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Conference Report

B2B: Bladder Cancer Summary

Peter C. Black [1,*,‡], Seth P. Lerner [2], Mihir M. Desai [3], Badrinath R. Konety [4,5], Shilpa Gupta [6], Amit Joshi [7], Karima Oualla [8], Senthil Rajappa [9], Vineet Talwar [10], Gagan Prakash [11,§] and Simon Tanguay [12,‡]

1 Department of Urologic Sciences, University of British Columbia, Vancouver, BC V6T 1Z4, Canada
2 Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, USA
3 Department of Urology, University of Southern California, Los Angeles, CA 90033, USA
4 Department of Urology, University of Minnesota, Minneapolis, MN 55455, USA
5 Rush Medical College, Chicago, IL 55454, USA
6 Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH 44195, USA
7 Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai 400012, India
8 Department of Medical Oncology, Centre Hospitalier Universitaire Hassan II, Fes 30050, Morocco
9 Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad 500034, India
10 Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi 110085, India
11 Department of Surgical Oncology, Tata Memorial Centre, Mumbai 400012, India
12 Department of Surgery, Division of Urology, McGill University, Montreal, QC H3A 0G4, Canada
* Correspondence: peter.black@ubc.ca
‡ Co-Chair, Scientific Programme Committee.
§ Local Lead, Scientific Programme Committee.

The 6th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 44th Annual Congress of the Société Internationale d'Urologie, was held on 25 October 2024, in New Delhi, India, and transmitted live on the *SIU@U* Congress platform. The first session, on bladder cancer (BCa), took place in the morning and was moderated by Dr. Peter C. Black (Canada). This session covered first-line treatments in non–muscle-invasive BCa (NMIBC), subtype-directed therapies in muscle-invasive BCa (MIBC), a debate on surgical approach for radical cystectomy (RC), an update on adjuvant therapy for MIBC, and a panel discussion on sequencing of systemic therapy in locally advanced and metastatic urothelial carcinoma (mUC). For the first time, the B2B programme featured a luncheon symposium dedicated to key advances in the management of GU cancers. This year, the symposium was dedicated to progress in intravesical drug delivery treatments in BCa.

Dr. Seth P. Lerner (United States) gave the first presentation, on the first-line treatment of intermediate-risk (IR) and high-risk (HR) NMIBC. He started his talk by noting that there is a global shortage of bacillus Calmette-Guérin (BCG), a mainstay of treatment for NMIBC. Therefore, clinicians must become familiar with which patients can receive alternative treatments and what those alternative treatment options are. An important first step in making treatment decisions is risk stratification. According to American Urological Association (AUA) [1] and European Association of Urology (EAU) [2] guidelines, most first-occurrence, low-grade (LG) solitary tumours are considered low risk (LR), and multifocal and/or recurrent LG BCa is typically categorized as IR. All remaining tumours that are high grade are considered HR. Dr. Lerner noted that, in the AUA guidelines, high-grade (HG) Ta tumours $\leq$ 3 cm have been reclassified from HR to IR. In addition, LG T1 tumours can also be treated as IR [1].

Among the IR population, approximately 10% to 15% are at risk of progressing to HG or invasive disease. The International Bladder Cancer Group (IBCG) has produced an

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updated risk stratification scheme for IR patients [3] that was validated by Soria et al. [4]. Kwong et al. are using artificial intelligence (AI) to improve precision in risk stratification of IR patients. In an analysis involving 34 academic and community centres and 11,713 patients (2935 of whom were IR-NMIBC), IR patients were separated into 3 risk strata using the following risk factors: multiple tumours, early recurrence (<1 year), frequent recurrence (>1/year), tumour size > 3 cm, and failure of previous intravesical treatment. The manuscript is currently under review for publication.

Dr. Lerner treats HR-IR patients (i.e., those with ≥3 risk factors) with BCG, similar to the treatment of HR NMIBC patients, but all other IR NMIBC patients he treats with intravesical chemotherapy. Patients suspected to have LG disease should receive a single dose of perioperative intravesical chemotherapy (IVC). Gemcitabine, mitomycin C (MMC), and anthracyclines (epirubicin, doxorubicin, pirarubicin) are the most effective agents in this context, reducing recurrence rates by about 35%. Interferon does not appear to be effective in this setting. IVC is contraindicated in patients with an obvious bladder perforation or resection into fat.

A recent meta-analysis demonstrated that a single-dose perioperative IVC after transurethral resection of bladder tumour (TURBT) in patients with stage pTa-pT1 urothelial carcinoma of the bladder slowed time to first recurrence but was not effective in patients with an European Organisation for Research and Treatment of Cancer (EORTC) risk score > 5 [5]. In a study by Messing et al., IVC using gemcitabine in LR or IR NMIBC patients reduced recurrence when compared with saline control [6]. According to Dr. Lerner's personal correspondence with the lead author, the treatment also produces substantial cost savings compared with either saline or MMC. In addition, Dr. Lerner stressed that MMC is a desiccant that can cause necrosis and calcification if it infiltrates the tissues surrounding the bladder.

For induction IVC, using an optimized MMC regimen can be very effective. In one trial, 119 patients with IR NMIBC were randomized to standard MMC (4 mg/40 mL) or a more concentrated (40 mg/20 mL) dose of MMC that was optimized with administration of oral sodium bicarbonate 1.3 g the night before or morning of the procedure. An alkaline environment promotes uptake of MMC into the bladder mucosa and submucosa. Patients must receive nothing by mouth after midnight the evening before the procedure, to ensure they are producing minimal urine so as not to dilute the concentration of MMC. An empty bladder is confirmed via ultrasound. In an intent-to-treat (ITT) analysis, patients in the optimized arm had a longer median time to recurrence (29.1 vs. 11.8 months) and a greater recurrence-free fraction (41.0% vs. 24.6%) at 5 years than patients in the standard arm [7].

In a recent trial, 117 IR NMIBC patients treated with TURBT were randomized to receive either intravesical gemcitabine or intravesical BCG weekly for 6 weeks. Outcomes were similar in both groups, but the rate of side effects was much lower with gemcitabine (13.6% vs. 44.8%, $p = 0.016$) [8].

In patients with HR NMIBC, the standard of care is BCG induction and maintenance out to 3 years. The benefits of this approach were demonstrated in the SWOG 8507 trial in which BCG-naïve HR NMIBC patients were randomized to BCG induction with or without 3 years of maintenance therapy delivered at 3, 6, 12, 18, 24, 30, and 36 months. Only 16% of patients lasted the entire 3 years of the trial, partly due to treatment toxicity. However, this experience has permitted improvement in management of toxicity over time, largely with dose reductions. The 2-year recurrence-free survival (RFS) was improved with maintenance therapy compared with no maintenance therapy (82% vs. 62%) as was 5-year RFS (60% vs. 41%). In addition, a composite endpoint termed worsening-free survival (consisting of the absence of any indication of progression to a worse disease state) was superior with maintenance therapy, at 87 vs. 102 events, $p = 0.04$) [9].

