know that for NMIBC, it is actually considered an advantage that you can put drugs into the bladder and avoid systemic therapy. So, we think that is a good thing. But of course, there's a lot of bladder toxicity, and a lot of catheters are being placed for BCG, once a week for 6 weeks, and then, you know, for a total of 27 times over 3 years; that is pretty invasive. And so the idea of being able to give a systemic therapy, whether it is intravenous, oral, or subcutaneous, may be attractive to a lot of patients, as long as the systemic toxicity is justifiable. So that is one thing. There are certainly a lot of patients, especially when you get into second- and third-line treatments who have problems holding the drugs in their bladder for the necessary period of time, so that [systemic therapy] might actually be a beneficial thing.

On the other hand, if we're going to be doing this early on, we do need to be aware of the immune-related and other adverse events, and systemic therapy for NMIBC would be a paradigm shift because it is not something we're used to. And so, we would need to get everybody on board, as you've already alluded to, Bernie, to make sure that we deal with those potential complications promptly and effectively [27].

The other element is just, you know, that as the landscape potentially shifts we will need more education and training, as you've also alluded to [15]. So you know the mechanisms of actions of the drugs: When should they be used? What patients need to be referred? How was the dosing and the schedule going to be? You know, what are the risks? And many other questions, These will also have a real impact on how we're practicing medicine for these patients with NMIBC.

Peter Black: So, Bernie, as we think of some of these issues that we need to address as we introduce checkpoint blockade for high-risk NMIBC. How can the urologists and the medical oncologists co-operate to help improve patient outcomes?

Bernie Eigl: Cooperation is key in this therapy and for patient safety and best outcomes. And I'm very lucky in the setting that we're in, you know, in an academic setting where we're across the street from each other, and I don't know if you're happy or not to know that you're on my speed dial. But, you know, the relationship between the urologist and the medical oncologist has to be very close when you're managing patients with bladder cancer.

In settings where the physical proximity is not necessarily so close, such as, you know, in the real world, I think this has to be something that is done with thought and actually active intention. So establishing regular communication channels, joint meetings, multidisciplinary tumor boards, and case discussions are all actions that allow for improved coordination and encourage shared decision-making, but also the sharing of what happens with these patients, so that you can learn from each event as you go. To promote multidisciplinary education and training programs and to maintain knowledge exchange between specialists, of course, and again involvement, we have rounds at least couple of times a year to which specialists who deal with the immune-related adverse events are invited. So, rheumatologists

come or endocrinologists, respirologists, etc., and we learn not only how these events are managed, but again, how to look for warning signs before they become serious events. We need to work through jurisdictions to develop standardized care pathways and treatment protocols once these agents are out in the real world. That involves the joint input of urologists, oncologists, and other specialists, and then, really, you know, the fostering of a culture of collaboration and implementing a team and patient-oriented approach. And again, this involves nurses and other allied HCPs specifically for NMIBC treatment [28].

Some urologists, I'll say uro-oncologists, may consider administering PD-(L)1 inhibitor therapies independent of medical oncologists. I think, you know, that the world may well evolve that way, in due course. If PD-(L)1 inhibitors are used more widely in the treatment of this disease, it may provide the necessary patient volume to gain experience for their independent use. But this will take time and education, and again, specialized knowledge and training on patient selection, contraindications, identification, and management of potential side effects. And so, systems would have to be developed to truly allow this, and I would say, in centers of expertise.

But, as I said, in most centers, the real, appropriate approach would be multidisciplinary care with medical oncologists and urologists both involved.

Peter Black: Yeah, I think, even if you know, for urologists to adopt this, it could only come out of a close cooperation with medical oncologists, learning from medical oncologists. I think you know that you often hear about, you know, that with the early introduction of immunotherapy there were severe adverse events, and even deaths that are attributed to inexperience. Things have gotten better as we've gotten better at recognizing the early signs. And really, the last thing we want to do is to relearn all those lessons at the expense of patient well-being. So, I think that it is just super critical that if new physicians are doing it, that they do it really in close collaboration. But ultimately, I think you're right. I think patients will be managed—co-managed—between us.

Peter Black: You know, one thing, Bernie, I was thinking about for education, is it just you talking to the patient during a consultation? Or is there a more formal education program, involving nurses that sit down? Or how does that work?

Bernie Eigl: Yeah, for sure. So, in the advanced setting, when we use immunotherapies, absolutely the first line of education would come when I'm doing initial consultation. But a nurse would have an education session with a patient as well prior to the initiation of therapy. And then at the time of infusion again, there's teaching, and there are teaching opportunities for nurses to provide to the patient while the drug is being infused.

We have a program in place in which we have nurse callouts during the first cycle to make sure that there are no emerging toxicities early and to enable the nurses to provide patient education and patient education materials so that the patient can identify their own immunotherapy and their part in it. So, it really is a multi-pronged, multidisciplinary approach to make sure that problems are identified early.

And you know, with the newer checkpoints, specifically with the PD-1-specific checkpoints as opposed to the first iteration of immunotherapies, you're right, the toxicities are less frequent. But again, they can be picked up early before they become a big problem, and that is key.

Peter Black: And these patients have potentially curable disease by other means. So, I think, there can be less tolerance for severe toxicity.

CLOSING SUMMARY

Peter Black: Good, well, Bernie, I think that we can wrap up this discussion. I think we've talked about how there really is compelling rationale to test PD-L1 or PD-1 therapy in NMIBC. And

you know, we have not talked about the trials, but the trials have been completed, and we're waiting for them to report out.[3] If positive, this will really cause a major shift in the landscape of NMIBC treatment and all the different things that go along with that.

Bernie Eigl: Yeah, Peter, I really enjoyed this conversation, and I agree, we're in the midst of very exciting times and, again, probably a paradigm shift in the management of this disease. And I think that the important take-home message is that with these agents, multidisciplinary care and collaboration are going to be key in providing the best care for our patients. So, I look forward to working even more closely with you.

Peter Black: As do I, and I would thank everybody for tuning in and listening.

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[3] Several clinical trials are currently investigating the safety and efficacy of utilising PD-1/PD-(L)1 inhibitors in combination with BCG. For example, phase 3 trials for atezolizumab (NCT03799835), sasanlimab (NCT04165317), durvalumab (NCT03528694), and pembrolizumab (NCT03711032) are ongoing with estimated primary completion estimated in April 2024, June 2024, October 2024, and December 2025, respectively.

Declarations

Conflict of Interest. Peter C. Black is a member of an advisory board or equivalent with a commercial organization: AbbVie, AstraZeneca, Astellas, Bayer, BMS, EMD-Serono, Ferring, Fergene, Janssen, Merck, miR Scientific, Nonagen, NanOlogy, Pfizer, Photocure, Prokarium, Protara Therapeutics, QED Bioscience, Roche, Sanofi, Sesen Bio, STIMIT, TerSera, Tolmar, Urogen, and Verity; is a member of a Speaker's bureau: Janssen, Minogue, Ferring, TerSera, and Pfizer; has received a grant(s) or an honorarium from a commercial organization: iProgen; is currently participating in or has participated in a clinical trial within the past 2 years: Genentech, Janssen, BMS, AstraZeneca, Therelase, Pacific Edge, and Pfizer; and shares a patent with: Veracyte. He has no other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity. Bernhard J. Eigl has received honoraria from: BMS, Janssen, EMD Serono, Seagen, Gilead; and has received honoraria and research funding from: Pfizer.

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