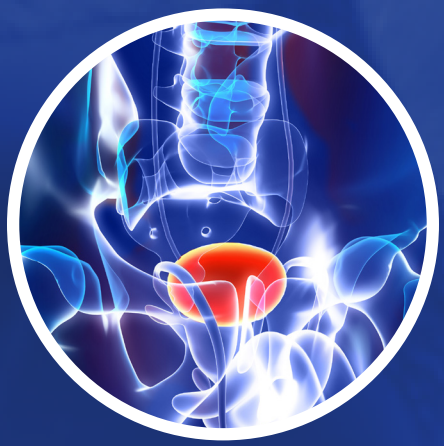
BENCH TO BEDSIDE
URO-ONCOLOGY
GU CANCERS TRIAD



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Bladder Cancer

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B2B: Bladder Cancer Summary

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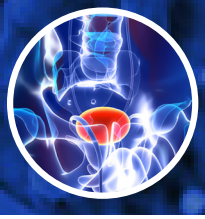
The 5th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 43rd Annual Congress of the Société Internationale d'Urologie, was held on October 13th, 2023, at the Istanbul Lutfi Kirdar International Convention and Exhibition Centre in Istanbul, Türkiye, and transmitted live on the *SIU@U* virtual platform. The session on bladder cancer (BCa) took place in the morning and was co-chaired by Drs. Sarah P. Psutka (United States) and Peter C. Black (Canada). This session covered novel methods of intravesical drug delivery and tumour ablation and the use of artificial intelligence (AI) to optimize cystoscopy, as well as a debate on the clinical utility of next-generation urine markers. This session also included two panel discussions, one on the use of molecular residual disease (MRD) to guide BCa treatment, and another on emerging systemic therapies for metastatic urothelial carcinoma (mUC), as well as an update on first-line therapy clinical trials in non–muscle-invasive BCa (NMIBC).

Dr. Psutka discussed novel strategies for intravesical drug delivery and methods of tumour ablation for the treatment of intermediate-risk NMIBC. The critical problem for clinicians in this setting is not only to improve treatment efficacy and outcomes, but also to reduce the therapeutic burden for patients with intermediate-risk NMIBC. During her presentation, Dr. Psutka presented several candidate strategies to de-escalate treatment, reduce burden, and ultimately improve outcomes, specifically focusing on direct drug delivery to the urothelium to reduce systemic toxicity.

BCa is a very prevalent disease. In the United States alone, more than 80 000 new cases of BCa are diagnosed annually[1]. The vast majority (~61 000) of BCa cases are NMIBC and most are low/intermediate risk[2]. While different clinical practice guidelines have differing definitions of intermediate-risk NMIBC, there is a general consensus for treatment recommendations[3–5]. Currently, intermediate-risk NMIBC is treated by a visually complete transurethral resection of bladder tumour (TURBT) followed by a single instillation of intravesical chemotherapy to reduce recurrence risk. Most guidelines also endorse adjuvant intravesical bacillus Calmette-Guérin (BCG) immunotherapy or chemotherapy and 1 year of maintenance treatment for patients who respond. Risk stratification and risk-adapted treatment are repeated upon disease recurrence, which is frequent.

While patients with intermediate-risk NMIBC are at high risk of recurrence, the risk can be mitigated to some extent with the addition of adjuvant intravesical therapy and maintenance treatment[6–10]. Dr. Psutka also emphasized that recurrences of low-grade NMIBC after TURBT are low grade in > 90% of cases; therefore,



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these are generally not life threatening. However, recurrences are associated with a substantial amount of emotional and treatment-associated burden for patients. For these reasons, in 2022 the International Bladder Cancer Group (IBCG) proposed a risk-adapted approach to the management of intermediate-risk NMIBC[11]. This approach is based on specific risk factors, which are the presence of multiple tumours, early recurrence (< 1 year), frequent recurrence (> 1/year), tumour size (> 3 cm), and failure of previous intravesical treatment. An intensity-modulated approach to the initial and adjuvant management of recurrent low-grade NMIBC is recommended according to the occurrence of 0, 1–2, or ≥ 3 risk factors. A multivariate analysis of 163 patients with low-grade NMIBC recently demonstrated that the 2022 IBCG risk stratification system is associated with the likelihood of undergoing subsequent TURBT vs. remaining on active surveillance[12].

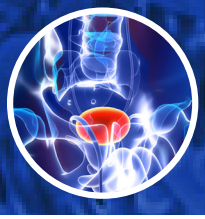
Dr. Psutka highlighted that there are critical concerns regarding the current paradigm of frequent resections and adjuvant therapy recommended for patients with recurrent low-grade NMIBC, particularly in a predominantly older and medically comorbid patient population. Treatment-related toxicities are not negligible, specifically with the risk of perioperative morbidity and, potentially, mortality. Importantly, recurrent exposure to general anesthetics may put patients at higher risk of postoperative delirium and long-term cognitive decline[13]. Additionally, the financial toxicity to patients and healthcare systems associated with repeat TURBTs and frequent surveillance should also be considered. In a recent study, the costs of care for intermediate-risk NMIBC over a 5-year period was estimated at US$146 250 per patient[14].

There are several strategies that can be considered to improve the therapeutic efficacy while reducing the treatment burden for patients with intermediate-risk NMIBC. These strategies include de-escalating care from TURBT to in-office fulguration, especially for small papillary recurrences; improving tissue penetration of the treatment agent; increasing the time of exposure of therapeutic agents to the urothelium; leveraging tumour biology through targeted therapies; and enhancing the response rate for adjuvant therapy[15,16].

The first strategy discussed by Dr. Psutka focused on the use of chemoablation with intensive intravesical mitomycin C. In a prospective, single-centre, nonrandomized study, 47 patients (group 1) received intravesical mitomycin C 3 times per week for 2 weeks and were compared with a cohort of 47 patients (group 2) who underwent TURBT as well as early instillation and weekly mitomycin C for 7 weeks. Both groups were evaluated for complete response (CR) 45 days after treatment. At the first follow-up, CR was similar between groups (72.3% in group 1 vs. 78.7% in group 2). More importantly, there were no systemic nor substantial increases in localized toxicity with the intensive chemoablation strategy. Therefore, the authors postulated that this strategy could lead to avoidance of TURBT in > 70% of patients following recurrence of low/intermediate-risk NMIBC[17].

The second strategy focuses on potentiating drug delivery to facilitate pharmacokinetic absorption. Both electromotive drug administration and chemohyperthermia can increase the permeability of the urothelium to intravesical agents[15]. In the open-label HIVEC-II trial, 259 patients were randomized to receiving either chemohyperthermia with mitomycin C at 43 °C or mitomycin C at room temperature. No significant differences in disease-free survival (DFS) and overall survival (OS) were observed between treatment arms. However, chemohyperthermia was associated with lower treatment completion rates of nearly 30%, related to technical issues as well as treatment toxicity[18]. Therefore, these results do not support the adoption of chemohyperthermia for intermediate-risk NMIBC.