Notably, among the 278 patients with carcinoma in situ (CIS), complete response (CR) rates at 3 months were similar between the 2 arms with and without maintenance (55% vs. 57%), as expected, but CR rates clearly favoured maintenance therapy by 6 months (84% vs. 68%) [9]. Dr. Lerner said that these findings highlight the fact that some patients have a delayed immune response, which mandates not abandoning BCG due to persistent CIS at 3 months. Patients should be treated with the 3 weekly maintenance BCG or reinduction should be considered. After 6 months, biopsy with enhanced cystoscopy is recommended to determine the pathologic response to BCG.

There is evidence that a gemcitabine-docetaxel (GD) regimen is beneficial in HR NMIBC, although all supporting data are retrospective in nature. A retrospective multisite study of sequential GD for the treatment of recurrent NMIBC with a history of BCG use revealed a 2-year overall RFS of 46% (50% in BCG unresponsive cases with CIS and 58% in papillary alone BCG unresponsive cases). The 2-year progression-free survival (PFS) was 7%, and there was a low rate of discontinuation due to side effects (3.3%) [10].

Several new studies are evaluating alternatives to BCG for HR-IR and HR NMIBC. In the ATLAS trial, IVC with UGN-102, a reverse thermal (RT) gel containing MMC, was evaluated in patients with new or recurrent LG IR NMIBC. Patients received UGN-102 plus TURBT or TURBT monotherapy. The estimated probability of disease-free survival (DFS) at 15 months was 72% with UGN-102 with or without TURBT vs. 50% for TURBT alone (hazard ratio = 0.45) [11].

Several trials in this space are either in the planning stage or ongoing. The ongoing phase 3 EA8212 BRIDGE study is randomizing patients with BCG-naïve HG NMIBC and no history of prostatic, urethral, or upper tract urothelial cancer to 6 weekly cycles of GD with monthly maintenance for 24 months or 6 weekly cycles of BCG with SWOG maintenance protocol. Patients are stratified by the presence of pure CIS, pure papillary disease, or mixed disease. The primary endpoint is event-free survival (EFS) [12]. For the phase 3 PIVOT-006 trial (NCT06111235), patients with IR NMIBC are being randomized to cretostimogene grenadenorepvec or observation following TURBT. Cretostimogene is a conditionally replicating, intravesically delivered adenovirus engineered to induce oncolytic immunotherapy (IO) by selectively replicating and lysing Rb-altered BCa cells via insertion of human E2F-1 promoter and producing granulocyte-macrophage colony-stimulating factor (GM-CSF). The primary outcome is RFS.

In the phase 3 ABLE-32 trial (NCT02773849), patients with IR NMIBC undergo TURBT, followed by either observation or quarterly instillations of nadofaragene firadenovec for 24 months. Nadofaragene firadenovec is a replication deficient adenovirus with the interferon-α2b transgene and is approved by the U.S. Food and Drug Administration (FDA) for treatment of BCG unresponsive CIS with or without papillary disease. The primary endpoint is RFS at 24 months. In the open-label phase 3 MoonRISe-1 study, patients with IR NMIBC are randomized to TAR-210, a novel erdafitinib intravesical delivery system, vs. IVC (investigator's choice of gemcitabine or MMC). Erdafitinib was selected because 50% to 80% of NMIBC have activating *FGFR* alterations. The primary outcome is DFS [13]. Finally, in SunRISe-3, another phase 3 open-label trial, patients with BCG-naïve HR NMIBC are randomized to monotherapy with TAR-200, a similar novel intravesical delivery system, this time providing local continuous gemcitabine release, TAR-200 plus cetrelimab, or BCG. The primary endpoint is EFS [14].

Dr. Lerner concluded by highlighting the need to be intentional with BCG, because of both supply issues and toxicity. BCG should be reserved for the highest risk patients and those with HR-IR disease who experience recurrences following IVC. Fortunately, the treatment landscape is rapidly expanding, soon offering several new options to patients.

Next, Dr. Black presented on the topic of subtype-directed therapy for MIBC. He explained that subtyping, at its essence, is about differentiating basal from luminal MIBC based on expression patterns of tumour RNA. The simplest, 2-group classifier was developed at the University of North Carolina, identifying high-expression basal genes and high-expression luminal genes [15]. At the same time, a group at MD Anderson described a 3-group classifier that included a group with high expression of stromal genes that was named p53-like subtype [16]. Based on these and other studies [17,18], an international group created a consensus classifier that includes 6 classes: luminal papillary (LumP), luminal non-specified (LumNS), luminal unstable (LumU), stroma-rich, basal/squamous (Ba/Sq), and neuroendocrine-like (NE-like) [19]. This consensus classifier has not been universally adopted, and individual research groups may still use their own classification systems.

The potential benefits of subtyping are to facilitate an understanding of the underlying biology of MIBC in the research setting as well as to classify tumours for treatment selection and prognostication. For instance, NE-like tumours may look like conventional MIBC but carry a worse prognosis. LumP tumours, on the other hand, have a favourable prognosis that could preclude the need for neoadjuvant chemotherapy [19]. Subtyping can help predict response to individual treatments. In exploratory studies, inflamed tumours with high stromal expression appeared to respond better to trimodal therapy (TMT) than non-inflamed tumours with low stromal expression, but the opposite was true in patients treated with RC with or without neoadjuvant chemotherapy [20]. Finally, molecular subtyping may be able to help identify the best candidates for chemotherapy vs. IO vs. no systemic therapy [21–25].

The MD Anderson group demonstrated that their 3-group classification system predicted response to neoadjuvant chemotherapy (NAC), with the p53-like subtype having the lowest response rate [16]. They later showed that the basal subtype was associated with better 5-year overall survival (OS) after NAC plus bevacizumab (91%), compared with the luminal (73%) and p53-like (36%) subtypes (p = 0.015). Metastases occurred in 53% of patients with the p53-like subtype and none of those with the basal and luminal subtypes [26].

Seiler et al. attempted to validate this subtype-based prediction of response to NAC in a multicentre cohort of 343 patients with MIBC. Transurethral resection specimens prior to cisplatin-based NAC were subtyped as claudin-low, basal, luminal-infiltrated, or luminal using a novel single-sample genomic subtyping classifier. The OS of each subtype in this group was compared with that of 476 published cases of patients who had not received NAC. Luminal tumours had the best OS with and without use of NAC, with claudin-low tumours having the worst prognosis. Basal tumours showed the most improvement in OS with the use of NAC, compared with surgery alone, with their survival rates approaching those of patients with luminal disease. The conclusion of this work was that patients with basal subtype MIBC may benefit the most from NAC [23].

