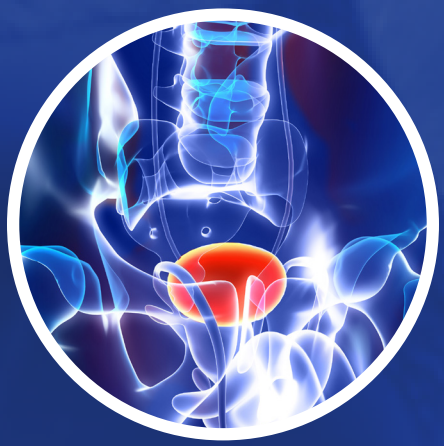
BENCH TO BEDSIDE
URO-ONCOLOGY
GU CANCERS TRIAD



# Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting

May 21–22, 2021

## Bladder Cancer

SOCIÉTÉ INTERNATIONALE D'UROLOGIE
SIU

www.siu-urology.org

#B2BGUCancerTriad

# B2B: Bladder Cancer Summary

DOI: 10.48083/NJCD1236

Peter C. Black,[a,*] Ashish M. Kamat,[b,†] Angela B. Smith,[c] Sima Porten,[d] Renu Eapen,[e,f] Carmen Mir,[g] Jeremy Teoh,[h] Tilman Todenhöfer,[i] Tian Zhang,[j] Kilian M. Gust,[k] Srikala Sridhar,[l] Simon Tanguay[m,‡]

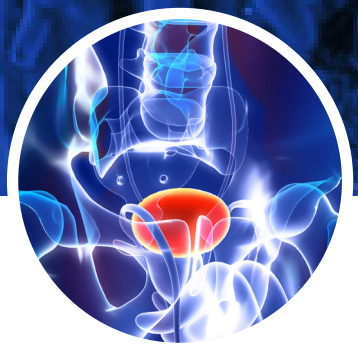
[a]Department of Urologic Sciences, University of British Columbia, Vancouver, Canada [b]Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, United States [c]Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, United States [d]Department of Urology, University of California, San Francisco, United States [e]Peter MacCallum Cancer Centre, Melbourne, Australia [f]Olivia Newton John Cancer Centre & Austin Health, Melbourne, Australia [g]Case Western Reserve University, Cleveland, United States [h]Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China [i]Eberhard-Karls University Tübingen, Tübingen, Germany [j]Department of Medicine, Duke Cancer Institute, Durham, United States [k]Department of Urology, Medical University of Vienna, Vienna, Austria [l]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada [m]Division of Urology, McGill University, Montreal, Canada *Chair of the Scientific Programme Committee [†]Co-Chair of the Scientific Programme Committee (BCa) [‡]Co-Chair of the Scientific Programme Committee (RCC)

The Bench-to-Bedside Uro-Oncology GU Cancer Triad Meeting was organized by the Société Internationale d'Urologie and was held online on May 21st and 22nd, 2021. The session on bladder cancer (BCa) took place on the morning of Friday, May 21st, and was chaired by Dr. Peter C. Black (Canada) and Dr. Ashish Kamat (United States). This session covered practice-changing advances on the horizon for BCa, the use of urine markers in BCa management, evolving therapies for non-muscle-invasive BCa (NMIBC), and recent advances for systemic therapy for muscle-invasive BCa (MIBC) and advanced urothelial carcinoma (UC). The faculty also discussed how to manage immune-related adverse events (AEs).

Dr. Angela Smith (United States) presented five practice-changing advances on the horizon across the disease spectrum of BCa and upper tract UC (UTUC). One of these advances is in the treatment of low-grade intermediate-risk NMIBC[1,2]. These are tumours that have high rates of recurrence but low risk of progression[2]. In this disease setting, transurethral resection of bladder tumour (TURBT) plus intravesical therapy is considered standard of care[1,3], with mitomycin and gemcitabine instillation after TURBT being shown to reduce the risk of recurrence[4,5]. However, repeat TURBTs expose patients to risks of repetitive anesthesia and surgically related complications[6].

The use of UGN-102, a thermoreversible hydrogel containing mitomycin, is being investigated for nonsurgical chemoablation in patients with low-grade intermediate-risk NMIBC in the phase 2b OPTIMA II trial[7]. In an interim analysis, complete response (CR) at 3 months was observed in 65% of patients (95% CI 52%–77%) following treatment with UGN-102. In the safety analysis, 91% of patients experienced ≥1 AE, with the most common AEs occurring in ≥5% of patients related to lower urinary tract symptoms (LUTS), such as dysuria (91%), pollakiuria (41%), and hematuria (19%)[7]. With an estimated durability of response at the 12-month follow-up of 60%, these interim data demonstrate that primary chemoablation of low-grade intermediate-risk NMIBC using UGN-102 results in a significant treatment response and encouraging durability, and may provide an alternative to TURBT treatment for patients in this disease setting[7]. Chemoablation with UGN-102 vs. TURBT is now being investigated in the phase 3 trial ATLAS[8].

There have been multiple advances in the treatment of high-grade bacillus Calmette-Guérin (BCG)-refractory NMIBC, including the U.S. Food and Drug Administration (FDA) approval of pembrolizumab in this setting for carcinoma in situ (CIS) and the recently published results of the novel gene therapy nadofaragene firadenovec in this population[9,10]. Among the developments on the horizon is the investigation of combination intravesical gemcitabine and pembrolizumab therapy to treat BCG-unresponsive NMIBC in the phase 2 Alliance A031803 trial[11]. This trial is also assessing correlations of tumour genomic aberrations with therapy response, the results of which may assist in future patient selection for treatment.



