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Conference Report

B2B: Five Practice-Changing Advances on the Horizon Summary

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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 fourth session, on the 5 practice-changing advances in genitourinary (GU) cancers, took place in the afternoon and was moderated by Dr. Peter C. Black (Canada) and Dr. Simon Tanguay (Canada).

The first presentation was by Dr. Black, who discussed the 5 practice-changing advances in bladder cancer (BCa). The first of these is perioperative chemoimmunotherapy in muscle-invasive BCa (MIBC). The current standard of care in this setting is dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) or gemcitabine-cisplatin (GC) in cisplatin- eligible patients, followed by radical cystectomy (RC). If there is residual disease, patients receive adjuvant immunotherapy (IO). Patients may also receive adjuvant chemotherapy if they did not receive neoadjuvant chemotherapy (NAC). Patients who are cisplatin ineligible will undergo RC and possibly receive adjuvant IO.

The NIAGARA trial introduced the potential for perioperative chemoimmunotherapy in this setting. Multiple single arm trials had previously tested neoadjuvant IO or neoadjuvant chemoimmunotherapy, but NIAGARA is the first randomized controlled trial (RCT) to compare perioperative chemoimmunotherapy with standard chemotherapy. For this trial, cisplatin- eligible patients with MIBC were randomized to GC alone or GC plus durvalumab in the neoadjuvant setting. Patients then underwent RC, and those in the durvalumab-containing arm continued to receive it postoperatively. The addition of durvalumab was associated with an improved event-free survival (EFS, hazard ratio = 0.68; 95% confidence interval [CI] 0.56–0.82; $p < 0.0001$) and overall survival (OS, hazard ratio = 0.75; 95% CI = 0.59–0.93; $p = 0.0106$). There was no difference between the 2 arms in terms of pathological complete response (pCR), although an unplanned re-analysis did reveal a nonsignificant difference that was larger than originally reported (37.3% with durvalumab vs. 27.5% without). All of this was attained with a manageable level of toxicity. Importantly, perioperative treatment did not delay or prevent surgery, nor did it increase the risk of perioperative complications [1].

Nevertheless, the NIAGARA trial did have its limitations. The trial included only cisplatin-eligible patients and only neoadjuvant GC chemotherapy was evaluated. Based on results of the VESPER trial [2], outcomes in NIAGARA may have differed with the inclusion of neoadjuvant ddMVAC as a comparator arm. Additionally, there was no adjuvant IO in the NAC arm, which makes it challenging to discern the actual benefit of neoadjuvant IO, which is the component of perioperative chemoimmunotherapy that is different from the current standard treatment algorithm. Finally, it remains unknown whether patients who have a complete response (CR) at the time of surgery will truly benefit from adjuvant IO.

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The second practice-changing advance projected by Dr. Black, also in the setting of MIBC, is neoadjuvant enfortumab vedotin (EV) plus pembrolizumab. Given that there is clear benefit for use of EV plus pembrolizumab when compared with chemotherapy in patients with metastatic urothelial carcinoma (mUC), Dr. Black predicts that this same combination may become standard of care in the neoadjuvant setting as soon as the relevant trials are completed and reported. He anticipates that EV plus pembrolizumab will be better tolerated than chemoimmunotherapy (as has been reported in the advanced setting), and will produce more pCRs, allowing for more bladder preservation with either surveillance or trimodal therapy. Importantly, cisplatin-ineligible patients, whose treatment options are limited, can receive this combination in the neoadjuvant setting.

Dr. Black's predictions are based on what has been observed in the mUC setting. In the EV-302 trial, OS was superior with EV plus pembrolizumab vs. chemotherapy (hazard ratio = 0.47) [3]. The magnitude of OS benefit observed in EV-302 was even greater than the one seen in the CheckMate 901 trial, which compared nivolumab plus GC with GC alone (hazard ratio = 0.78) [4].