Subsequently, Lotan et al. investigated 601 MIBC patients from 4 different cohorts, 247 of whom received cisplatin-based NAC and 354 of whom did not. In contrast to the study from Seiler et al. [23], all patients had their tumour molecular subtypes profiled on the same platform. Patients with luminal tumours had similar 3-year survival outcomes with or without use of NAC (63% vs. 65%, p = 0.07). Among the other subtypes, however, NAC was associated with a greater 3-year survival rate (71% vs. 61%, p = 0.01) [27]. These findings suggest that patients with luminal subtypes may not require NAC because they have relatively favorable outcomes after RC alone. Other molecular subtypes, however, may benefit from NAC, with a similar a degree of response among the subtypes.

Additional reports appear to contradict these findings. Sjödhal et al. found that patients with luminal subtypes actually had a better response to cisplatin-based NAC than patients with Ba/Sq subtype tumours [25]. Three studies have shown that the Ba/Sq subtype responds poorly to cisplatin-based NAC [28–30], but these studies all lacked a comparison cohort treated without NAC, so it is impossible to draw conclusions about the relative benefit in each subtype. Dr. Black suggested these conflicting findings may be due to differences in study design, endpoints, and subtype classifiers as well as heterogeneity in the patient populations studied. For instance, different patients are classified as basal by different classifiers.

To obtain more clarity on which tumour subtypes respond best to individual therapy, future clinical trials must classify patients by tumour subtype and subsequently tailor the treatment arms to those subtypes. Following this approach, each subtype would be randomized to standard of care vs. an alternative option that can be rationalized based on subtype. For instance, LumP tumours frequently have *FGFR3* alterations and thus could be treated with an FGFR inhibitor.

The ongoing GUSTO trial is randomizing patients to standard of care, without genotyping, or molecular subtype-guided treatment (NAC, IO, or no systemic therapy), with patients subtyped as basal, luminal infiltrated, or lumP/luminal [31].

Looking forward, there is potential to select ADC therapy based on molecular subtype. This is a nascent field that requires further study. For instance, DLL3 is being explored in NE tumours outside the BCa setting. If these studies prove successful, it could be evaluated in NE-like MIBC tumours [19].

Next was a debate on robotic vs. open RC, moderated by Dr. Black. The pro-robotic approach was presented by Dr. Mihir M. Desai (United States). Dr. Desai pointed out that BCa is one of the few areas where randomized controlled trials (RCTs) have been conducted to directly compare robotic with open surgical approaches. However, most of these trials compared open surgery with extracorporeal urinary diversion as their robotic method of choice. Since diversion drives morbidity, this approach can limit the ability to compare perioperative outcomes. Nevertheless, a few trials did use an intracorporeal approach.

When determining whether to invest in the undoubtedly more expensive robotic approach, it is necessary to consider what proportion of patients are eligible for a robotic approach and whether it offers oncologic equivalence, reductions in morbidity, and/or improvements in health-related quality of life (HRQOL) and functioning.

With regard to patient eligibility, robotic RC has virtually no contraindications in experienced hands. In fact, following pelvic floor irradiation, the robotic magnification can help minimize rectal complications. A robotic approach can be used for patients with locally advanced disease, the majority of whom will have received NAC, in both males and females, and using all forms of diversions.

Only the RAZOR trial, comparing robotic with open RC, was powered to an oncologic endpoint. This study had a non-inferiority design, and the 2-year PFS was similar between the 2 groups (72.3% robotic vs. 71.8% open in a modified ITT analysis), as were rates of atypical patterns of recurrence, positive margins, and other surrogates [32]. Oncologic equivalence was also supported by a systematic review and meta-analysis of RCTs, in which no differences in PFS or OS for robotic vs. open RC was observed [33]. Although a few low-quality studies have suggested atypical recurrence patterns after robotic cystectomy [34], as well as with robotic extirpation of other solid tumour cancers [35,36], none of the high quality prospective randomized trials have shown this. Dr. Desai emphasized the importance of surgical technique and handling, regardless of whether robotic or open approaches are used.

In terms of perioperative morbidity, a robotic approach shows benefits in terms of blood loss and need for transfusion, while the open approach shortens the time in the operating room (OR) [33]. While length of hospital stay is an important endpoint, it is a weak surrogate marker of recovery, because it is often driven by physician preference. Also, these patients have about a 25% chance of requiring readmission. For the iROC study, in which intracorporeal diversion was performed in the robotic surgery arm, Catto et al. examined how long patients spent alive and out of the hospital during the first 90 days after index surgery. They found an advantage of 2 days with the open vs. robotic approach (80 vs. 82 days, $p = 0.01$) [37]. However, the clinical importance of this difference is unclear. In the meta-analysis, length of hospital stay was shorter with a robotic approach in the United States and United Kingdom, but not Europe [33].

With respect to complications, the rate of thromboembolic events was higher with open than robotic surgery (8.3% vs. 1.9%) in the iROC study [37]. This study included a fairly standardized clinical pathway, with similar thromboembolic prevention in both groups.

When looking out to 3 to 6 months following surgery, HRQOL is unlikely to be driven by surgical approach. Rather, it is driven by cancer state, use of systemic therapy, and type of diversion. Thus, the perioperative setting is the critical time to examine differences in HRQOL based on surgical approach. In the iROC study, the investigators looked at 5 domains of HRQOL at 1 and 3 months and found that most of these domains favoured the robotic approach [37]. Dr. Desai emphasized that the importance of short-term changes in HRQOL should not be underestimated.

Information on functional outcomes comparing open with robotic RC is lacking. However, an Italian group that uses a Padua stapled pouch that is not commonly used elsewhere in the world demonstrated benefits with the open approach in terms of continence outcomes [38].

With regard to cost-effectiveness, the iROC study demonstrated the robotic approach was more expensive by US $1622 with regard to operative and surgical costs. When taking into account downstream costs, such as care in the intensive care unit and length of hospital stay, there was a quality-adjusted life-year (QALY) gain of 0.001124 with the robotic approach. This gain, however, did not reach the QALY metric of $20,000 for 1 additional QALY. Interestingly, the higher-risk groups, such as older patients with more advanced disease and worse performance status, were more likely to be treated more cost effectively with a robotic approach [39].

In summary, Dr. Desai pointed out that a robotic approach can presently be offered to all-comers, offers oncologic equivalence, has fewer perioperative complications, and offers a brief improvement in HRQOL. The functional benefits, compared with open surgery, are unknown, and the robotic approach is currently more expensive. If access to the technology and expertise is available, Dr. Desai believes robotic surgery should be considered.

Dr. Badrinath R. Konety (United States) followed by defending the open cystectomy approach. He pointed out that, with RC, the primary goals are to minimize bleeding, duration of hospital stay, and complication rates. In addition, it is important to improve HRQOL, ensure complete cancer resection, and minimize costs. Novel surgical approaches that increase costs, have a steep learning curve, are associated with longer OR time, and/or can result in either higher rates of inadequate node dissection or over-dissection of the ureter are, therefore, not advantageous.