# B2B: Bladder Cancer Summary

In the localized MIBC space, RETAIN BLADDER is a phase 2 trial investigating a risk-adapted approach to treatment that may result in bladder preservation[12]. Treatment was determined according to tumour stage and mutation status following neoadjuvant chemotherapy (NAC) and TURBT. Patients with no residual tumour (cT0) and positive mutations proceeded to active surveillance. In an interim analysis of clinically meaningful endpoints, 39% of patients proceeded to active surveillance. At the data cut-off, 77% of patients on active surveillance were alive, had not developed metastasis, and had not undergone radical cystectomy. Based on these favourable results, the phase 2 RETAIN trial was initiated to investigate a risk-enabled treatment approach following neoadjuvant immunochemotherapy in MIBC[13].

Dual immunotherapy is showing encouraging results in the first-line treatment of locally advanced or metastatic BCa. In an updated analysis of cisplatin-ineligible patients in the EV-103 trial, enfortumab vedotin plus pembrolizumab resulted in a 73.3% confirmed objective response rate (ORR), regardless of programmed death-ligand 1 (PD-L1) expression, and promising 93% tumour reduction[14]. Response to treatment appears to occur relatively quickly, with 88% of patients demonstrating response at first assessment (week 9±1 week). The median progression-free survival (PFS) in this patient cohort was 12.3 months and both median overall survival (OS) as well as duration of response (DOR) have not been reached. In addition to the positive efficacy results, treatment with enfortumab vedotin plus pembrolizumab has a favourable toxicity profile, with only 16% of patients experiencing serious treatment-related AEs (TRAEs).

In the UTUC setting, the phase 3 trial PROOF 302 is evaluating the efficacy and safety of infigratinib as adjuvant therapy in patients with high-risk invasive UC and susceptible FGFR3 alterations[15]. As a large proportion of patients with UTUC shows alterations in FGFR3[16], infigratinib, a fibroblast growth factor receptor (FGFR) inhibitor, may be an attractive therapeutic agent for this population.

During the Q&A period, Dr. Smith was asked how the toxicities of novel bladder-sparing treatments will compare to those of current therapeutic options. According to Dr. Smith, patient-reported outcomes will play an important role in the toxicity evaluation of new therapies, which will also impact the treatment selection. As she pointed out, different treatments may differ considerably in terms of patient experience, regardless of similar efficacy. Another important aspect that will affect treatment selection is the frequency of treatment delivery. Therapies that require fewer visits to the hospital may pose a reduced logistical and financial burden that would ultimately benefit the patient.

The following session was a panel discussion hosted by the SIU Innovators and provided insights on the selection and use of urinary biomarkers in the various stages of BCa diagnosis, management, and follow-up. Dr. Sima Porten (United States) moderated the discussion with input from a panel of experts comprising Dr. Renu Eapen (Australia), Dr. Carmen Mir (Spain), and Dr. Jeremy Teoh (Hong Kong).

The case was a 50-year-old male who received initial treatment with TURBT with gemcitabine for a low-grade Ta tumour. At the 3-month follow-up, cytology showed atypical urothelial cells (Paris 3 classification), despite no evidence of disease by cystoscopy. The panelists discussed if cytology is commonly performed at the time of cystoscopy, the use of the Paris classification by cytopathologists, and whether other urinary biomarkers are routinely used for BCa diagnosis. The use of cytology at the time of surveillance cystoscopy is variable and not always performed for low-grade tumours, and the Paris classification is not always adopted. While cytology is considered the gold standard in this setting, the panelists highlighted other commercially available urinary biomarker tests that may be used in adjunction. ADXBLADDER™ is an enzyme-linked immunosorbent assay (ELISA) test that detects MCM5 in urine, a known biomarker for bladder tumours[17]. Other options include gene expression analysis with messenger RNA (mRNA)-based tests for BCa biomarkers, such as Xpert® Bladder Cancer Monitor[18] and Cxbladder Monitor™ tests[19]. Another biomarker test is UroVysion™, a multi-colour fluorescence in situ hybridization (FISH) assay to detect chromosome aberrations associated with urothelial tumour cells[20].

# B2B: Bladder Cancer Summary

The discussion continued on to which steps would be taken following a positive cytology for Paris 4 or Paris 5, which indicate a higher risk for high-grade UC[21]. If no evidence of disease is seen by cystoscopy, enhanced imaging techniques, such as photodynamic diagnosis or narrow band imaging (NBI)[22], should be implemented to evaluate the presence of UC. Random biopsies of the bladder as well as selective upper tract urine cytology may also be considered, particularly in patients with unexplained positive urine cytology. Upper tract urine cytology may be performed by urine aspiration or lavage cytology and has a high sensitivity of up to 69.9% for high-grade UTUC[23].

Next, the case proceeded with the patient being diagnosed with high-risk NMIBC and starting BCG induction. While not routinely used in clinical practice, urinary biomarkers may play an important role in predicting response to BCG therapy and evaluating patient prognosis. UroVysion FISH analysis has been shown to predict disease recurrence and progression in patients receiving BCG[24]. This may be particularly useful for guiding treatment discussions with patients.

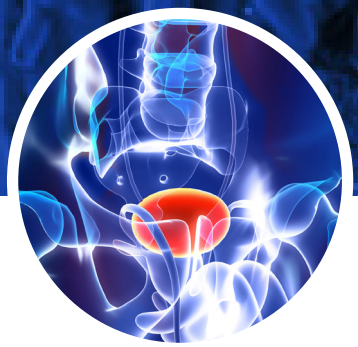
Following BCG maintenance, no evidence of disease was found by cystoscopy and cytology was negative during surveillance for the patient case. However, the number of procedures, frequency of hospital visits, and current risk of COVID-19 may pose an important burden on the patient. In this setting, some urinary biomarker tests demonstrate potential for providing a noninvasive alternative to cystoscopy. Bladder EpiCheck is a kit that detects disease-specific DNA methylation patterns in BCa patients with high negative predictive values (NPV)[25]. However, this test is not routinely implemented in the clinical practice. Other options for patient surveillance may include ADXBLADDER[26] and Xpert Bladder Cancer Monitor[27], both of which have shown high NPV. Dr. Porten highlighted the use of Cxbladder Monitor during the COVID-19 pandemic as an option for patient surveillance at home that has been adopted at the UCSF Medical Center.