An ongoing trial of EV plus pembrolizumab in the MIBC setting is the phase 3 EV-304/KEYNOTE-B15 trial, in which cisplatin-eligible patients are being randomized to EV plus pembrolizumab or GC preoperatively, followed by RC plus pelvic lymph node dissection (PLND). The EV plus pembrolizumab group will then continue this therapy postsurgically, while the GC group will undergo observation only [5]. The treatment of cisplatin-ineligible patients is under evaluation in the phase 3 EV-303/KEYNOTE-866 trial. Patients are randomized to either neoadjuvant pembrolizumab or EV plus pembrolizumab followed by RC plus PLND. In each arm, adjuvant therapy will match the treatment received in the neoadjuvant setting. These 2 arms will be compared to a standard-of-care arm in which patients receive RC and PLND alone. The 2 treatment arms will be compared with surgery alone, but they will not be compared directly with each other [6].

The third practice-changing advance is intravesical fibroblast growth factor receptor (FGFR) inhibition for non–muscle- invasive BCa (NMIBC). *FGFR* mutations, particularly *FGFR3* mutations, are common in NMIBC, particularly in low-grade disease [7]. The first evidence of the efficacy of FGFR inhibition was seen in the THOR-2 trial, which compared oral erdafitinib with intravesical chemotherapy. Recurrence-free survival (RFS) was observed with erdafitinib (hazard ratio = 0.28; 95% CI = 0.1–0.6) [8]. It is important to note, however, that the side effects of oral erdafitinib limit its use in early-stage disease.

A more promising avenue is intravesical FGFR-targeted therapy. This has been investigated using the pretzel-shaped TAR-210 intravesical drug delivery system. Once deployed into the bladder, the device elutes erdafitinib in a slow, controlled manner over 90 days. The first-in-human trial investigating this approach was conducted in patients with high-risk (HR) and intermediate-risk (IR) NMIBC, using several different doses of erdafitinib. Results were encouraging, with an estimated 12- month RFS of 90% among the 21 participants of cohort 1 (HR), who were treated after complete tumour resection, and a 93% CR rate at 12 weeks among 31 evaluable participants in cohort 3 (IR) who were left with tumour for chemoablation [9].

Looking to the future, said Dr. Black, use of urine tumour DNA (utDNA) testing to detect *FGFR3* alterations will become important. Moreover, the phase 3 MoonRISe-1 trial is comparing TAR-210 with erdafitinib vs. investigator's choice of intravesical therapy [10].

However, several unanswered questions remain. For example, can all low-grade disease be targeted regardless of the results of *FGFR3* alterations, given that many of these tumours have high expression of *FGFR3* even without mutations? Is primary ablative therapy without transurethral resection of bladder tumour an option, particularly if there

is a prior history of low-grade tumour? Will a device similar to TAR-210 be developed for cancers in the upper tract, where *FGFR3* alterations occur at higher rates?

The fourth advance was targeting the human epidermal growth factor receptor 2 (HER2) with antibody-drug conjugates (ADCs) in the setting of metastatic disease. There has been an explosion of novel therapies for advanced BCa, and it appears that ADCs targeting HER2 are next, since HER2 is frequently overexpressed, amplified, or mutated in MIBC [11]. Over the years, several HER2-targeting agents, including tyrosine kinase inhibitors (TKI) and inhibitory antibodies, have proven ineffective in BCa trials, and the biology of HER2 in BCa remains poorly understood [12]. ADCs, on the other hand, simply use the cell surface marker target to get the drug into the cancerous cells. In this scenario, the underlying biologic mechanisms of HER2 in BCa may be of less importance [12].

Notably, some ADCs that have shown promise in this setting include trastuzumab deruxtecan and disitamab vedotin. The DESTINY-PanTumor02 trial tested trastuzumab deruxtecan in multiple tumour types, and responses were observed in HER2-positive tumours, including some urothelial tumours [13]. Based on this trial, this ADC received a tumour-agnostic approval for HER2-positive solid tumours by the U.S. Food and Drug Administration (FDA). In the RC48G001 trial, disitamab vedotin demonstrated efficacy in the first-line treatment of mUC expressing HER2 [14].