Several RCTs have examined these features with regard to robotic vs. open RC. Nix et al. revealed that node dissection with the robotic approach is non-inferior to the open approach, with a mean node yield of 19 in the robotic arm and 18 in the open surgery arm [40]. Bochner at al. compared complication rates between the 2 approaches, but the

study stopped early because the prespecified goal of reducing complication rate by ≥20% was not met. The 2 groups were similar with regard to complications, length of hospital stay, and HRQOL. Robotic surgery was associated with less blood loss (about 159 mL), but the OR time was more than 2 h longer [41,42].

In the RAZOR trial, which yielded similar oncologic endpoints for robotic and open RC, length of hospital stay, estimated blood loss, and OR time were all similar between the 2 groups. The major criticism of this trial, as pointed out by Dr. Desai, is that all diversions were performed as open diversions, which could minimize the potential benefits of the robotic approach. There is evidence, however, that an intracorporeal approach may not confer substantial benefits. The International Robotic Cystectomy Consortium (IRCC) demonstrated in over 4000 cases that patients who underwent completely intracorporeal cystectomy and urinary diversions had decreased blood loss and transfusion rates, but no other major benefits were observed with the completely robotic approach. Multivariable analysis revealed no difference in complication or mortality rates with the intracorporeal or extracorporeal approaches [43].

The iROC study failed to show differences between robotic or open approaches in terms of length of hospital stay [37]. Looking at the outcomes of both the RAZOR and iROC studies together reveals that both showed longer OR times with the robotic arm and no difference in complications. The benefits with the robotic approach were limited to a slightly shorter length of hospital stay (by about 1 day), minor improvements in HRQOL [32,37], and slightly less blood loss (about 200 mL). While iROC did reveal 2 fewer days in hospital over 90 days, Dr. Konety pointed out that many of these patients are older and have poor caregiving situations at home and thus may benefit from more time in hospital.

While benefits are minimal, some serious problems can result from performing robotic RC, especially when performed by inexperienced surgeons. The overall published positive margin rate from the IRCC is 9% [43], compared with about 6% in most studies of open RC. More alarmingly, for T3-T4 disease, the positive margin rate for robotic RC is as high as 17% [32,44–47], which Dr. Konety characterized as "virtually a death sentence". He agreed with Dr. Desai that unusual patterns of recurrence with robotic RC were generally observed only in early trials [34]. However, even the IRCC data had a concerning 0.4% port site recurrence rate [43].

While it may not be an issue in experienced hands, serious mishaps may occur with robotic RC among surgeons doing their first few procedures. Research shows that the learning curve does not plateau until surgeons have performed 60 to 70 robotic RCs [44]. In the United States, based on American Board of Urology reviews of case logs, the average number of RCs done by urologists in the United States is about 2 over an 18-month period. Recent IRCC data suggest that the overall complication rate persists at 60% even with experience. Unexpectedly, higher complication rates have been observed at higher volume institutions [48]. This may reflect referral bias. In particular, higher rates of postoperative cognitive dysfunction in elderly patients are being observed [48], and intracorporeal neobladders have a high readmission rate [49].

A systematic review and meta-analysis of robotic vs. open RC revealed a higher rate of ureteric strictures with the robotic approach (9.6% with open surgery with open conduit vs. 12.4% with robotic surgery and open conduit vs. 15% with robotic surgery and intracorporeal conduit) [50]. Later, Dr. Desai noted that the risk of ureteric strictures has been virtually eliminated by using indocyanine green. In fact, this technique is also being used in open surgery.

Dr. Konety confirmed that the robotic approach is more expensive [39], although he expects the price to come down as lower-cost technology is made available. However, even if costs are equivalent, the robotic approach may not be the best option given the risks

involved. These risks include positive margins (particularly with bulky disease), longer OR times, steep learning curves, fewer neobladders being performed, and more ureteric strictures. Such risks may not be worth the potential benefits of slightly less blood loss and slightly shorter length of hospital stay.

During a Q&A period, a participant highlighted the importance of communication and learning between open and robotic surgeons in an effort to improve outcomes. In particular, measuring the quality of node dissections with robotic vs. open RC has been important. Moving forward, further improvements in programs of enhanced recovery after surgery will be important in this setting, given the high rate of hospital readmissions. It has been disappointing that a robotic approach does not appear to have improved that.

Another participant asked Dr. Konety, who performs both robotic and open RCs, what indications he considers for performing a robotic approach. Dr. Konety replied that these include patient preference for robotic RC, as well as patients who are obese and those who have undergone radiation.

A third participant raised the issue of how to ensure that future generations of surgeons are prepared to tackle the challenging cases that may not be good candidates for robotic surgery if their training is focused on using robotic technology. Dr. Desai replied that trainees will learn to perform the procedures for which there is the greatest need. Dr. Konety said that it will be important to teach open surgery techniques to trainees, and RC offers a good opportunity for this since most are still performed using the open technique.

Next, Dr. Shilpa Gupta (United States) discussed adjuvant therapy for MIBC. BCa carries a considerable societal and financial burden [51–53]. Globally, over 550,000 new cases are diagnosed every year. In the United States, the estimated total cost of BCa treatment amounts US $5 billion. In addition, surgery has a mortality rate of 2% to 13% and results in a significant impact on HRQOL. Finally, recurrence rates are high, and racial and gender disparities exist with respect to access to care.

The landmark SWOG 8710 [54] and EORTC 30984 [55] studies demonstrated that cisplatin-based NAC prior to RC improves OS in cisplatin-eligible MIBC patients compared with upfront RC. Meta-analyses have also suggested an absolute improvement of 8% in 5-year OS with NAC [56,57]. Standard chemotherapy options include dd-MVAC or GC, but recurrence risk is high even with NAC and surgery. As many as 50% of patients are not eligible for cisplatin or refuse NAC [57–59]. Moreover, there is a lack of NAC treatment options for cisplatin-ineligible patients.

In the adjuvant setting, the goal is to improve DFS and OS. No RCTs have demonstrated improvements in these outcomes with use of adjuvant chemotherapy (AC) vs. no AC. The EORTC 30994 trial failed to demonstrate a difference in OS when comparing immediate vs. deferred cisplatin-based chemotherapy after RC in patients with pT3 to pT4 or node-positive M0 BCa [60]. Nevertheless, the ABC meta-analysis revealed a 6% absolute improvement in 5-year OS with the use of AC [61].

Outcomes improved with the advent of IO. Disappointingly, no DFS or OS improvement was observed with adjuvant atezolizumab vs. observation in patients with HR muscle-invasive urothelial cancer (including both BCa and upper tract urothelial cancer) [62], but CheckMate 274 revealed superior DFS with adjuvant nivolumab vs. placebo in a similar patient population, with 3-year OS trending toward improvement as well. Exploratory subgroup analyses of CheckMate 274 revealed that results were best among patients who were programmed death-ligand 1 (PD-L1)–positive and, indeed, nivolumab is approved in Europe only in MIBC for PD-L1–positive patients. Notably, patients who were ineligible for cisplatin-based NAC or did not receive any systemic NAC did not benefit from nivolumab, so lack of treatment options in this patient population remains an issue [63].