In the patient case, surveillance with Cxbladder Monitor showed values above cut-off. Cystoscopy was performed, leading to a diagnosis of MIBC. The patient received NAC followed by radical cystoprostatectomy with lymph node dissection and neobladder diversion with favourable pathology. Given the limited evidence for urinary biomarkers in this setting, computed tomography (CT) scans and urine cytology are typically the routine options for patient surveillance. However, emerging data may provide new insights on the use of urinary biomarkers for post-urinary diversion surveillance.

Next, Dr. Tilman Todenhöfer (Germany) discussed the evolving treatments for NMIBC by focusing on three main topics: 1) identifying predictive molecular markers of BCG treatment response, 2) emerging treatment options for BCG-unresponsive patients, and 3) novel therapy delivery approaches in NMIBC.

Recent studies examining the molecular alterations of NMIBC have led to significant improvements in understanding the disease. In a recent report of the UROMOL project, four molecular subtypes of NMIBC with differing recurrence rates were identified based on the transcriptomic analysis of 834 patients[28]. In the same study, chromosomal instability was also analyzed, leading to the identification of three genomic classes associated with varying risk of disease progression. Both the molecular subtype and genomic class may have important implications for predicting treatment response.

BCG is currently the gold standard for treatment of BCG-naïve NMIBC and results in high rates of high-grade recurrence-free survival (RFS), as demonstrated in a recent retrospective analysis of a contemporary patient cohort[29]. Despite these excellent outcomes, there is an ongoing need for alternative treatment approaches to BCG in NMIBC. First, BCG shortage is an ongoing issue and limits the access of a high proportion of patients to this therapy, leading to significant impact on patient outcomes[30]. Second, BCG intolerance is an ongoing issue, regardless of recent decreases in treatment discontinuation due to TRAEs. Lastly, many patients with NMIBC do not respond to BCG therapy and require other treatment approaches. Therefore, predicting BCG response is important to guide treatment decisions in NMIBC. Recent studies have further advanced this field by identifying genomic and histological markers for patient stratification and treatment outcome prediction[31–33].



# B2B: Bladder Cancer Summary

Treatment of BCG-unresponsive disease continues to be a major challenge in NMIBC. Novel treatment options under investigation in this setting include intravesical approaches with nadofaragene firadenovec[34], oportuzumab monatox[35], and N803/BCG[36], as well as systemic options with immune checkpoint inhibitors (ICIs), such as atezolizumab[37] and pembrolizumab[38]. While all of these agents are showing encouraging outcomes, treatment tolerability in this setting appears slightly improved with intravesical approaches. However, the role of ICI may increase in the NMIBC setting as the results of multiple ongoing trials in BCG-naïve high-risk disease (Potomac, Alban, and CREST), BCG induction failure (KN676 and CheckMate 7G8), and BCG-unresponsive NMIBC (CheckMate 9UT and A031803) become available. In addition, a novel approach for ICI therapy was recently presented. In SUBDUE-1, a dose-finding phase 1b trial, intravesical injection of durvalumab is under investigation for patients with NMIBC[39], an approach that has shown promising results in the pre-clinical studies[40].

Several ongoing trials are also investigating the use of targeted systemic therapies, currently approved for metastatic BCa, in patients with BCG-unresponsive disease. A recent study in patients with FGFR-positive NMIBC demonstrated promising efficacy results following treatment with infigratinib. However, TRAE in all patients led to discontinuation of treatment[41]. In order to improve tolerability of FGFR-targeted therapy in NMIBC, ongoing trials are evaluating FGFR inhibitor doses lower than those used in the metastatic setting. In a current phase 2 trial led by Dr. Noah Hahn at Johns Hopkins, a 9-mg dose of pemigatinib is being investigated to treat patients with NMIBC, which corresponds to only two-thirds of the dose used in metastatic BCa[42].

Other studies are focusing on improving the efficacy and delivery of intravesical chemotherapy. Hyperthermia-induced mitomycin, an approach frequently used in centres in Europe, has become the focus of recent investigations. In a retrospective study of patients with BCG-unresponsive NMIBC, conductive chemohyperthermia with mitomycin led to 12-month RFS rates >50% in patients with CIS[43]. Another way of improving the efficacy of intravesical treatment is the use of a slow-delivery device (TAR-200, GemRIS™) that is inserted in the bladder, which allows continuous delivery and exposure to chemotherapy[44]. Two clinical trials will evaluate the use of TAR-200 in patients with NMIBC. In an ongoing, prospective, randomized phase 2b trial, treatment delivery with TAR-200 is being compared with standard of care intravesical chemotherapy in patients with BCG-unresponsive disease as monotherapy or in combination with the ICI cetrelimab[45]. Another randomized, phase 3 clinical trial will investigate the efficacy of TAR-200 chemotherapy in combination with cetrelimab compared to BCG therapy in BCG-naïve NMIBC, with disease-free survival (DFS) as the primary endpoint.