The third strategy aims to develop ways to enhance the contact between the therapeutic agent and the urothelium. UGN-102 is a mitomycin-containing thermal hydrogel that solidifies at body temperature to extend the contact time with the urothelium. The phase 2b, open-label, single-arm Optima II trial investigating chemoablation with UGN-102 demonstrated an encouraging 3-month CR rate of 65% and a 12-month DFS rate of 40%[19]. The use of primary chemoablation as an alternative to repeat TURBT in intermediate-risk NMIBC is being further investigated in the phase 3 ENVISION trial (NCT05243550).



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Another approach for enhancing the length of contact between a therapeutic agent and the tumour is observed with the TAR-200 drug delivery system. This is a dual lumen silicone tube containing gemcitabine tablets that are osmotically released, resulting in sustained levels of drug delivery locally, within the bladder. The device is inserted in the clinic and retained in the bladder due to a super-elastic nitinol wireform that maintains the device in a so-called "pretzel" shape until it is removed cystoscopically[20]. Results of the phase 1 TAR-200-103 study in patients with muscle-invasive BCa (MIBC) were recently published[21]. While 43% of patients experienced a treatment-emergent adverse event (TEAE), only 2 patients (5.7%) experienced TEAEs that led to the removal of TAR-200. TAR-200–related TEAEs occurred in 15 patients (42.9%) and were mostly grade ≤ 2. Additionally, the 12-month progression-free survival (PFS) in responders was 68%. TAR-200 alone or in combination with cetrelimab in BCG-unresponsive high-risk NMIBC is under investigation in the phase 3 SunRISe-3 trial (NCT05714202).

The fourth strategy leverages the knowledge of intermediate-risk NMIBC tumour biology for targeted therapy. Around 60% of low-grade papillary tumours are characterized by overexpression of activating *FGFR3* mutations[2], which may make them amenable to targeting with fibroblast growth factor receptor (*FGFR*) inhibitors. TAR-210 is an intravesical drug delivery system containing erdafitinib, a tyrosine kinase inhibitor (TKI) of *FGFR1–4*. Erdafitinib is currently approved in adults with locally advanced and metastatic urothelial carcinoma (UC) who progress after at least 1 line of platinum-based chemotherapy. Currently, TAR-210 is under investigation in multiple different study populations with confirmed susceptible *FGFR* alterations, including a cohort of patients with recurrent low-grade papillary NMIBC not planned for radical cystectomy (NCT05316155). Another strategy, this time employing a systemic approach, is the phase 2 window-of-opportunity trial, led by Dr. Noah Hahn, which will evaluate pemigatinib, an oral *FGFR* inhibitor, in patients with recurrent low- and intermediate-risk NMIBC (NCT03914794).

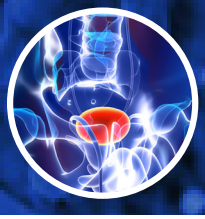
The last strategy is to consider intravesical therapies to enhance the response rate for adjuvant therapy and reduce disease recurrence. In the landmark phase 3 study of nadofaragene firadenovec, a replication deficient adenovirus-based gene therapy encoding IFN-α2b, a CR rate of 53%, along with durable high-grade recurrence-free survival (RFS), was observed in BCG-unresponsive, heavily pretreated patients. Treatment was also well tolerated[22]. Dr. Psutka also pointed out that the drug is administered only once every 3 months, likely reducing the burden on patients. Nadofaragene firadenovec is also under investigation in the adjuvant setting in patients with intermediate-risk NMIBC in the phase 3 randomized ABLE-32 trial, led by Dr. Trinity Bivalacqua.

To conclude, Dr. Psutka stressed the need to prioritize meaningful patient-focused endpoints in clinical trials of intermediate-risk NMIBC. These should include RFS, the rate of reclassification from intermediate- to high-risk disease, and the toxicity, harms, and complications associated with treatment. Additionally, trials should assess patient-reported quality of life (QoL), treatment burden, financial toxicity and costs, and resource utilization associated with the different treatments evaluated.

Ultimately, many NMIBCs will chronically relapse; however, most of these will not be life threatening. As a result, the traditional treatment paradigm leads to overtreatment, with unacceptable risk of harm, costs, and reduction in QoL. As the treatment paradigm for intermediate-risk NMIBC continues to evolve, novel intravesical and systemic strategies under evaluation may help to reduce treatment burden, minimize overtreatment, and reduce recurrences and progression.

In a subsequent Q&A session, Dr. Psutka discussed developments in intravesical immunotherapy, particularly in the BCG-unresponsive setting, where multiple trials are ongoing evaluating several different agents alone or in combination with standard of care. Dr. Psutka expressed that these are a potentially interesting avenue for the traditional paradigm of TURBT followed by adjuvant therapy.

Next, Dr. Jeremy Yuen-Chun Teoh (Hong Kong) discussed the use of AI to optimize the detection of BCa. Cystoscopy plays a critical role in BCa management. Patients presenting with hematuria require cystoscopy



for the diagnosis of BCa. An adequate visualization and inspection of the bladder during TURBT is also critical, not only for improving surgical outcomes but also for supporting patient surveillance after TURBT. Cystoscopy during TURBT can be improved with the use of enhanced imaging approaches, such as narrow band imaging[23] and photodynamic diagnosis[24]. While useful, these approaches also present limitations. First, enhanced imaging changes the colour of the image, which makes tumour resection more challenging. Second, enhanced imaging may make it difficult to distinguish between cystitis and an actual bladder tumour. Therefore, there is an ongoing need to optimize cystoscopic imaging and optimize TURBT outcomes.

AI-based cystoscopy represents an important approach to optimize BCa resection. The development of AI-based cystoscopy requires building up a large database of photos and videos of cancerous as well as health bladder mucosa. All images must be pre-processed for image ratio, and tumours must be manually annotated. The database is then used to develop an AI model using a deep learning algorithm, followed by training, validation, and testing[25].

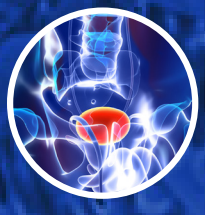
Several AI-based systems for BCa cystoscopy have been recently published. In a multicentre diagnostic study from 6 hospitals in China published in 2022, an AI-based system was developed using 69 204 images obtained from 10 729 patients[26]. This AI algorithm produces a heatmap that indicates the likelihood of BCa and can be projected on the cystoscopic image. While the area under the curve (AUC) was generally > 0.9 for multiple parameters, Dr. Teoh cautioned that these results should be carefully interpreted, as the AUC generally drops to ≥ 0.8 upon AI validation, as seen in this and other studies. In addition, AI studies often present with limitations. In this particular study, 12% of the cohort was excluded from the dataset due to inadequate cystoscopic images, which may incur performance bias.

In a study from Japan published in 2022, the authors used 1790 cystoscopic images obtained from converting videos from 120 patients who underwent TURBT to develop 2 AI models, resulting in a black and white output image[27]. The results of this study are still exploratory and lack validation. Because the images were extracted from videos, the quality of the photos can be an issue. Real-time assessment was also not reported in the study, which makes application to clinical practice challenging.

Another study published in 2020 used a deep convolutional neural network (DCNN) to develop an AI tumour classifier based on a total of 2102 cystoscopic images, of which 1671 were of normal tissue and 431 were of BCa lesions[28]. More interestingly, the DCNN model used in this study had been pre-trained on a large dataset of generic images as an initial setting for fine-tuning. The resulting AI model performed with an AUC of 0.980 (across different T stages, inclusive), sensitivity of 0.897, and specificity of 0.940. While promising, this AI model requires further validation.