More recently, the AMBASSADOR trial also revealed improvement in DFS, but not OS, with adjuvant pembrolizumab vs. observation among HR patients with MIBC. Unlike in CheckMate 274, however, patients with PD-L1–positive tumours actually had poorer outcomes with pembrolizumab [64].

Upper tract urothelial cancer is considered to be quite a different disease from BCa. In the POUT trial, adjuvant platinum-based chemotherapy following nephroureterectomy improved DFS over observation [65]. The best outcomes were achieved with GC chemotherapy, but many patients who undergo nephroureterectomy are not good candidates for this regimen. Unfortunately, atezolizumab, nivolumab, and pembrolizumab have all failed to improve outcomes in this setting [62–64].

Circulating tumour DNA (ctDNA) is highly prognostic in MIBC [62,66]. IMvigor010, despite failing to show a benefit of adjuvant atezolizumab in patients with muscle-invasive urothelial carcinoma, did reveal a benefit in both OS and DFS among patients who were ctDNA-positive following surgery in a post hoc analysis [67].

In terms of ongoing trials, for IMvigor011, patients with muscle-invasive urothelial carcinoma who become ctDNA positive within 12 months of RC are being randomized to surveillance or to either atezolizumab or placebo [68]. For the MODERN trial (NCT05987241), outcomes with nivolumab are being compared between 2 cohorts based on ctDNA status. Patients who are ctDNA negative after RC are randomized to adjuvant nivolumab or active ctDNA surveillance. Patients who are ctDNA positive at the time of study registration are being randomized to adjuvant nivolumab alone or nivolumab plus the LAG3–blocking antibody relatlimab.

Several perioperative trials are also ongoing in MIBC. Studies that are exploring various combinations of standard-of-care GC chemotherapy, IO, and enfortumab vedotin (EV) plus pembrolizumab include the KEYNOTE-866 trial (GC vs. GC plus pembrolizumab) [69], KEYNOTE-B15/EV-304 (GC vs. pembrolizumab plus EV) [70], ENERGIZE (GC vs. GC plus nivolumab) [71], and NIAGARA (GC vs. GC plus durvalumab) [72]. For cisplatin-ineligible patients, KEYNOTE-905/EV-303 is comparing RC vs. pembrolizumab vs. pembrolizumab plus EV [73]. In VOLGA, the comparators are RC vs. durvalumab plus tremelimumab plus EV vs. durvalumab plus EV [74].

In the NIAGARA trial, 530 patients received 4 cycles of neoadjuvant GC, and 533 received 4 cycles of neoadjuvant GC plus durvalumab. All patients subsequently underwent RC. Those in the durvalumab-containing arm continued to receive this therapy for 8 cycles, with no additional treatment given in the adjuvant setting in the GC monotherapy arm. This trial includes patients with different types of histology, and the bar for cisplatin eligibility was low (creatinine clearance rate $\geq$ 40 mL/min). The dual primary endpoints are EFS and pathologic CR (pCR). In early results, the pCR endpoint was not met, but EFS and OS were both significantly improved with the addition of durvalumab. In an ITT analysis, the hazard ratio for EFS was 0.68 (95% CI = 0.56–0.82) in the durvalumab-containing arm [72].

Results of these ongoing trials will help inform whether there are benefits to adding IO to GC. It is worth noting, however, that the control arms in the perioperative trials do not include nivolumab, making them suboptimal. As such, these trials cannot help determine whether the addition of IO would remain beneficial in comparison with GC plus nivolumab. The trials will also help to elucidate whether EV plus pembrolizumab is superior to GC, and whether EV plus pembrolizumab in cisplatin-ineligible patients is superior to upfront RC. Remaining questions not being addressed by these trials include whether adjuvant IO with EV intensification is needed in patients who achieve pCR, whether adjuvant IO is needed for patients who have upstaging at RC after IO, and whether patients with node-positive histology or predominant-variant histology benefit from these experimental options (these

patients are excluded from the trials). Finally, it will remain unknown which aspects of treatment (neoadjuvant, adjuvant, or both) provide the most benefit.

Given the efficacy of currently available treatments, the question remains whether all patients still require RC or whether the disease can be sufficiently downstaged to allow treatment with radiotherapy or intravesical therapy using a new technology such as TAR-200. In the breast cancer setting, new drugs are first launched in the localized setting and, if effective, move to the metastatic setting. In BCa, the tradition has been to test new drugs in the metastatic setting and then adopt those drugs in less advanced disease. This results in the most effective regimens being approved only for advanced disease. Dr. Gupta feels it would be wiser to conduct smaller studies in localized disease and then move onto the metastatic setting.

Dr. Gupta concluded that the perioperative space in MIBC is evolving rapidly. While adjuvant IO is effective in select patients, not all patients with HR disease are likely to require this approach. Notably, most patients who benefit also received cisplatin-based NAC. In addition, IO is not effective in upper tract disease and not financially feasible in many countries. There is promise for ctDNA as a biomarker to help guide patient selection for adjuvant IO, sparing patients from unnecessary treatment. Lastly, efforts should be made to help address global disparities in access to novel treatments.

Following the presentation, Dr. Gupta moderated a panel discussion on the sequencing of systemic therapy in mUC. Panellists were Dr. Amit Joshi (India), Dr. Karima Oualla (Morocco), Dr. Senthil Rajappa (India), and Dr. Vineet Talwar (India). The discussion started with a presentation of the case of a 69-year-old male ex-smoker (40 pack years) with gross hematuria. TURBT revealed HG, cT $\geq$ 2 urothelial carcinoma. Workup revealed metastatic disease in the lungs, and the patients' glomerular filtration rate (GFR) was 35 mL/min. Dr. Gupta asked whether PD-L1 testing was widely available in the panellists' countries and whether they use it. She noted that she herself does not use it to guide treatment decision-making, but colleagues in Europe often do because PD-L1 positivity is required for access to adjuvant nivolumab. In Morocco, Dr. Oualla reported that they do have access to some IO, including atezolizumab and pembrolizumab, so PD-L1 testing is performed to determine eligibility for IO monotherapy among patients who are not eligible for chemotherapy. They do not have access to pembrolizumab plus EV, but avelumab will be available in 2025, which will allow them to use this agent as maintenance therapy following GC. Phase 2 trials do demonstrate the benefits of pembrolizumab as maintenance therapy, but this is not routine practice in Morocco.

Dr. Rajappa said that, in India, this patient would be treated with GC followed by avelumab maintenance. Pembrolizumab plus EV is not readily available in India, and they would not do PD-L1 testing in this patient. In early 2025, EV will be launched in India, but Dr. Talwar said that cost may limit its use. A similar issue regarding cost arose with avelumab, which was addressed by the manufacturer with patient assistance plans. Dr. Joshi pointed out, however, that the high toxicity of EV may limit its uptake in India even if the cost were reasonable. Management of toxicity will also be a problem for combinations of IO and ADC. Dr. Gupta said that education on how to manage toxicity will be important following the launch of these drugs.