In the Q&A period, Dr. Todenhöfer provided his highlights of treatment advances in NMIBC to look forward to in the next year. One of the highlights is the development of new drug classes that exceed the efficacy of chemotherapy, such as nadofaragene firadenovec and oportuzumab monatox. According to Dr. Todenhöfer, these therapies may have an important role not only in the treatment of BCG-unresponsive patients, but also in earlier settings. Another highlight is the advance of systemic therapy for NMIBC. As pointed out by Dr. Todenhöfer, these advances will be influenced by important treatment-related toxicities, which may be less tolerable in patients with NMIBC.

The following talk was by Dr. Tian Zhang (United States) who discussed the advances in systemic therapy for MIBC and advanced UC in 2021. The current treatment landscape for metastatic UC comprises platinum-based chemotherapy as first-line regimen and switch maintenance with the PD-L1 inhibitor avelumab, recently highlighted in the JAVELIN Bladder 100 study[46]. Treatment then may follow with enfortumab vedotin for all patients or erdafitinib for those presenting with FGFR2 and FGFR3 genomic alterations. Multiple clinical trials are ongoing and sacituzumab govitecan recently received FDA accelerated approval in the third-line setting[47].

The successful results of different immunotherapeutic agents for metastatic disease have fomented several trials aiming to bring those treatment advances into earlier disease settings. In MIBC, chemotherapy in combination with pembrolizumab was investigated

# B2B: Bladder Cancer Summary

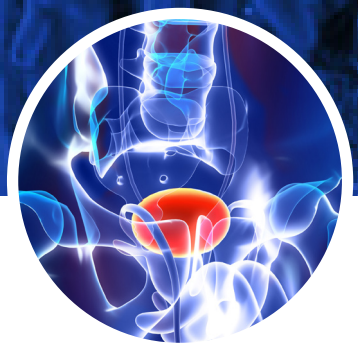
as neoadjuvant therapy prior to radical cystectomy in the LCCC 1520 trial[48]. The primary endpoint has been met, with 56% of patients achieving a down-staging pathologic response rate <pT2N0M0 and 36% having a pathologic CR to treatment, along with a generally safe toxicity profile. A number of clinical trials have been reported in recent years using neo-adjuvant immunotherapy or combination chemoimmunotherapy in MIBC[48–53]. Most of these studies have enrolled patients with T2, T3, T4, or N1 disease and demonstrated the effect of immunotherapies on pathologic response at the time of cystectomy. Several trials are ongoing and aim to examine the role of ICIs, antibody-drug conjugates (ADCs), and combination therapy in the neoadjuvant treatment of MIBC.

In the adjuvant setting, the CheckMate 274 trial investigated the role of nivolumab in the treatment of MIBC following cystectomy, in both patients with prior neoadjuvant cisplatin-based chemotherapy and those without NAC and ineligible for adjuvant treatment[54]. Treatment with nivolumab compared to placebo resulted in a significantly longer median DFS, the primary endpoint, in the intent-to-treat (ITT) population (21.0 vs. 10.9 months, HR=0.70 [98.31% CI 0.54–0.89]; P<0.001), as well as in a subset of patients with PD-L1 expression ≥1% (not reached vs. 10.8 months, HR=0.53 [98.87% CI 0.34–0.84]; P<0.001). Common AEs included pruritus, fatigue, diarrhea, rash, and increased lipase, which are expected reactions from treatment with immunotherapies. Additional trials currently enrolling patients to examine the role of adjuvant immunotherapies in MIBC and UTUC include the AMBASSADOR trial (pembrolizumab vs. observation[55]) and, with targeted therapies for FGFR-altered urothelial cancer, the PROOF-302 trial (infigratinib vs. placebo[15]).

Results of the JAVELIN Bladder 100 trial have changed practice in the locally advanced and metastatic UC setting. In patients with unresectable disease, treatment with avelumab and best supportive care (BSC) resulted in significant improvements in OS (HR=0.69 [95% CI 0.56–0.86]; P<0.001) and PFS (HR=0.62 [95% CI 0.52–0.75]; P<0.001) compared to BSC alone[46]. The benefit of adding avelumab to BSC was observed in patients who had achieved CR, partial response (PR), or stable disease (SD) after initial chemotherapy. While shorter median OS and PFS were observed in patients with PR or SD, additional treatment options may be available for this very frail patient population in the post-avelumab setting.

Additionally, in the metastatic UC setting, the positive results of the phase 3 trial EV-301 have cemented enfortumab vedotin for treatment of patients with refractory disease and prior immunotherapy[56]. In the trial, treatment with enfortumab vedotin resulted in significantly improved OS (12.88 vs. 8.97 months, HR=0.70 [95% CI 0.56–0.89]; P=0.0142) and PFS (5.554 vs. 3.72 months, HR=0.62 [95% CI 0.51–0.75]; P<0.00001) compared to chemotherapy. Among the grade 3 or higher AEs observed in this trial, maculopapular rash occurred more frequently in patients who received enfortumab vedotin (7% vs. 0%), whereas decreased neutrophil count (6% vs. 13%), decreased white blood cell (1% vs. 7%), and febrile neutropenia (1% vs. 5%) were more frequently observed in the chemotherapy group. Other ongoing trials (EV-302 and EV-103) are evaluating the use of enfortumab vedotin alone or in combination with pembrolizumab or chemotherapy as a first-line treatment option for metastatic UC[51,57].