In 2019, researchers published the first results of CystoNet, a convolutional neural network (CNN)-based image analysis platform for automated BCa detection developed from a dataset of 95 patients for algorithm training and 5 patients for testing; it was validated prospectively in an additional 54 patients[29]. The model aims to provide real-time assessment of images during cystoscopy; however, the processing required for the number of images in every 1-second frame results in time lag that may hinder real-time assessment.

Dr. Teoh also discussed the results of a study conducted at his centre[30]. Using cystoscopic videos from 100 patients undergoing flexible cystoscopy or TURBT, Dr. Teoh and colleagues were able to obtain 4019 images with good quality. A segmentor was used to segment the tumour at pixel level and a classifier was employed to distinguish malignant from benign lesions in the images. From the dataset, 3294 images were used to train a deep learning endoscopic system, whereas 725 images were used to test the system. The AI system performed with an AUC of 0.906, sensitivity of 0.808, and specificity of 0.913. Despite the success of its high performance, Dr. Teoh cautioned that sometimes the AI model will fail to detect BCa during cystoscopy. Some circumstances that may lead to failed detection include the position of the tumour (e.g., at the edge of the image), tumours located outside the bladder (e.g., in the urethra), as well as images that are out of focus. These cases highlight the



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importance of diversifying the images included in the dataset to train the AI model, particularly those images that may not be considered of good quality.

Lastly, Dr. Teoh discussed a novel endoimaging system that aims to reconstruct 3D bladder models from cystoscopy videos, which can then be visualized through an online platform[31]. This phantom digital 3D bladder model can be used to help visualization of difficult cases, as well as implemented to support training.

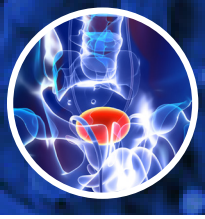
To conclude, Dr. Teoh emphasized that AI cystoscopy has an excellent performance in BCa detection, but most systems are still exploratory and their real value remains to be determined upon further validation. There are still several obstacles that need to be overcome, such as the ability to assess images of lower quality and to ensure real-time transmission. Once the system has been developed and is validated, it is also important to consider how the system may improve clinical endpoints, as well as to consider the regulatory approval process for use of the AI in daily clinical practice. Most importantly, Dr. Teoh emphasized that AI cystoscopy should be viewed as a complementary, rather than competitive, tool in the management of BCa.

During his Q&A session, Dr. Teoh discussed whether AI cystoscopy may evolve to allow for BCa prognosis by providing information on tumour grading and staging. While this may eventually be feasible, the current issue with most AI systems is how labour intensive it is to not only capture the image, but also to resect the tumour, send it for histology, and then match the image with the actual histology results. As this field continues to develop, scaling up these models and making them widely available will certainly have an important contribution.

Dr. Teoh's presentation was followed by a debate on whether next-generation urine markers have utility in clinical practice, with Dr. Öner Sanli (Türkiye) presenting the pro side and Dr. Carmen Mir (Spain) presenting the con side. Dr. Sanli started the debate by pointing out that despite urine cytology and cystoscopy being standard of care for diagnosing and surveilling BCa, both present limitations. For instance, the sensitivity of cytology is low (38% to 45%), despite the high specificity (95% to 97%)[32]. The performance of cystoscopy, on the other hand, is operator dependent and may result in side effects (such as pain during urination, increased urinary frequency, macroscopic hematuria, and infection)[33,34]. Cystoscopy also has high variability in sensitivity (62% to 84%) and specificity (43% to 98%), which is dependent on the tumour type, stage, and grade[34]. Despite the limitations of both approaches, patients are willing to accept a urine test as replacement to cystoscopy only if the test is ≥ 95% accurate[35].

Urine biomarkers have greatly improved in recent years with the development of messenger RNA (mRNA)- and DNA-based next-generation multiplex assays, which have higher sensitivity (74% to 95%) and specificity (80% to 100%)[36]. While urine markers have several applications in clinical practice, such as the prediction of recurrences, identification of high-risk tumours or MIBC, and assessment of response to BCG treatment, Dr. Sanli focused on those that can be used in the diagnosis and surveillance of BCa.

First, Dr. Sanli discussed next-generation urine markers used in BCa diagnosis. AssureMDx™ is a commercially available urine-based genomic assay used in BCa diagnosis, particularly in patients who present with hematuria. The assay was evaluated prospectively in diagnosing 838 patients with hematuria. In the full cohort, the AUC was 0.957 and sensitivity was 96%. The assay also showed good performance in patients with microhematuria (n = 381, AUC = 0.971)[37], suggesting that AssureMDx may replace cystoscopy in select patients. Cxbladder™ is a multigene urine test developed through a cohort of 485 patients presenting with macrohematuria. Cxbladder had an AUC of 0.87, sensitivity of 81.8%, and specificity of 85%[38]. Overall, Cxbladder detected 82% of tumours, including 97% of the high-grade tumours and 100% of T1 or greater stage tumours. This test is currently under investigation in patients with microhematuria in the STRATA study (NCT03988309). UroSEEK is another urinary marker assay incorporating parallel sequencing for mutations in 11 genes and copy number changes in 39 chromosome arms. Combined with cytology, UroSEEK demonstrated sensitivity of 95% and specificity of



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93% in an early detection cohort of 570 patients[39]. The diagnostic performance of UroSEEK was also investigated in patients after equivocal cytology, where it showed a sensitivity of 96% and specificity of 88%[40]. Lastly, UroMark is a biomarker panel assay of 150 loci that targets epigenetic DNA changes. The assay was validated in an independent cohort (non-cancer, n = 274; BCa, n = 107) with an AUC of 97%, sensitivity of 98%, and specificity of 97%[41].

Second, Dr. Sanli focused on urinary biomarker assays used in BCa surveillance. EpiCheck™ uses 15 proprietary DNA methylation biomarkers that were validated in a multicentre study of 353 patients undergoing surveillance. The overall sensitivity of EpiCheck was 68.2% and the AUC was 0.82. After excluding low-grade Ta recurrences, the sensitivity increased to 91.7% and the AUC to 0.94[42]. According to Dr. Sanli, a considerable challenge of EpiCheck is the need for a dedicated laboratory facility and well-trained personnel. Cxbladder™ Monitor was compared prospectively with other commercially available urine markers as well as cytology using samples from 803 patients recruited from 10 centres in the United States. The assay demonstrated sensitivity of 91%, performing considerably better than the comparator tests[43]. Xpert® Bladder Cancer Monitor measures the expression of 5 mRNAs. The test was evaluated in 11 prospective studies that included 2896 patients, resulting in a pooled sensitivity of 73% and specificity of 77% in meta-analysis[44]. It has moderate sensitivity (58%) in low-grade tumours[44]. UroSEEK in combination with cytology can also be used in BCa surveillance (sensitivity = 71%; specificity = 80%), although the outcomes for surveillance are not as good as for diagnosis[39]. The main advantage of this assay is its ability to detect low-grade tumours within 6 months, Dr. Sanli highlighted.