Next, Dr. Gupta asked what the frontline therapy preference would be for this patient if he had a perfect GFR. In an ideal world, Dr. Oualla feels that a chemotherapy-free regimen would be a good option. For eligible patients, GC is a good choice, but in Morocco, she cannot access maintenance avelumab for these patients. Ideally, she would offer pembrolizumab plus EV, but if that is not accessible, then it would be platinum-based chemotherapy followed by avelumab. She does not have access to GC plus nivolumab. Dr. Rajappa added that he also does not use GC plus nivolumab in India. They would

both use pembrolizumab plus EV if it were accessible, and they felt comfortable managing potential toxicities.

Dr. Gupta said that despite pembrolizumab plus EV being available for nearly 2 years in the United States, there is little clarity on what to do when patients progress. In the EV-302 study, patients who progressed were given platinum-based chemotherapy, with a 30% response rate [75]. The only other option in this setting, sacituzumab govitecan, was just withdrawn from the market because in the phase 3 trial it failed to show benefits over taxanes and was more toxic than chemotherapy. The panellists agreed that GC will likely re-emerge in the second-line setting. Dr. Talwar pointed out that, as pembrolizumab plus EV is moved into the neoadjuvant setting, the only fallback in the second-line setting will be traditional chemotherapy drugs.

Dr. Gupta then asked which regimen would be preferred, pembrolizumab plus EV or GC plus durvalumab, if both are approved in the perioperative space. She noted that patients often have trouble tolerating EV in the immediate postsurgical period. Dr. Rajappa replied that, hopefully, using pembrolizumab plus EV in the neoadjuvant setting will eliminate the need for RC in some patients. If surgery is planned, then the incentive to use pembrolizumab plus EV will be lower, unless a future trial reveals a major OS benefit. Dr. Talwar added that, with mUC, when going from first- to second-line setting, there is a substantial reduction in the number of patients who come in for treatment. It would be more sensible to treat with pembrolizumab plus EV sooner rather than later. Dr. Oualla added that it will be necessary to conduct appropriate biomarker testing before initiating IO plus ADC therapy. This will be available in Morocco soon. In India, *FGFR* testing is offered only to patients who are able to afford the relevant drugs. Dr. Talwar noted that there are data showing that 15% to 20% of BCa patients have the somatic *BRCA* mutation, so they test for that since generic olaparib and rucaparib are available and affordable. He also likes to request *HER2* testing, but cost can be a barrier.

Dr. Talwar asked whether dd-MVAC would be considered in this patient, particularly if he were younger. Dr. Gupta replied that, for a younger patient, she would be more likely to use pembrolizumab plus EV. Dr. Oualla pointed out that not all patients are eligible for this regimen, however. Particularly given that EV is a new drug, it is not yet clear what performance status, comorbidities, or organ dysfunction may make patients unable to tolerate it.

Next, Dr. Oualla asked whether patients similar to the presented case, with only 2 metastases on conventional imaging, would be considered for local treatment only if they are good responders. Dr. Gupta replied that she does not use EV indefinitely in her practice, unlike the EV-302 study. If the patient has a good response, consolidation with stereotactic body radiation therapy is an option to give them a break from systemic therapy.

Dr. Talwar asked if there are any data on reducing the dose of EV to help manage toxicity. Dr. Gupta replied that there was a presentation by Dr. Petrylak at the 2024 American Society of Clinical Oncology meeting on the pharmacokinetics of EV, suggesting it is better to start at a full dose and then decrease or hold the dose, as needed [76]. If a patient is frail and elderly, it is reasonable to start with a lower dose, however. Dr. Gupta's institution will be initiating a study to evaluate the outcomes of stopping EV after 4 to 6 cycles.

Dr. Black pointed out that Canada also faces many of the access limitations to novel therapies that Morocco and India do. For instance, *FGFR* testing is difficult to access, and while pembrolizumab plus EV is available, it is not yet reimbursed by provincial payers. He noted that patients who are node positive or clinical T4b with fully resectable tumours may still receive chemotherapy with neoadjuvant intention, even if they technically meet the criteria for locally advanced metastatic disease. He suggested that it is justified to

use pembrolizumab plus EV in these patients. Dr. Gupta agreed, given the patient has locally advanced disease. In the United States, pembrolizumab plus EV is being used in an increasingly wider range of patients.

Dr. Oualla added that GC plus nivolumab has showed excellent response rates in node-positive disease, so she asked Dr. Gupta if these patients who are M+ or M0 would be considered for local treatment in the form of surgery or radiotherapy. Dr. Gupta would definitely consider such patients for consolidative surgery. She noted that node-positive patients tend to do well no matter what they receive, including chemotherapy followed by nivolumab or pembrolizumab plus EV. If these patients respond well, then consolidative surgery is a good option.

An attendee asked why, in the SWOG 8710 study, those with a CR were essentially cured [54], but in the NIAGARA trial, there was no correlation between tumour response and long-term outcomes, even though they received standard-of-care chemotherapy [72]. Dr. Gupta agreed this was unexpected. The pCR was much lower than expected, even in the control arm. With IO, it appears that focus on pCR is unwarranted if improvements in EFS and OS are demonstrated, with the caveat being that it is not yet known what subsequent therapies patients received in the control arm (including use of IO).

Another attendee asked what solutions there might be to this ever-escalating cost of new drugs. Dr. Gupta believes that the pharmaceutical industry will have to collaborate with academic physicians to help influence regulatory bodies. To ensure regulatory approval, price decrease is often essential. Dr. Rajappa added that much can be learned from the experience at Tata Memorial, including the potential to achieve similar outcome with lower drug doses and shorter exposures and getting biosimilars into the market more quickly. In addition, the science of biomarkers must move more rapidly. This would allow the use of biomarkers to identify which patients are most likely to respond to specific drugs. Dr. Talwar added that, as treatments move increasingly toward molecular targets, it will be easier to tailor specific treatments to individual patients. Finally, Dr. Joshi said that ethnic variations with regard to propensity to harbour certain genetic mutations should be taken into account in clinical trials. Conversely, Dr. Rajappa noted that reproducibility of these findings in laboratories all over the world could be a challenge.

The BCa session of the meeting concluded with the first-ever B2B GU Cancers luncheon symposium on progress in intravesical drug delivery treatments. Dr. Lerner, the symposium chair, set the stage by reminding attendees about the BCG supply crisis and the need to use it judiciously as well as the hope that new drug development will help ease this crisis by offering novel treatment options. He noted that the FDA guidance document on the development of new drug and biologic products for the treatment of BCG-unresponsive NMIBC set the stage for rapid development of new therapeutics in this setting, particularly since it allows for single-arm trials [77].