During the Q&A, Dr. Zhang provided her insights on first- and second-line therapy recommendations for metastatic UC. Platinum-based chemotherapy is still the primary option for eligible patients. Once achieving SD, Dr. Zhang recommends that patients undergo maintenance treatment with avelumab. Second-line options will often include enfortumab vedotin for all patients or erdafitinib for patients with FGFR alterations. With each line of therapy in metastatic UC, the goal is to extend patient survival while preserving quality of life. She also pointed out that other options may become available in earlier disease settings, as many ongoing clinical trials are evaluating systemic therapy options in the localized and adjuvant settings. In addition, Dr. Zhang addressed the ideal timing to sequence tumour tissue in order to guide treatment decisions in the metastatic setting. She recommends that sequencing be performed following cystectomy, given the amount of tumour tissue available, particularly for patients who have residual disease after neoadjuvant treatment.



# B2B: Bladder Cancer Summary

The session concluded with a case-based discussion on management of immune-related AEs and toxicities, not specifically related to BCa. This was led by Dr. Kilian Gust (Austria), with the discussion based on the input of Dr. Srikala Sridhar (Canada), Dr. Tilman Todenhöfer (Germany), and Dr. Tian Zhang (United States).

The first case was a 54-year-old female initially diagnosed with and treated for high-risk NMIBC who progressed to MIBC. Following a radical cystectomy, the patient presented with lymph node metastasis in the surgical field. At this time, the patient started treatment with atezolizumab after enrolling in the SAUL trial[58]. After the first treatment cycle, the patient presented with a marked increase in thyroid-stimulating hormone (TSH), characteristic of thyroiditis. This AE is commonly observed in patients receiving immunotherapies. If the patient is asymptomatic or presents mild symptoms, immune-related thyroid dysfunction does not require immediate management or discontinuation of immunotherapy. Changes in TSH, T3, and T4 hormone levels should be closely monitored. Early referral to an endocrinologist may be considered[59]. The patient continued treatment with atezolizumab and reached CR. Over time, she developed hypothyroidism, which was managed with thyroid hormones. At cycle 49 of atezolizumab, the patient relapsed and was treated with chemotherapy, after which she achieved PR and was put on avelumab maintenance. After receiving the first dose, the patient presented with fever and chills. These infusion reactions are commonly seen with avelumab[46] and may be prevented with premedication.

The second case was a 76-year-old male with poor prognosis for MIBC. After the patient refused NAC, he underwent radical cystectomy and recovered well after surgery. Results of CheckMate 274 trial suggest that this patient could benefit from adjuvant treatment with nivolumab[54], which is not yet approved in this setting. Two weeks after receiving the first dose of nivolumab, the patient reported feeling unwell. His blood work showed altered liver function. At this point, it is important to put the immunotherapy treatment on hold, discuss with the patient the possibility of a TRAE, and consider referral to a hepatologist. Management of altered liver function may include prednisolone. If tests do not show improvement, a liver biopsy may be performed to guide alternative management decisions[59]. The patient in this case responded well to intravenous methylprednisolone and resumed immunotherapy with close monitoring of liver function. In an alternative scenario in which the patient had received NAC, it would be important to discuss potential TRAEs prior to starting treatment with nivolumab. Patients in this setting who have no signs of active disease may be less tolerant to AEs resulting from immunotherapy.

The last case was a 67-year-old male with intermediate-risk renal cell carcinoma (RCC) who underwent cytoreductive nephrectomy prior to enrolling in the phase 3 CLEAR trial, in which the patient received pembrolizumab plus lenvatinib[60]. At his first visit, the patient presented with grade 1 nausea and grade 1 hypertension. Later, he also developed grade 2 rash on the back of the legs, corresponding to 18% of the body surface area (BSA). In this scenario, management of rash includes topical steroids, which may be complemented by oral antihistamines. Early referral to a dermatologist is advised[59]. The patient continued combination therapy and started treatment with topical steroids, until developing intense grade 3 rash on the legs, corresponding to a BSA of 36%. In this case, the patient requires management with systemic steroids and a dermatological review is indicated[59]. Therapy should be put on hold and continued only after symptoms have improved. Combination therapy was resumed after symptoms had improved, until recurrent grade 3 rash led to permanent discontinuation of first pembrolizumab and later lenvatinib, due to tyrosine kinase inhibitor (TKI)-related rash. In some practices, TKI may be discontinued prior to ICI due to its shorter-acting effects. Steroid treatment may be considered if rash persists after TKI discontinuation. If rashes improve after treatment discontinuation, treatment dose reduction may be considered. When evaluating additional treatment options, it is also important to keep the patient's quality of life, which may be deeply impacted by skin rashes, in mind.

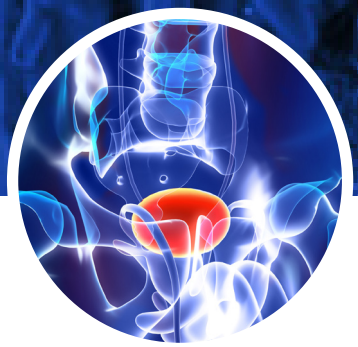
# B2B: Bladder Cancer Summary

## Abbreviations Used in the Text

| | |
|---|---|
| ADC | antibody-drug conjugate |
| AE | adverse event |
| BCa | bladder cancer |
| BCG | bacillus Calmette-Guérin |
| BSA | body surface area |
| BSC | best supportive care |
| CI | confidence interval |
| CIS | carcinoma in situ |
| CR | complete response |
| CT | computed tomography |
| DFS | disease-free survival |
| DOR | duration of response |
| ELISA | enzyme-linked immunosorbent assay |
| FDA | U.S. Food and Drug Administration |
| FGFR | fibroblast growth factor receptor |
| FISH | fluorescence in situ hybridization |
| HR | hazard ratio |
| ICI | immune checkpoint inhibitor |
| ITT | intent-to-treat |
| LUTS | lower urinary tract symptom |
| MIBC | muscle-invasive bladder cancer |
| mRNA | messenger RNA |
| NAC | neoadjuvant chemotherapy |
| NBI | narrow band imaging |
| NMIBC | non-muscle-invasive bladder cancer |
| NPV | negative predictive value |
| ORR | objective response rate |
| OS | overall survival |
| PD-L1 | programmed death-ligand 1 |
| PFS | progression-free survival |
| PR | partial response |
| RCC | renal cell carcinoma |
| RFS | recurrence-free survival |
| SD | stable disease |
| TKI | tyrosine kinase inhibitor |
| TRAE | treatment-related adverse event |
| TSH | thyroid-stimulating hormone |
| TURB | transurethral resection of bladder tumour |
| UC | urothelial carcinoma |
| UTUC | upper tract urothelial carcinoma |