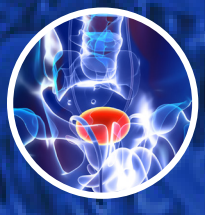
Lastly, Dr. Sanli discussed a microsatellite analysis to predict the risk of future recurrence. In this study of 1012 urine samples, the analysis demonstrated sensitivity of 58% and specificity of 73%. More importantly, the authors identified an 83% 2-year risk of recurrence when microsatellite analysis was persistently positive vs. 22% risk when the analysis was persistently negative[45].

In summary, Dr. Sanli noted that next-generation urine markers have improved sensitivity and better negative predictive value (NPV) relative to traditional tests. However, the assays are still relatively complex, require dedicated infrastructure for analyses, and samples may take time to process. Additionally, most assays are currently more expensive than cytology and cystoscopy. Despite the present limitations, urine markers have a future in clinical practice. No single test in available for all clinical scenarios, but there is a test for every clinical scenario and many tests have sensitivity and specificity ≥ 90%.

Arguing against the clinical utility of next-generation urine markers, Dr. Mir explained that no urinary molecular markers have been accepted for the routine diagnosis and follow-up of patients with BCa by any clinical guidelines to date[46]. When recommended as part of BCa management, the National Comprehensive Cancer Network (NCCN) Guidelines® classify the recommendation as weak due to the lack of randomized controlled trials[5].

BCa poses a high economic burden on patients and healthcare systems. In Europe, the annual cost to healthcare systems is €2.9 billion, with inpatient care accounting for the major cost component (58%)[47]. Disease progression has the highest cumulative cost of care, and this cost is considerably more elevated in patients with intermediate- and high-risk BCa[14]. Therefore, early detection of disease progression is key not only to optimize treatment outcomes but also to reduce the economic burden of BCa management.

A proposed algorithm for the screening and early management of BCa may start with the identification of hematuria to trigger initial evaluations of biomarkers, followed by cystoscopy and cytology for accurate diagnosis. However, there are limitations to this algorithm. First, hematuria has demonstrated poor performance in defining populations at risk for BCa in cohort studies[48]. Looking at biomarkers, clinicians should be interested in those that show high specificity, i.e., the percentage of patients without disease who test negative. This is important to avoid invasive procedures in patients who do not require them. Of the commercially available biomarker tests, ADXBLADDER™ has specificity of 68%[49]. This test detects levels of MCM5



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(a protein that can become overexpressed in other pathologies than BCa, such as bladder inflammation) in urine. Xpert® Bladder Cancer and Cxbladder Triage, which are molecular assays also available commercially, have specificity of 84% and 96%, respectively[50,51]. However, what would be an acceptable cutoff for false positives detected with biomarker tests? Based on published data, Dr. Mir estimated that 132 unnecessary cystoscopies were performed after a false positive result with Xpert Bladder Cancer and 39 after ADXBLADDER, highlighting the limitations of current assays. Prospective validation of commercially available biomarker tests is still ongoing.

Focusing on surveillance and follow-up, clinicians should select urine biomarkers that have high sensitivity and high NPV. In a meta-analysis of biomarker data in the surveillances setting[52], the protein-based assay ADXBLADDER demonstrated a pooled sensitivity of 57%; mRNA-based assays Xpert Bladder Cancer and Cxbladder had sensitivity of 72% and 91%, respectively; and DNA-based assays EpiCheck and UroMonitor® had sensitivity of 73% and 74%, respectively. NPV ranged from 82% to 98% across assays. Overall, both sensitivity and NPV were improved for the detection of high-grade tumours[52].

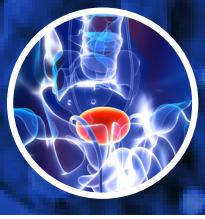
To guide management decisions in the surveillance setting, clinicians should consider the oncological outcomes, the rate of false negatives, and the impact of surveillance on patient QoL. Patients with low-risk superficial BCa are at low risk for progression and can be maintained in active surveillance without the need for surveillance intensification, as seen in the Bladder Cancer Italian Active Surveillance study[53]. It is also known that cystoscopy is overused in the surveillance of low-risk NMIBC. In a recent national study of the Department of Veterans Affairs in the United States, it was found that overuse of cystoscopy occurred in 75% of patients (852/1135). A total of 1846 cystoscopies more than recommended were performed[54]. The overuse of surveillance testing, including cystoscopy, may have an additional cost of at least US$10 000 to the patient[55]. Because cystoscopy is an invasive endoscopic procedure, it can also cause substantial discomfort and anxiety to patients. However, patients are not willing to accept an alternative diagnostic test over cystoscopy, such as a urine biomarker, unless it has sensitivity of ≥ 90%[35,56].

How many cystoscopies are avoided with the use of a urine biomarker? According to results of a meta-analysis, the number of cystoscopies avoided ranges from 500 to 740, depending on which biomarker is used. On the other hand, the number of recurrences missed with a biomarker varies from 10 to 78[52]. Importantly, prospective validation of commercially available biomarker tests is also ongoing in the surveillance setting.

To summarize, Dr. Mir reiterated that current guidelines do not support the use of urine biomarkers, neither for hematuria screening nor for surveillance after BCa diagnosis. In the future, biomarkers may be used to extend intervals of surveillance for patients with low-grade NMIBC, whereas in those with high-grade NMIBC, biomarkers may be used to trigger cystoscopic evaluation. She emphasized that there is an ongoing concern about the overuse of different tools during surveillance, and efforts should be made to limit the use of these tools only to necessary cases.

During the discussion, Dr. Psutka enquired about the current use by Drs. Sanli and Mir of urine biomarker assays and what steps should be taken to accelerate the integration of these biomarkers into clinical practice. Dr. Sanli highlighted that, based on his experience with EpiCheck, one of the main limitations is establishing a laboratory facility and training the personnel, which may take some time. Another challenge is the cost of biomarker assays, which are generally more expensive than standard cytology and cystoscopy. Despite these challenges, Dr. Sanli expects that biomarkers will likely replace more than 50% of cystoscopies in the future.

A case-based panel discussion on the use of MRD to guide BCa treatment followed, moderated by Dr. Black. On the panel were Drs. Shilpa Gupta (United States), Andrea Necchi (Italy), and Karima Oualla (Morocco). Dr. Black started by explaining that MRD was initially defined as *minimal* residual disease. This concept evolved over time with the availability of molecular tests to detect persistent cancer in the absence of other clinical findings. Some examples of molecular tests include circulating tumour cells (CTC),



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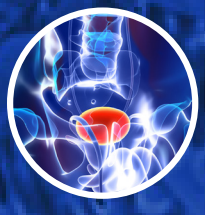
urine tumour DNA (utDNA), and plasma circulating tumour DNA (ctDNA), which was the focus of this discussion. Importantly, Dr. Black emphasized that the clinical utility of these molecular tests remains investigational.