Finally, Dr. Black discussed the use of utDNA. There are some very promising urine biomarkers being developed for BCa, he said, with an evolution from single markers to multiplex markers, which are primarily based on RNA or DNA methylation. Research in this area is focused on the detection of tumours in the diagnostic or surveillance setting. Next- generation utDNA may become a better diagnostic tool as sequencing improves and becomes accessible at a reasonable price, but it is also valuable due to the insight it offers into tumour biology, which can provide important information about potential response to various therapeutic modalities.

utDNA is advantageous because it is not affected by benign conditions (with the exception of the risk of field cancerization) and it provides easily accessible longitudinal information about the molecular evolution of the tumour with treatment. The expectation for the future is that cost will decrease and depth of sequencing will increase. Disadvantages of utDNA, other than potential cost, currently include methodologic considerations and false positive tests caused by field cancerization.

Dr. Black has been involved in testing UroAmp, produced by Convergent Genomics, in a clinical trial. This utDNA analysis platform employs next-generation sequencing of a 60-gene panel and low-pass whole genome sequencing to identify aneuploidy. A weighted analysis using a machine learning algorithm that takes into account type and number of alterations as well as allele frequency determines if the test is positive or negative [15].

This platform was used to analyze utDNA from 89 patients with bacillus Calmette-Guérin (BCG)–unresponsive NMIBC treated with atezolizumab as part of the SWOG 1605 trial. The test provided a wealth of genomic information on individual patient tumours, both before and after treatment. Those with a positive test at the outset of the trial had a much poorer EFS than those with a negative test, at both 12 months (26% vs. 67%) and 18 months (23% vs. 51%). In this trial, patients with papillary (Ta/T1) disease required complete resection of their disease to be included. Despite this, about half were UroAmp positive, suggesting that current mechanisms used to identify residual disease are lacking [16].

During a Q&A session, Dr. Tanguay asked whether utDNA could be used to determine which patients require surgery or radiotherapy (RT) now that there is an increasing number of CRs to neoadjuvant treatment of MIBC. Dr. Black replied that this is increasingly becoming an area of interest, especially with the possible use of EV plus pembrolizumab

in the future, where patients with a clinical CR may undergo surveillance alone, but that there is a risk of field cancerization producing a false positive. Circulating tumour DNA in plasma and magnetic resonance imaging of the bladder are also exciting options to address this question.

Next, Dr. Faiz Mumtaz (United Kingdom) described the 5 practice-changing advances on the horizon for renal cell carcinoma (RCC). The first is the evolving role of cytoreductive nephrectomy (CN) in the era of systemic therapy combinations. The combination of IO-IO or IO-TKI was established as the standard of care in the first-line treatment of advanced/metastatic clear cell RCC (ccRCC) based on the results of the KEYNOTE-426 [17], CheckMate 214 [18], and JAVELIN Renal 101 [19] trials. What remains unknown is how best to incorporate CN into the management of metastatic ccRCC in the context of IO-IO or IO-TKI regimens. Importantly, the CARMENA [20] and SURTIME [21] trials have demonstrated that deferred nephrectomy is probably the best option in this setting, with upfront sunitinib as the likely way forward.

New trials are needed in the IO era for CN. In the main IO clinical trials, 70% of the patients underwent radical nephrectomy prior to treatment with immune checkpoint inhibitors (ICIs), creating a patient selection bias. Thus, it will be important to evaluate benefits of IO in patients who have not received CN. In addition, the TracerX Renal study revealed significant heterogeneity changes at the primary and metastatic sites [22], which suggests there is a need to reduce tumour burden and its genetic complexity in order to diminish the impact of resistant clones. This will hopefully reduce metastatic seeding and slow disease progression in low metastatic burden patients. CN may reduce the immunosuppressive response and enhance response to ICIs and in-house immune response. All this raises the question of the role of ICIs in metastatic RCC and how CN may improve outcomes.