Next was a presentation by Dr. Black on novel intravesical agents. BCG remains the standard of care in HR disease and plays a foundational role in IR disease, he said, but it remains limited not only by supply issues but also by contraindications, toxicity, and risk of recurrence.

The potential to enhance the efficacy of BCG by selecting specific strains is being evaluated (e.g., EVER trial [NCT05037279], S1601 trial [78]). The recombinant BCG VMP1002 has shown promise in a phase 1/2 trial [79]. The S1602 trial is also examining whether intradermal vaccination can enhance BCG efficacy [78]. The use of adjuncts together with BCG is also being evaluated, such as encapsulated rapamycin (eRapa) [80] or checkpoint inhibitors. An alternative strategy in patients with BCG-naïve NMIBC is to test alternatives to BCG. The BRIDGE trial, for example, is investigating use of gemcitabine-docetaxel (GD) vs. BCG as a first-line therapy in HR NMIBC [12].

Most novel therapeutics are intravesical agents that have been tested primarily in patients with BCG-unresponsive NMIBC. Trials have typically been single arm trials in patients with CIS, with CR as the primary endpoint. Some trials have a separate arm for patients with papillary disease (Ta/T1) and no CIS, with the primary endpoint being RFS or EFS. An example is nadofaragene firadenovec, an adenovirus carrying interferon-α2b [81], which revealed a CR rate of 53% at 3 months, which was maintained to 12 months in 24% of all patients. Patients with Ta/T1 disease had an EFS of 44% at 12 months [81].

Another novel therapeutic is nogapendekin alfa inbakicept (N-803), a recombinant protein that acts as an interleukin (IL)-15 superagonist. This agent led to a CR rate of 71% at 3 or 6 months in a single-arm trial of patients with BCG-unresponsive CIS. Reinduction was permitted in this trial, unlike with nadofaragene firadenovec, which may contribute to the superior CR. Approximately 40% of patients were in durable CR at 1 year after treatment with N803 [82]. The EFS at 12 months was 55% in patients with Ta/T1 tumours without CIS.

Cretostimogene grenadenorepvec is an oncolytic adenovirus that replicates specifically in cancer cells due to abnormalities in Rb and E2F signalling in cancer cells. It also releases GM-CSF, which activates the immune system. In the BOND-3 trial in patients with BCG-unresponsive CIS, the agent had a 73% CR at any time, with an ongoing CR at 12 months of 41% [83].

Detalimogene voraplasmid (EG70) is a non-viral DNA plasmid acting locally in the bladder that induces secretion of IL-12, which stimulates the adaptive immune system, and 2 double-stranded RNA activators of the intracellular innate immunity regulator, RIG-I. In a small trial of 22 patients with BCG-unresponsive CIS, the CR rate at any time was 73% (68% at 3 months and 45% at 6 months), with minimal toxicity. A phase 2 trial evaluating this agent in 100 patients is ongoing [84].

As these new drugs become available, it will be imperative to learn how best to sequence or combine them. Many in the field believe that it is time to move from single-arm to multi-arm trials. Likely these drugs will migrate from BCG-unresponsive disease to earlier disease states. It will also be relevant to determine how resulting changes in first-line approaches impact downstream options. Importantly, in patients who really need it, RC should remain a mainstay of therapy.

Next, Dr. Gagan Prakash (India) discussed device-based intravesical treatment for BCa. He explained that the goal of such systems is to increase efficacy of therapeutics by enhancing penetration, which can be accomplished by increasing their temperature, as well as by maximizing contact time with the bladder, which can be accomplished by one of the TAR devices or via a gel technology. This new technology can be used as adjuvant or ablative therapy, the latter of which eliminates the need for surgical resection.

The rationale for chemohyperthermia is that it increases the concentration of the drug in the bladder tumour and enhances its effects [85]. Hyperthermic Intra-VEsical Chemotherapy (HIVEC) delivered via the COMBined Antineoplastic Thermotherapy Bladder Recirculation System (COMBAT BRS) has been evaluated in 2 RCTs: HIVEC-I and HIVEC-II. Both trials compared regular MMC with HIVEC MMC in patients with IR NMIBC, and neither showed significant differences in outcomes between the 2 study arms [86,87].

Radiofrequency-induced thermo-chemotherapeutic effect (RITE) treatment for BCa has demonstrated efficacy in clinical trials in IR, HR, and papillary-only BCG-naïve NMIBC. Among patients who have experienced a recurrence on BCG therapy, subgroup analyses have demonstrated nonsignificant improvements using RITE among patients with papillary-only disease [85].

While there is currently no rationale to use HIVEC in the setting of IR NMIBC, it might be considered in individuals who have experienced recurrence following adjuvant normothermic MMC. In BCG-naïve HR NMIBC, it could be an alternative approach in cases of BCG paucity, intolerance, or contraindication.

RT gel technology is a gel that is a liquid at cooler temperatures, so it can be delivered into the bladder, and becomes a solid once it warms up inside the bladder. This increases contact time with the bladder tissue, even in the upper tract. UGN-102 is an RT hydrogel containing MMC. In 1 trial, TURBT alone was compared with UGN-102 plus TURBT among patients with LG IR NMIBC. The 15-month DFS was 72% with UGN-102 plus TURBT compared with 50% with TURBT monotherapy [11]. ENVISION is an ongoing trial in which UGN-102 is being evaluated in a single arm among patients with LG IR NMIBC who did *not* undergo surgical resection. The CR was 79.6% at 3 months, and there was a 12-month estimated duration of response of 82.3% at 3 months [88].

The TAR-200 and TAR-210 devices are being investigated in the SunRISe and MoonRISe trials, respectively, in both NIMBC and MIBC. In each case, the drug is installed into the device, which is shaped like a pretzel, and the device stays in the bladder for 3 weeks (TAR-200) or 3 months (TAR-210). A recent update of the ongoing SunRISe-1 trial, which investigated TAR-200 in patients with BCG-unresponsive HR NMIBC, demonstrated that TAR-200 monotherapy is as effective as TAR-200 combined with cetrelimab and is superior to cetrelimab monotherapy (CR 83.5% vs. 46.4%) [89]. TAR-210, containing erdafitinib, has been studied in IR and HR NMIBC patients with select *FGFR* alterations. In patients with BCG-exposed HR NMIBC, the estimated 12-month RFS was 90% (95% CI = 66–97). Among IR NMIBC patients, 90% (95% CI = 74–98) achieved a CR at week 12 [90]. Based on these findings, the MoonRISe-1 trial is being conducted, which will compare erdafitinib-containing TAR-210 with standard-of-care intravesical therapy in patients with IR NMIBC and susceptible *FGFR* alterations [13].

Looking into the future, Theralase is a device that uses a photosensitizer and laser light inside the bladder to destroy tumours (NCT03945162). The ADC belzupacap sarotalocan is being injected directly into the bladder for the treatment of NMIBC (NCT05483868). Finally, a series of studies are using the concept of nanoplatforms for BCa.