The first case focused on neoadjuvant therapy for MIBC. A 67-year-old male with cT2N0M0 UC had a 3-cm mass completely resected by TURBT. The baseline staging by computed tomography (CT) of the chest/abdomen/pelvis, performed after TURBT, showed bladder wall thickening and no clear 3D mass. The patient received 4 cycles of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC), as per clinical practice guidelines. Restaging with CT showed mild improvement of bladder wall thickening after chemotherapy. The patient did not want to undergo cystectomy or radiotherapy. Based on data from the phase 2 RETAIN trial, which assessed a risk-adapted approach to MIBC management after completion of chemotherapy, bladder preservation would not be recommended[57]. In the trial, patients who presented with no residual tumour and had a mutation in a DNA damage repair (DDR) gene *(ATM, RB1, FANCC,* or *ERCC2)* were offered active surveillance. Out of 26 patients on active surveillance, 10 (38%) developed metastatic disease.

Dr. Black asked whether the panelists would consider any additional investigation for this patient to determine that bladder preservation would be an adequate management. Dr. Oualla explained that active surveillance in this setting is not supported by current clinical evidence and the focus should be on discussions on local treatment options, such as surgery or radiotherapy. Dr. Gupta recommended performing a repeat cystoscopy to investigate for any residual disease, followed by repeat TURBT. If indeed the patient had no evidence of residual cancer, then the risks and benefits of bladder preservation could be discussed with the patient. Dr. Black enquired about the use of ctDNA, if available. Dr. Gupta said she would consider ctDNA analysis. In fact, she has been performing ctDNA testing routinely for post-surgery monitoring, but not to guide decision-making regarding cystectomy. Drs. Oualla and Black pointed out that ctDNA testing might be most valuable by comparing results before and after chemotherapy to assess change over time. Dr. Black also emphasized that neither ctDNA testing nor bladder preservation are currently standard of care. The patient underwent repeat TURBT with no evidence of residual disease (ypT0) and had a negative ctDNA test (Signatera™). Ultimately, the patient proceeded with trimodal therapy.

The second case was a 54-year-old female with cT3N0M0 UC without any histologic subtype. The patient was included in the NURE-Combo trial (NCT04876313) of nivolumab in combination with nab-paclitaxel, to be followed by cystectomy and adjuvant nivolumab. Baseline genomic profiling revealed no alterations that could impact first-line treatment. Staging was performed with magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT. The patient underwent 4 cycles of nivolumab plus nab-paclitaxel. As per trial protocol, ctDNA testing (Signatera) revealed no mutations after neoadjuvant treatment. Radiographic imaging (MRI and PET/CT) showed clinical CR (cCR). Dr. Black asked whether the panelists would consider bladder preservation. Dr. Necchi, who provided the case, explained that the discussion regarding radical cystectomy was based on the depth of response observed and imaging. These discussions are becoming more frequent in daily clinical practice. Dr. Necchi strongly advocated for the use of MRI for staging and tumour reassessment after treatment. He suggested that clinicians should be able to discuss with patients alternative management options to radical cystectomy if there is no evidence of residual tumour on imaging after chemotherapy.

Dr. Black focused on data recently published from the phase 2 HCRN GU16-257 trial[58]. Neoadjuvant therapy was nivolumab in combination with gemcitabine and cisplatin. Patients achieving cCR after neoadjuvant therapy were offered adjuvant nivolumab (8 cycles) without cystectomy regardless of any candidate biomarkers. Bladder preservation was elected by 32 of 33 patients who achieved cCR. The median follow-up for patients achieving cCR was 30 months (range, 18 to 42 months). There was local recurrence in 8 of 32 patients who then underwent cystectomy, including 1 patient with abnormal MRI scan but no evidence of recurrence. Two patients had metastatic



recurrence. Cross-trial comparisons notwithstanding, Dr. Gupta believes that the addition of immunotherapy to the treatment plan in HCRN GU16-257 might have contributed to the durability of responses with respect to the RETAIN trial, in which 38% of patients developed metastatic disease. Dr. Black pointed out that ctDNA was measured in the HCRN GU16-257 trial but not used for decision-making. These data have not yet been reported. He also mentioned that methods to re-assess the bladder after neoadjuvant therapy might have been different in this trial compared to RETAIN, with a formal requirement for repeat TURBT in this trial. In the case, the patient underwent repeat TURBT, revealing a high-grade Ta tumour. Despite the downstaging after treatment, Dr. Oualla would still recommend local treatment for the patient because the tumour was initially cT3. She emphasized that while negative ctDNA after neoadjuvant treatment is an indicator of good prognosis, it is not sufficient to avoid radical cystectomy. Dr. Black pointed out that in the RETAIN trial, there were patients with high-risk NMIBC who had bladder preservation and ultimately recurred and/or progressed. He stated that bladder preservation is still an open question in patients with residual high-grade non–muscle-invasive tumours, especially T1 tumours. In the case, the patient opted for bladder preservation and underwent adjuvant nivolumab and intravesical BCG.

Another consideration raised in the panel discussion was that ctDNA testing may be useful to avoid neoadjuvant chemotherapy in patients with MIBC if the ctDNA is negative after TURBT. This paradigm and the potential use of ctDNA to avoid radical cystectomy after neoadjuvant therapy both require investigation in clinical trials. Furthermore, Dr. Black suggested that ctDNA could be used after treatment to refine surveillance schedules. Patients who are ctDNA negative would undergo less intense surveillance, whereas ctDNA-positive patients would be followed more closely.

The third case focused on M1a disease. The patient was a 57-year-old female who initially presented with high-grade T1 UC with no adverse risk features. No residual disease was found on repeat TURBT, and the patient completed 3 years of BCG without recurrence. One year after completing BCG, routine upper tract imaging revealed pelvic (up to 3 cm) and retroperitoneal (up to 1.9 cm) lymphadenopathy. The largest lymph node was biopsied and shown to be UC. No sign of tumour was found in the bladder on cystoscopy or imaging. The patient underwent 4 cycles of gemcitabine-cisplatin and achieved cCR.

Dr. Black asked the panel what the optimal subsequent therapy for this patient with cCR after chemotherapy for M1a disease should be, and whether ctDNA could aid in decision-making. Dr. Gupta would use avelumab, according to results of the JAVELIN Bladder 100 trial[59], and not recommend retroperitoneal lymph node dissection (RPLND). She would also use ctDNA to monitor ongoing response. If ctDNA were negative, Dr. Gupta would discuss avelumab discontinuation with the patient at some point. Dr. Necchi pointed out that, despite a clear standard of care for M1a tumours, this case falls into the oligometastatic disease state, where RPLND may have a role. This may be relevant for patients who have concerns about the duration of maintenance avelumab, which has no clear timeline for discontinuation. Dr. Necchi may favour RPLDN if the patient is ctDNA negative. However, he emphasized the importance of personalizing the decision-making process with the patient. He also emphasized the importance of biopsy to confirm oligometastatic relapse prior to starting chemotherapy, especially if the relapse occurs 1 year after the completion of prior treatment.

Dr. Oualla then presented on the next frontier in systemic therapy for mUC. In recent years, there have been important changes in the treatment landscape of BCa, particularly in the advanced setting. Improved understanding of BCa biology has opened the door to the development of new therapies through the identification of new treatment targets, as well as better use of immunotherapy in this setting. One of the first questions faced by clinicians is patient fitness for chemotherapy. Patients can be cisplatin fit, cisplatin unfit (but fit for carboplatin), or platinum unfit. In the last 20 years, limited advances have been achieved with the use of systemic chemotherapy[60].