To date, studies of ICIs with deferred or upfront CN are retrospective in nature, revealing variable responses of the primary lesion compared with metastatic sites [23]. Survival has been shown to be higher in patients who receive ipilimumab plus nivolumab, but there is no conclusive evidence to demonstrate whether upfront or deferred CN offers superior outcomes.

There is a clear need for large RCTs in this setting to better understand the ideal timing for CN in combination with systemic therapies in metastatic ccRCC—and several trials are upcoming. The SEVURO-CN trial is exploring the role of CN in patients with metastatic RCC. Patients are stratified as HR or low risk (LR), and HR patients receive ipilimumab plus nivolumab. Those who respond and are eligible for surgery are then randomized to nivolumab maintenance with or without CN. Those who are ineligible for surgery receive nivolumab maintenance. The LR patients are randomized to ipilimumab plus nivolumab and deferred CN vs. upfront CN followed by ipilimumab plus nivolumab. All receive nivolumab maintenance therapy [24].

For the NORDIC-SUN trial, patients with treatment-naïve metastatic IR and HR RCC receive ipilimumab plus nivolumab. Eligible patients are then randomized to undergo CN or receive maintenance nivolumab. Surgery-ineligible patients receive nivolumab, and their eligibility for CN is then re-evaluated to see if they can undergo similar randomization. All patients receive maintenance nivolumab [25].

The PROBE trial involves giving treatment-naïve patients with metastatic RCC FDA-approved ICI therapy for 12 weeks. Responders are randomized to CN followed by maintenance ICI or maintenance ICI alone. Nonresponders leave the trial [26].

In Cyto-KIK, a similar population is treated with nivolumab plus cabozantinib and is then divided into cohort 1, whose population undergoes a 21-day pause in systemic therapy, or cohort 2, whose population undergoes a 14-day pause. All patients then undergo CN

and continue on maintenance IO-TKI therapy until progression [27]. These 4 trials, said Dr. Mumtaz, could help define the best time to offer CN.

The second practice-changing advance in RCC is the advent of new biomarkers to guide management of RCC. Kidney injury molecule-1 (KIM-1) is potentially the first serum-based marker in this setting. It was used in 418 patients from the ECOG-ERIN E2805 (ASSURE) trial who underwent nephrectomy for RCC. KIM-1 levels were measured 4 to 12 weeks post nephrectomy, and higher levels were associated with worse disease-free survival (DFS) and OS. The investigators suggested that circulating KIM-1 is likely a reflection of residual microscopic tumour burden [28].

Based on those findings, KIM-1 was tested in the IMmotion010 trial patients, with 86 used as a cut-off to determine high and low levels (the ideal cut-off remains contentious) [29]. High KIM-1 levels were again associated with poorer prognosis and DFS, and high baseline KIM-1 correlated with advanced disease. Importantly, high baseline KIM-1 also predicted improved survival benefit from ICI therapy, so there could be a predictive role for KIM-1 in patients treated with ipilimumab plus nivolumab, possibly working as a surrogate marker for T-cell activation. Before being introduced into clinical practice, however, this test requires validation.

Another biomarker of interest is molecular cluster identification. In the IMmotion151 trial, 7 molecular clusters were identified: angiogenic/stromal, angiogenic, complement/Ω-oxidation, T-effector/proliferative, proliferative, stromal/ proliferative, and small nucleolar RNA (snoRNA). While no difference in OS was observed in this trial between atezolizumab plus bevacizumab vs. sunitinib, there was evidence that these biomarker clusters had some prognostic value. Patients with angiogenic/stromal markers responded better to TKIs and those with more T-effector/proliferative and snoRNA markers responded better to ICI therapy [30]. To explore the prognostic value of these molecular clusters, the OPTIC trial is using them to guide selection of therapy (ipilimumab plus nivolumab or cabozantinib plus nivolumab) [31].