## References


1. Kamat AM, Witjes JA, Brausi M, et al. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. *Journal of Urology.*2014;192(2):305-315. doi:10.1016/j.juro.2014.02.2573
2. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: acombined analysis of 2596 patients from seven EORTC trials. *European Urology.*2006;49(3):466-477. doi:10.1016/j.eururo.2005.12.031
3. Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *Journal of Urology.*2007;178(6):2314-2330. doi:10.1016/j.juro.2007.09.003
4. Chou R, Selph S, Buckley DI, et al. Intravesical Therapy for the treatment of nonmuscle invasive bladder cancer: a systematic review and meta-analysis. *Journal of Urology.* 2017;197(5):1189-1199. doi:10.1016/j.juro.2016.12.090
5. Bosschieter J, Nieuwenhuijzen JA, van Ginkel T, et al. Value of an Immediate Intravesical Instillation of Mitomycin C in Patients with Non–muscle-invasive Bladder Cancer: A Prospective Multicentre Randomised Study in 2243 patients [Figure presented]. *European Urology.*2018;73(2):226-232. doi:10.1016/j.eururo.2017.06.038
6. Avallone MA, Sack BS, El-Arabi A, et al. Ten-Year Review of Perioperative Complications After Transurethral Resection of Bladder Tumors: Analysis of Monopolar and Plasmakinetic Bipolar Cases.*Journal of Endourology.* 2017;31(8):767-773. doi:10.1089/end.2017.0056
7. Huang W, Chevli K, Trainer A, et al. Can TURBT be avoided? Primary chemoablation with a reverse thermal gel containing mitomycin (UGN-102) in patients with low grade intermediate risk non-muscle invasive bladder cancer. *Journal of Urology.*2020;203(Supplement 4). doi:10.1097/ju.0000000000000958.03



# B2B: Bladder Cancer Summary


8. A phase 2b study of UGN-102 for low grade intermediate risk non-muscle-invasive bladder cancer. Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT03558503

9. FDA approves pembrolizumab for BCG-unresponsive, high-risk non-muscle invasive bladder cancer. Accessed June 1, 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer

10. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *The Lancet Oncology*.2021;22(1):107-117. doi:10.1016/S1470-2045(20)30540-4

11. Testing the Addition of an Anti-cancer Drug, Pembrolizumab, to the Usual Intravesical Chemotherapy Treatment (Gemcitabine) for the Treatment of BCG-Unresponsive Non-muscle Invasive *Bladder Cancer*. Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT04164082

12. Geynisman DM, Abbosh P, Ross EA, et al. A phase II trial of risk enabled therapy after initiating neoadjuvant chemotherapy for bladder cancer (RETAIN BLADDER): interim analysis. *Journal of Clinical Oncology*. 2021;39(6_suppl):397. doi:10.1200/jco.2021.39.6_suppl.397

13. A study of risk enabled therapy after neoadjuvant immunochemotherapy for bladder cancer. Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT04506554

14. Rosenberg JE, Flaig TW, Friedlander TW, et al. Study EV-103: preliminary durability results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. *Journal of Clinical Oncology*. 2020;38(6_suppl):441. doi:10.1200/jco.2020.38.6_suppl.441

15. Daneshmand S, Grivas P, Sridhar SS, et al. PROOF 302: a randomized, double-blind, placebo-controlled, phase III trial of infigratinib as adjuvant therapy in patients with invasive urothelial carcinoma harboring susceptible FGFR3 alterations. *Journal of Clinical Oncology*. 2020;38(15_suppl):TPS5095. doi:10.1200/jco.2020.38.15_suppl.tps5095

16. Sfakianos JP, Cha EK, Iyer G, et al. Genomic characterization of upper tract urothelial carcinoma. *European Urology*. 2015;68(6):970-977. doi:10.1016/j.eururo.2015.07.039

17. Dudderidge T, Stockley J, Nabi G, et al. A novel, non-invasive test enabling bladder cancer detection in urine sediment of patients presenting with haematuria—a prospective multicentre performance evaluation of ADXBLADDER. *European Urology Oncology*. 2019;3(1):42-46. doi:10.1016/j.euo.2019.06.006

18. Pichler R, Fritz J, Tulchiner G, et al. Increased accuracy of a novel mRNA-based urine test for bladder cancer surveillance. *BJU International*.2018;121(1):29-37. doi:10.1111/bju.14019

19. Lotan Y, O'Sullivan P, Raman JD, et al. Clinical comparison of noninvasive urine tests for ruling out recurrent urothelial carcinoma. *Urologic Oncology: Seminars and Original Investigations*.2017;35(8):531.e15-531.e22. doi:10.1016/j.urolonc.2017.03.008

20. Reid-Nicholson MD, Ramalingam P, Adeagbo B, et al. The use of Urovysion™ fluorescence in situ hybridization in the diagnosis and surveillance of non-urothelial carcinoma of the bladder. *Modern Pathology*. 2009;22(1):119-127. doi:10.1038/modpathol.2008.179