The paradigm started to shift with the results of the phase 3 JAVELIN Bladder 100 trial, which established

maintenance with avelumab as standard of care for patients with mUC who do not progress with first-line platinum chemotherapy[59]. For patients with mUC who are cisplatin ineligible, pembrolizumab and atezolizumab were initially approved based on outcomes of the phase 2 trials KEYNOTE-052[61] and IMvigor210[62], respectively. The current first-line indication of each agent differs between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Given the independent benefits of chemotherapy and immunotherapy, researchers have hypothesized a potential benefit of combining the 2 treatment strategies. However, trials have failed to demonstrate an OS benefit of combining chemotherapy with pembrolizumab (KEYNOTE-361)[63], atezolizumab (IMvigor130)[64], or durvalumab (DANUBE)[65].

Another combination, this time with cabozantinib and atezolizumab, was investigated in cohort 3 (no prior systemic therapy and cisplatin ineligible), cohort 4 (no prior systemic therapy and cisplatin eligible), and cohort 5 (1 prior immune checkpoint inhibitor and no prior vascular endothelial growth factor receptor [VEGFR]-TKI therapy; ≤ 2 line of therapy) in the phase 1b COSMIC-021 trial[66]. While the objective response rate (ORR) was modest in all cohorts, the observed disease control rate was encouraging, particularly in cohort 3. Further investigation with this treatment combination is promising.

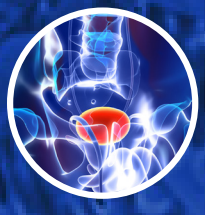
The phase 2 NORSE trial investigated erdafitinib in combination with cetrelimab in patients with mUC who are systemic-therapy naïve, ineligible for cisplatin, and have FGFR alterations. The trial enrolled 90 patients who were randomized to either the combination or erdafitinib alone. Final results of the trial reported in 2023 revealed an ORR of 54.5% in the erdafitinib plus cetrelimab arm compared to 44.2% in the erdafitinib monotherapy arm[67].

Also in the first-line setting, the phase 1/2, multicohort, dose-escalation and dose-expansion KEYNOTE-869/EV-103 trial (NCT03288545) investigated the treatment with pembrolizumab ± enfortumab vedotin in patients with mUC. Dr. Oualla focused on the results of cohort A (pembrolizumab plus enfortumab vedotin) and cohort K (pembrolizumab plus enfortumab vedotin or enfortumab vedotin monotherapy), both in cisplatin ineligible populations. In cohort A, the ORR was 73.3% in the overall population and 57.1% in patients with liver metastasis[68]. In cohort K, the confirmed ORR was 64.5% for the combination and 45.2% for the monotherapy[69]. More recently, it has been announced that the phase 3 KEYNOTE-A39/EV-302 trial, investigating the combination of pembrolizumab and enfortumab vedotin compared to chemotherapy, has met its dual primary endpoints of OS and PFS in previously untreated patients with mUC.

What about emerging treatment combinations in mUC? The phase 3 CheckMate 901 trial investigated nivolumab in combination with gemcitabine-cisplatin (cisplatin eligible) or with ipilimumab (cisplatin ineligible) as a first-line option. In the cisplatin-eligible arm, patients were randomized to either the nivolumab-chemotherapy combination followed by nivolumab monotherapy or chemotherapy alone. With a median follow-up of 33.6 months, the OS was significantly longer with the nivolumab-chemotherapy combination (21.7 months) compared with chemotherapy alone (18.9 months; hazard ratio [HR] = 0.78; 95% confidence interval [CI], 0.63 to 0.96; $P = 0.02$). PFS was also longer with the nivolumab-chemotherapy combination (7.9 months) compared with chemotherapy alone (7.6 months; HR = 0.72; 95% CI, 0.59 to 0.88; $P = 0.001$)[70].

With several improvements in the first-line setting, there is a greater proportion of patients who may progress to second and subsequent lines of treatment. Presently, pembrolizumab is the only agent approved as second-line therapy after chemotherapy based on phase 3 data (KEYNOTE-045 trial)[71]. Atezolizumab and durvalumab, which had initially received accelerated approvals, have been withdrawn from the second-line indication since 2021. In this setting, avelumab and nivolumab may also be considered as a second-line option if not previously given.

Results of the phase 3 THOR-2 trial have become available recently. This trial investigated treatment with erdafitinib compared with chemotherapy in patients with *FGFR2/3*-altered mUC who progressed after 1 or 2 lines of treatment. A total of 236 patients



underwent randomization. With a median follow up of 15.9 months, the OS was significantly longer with erdafitinib (12.1 months) compared with chemotherapy (7.8 months; HR = 0.64; 95% CI, 0.47 to 0.88; $P = 0.005$). PFS was also significantly improved with erdafitinib (5.6 months) compared with chemotherapy (2.7 months; HR = 0.58; 95% CI, 0.44 to 0.78; $P < 0.001$)[72]. These results establish erdafitinib as a standard second- or third-line treatment option in patients with mUC with *FGFR2/3* alterations.

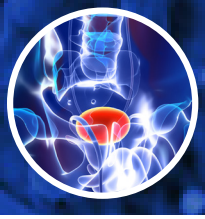
Enfortumab vedotin is a third-line treatment option based on results of the open-label phase 3 EV-301 trial[73]. At the median follow-up of 11.1 months, treatment with enfortumab vedotin vs. chemotherapy resulted in significantly longer OS (12.88 vs. 8.97 months, respectively; HR = 0.70; 95% CI, 0.56 to 0.89; $P = 0.001$), as well as PFS (5.55 vs. 3.71 months, respectively; HR = 0.62; 95% CI, 0.51 to 0.75; $P < 0.001$).

Sacituzumab govitecan is another antibody-drug conjugate available in the third-line setting. The agent demonstrated positive activity in heavily pretreated patients in cohort 1 of the multicohort, open-label, single-arm, phase 2 TROPHY-U-01 trial. With median follow-up of 10.5 months, sacituzumab govitecan resulted in ORR of 28%, as well as 12-month rates of 14% PFS and 45% OS[74]. The ongoing, randomized phase 3 TROPiCS-04 trial (NCT04527991) is investigating sacituzumab govitecan vs. chemotherapy in the third-line setting.

In this rapidly evolving field, novel treatment approaches and combinations may soon be changing the current standard of care for patients with mUC. Following Dr. Oualla's presentation, the discussion continued with the panelists Drs. Andrea Necchi, Petros Grivas (United States), and Tian Zhang (United States). Dr. Necchi started by acknowledging that the field for mUC will likely be impacted by important progress in earlier settings. Around 70% of patients with mUC will likely have received one form of systemic therapy for organ-confined BCa. He highlighted the example of positive, recently reported DFS benefit with adjuvant pembrolizumab vs. observation for MIBC from the phase 3 AMBASSADOR trial (NCT03244384) and how this may impact the approval of pembrolizumab in the adjuvant setting. In addition, the highly anticipated results of the EV-302 trial (NCT04223856) will likely lead to the combination of pembrolizumab with enfortumab vedotin in the first-line mUC setting. This poses an important question on predicting how the field of systemic therapies in mUC may further evolve. On the other hand, the field of targeted systemic therapies, such as erdafitinib for *FGFR2/3*-altered mUC, may also evolve over time with progress in key ongoing trials. Dr. Necchi also pointed out that, for most patients, only small increments in OS benefit have been seen with new agents and/or treatment combinations, while we wait for the results of the EV-302 trial.