The third practice-changing advance is use of the second-generation hypoxia-inducible factor (HIF)-2α inhibitor belzutifan in RCC, which represents a first-in-class oral drug for this setting. In a phase 2, open-label, single-group trial of patients with RCC associated with von Hippel-Lindau (VHL) disease treated with 120 mg belzutifan once daily, objective responses occurred in 49% after 21.8 months of follow-up, with no disease progression [32]. This is in line with what is observed with ICIs, said Dr. Mumtaz. Based on these findings, the agent has received approval from both the National Institute for Health and Care Excellence (NICE) and the FDA and has begun to be used in clinical practice.

For the phase 3 LITESPARK-005 study, response to belzutifan vs. everolimus was compared among patients with previously treated, advanced ccRCC. Initial findings revealed improvement in progression-free survival (PFS) (33.7% vs. 27.6% at 12 months) and overall response rate (ORR) with belzutifan. The CR was 3.5% with belzutifan and 0% with everolimus. Discontinuation rate due to any adverse event was 17.6% with everolimus vs. 5.9% with belzutifan [33]. In a final outcomes analysis, PFS and ORR continued to be superior with belzutifan. Median OS was 21.4 months with belzutifan vs. 18.2 month with everolimus, buta significant improvement in OS was not observed. With belzutifan, there was also a lower discontinuation rate from adverse events (5.9% vs. 14.7%) [34].

In the phase 3 LITESPARK-012 trial, pembrolizumab plus lenvatinib is being compared with and without belzutifan as well as in combination with quavonlimab in advanced ccRCC [35]. Dr. Mumtaz believes that these findings will bring about a change in clinical practice, but whether belzutifan becomes a first-line therapy remains to be seen.

The fourth practice-changing advance is stereotactic ablative body RT (SABR). In the setting of RCC, RT can now be given in high fraction doses, and the mechanism behind

its effects appears to be based on apoptosis of vascular tumours and its abscopal effect. The role of SABR will primarily be for patients who are unfit for surgery or ablative therapy. Five- year data published by the International Society of Stereotactic Radiosurgery examined 822 patients from 36 studies and revealed a median local control rate of 94.1%, a 5-year PFS of 80.5%, and a 5-year OS of 77.2%. The optimal dose was determined to be 25 to 26 Gy in 1 fraction or 42 to 48 Gy in 3 fractions. Routine post-treatment biopsy is not recommended, as it is not predictive of outcomes [36]. Instead, guidelines recommend surveillance imaging every 6 months.

The single-arm phase 1/2 RAPPORT trial examined the role of SABR and pembrolizumab for oligometastatic RCC tumours. Overall, 37 patients with 83 oligometastatic lesions who had previously received up to 2 lines of therapy were treated with SABR followed by pembrolizumab. Freedom from local progression at 2 years was 92% [37].

The nonrandomized phase 2 FASTRACK II study was the first multicentre prospective clinical trial in this setting. Patients with a median tumour size of 4.6 cm received a single fraction of 28 Gy of SABR or 3 fractions of 47 Gy. After a median follow-up of 3.5 years, local control rate was 100%, and there were no treatment-related deaths [38]. These promising findings in terms of halting disease progression will likely bring about a change in clinical practice, said Dr. Mumtaz.

Notably, SABR can be used for RCC with renal vein/vena caval involvement. In patients who are not suitable for cable thrombectomy, the disease can be stabilized with SABR. In a single-arm phase 2 study, neoadjuvant SABR (40 Gy in 5 fractions) was followed by radical nephrectomy (RN) and thrombectomy. The primary endpoint was absence of grade 4 or 5 adverse events. The treatment was feasible, with no grade 4 or 5 adverse events, and only a 4% rate of grade 3 adverse events. A limitation of the study, however, is that only 6 patients were in the final analysis [39]. In the future, an RCT comparing SABR with surgery and/or ablation is needed to fully characterize the optimal role of SABR in this setting [40].