The treatment pathways for NMIBC are likely to change substantially in the future. Some tumours may be treated with ablation rather than resection. Others may be targeted based on their mutations. Risk stratification and BCG status will continue to be key considerations when investigating and selecting appropriate therapies.

Finally, Dr. Gupta discussed the impact of IO and ADC in NMIBC. The 2 trials investigating systemic IO in BCG-refractory NMIBC are KEYNOTE-057 and S1605. In KEYOTE-057, activity with pembrolizumab at 3 months was promising, with a CR of 41% at 3 months, but that fell to 19% at 12 months [91]. While the drug is approved for use in this indication, questions remain as to whether its limited efficacy is worth the expense, especially in resource-poor settings. Notably, outcomes were superior among patients with papillary disease without CIS. In this group, median DFS was 7.7 months (95% CI = 5.5–13.6). An additional cohort is enrolling, targeting patients with anti–LAG-3 (favezelimab) and anti-TGIT (vibostolimab) specific antibodies. In S1605, a similar population of patients had a similar response with atezolizumab, with a 12-month CR of 20% [92].

Ongoing phase 3 trials in HR NMIBC include the POTOMAC trial, comparing BCG induction plus durvalumab vs. BCG induction and maintenance plus durvalumab vs. BCG induction and maintenance alone [93]. A similar design has been used to test sasanlimab (CREST trial) and atezolizumab (ALBAN trial). The KEYNOTE-676 trial is comparing

BCG plus pembrolizumab vs. BCG monotherapy in patients who have a recurrence after induction BCG [94].

Phase 3 trials that are exploring the benefits of systemic agents for BCG-naïve HR NMIBC include SunRISe-3, comparing TAR-200 containing gemcitabine plus cetrelimab vs. BCG induction and maintenance vs. TAR-200 containing gemcitabine monotherapy [14].

Use of intravesical pembrolizumab was investigated in a small trial of 9 patients with BCG-unresponsive disease. The trial was halted early due to the COVID-19 pandemic. Urinary symptoms were manageable, and diarrhea was a dose-limiting toxicity. There was 1 toxic death from myasthenia gravis [95]. Intravesical EV is currently being evaluated in patients with BCG-unresponsive CIS NMIBC in the phase 1 EV-104 trial [96].

As the NMIBC treatment landscape evolves, Dr. Gupta concluded, the hope is that many patients will be able to avoid RC for BCG-refractory disease. There is also a need to develop biomarkers to help customize care and improve global access to novel therapies.

The session came to an end with a Q&A led by Dr. Lerner. An attendee asked Dr. Black if it is possible to develop node positivity while undergoing intravesical therapy. He replied that this is a concern. If individual therapies are introduced sequentially over time, patients may begin to progress. Dr. Lerner then brought up concern about the development of extravesical second primary tumours while intravesical treatment is clearing the bladder of CIS, particularly in the upper urinary tract. Dr. Prakash agreed it is a valid concern. Trials that are investigating the ability to delay RC should include outcome measures evaluating extra-vesical disease. Dr. Lerner replied that most guidelines agree that RC is the treatment of choice for BCG-unresponsive NMIBC and asked Dr. Black which patients should get upfront RC. Dr. Black said that when trials report early results showing no progression, this should not be misconstrued to mean that the drug is preventing progression. In fact, this likely represents the natural history of the disease. Without a CR, it is not possible to examine if the drug demonstrates activity. It is difficult to determine how many cycles of treatment can be administered safely before considering RC. He usually recommends RC at first HG recurrence after a second line of intravesical therapy after prior BCG. Patients requiring upfront RC generally have a combination of adverse features, such as large or multifocal tumours.

An attendee reported that, in Australia, there has been a small phase 1/2 trial of submucosal injections of durvalumab that has shown some good immune response within the bladder wall, including one CR. He asked Dr. Gupta how she views the interplay between systemic and local treatment options. She replied that virtually any drug can be delivered intravesically, but for now other injectable localized treatment options remain experimental.

Another attendee asked why different agents have not been tried with HIVEC. Dr. Prakash explained that agents are selected based on the success of HIVEC therapy in other cancers and the likelihood that they have an enhanced effect at higher temperatures.

Dr. Lerner then asked Dr. Black about his work on biomarkers unique to BCa. Dr. Black replied that the genomic information that can be derived from urine tumour DNA may help determine which patients are likely to progress rapidly and should receive upfront RC, who should receive standard-of-care therapy, and who might respond well to a de-escalated approach. Dr. Lerner noted that those involved in clinical trial design should be incorporating predictive diagnostic biomarkers into trials for NMIBCs, make efforts to validate the findings, and then design trials using these biomarkers, with escalation and de-escalation arms.

An attendee asked about the role of radiotherapy in HG NMIBC. Dr. Black replied that TMT with sensitizing radiation has a role for T1 disease. He would not recommend it for CIS. The notion has been put forward of using radiation in BCG-unresponsive

CIS to increase immunogenicity, followed by IO. Dr. Lerner noted that this highlights the importance of actively looking for CIS in patients, which is a limitation of bladder-sparing trials.

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Abbreviations

AC	adjuvant chemotherapy
ADC	antibody-drug conjugate
AUA	American Urological Association
Ba/Sq	basal/squamous
BCa	bladder cancer
BCG	bacillus Calmette-Guérin
CI	confidence interval
CIS	carcinoma in situ
CR	complete response
ctDNA	circulating tumour DNA
dd-MVAC	dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DFS	disease-free survival
EAU	European Association of Urology
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
EV	enfortumab vedotin
FDA	U.S. Food and Drug Administration
GC	gemcitabine-cisplatin
GD	gemcitabine-docetaxel
GFR	glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
HG	high grade

HIVEC	hyperthermic intra-vesical chemotherapy
HR	high risk
HRQOL	health-related quality of life
IBCG	International Bladder Cancer Group
IL	interleukin
IO	immunotherapy
IR	intermediate risk
IRCC	International Robotic Cystectomy Consortium
ITT	intent-to-treat
IVC	intravesical chemotherapy
LG	low grade
LR	low risk
LumP	luminal papillary
MIBC	muscle-invasive bladder cancer
MMC	mitomycin C
mUC	metastatic urothelial carcinoma
NAC	neoadjuvant chemotherapy
NE	neuroendocrine
NMIBC	non–muscle-invasive bladder cancer
OR	operating room
OS	overall survival
pCR	pathologic complete response
PD-L1	programmed death-ligand 1
PFS	progression-free survival
QALY	quality-adjusted life-year
RC	radical cystectomy
RCT	randomized controlled trial
RFS	recurrence-free survival
RITE	radiofrequency-induced thermo-chemotherapeutic effect
RT	reverse thermal
TMT	trimodal therapy
TURBT	transurethral resection of bladder tumour

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