Dr. Zhang added that it has not been long since treatment options for mUC were very limited. What is very encouraging now is that there are several life-extending therapies available. Despite the improvements in OS being small/incremental with each individual therapy, the possibility of sequencing those therapies may ultimately help to achieve a much better outcome for an individual patient. She highlighted that in her practice she sees several patients with mUC who experience early metastatic visceral crises. In those patients, it is very important to achieve early disease control with chemotherapy and then try to maintain disease control with switch maintenance avelumab, which is why results of the JAVELIN Bladder 100 trial[59] are so important for current clinical practice. Dr. Zhang also hopes that closer follow-up may allow clinicians to intervene before patients experience metastatic visceral crisis.

Dr. Grivas underlined the importance of the positive results from the phase 3 trials KEYNOTE-A39/EV-302 and CheckMate 901, which were subsequently presented at the European Society of Medical Oncology (ESMO) 2023 meeting in Madrid, for the current treatment of mUC. He also emphasized the impact that adjuvant pembrolizumab for MIBC may have for the subsequent treatment of patients who experience metastasis after adjuvant anti–programmed cell death-1 (PD-1) therapy, based on recently announced results from the AMBASSADOR trial. Dr. Grivas stressed the need for clinical trials examining the efficacy of immune checkpoint inhibition rechallenge in the mUC setting.



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Despite the rapid evolution in treatment options for mUC, Dr. Grivas highlighted that global access to new therapies is an ongoing challenge. Differences in access to life-prolonging therapies will continue to influence how patients are treated worldwide. He noted that, while important for guiding management decisions, clinical trial data are relatively limited to a select patient population. Real-world data, collected from patients with distinct sets of comorbidities, are also important to complement the results of clinical trials and offer the opportunity for international collaboration across multiple centres.

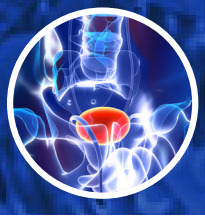
Another consideration is the importance of clinical trials investigating treatment de-escalation. In the context of the results of KEYNOTE-A39/EV-302, could enfortumab vedotin be de-escalated at some point in the management course? Trials designed by cooperative groups may provide an answer to this question. Regarding the developments in targeted therapy, Dr. Grivas emphasized the importance of tumour genomic testing at the time of diagnosis of metastatic disease to inform subsequent treatment options. Lastly, Dr. Grivas noted the relevance and need of biomarker validation to further advance personalized medicine for mUC.

Dr. Necchi added that disparities in treatment access have increased with the availability of more therapeutic options based on recent clinical trial progress. As an example, he mentioned that reimbursement for switch maintenance with avelumab is challenging in several countries. This scenario may become more complicated with the upcoming approvals in first-line setting mUC. He noted that, while there is a tendency to focus on forefront research, most patients worldwide are very far from forefront treatment. Coming from Morocco, Dr. Oualla expressed how frustrating it is, not only for doctors but also for patients, to be aware of all the emerging data and survival benefits of new therapies when access to those treatments is limited. She stressed the critical need for more equitable treatment and access to healthcare systems across the globe.

Dr. Psutka noted that there were common themes throughout the BCa session, spanning from nonlethal NMIBC to multidrug-exposed mUC. New strategies to detect earlier levels of disease, prognosticate, restratify disease, and escalate or de-escalate treatment, as well as translational approaches, such as urine biomarkers and ctDNA, are all important to avoid unnecessary treatment and related toxicities, related not only to side effects but also to financial toxicity. There is a clear issue regarding the cost of treatments worldwide, and clinicians must work together to ensure more equitable access for their patients.

Regarding *FGFR* testing, Dr. Necchi enquired about the optimal timing for testing. Dr. Grivas emphasized the importance of tumour genomic sequencing for *FGFR2/3* activating mutation or fusion at time of diagnosis for mUC, because these results may inform management if the patient progresses to a subsequent line of therapy. He mentioned that sometimes he also requests ctDNA testing at the same time, which may capture tumour heterogeneity; *FGFR3* mutations are usually captured from sequencing of TURBT or radical surgery tissue samples, whereas *FGFR2* might also be captured from ctDNA in plasma. Dr. Grivas noted the challenges faced by community oncologists in interpreting genomic reports and the importance of establishing molecular tumour boards in community oncology hospitals. Dr. Zhang added that urologists at her institution reflexively send cystectomy tissue for genomic sequencing, which helps guide treatment decisions by medical oncologists at the time of recurrence or metastatic disease, as well as guide patient inclusion in clinical trials. Drs. Psutka and Grivas both commented on the importance of multidisciplinary collaboration across different specialties to drive evolutions in the field and help provide the best care for patients.

The last presentation in the BCa session was by Dr. Black, who provided an update on key, ongoing clinical trials in first-line therapy for NMIBC. NMIBC is categorized as low, intermediate, or high risk, which has implications for routine treatment and clinical trials. Different guidelines use different risk stratification criteria. In clinical practice, Dr. Black follows the older risk groupings of the European Association of Urology (EAU), given their simplicity. According to this classification, low-risk NMIBC is defined as a single, first occurring, low-grade tumour of < 3 cm in diameter and



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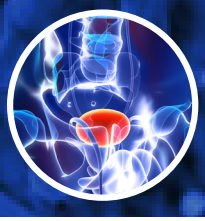
includes papillary urothelial neoplasm of low malignant potential (PUNLMP). High-risk NMIBC includes any high-grade (including carcinoma in situ [CIS]) and any T1 tumour. All other NMIBC tumours are classified as intermediate-risk NMIBC, which includes low-grade tumours that are multifocal, recurrent, or > 3 cm in diameter[46]. High-risk NMIBC can be further defined according to exposure to BCG. BCG naïve indicates no prior exposure to BCG therapy, whereas BCG unresponsive includes BCG refractory (tumour is persistent or recurrent after initial adequate BCG therapy) and early relapse after initial disease-free interval. BCG exposed includes high-grade recurrence after BCG induction only or late relapse. BCG intolerance indicates BCG discontinuation due to adverse effects[75]. Distinguishing among these subgroups is key for clinical practice and clinical trial design.

The current treatment of NMIBC involves a risk-adapted approach. Low-risk NMIBC is treated with TURBT plus a single dose of postoperative intravesical chemotherapy, whereas the treatment of high-risk disease includes TURBT followed by BCG with 3 years of maintenance. In intermediate-risk NIMBC, treatment involves TURBT followed by adjuvant chemotherapy or BCG at the physician's discretion, and 1 year of BCG maintenance[46].

It is remarkable how long BCG has been recommended as a treatment in BCa, since its first use in patients by AI Morales and colleagues 50 years ago[76]. BCG induction followed by maintenance remains the standard first-line therapy for intermediate- and, particularly, high-risk NMIBC. This should not be interpreted as a lack of progress in the field, but instead as evidence that BCG remains a highly effective therapy. However, there are limitations to BCG. For instance, BCG is associated with important toxicities and is contraindicated in patients who are immunosuppressed (e.g., patients after organ transplant). Additionally, BCG recurrence and progression are common events, and one of the biggest unmet clinical needs that has been the focus of extensive research over the past decades is the lack of effective treatments in the second line. New treatments can be classified as agents that enhance BCG or those that aim to replace BCG.