The final advance described by Dr. Mumtaz is artificial intelligence (AI)–enhanced renal cancer surgery. This includes AI-based 3D models for surgical planning, which are now in their fourth generation. Digital twin models created from images offer improved visualization of architectural and textural properties of tumours and the surrounding tissue. Perfusion models can help identify the segmental blood supply, allowing for better localization of tumours in relation to the blood supply. 3D imaging–aided robotic surgery is currently being used in clinical practice and is especially useful for complex tumours or horseshoe kidneys [41].

Dr. Mumtaz and his team have initiated the world's largest RCT to date comparing 2D vs. 3D virtual imaging for surgical planning. The primary outcome is 20% reduction in console time. Secondary outcomes include warm ischemia time, complication rate, and overall surgical time [42,43]. Results are expected by mid-2025.

An evolution is taking place now with use of 3D images in surgical navigation, where the images are overlaid onto the tumour during surgery [44]. Much work still remains to determine how best to overlay the images onto the tumour in real time, said Dr. Mumtaz. For instance, investigators have used indocyanine green (ICG) to mark the location of the kidney and then overlay the 3D image [45]. In another study, a new software (iKidney) allowed for automatic anchorage of the 3D model to the kidney, eliminating the need for ICG [46].

The evolution from 3D data to integrated diagnostics can lead to further advances, including radiomics and radiogenomics. Diagnostics can be integrated with histopathology and with electronic health record data, enabling improved decision- making and risk stratification, concluded Dr. Mumtaz.

In a Q&A, Dr. Tanguay asked whether 3D reconstruction is available with standard equipment or whether it requires specific software. Dr. Mumtaz replied that segmentation algorithms are now available through a variety of providers and can be used on standard equipment.

This session concluded with Dr. Caroline Moore (United Kingdom), who presented on the 5 practice-changing advances in prostate cancer (PCa). Dr. Moore discussed modern approaches to PCa screening and active surveillance, the use of RT for low- to intermediate-risk PCa as well as RT post radical prostatectomy, and consideration for androgen deprivation therapy (ADT) vs. orchidectomy in advanced hormone-sensitive PCa (aHSPC). Per request of the speaker, a summary of her presentation was not included in these proceedings.

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Abbreviations

ADC	antibody-drug conjugate
AI	artificial intelligence
BCa	bladder cancer
BCG	bacillus Calmette-Guérin
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
CN	cytoreductive nephrectomy
CR	complete response
ddMVAC	dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DFS	disease-free survival
EFS	event-free survival
EV	enfortumab vedotin
FDA	U.S. Food and Drug Administration
FGFR	fibroblast growth factor receptor
GC	gemcitabine-cisplatin
HER2	human epidermal growth factor receptor 2
HR	high risk
ICG	indocyanine green
ICI	immune checkpoint inhibitor
IO	immunotherapy
IR	intermediate risk
KIM-1	kidney injury molecule-1
LR	low risk
MIBC	muscle-invasive bladder cancer
mUC	metastatic urothelial carcinoma

NAC	neoadjuvant chemotherapy
NMIBC	non–muscle-invasive bladder cancer
ORR	overall response rate
OS	overall survival
PCa	prostate cancer
pCR	pathological complete response
PFS	progression-free survival
PLND	pelvic lymph node dissection
RC	radical cystectomy
RCC	renal cell carcinoma
RCT	randomized controlled trial
RFS	recurrence-free survival
RT	radiotherapy
SABR	stereotactic ablative body radiotherapy
snoRNA	small nucleolar RNA
TKI	tyrosine kinase inhibitor
utDNA	urine tumour DNA

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