21. Rosenthal DL, Wojcik EM, Kurtycz DFI, eds. The Paris System for Reporting Urinary Cytology. *Springer International Publishing*.2016. doi:10.1007/978-3-319-22864-8

22. Kutwin P, Konecki T, Cichocki M, et al. Photodynamic diagnosis and narrow-band imaging in the management of bladder cancer: a review. *Photomedicine and Laser Surgery*.2017;35(9):459-464. doi:10.1089/pho.2016.4217

23. Potretzke AM, Knight BA, Vetter JM, et al. Diagnostic Utility of Selective Upper Tract Urinary Cytology: A Systematic Review and Meta-analysis of the Literature. *Urology*.2016;96:35-43. doi:10.1016/j.urology.2016.04.030

24. Kamat AM, Dickstein RJ, Messetti F, et al. Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guérin therapy for bladder cancer: Results of a prospective trial. *Journal of Urology*.2012;187(3):862-867. doi:10.1016/j.juro.2011.10.144

25. Mancini M, Righetto M, Zumerle S, et al. The Bladder EpiCheck Test as a non-invasive tool based on the identification of dna methylation in bladder cancer cells in the urine: a review of published evidence. International *Journal of Molecular Sciences*.2020;21(18):6542. doi:10.3390/ijms21186542

26. Roupret M, Gontero P, McCracken SRC, et al. Diagnostic accuracy of MCM5 for the detection of recurrence in nonmuscle invasive bladder cancer followup: a blinded, prospective cohort, multicenter european study. *Journal of Urology*.2020;204(4):685-690. doi:10.1097/JU.0000000000001084

# B2B: Bladder Cancer Summary


27. Elsawy AA, Awadalla A, Elsayed A, et al. prospective validation of clinical usefulness of a novel mRNA-based urine test (Xpert® *Bladder Cancer* Monitor) for surveillance in non muscle invasive bladder cancer. *Urologic Oncology: Seminars and Original Investigations.*2021;39(1):77.e9-77.e16. doi:10.1016/j.urolonc.2020.07.013

28. Lindskrog SV, Prip F, Lamy P, et al. An integrated multi-omics analysis identifies prognostic molecular subtypes of non-muscle-invasive bladder cancer. *Nature Communications.* 2021;12(1):2301. doi:10.1038/s41467-021-22465-w

29. Matulay JT, Li R, Hensley PJ, et al. Contemporary outcomes of patients with nonmuscle-invasive bladder cancer treated with bacillus Calmette-Guérin: Implications for clinical trial design. *Journal of Urology.*2021;205(6):1612-1621. doi:10.1097/JU.0000000000001633

30. Lee S, Lim B, You D, et al. Association of bacillus Calmette–Guerin shortages with bladder cancer recurrence: a single-center retrospective study. *Urologic Oncology: Seminars and Original Investigations.*2020;38(11):851.e11-851.e17. doi:10.1016/j.urolonc.2020.07.014

31. Robertson AG, Groeneveld CS, Jordan B, et al. Identification of differential tumor subtypes of T1 bladder cancer. *European Urology.*2020;78(4):533-537. doi:10.1016/j.eururo.2020.06.048

32. de Jong FC, Hoedemaeker RF, Kvikstad V, et al. T1 substaging of nonmuscle invasive bladder cancer is associated with bacillus Calmette-Guérin failure and improves patient stratification at diagnosis. *Journal of Urology.*2021;205(3):701-708. doi:10.1097/JU.0000000000001422

33. Bellmunt J, Kim J, Reardon B, et al. Genomic predictors of good outcome, recurrence, or progression in high-grade T1 non–muscle-invasive bladder cancer. *Cancer Research.*2020;80(20):4476-4486. doi:10.1158/0008-5472.CAN-20-0977

34. Boorjian S, Dinney C, The Society of Urologic Oncology Clinical Trials Consortium. A phase III study to evaluate the safety and efficacy of intravesical nadofaragene firadenovec for patients with high-grade, BCG unresponsive non-muscle invasive bladder cancer: papillary disease cohort results. *Journal of Urology.*2020;203:e261. doi:10.1097/JU.0000000000000846.07

35. Dickstein R, Wu N, Cowan B, Franks M, Wolk F. VISTA, phase 3 trial of vicineum, an EpCAM-targeted pseudomonas exotoxin, in bcg-unresponsive non-muscle invasive bladder cancer. In: *Global Congress on Bladder Cancer 2018.*2018.

36. Chamie K, Chang S, Gonzalgo ML, et al. Phase II/III clinical results of IL-15R$\alpha$Fc superagonist N-803 with BCG in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS) patients. *Journal of Clinical Oncology.*2021;39(6_suppl):510. doi:10.1200/JCO.2021.39.6_suppl.510

37. Black PC, Tangen C, Singh P, et al. Phase II trial of atezolizumab in BCG-unresponsive non-muscle invasive bladder cancer: SWOG S1605 (NCT #02844816). *Journal of Clinical Oncology.*2020;38(15_suppl):5022. doi:10.1200/JCO.2020.38.15_suppl.5022

38. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab (pembro) for the treatment of patients with Bacillus Calmette-Guérin (BCG) unresponsive, high-risk (HR) non–muscle-invasive bladder cancer (NMIBC): over two years follow-up of KEYNOTE-057. *Journal of Clinical Oncology.*2020;38(15_suppl):5041. doi:10.1200/JCO.2020.38.15_suppl.5041

39. Viswambaram P, Moe A, Liow ECH, et al. Sub-urothelial durvalumab injection-1 (SUBDUE-1): A novel approach to immunotherapy for bladder cancer. *Journal of Clinical Oncology.*2021;39(6_suppl):TPS503. doi:10.1200/JCO.2021.39.6_suppl.TPS503