Strategies to enhance BCG therapy are relevant to overcome limitations associated with toxicity and frequency of recurrence/progression. There are ongoing trials investigating alternative BCG strains, which may prove at least noninferior to the current strain (TICE® BCG), such as the SWOG S1602 trial (NCT03091660) and the EVER trial (NCT05037279). Another approach is dermal BCG vaccination prior to standard intravesical BCG, which is also being testing in the SWOG S1602 trial (NCT03091660). Recombinant BCG may provide an opportunity to overcome BCG shortage as well as enhance immune response while reducing toxicity from treatment. An example of a recombinant BCG is VPM1002, which has been modified to express the listeria toxin (listeriolysin). VPM1002 has shown encouraging results in patients who recurred after BCG in the single-arm phase 1/2 SAKK 06/14 trial[77]. An additional strategy involves the administration of adjunct agents to enhance BCG activity. Low-dose, oral encapsulated rapamycin (eRapa), an antineoplastic, is under investigation in a double-blind, randomized phase 2 trial (NCT04375813). BCG-naïve patients with low- or high-grade NMIBC will be treated according to standard of care and then randomized to the addition of 0.5 mg eRapa or placebo. Currently, there are four phase 3 trials investigating the combination of BCG and an immune checkpoint inhibitor in BCG-naïve, high-risk NMIBC: durvalumab in POTOMAC (NCT03528694), atezolizumab in ALBAN (NCT03799835), pembrolizumab in KEYNOTE-676 (NCT03711032), and subcutaneous sasanlimab in CREST (NCT04165317). Most of these trials have accrued and results are much anticipated.

Another strategy is the investigation of novel agents that can replace BCG, especially for patients who are intolerant or have contraindications, and also in the setting of BCG shortages. In the ongoing phase 3 BRIDGE trial (NCT05538663), patients with BCG-naïve high-grade NMIBC are being randomized to sequential gemcitabine-docetaxel (6 weekly cycles with monthly maintenance) or BCG (6 weekly cycle with SWOG protocol maintenance). The primary endpoint is event-free survival. The multicohort phase 2 THOR-2 trial (NCT04172675) is investigating erdafitinib in various NMIBC states with *FGFR2/3* mutations or fusions. In the exploratory cohort 3, erdafitinib is being



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evaluated as a first-line option in intermediate-risk low-grade NMIBC. Preliminary results for cohort 3 were presented earlier in 2023 for 11 patients enrolled. After a median follow-up of 5.7 months, CR was observed in 6 of 8 evaluable patients[78]. Chemoablation with UGN-102 in the Optima II trial[19] and chemoresection with mitomycin C in the DaBlaCa-13 study[79] may also offer alternative therapies in first-line NMIBC.

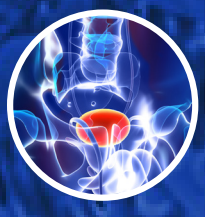
Looking into the future, any agent with efficacy in BCG-unresponsive NMIBC is also attractive for study in first-line intermediate- and high-risk NMIBC. This is the case of nadofaragene firadenovec in the ABLE trial and cretostimogene grenadenorepvec (CG0070) in CORE-008. One potential limitation of alternatives to BCG, however, may be the cost of treatment compared to BCG. Potential major paradigm shifts that may come to clinical practice in upcoming years include the use of systemic therapies (immunotherapy or *FGFR* inhibitors) for intermediate-/high-risk NMIBC, as well as chemoablation instead of primary TURBT for intermediate-risk NMIBC.

In summary, there has been a gradual shift in the clinical trials landscape from BCG-unresponsive to first-line BCG-naïve NMIBC. The majority of trials are most advanced in high-risk NMIBC, although trials in intermediate-risk disease are also on the horizon. The main objective of these trials is to enhance or replace BCG as standard of care.

During the Q&A session, Dr. Black clarified that the THOR2 trial includes a high-risk NMIBC cohort and a BCG-unresponsive cohort. These patients, however, are less likely to have an FGFR alteration and, if they do, that alteration may be less likely to be driving tumour growth. Conversely, low-grade tumours in intermediate-risk NMIBC are more likely to have *FGFR3* alterations, and they are more homogenous at a molecular level so that the *FGFR3* alteration is likely to be driving tumour growth, suggesting that erdafitinib would likely show activity in these patients. Dr. Black suggested that intravesical delivery of erdafitinib with the TAR-210 system is particularly attractive, given its potential to avoid systemic toxicity.

Dr. Black also addressed trial design for novel agents in the BCG-unresponsive setting, given the advent of new treatment options in this space. Recent trials in this space were single arm because of the lack of an adequate comparator. There are now several options that could be used as a standard comparator derived from recent trials and retrospective, multicentre evidence for sequential gemcitabine-docetaxel. This would allow for prospective, randomized-controlled trials to be conducted, and such a trial is under development in the cooperative groups. Novel trials will test combination therapies, which will likely require comparison to one or both agents in the combination as monotherapy.

Lastly, Dr. Black discussed his current approach for high-risk BCG-unresponsive NMIBC in patients not undergoing cystectomy. Sequential gemcitabine-docetaxel has become a popular alternative to BCG given its tolerability, although the supporting data are retrospective. This therapy is also applicable if BCG is unavailable or if a patient is ineligible or intolerant to BCG.



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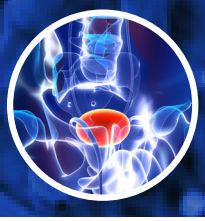
Abbreviations Used in the Text

AI	artificial intelligence
AUC	area under the curve
BCa	bladder cancer
BCG	bacillus Calmette-Guérin
cCR	clinical complete response
CI	confidence interval
CR	complete response
CT	computed tomography
ctDNA	plasma circulating tumour DNA
DCNN	deep convolutional neural network
DFS	disease-free survival
eRapa	encapsulated rapamycin
FGFR	fibroblast growth factor receptor
HR	hazard ratio
IBCG	International Bladder Cancer Group
MIBC	muscle-invasive bladder cancer
MRD	molecular residual disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
mUC	metastatic urothelial carcinoma
NMIBC	non–muscle-invasive bladder cancer
NPV	negative predictive value
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PUNLMP	papillary urothelial neoplasm of low malignant potential
QoL	quality of life
RFS	recurrence-free survival
RPLND	retroperitoneal lymph node dissection
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TURBT	transurethral resection of bladder tumour
UC	urothelial carcinoma



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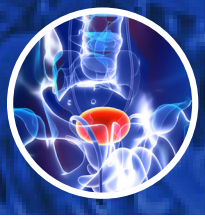

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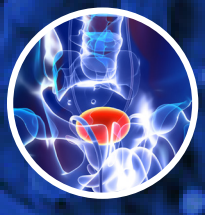

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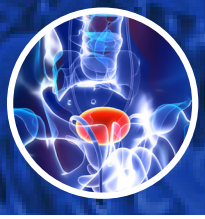

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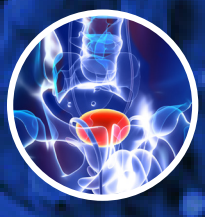

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