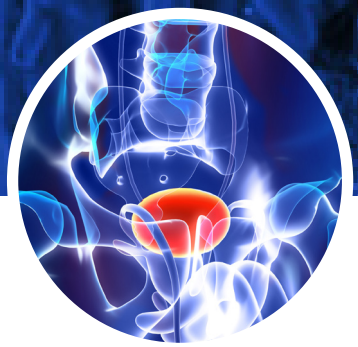
40. Kirschner AN, Wang J, Rajkumar-Calkins A, et al. Intravesical anti-PD-1 immune checkpoint inhibition treats urothelial bladder cancer in a mouse model. *Journal of Urology.*2021;205(5):1336-1343. doi:10.1097/JU.0000000000001576

41. Cha EK, Iyer G, Funt SA, et al. Marker lesion study of oral FGFR inhibitor BGJ398 in patients with FGFR3-altered intermediate-risk nonmuscle-invasive bladder cancer. *Journal of Clinical Oncology.*2020;38(6_suppl):510. doi:10.1200/JCO.2020.38.6_suppl.510

42. A study of pemigatinib in non-muscle invasive bladder cancer patients with recurrent low- or intermediate-risk tumors. Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT03914794

43. de Jong JJ, Hendricksen K, Rosier M, et al. Hyperthermic intravesical chemotherapy for BCG unresponsive non-muscle invasive bladder cancer patients. *Bladder Cancer.*2018;4(4):395-401. doi:10.3233/BLC-180191

44. Grimberg DC, Shah A, Inman BA. Overview of Taris GemRIS, a novel drug delivery system for bladder cancer. *European Urology Focus.*2020;6(4):620-622. doi:10.1016/j.euf.2019.09.006



# B2B: Bladder Cancer Summary


45. A Study of TAR-200 in combination with cetrelimab, TAR-200 alone, or cetrelimab alone in participants with non-muscle invasive bladder cancer (NMIBC) unresponsive to intravesical bacillus calmette-guerin who are ineligible for or elected not to undergo radical cystectomy . Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT04640623

46. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *New England Journal of Medicine.*2020;383(13):1218-1230. doi:10.1056/NEJMoa2002788

47. FDA grants accelerated approval to sacituzumab govitecan for advanced urothelial cancer. Accessed June 1, 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer

48. Rose TL, Harrison MR, Deal AM, et al. Phase II study of gemcitabine and split-dose cisplatin plus pembrolizumab as neoadjuvant therapy prior to radical cystectomy (RC) in patients with muscle-invasive bladder cancer (MIBC). *Journal of Clinical Oncology.*2021;39(6_suppl):396. doi:10.1200/JCO.2021.39.6_suppl.396

49. Bandini M, Ross JS, Raggi D, et al. Predicting the pathologic complete response after neoadjuvant pembrolizumab in muscle-invasive bladder cancer. *Journal of the National Cancer Institute.*2021;113(1):48-53. doi:10.1093/JNCI/DJAA076

50. Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. *Nature Medicine.*2019;25(11):1706-1714. doi:10.1038/s41591-019-0628-7

51. van der Heijden MS, Gupta S, Galsky MD, et al. Study EV-302: a 3-arm, open-label, randomized phase III study of enfortumab vedotin plus pembrolizumab and/or chemotherapy, versus chemotherapy alone, in untreated locally advanced or metastatic urothelial cancer. *Annals of Oncology.*2020;31 :S605-S606. doi:10.1016/j.annonc.2020.08.2069

52. Gao J, Navai N, Alhalabi O, et al. Neoadjuvant PD-L1 plus CTLA-4 blockade in patients with cisplatin-ineligible operable high-risk urothelial carcinoma. *Nature Medicine.*2020;26(12):1845-1851. doi:10.1038/s41591-020-1086-y

53. Gupta S, Sonpavde G, Weight CJ, et al. Results from BLASST-1 (*Bladder Cancer* Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in muscle invasive bladder cancer (MIBC) undergoing cystectomy. *Journal of Clinical Oncology.*2020;38(6_suppl):439. doi:10.1200/JCO.2020.38.6_suppl.439

54. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *New England Journal of Medicine.* 2021;384(22):2102-2114. doi:10.1056/NEJMoa2034442

55. Apolo AB, Rosenberg JE, Kim WY, et al. Alliance A031501: phase III randomized adjuvant study of MK-3475 (pembrolizumab) in muscle-invasive and locally advanced urothelial carcinoma (MIBC) (AMBASSADOR) versus observation. *Journal of Clinical Oncology.* 2019;37(7_suppl):TPS504. doi:10.1200/JCO.2019.37.7_suppl.TPS504

56. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *New England Journal of Medicine.*2021;384(12):1125-1135. doi:10.1056/NEJMoa2035807

57. Hoimes CJ, Rosenberg JE, Petrylak DP, et al. EV-103: enfortumab vedotin plus pembrolizumab and/or chemotherapy for locally advanced or metastatic urothelial cancer. *Journal of Clinical Oncology.*2019;37(15_suppl):TPS4593. doi:10.1200/JCO.2019.37.15_suppl.TPS4593

58. Sternberg CN, Loriot Y, James N, et al. Primary results from SAUL, a multinational single-arm safety study of atezolizumab therapy for locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract. *European Urology.*2019;76(1):73-81. doi:10.1016/j.eururo.2019.03.015

59. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.*2017;28:iv119-iv142. doi:10.1093/annonc/mdx225

60. Motzer R, Alekseev B, Rha S-Y, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *New England Journal of Medicine.* 2021;384(14):1289-1300. doi:10.1056/nejmoa2035716