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URO-ONCOLOGY
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Five Practice-Changing Advances on the Horizon Summary

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PrOPDIVO® (nivolumab)

B2B: Five Practice-Changing Advances on the Horizon Summary

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The 4th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 42nd Annual Congress of the Société Internationale d'Urologie, was held on November 11th, 2022, at the Palais des congrès de Montréal in Canada, and transmitted live on the *SIU@U* virtual platform. The programme concluded with a special session dedicated to the Five Practice-Changing Advances on the Horizon for bladder, kidney, and prostate cancers, which was chaired by Dr. Simon Tanguay and Dr. Peter C. Black (Canada).

Dr. Sarah P. Psutka (United States) discussed key advances on the horizon within the continuum of bladder cancer (BCa) management. First, Dr. Psutka focused on recent progress in the molecular characterization of BCa. While extensive research has been conducted on muscle-invasive BCa (MIBC), it's only more recently that next-generation sequencing studies have led to a better understanding of non–muscle-invasive BCa (NMIBC) at the molecular level and contributed to the development of a molecular classification system. Implementing these advances in the clinical practice may lead to more precise risk stratification and prognostication to help guide treatment decision-making. One example is the molecular classification system initially developed in the UROMOL study, which used comprehensive transcriptomic analysis to classify early-stage NMIBC into three classes: class 1, early cell cycle activation; class 2, epithelial-mesenchymal transition and enriched for immune infiltration; and class 3, high expression of *FGFR3*-coexpressed genes and depleted immune contexture[1]. A more recent transcriptomic analysis of 834 patients with NMIBC has further stratified the UROMOL system into four classes (1, 2a, 2b, and 3), which reflect tumour biology and disease aggressiveness[2]. Adding transcriptomic signatures to traditional risk stratification tools resulted in increased specificity and accuracy in patient characterization and prediction of treatment outcome. This molecular classification provides not only a framework for biomarker discovery, but also presents an opportunity to optimize treatment selection and surveillance guidance with respect to balancing efficacy, toxicity, and logistics.

The second, key advance discussed by Dr. Psutka was emerging strategies to personalize treatment selection in BCa. One of the ongoing challenges in BCa management is the high proportion of patients who do not respond to initial treatment and therefore experience recurrence and/or progression, which ultimately may result in death. A key limitation in clinical practice is the lack of personalized tools to predict response to individual treatments. In recent years, several biological pathways have been identified that may be involved in cellular response to chemotherapy[3]. Patient-derived xenografts represent one potential avenue to build on this new knowledge and determine chemoresistance profiles in individual tumours. In the Bladder Cancer Tissue Acquisition at Necropsy programme, a rapid necropsy sampling of all metastatic sites is performed in patients with advanced BCa upon their death. Tissue samples are grown in culture or implanted into immunodeficient mice with the goal of developing patient-derived xenografts[4]. To date, 28 rapid necropsies have been performed at the University of Washington, and over 500 specimens have been collected, leading to development of not only xenografts of conventional urothelial carcinoma but also of histologic subtypes. This approach presents the opportunity to further characterize the molecular

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signatures of BCa and to develop organoids in the laboratory with important translational applications[5–7].

The third advance on the horizon highlighted by Dr. Psutka is the development of artificial intelligence (AI) to overcome challenges related to subjectivity in the diagnosis and staging of BCa. To that end, in recent years several studies have leveraged AI to improve the diagnosis, staging, and outcome prediction of BCa[8]. One example is the development of artificial neural network models, a type of machine learning algorithm, that have been shown to predict 5-year overall survival (OS) and disease-specific survival with better or similar accuracy compared to traditional multivariable models[9]. Other examples leveraging AI in BCa include the use of multiparametric magnetic resonance imaging (mpMRI) features to allow preoperative discrimination between NMIBC and MIBC[10], as well as development of a blue light-based diagnostic imaging platform to assist with the detection, staging, and grading of BCa[11]. While AI and deep learning have the potential to improve diagnostic efficiency, overcome subjectivity in assessments, increase consistency, and generate detailed risk estimates using integrated data sources, questions and concerns remain. Before implementation in clinical practice, external validation is required, sharing of algorithms is necessary to scale use, and real-world applicability of models must also be considered.

The fourth BCa advance centres on improving functional outcomes for female patients after radical cystectomy through better characterization of female pelvic anatomy (Komisaruk BR & Goldstein I, in prep), developments in pelvic organ sparing procedures[12], and understanding of female sexual health outcomes after radical surgery[13]. Despite guideline recommendations regarding the effects of radical cystectomy on female sexual function[14,15], bladder sparing approaches remain largely underutilized. However, recent efforts may start to change the current clinical practice for women with MIBC. Recently, there have been several advances in the development of sexual function-preserving surgical techniques[16], as well as improved guidance for patient selection and counselling[17,18], which may improve functional outcomes for female patients.

Lastly, the fifth advance on the horizon for BCa is improved survivorship care and patient quality of life (QoL). Dr. Psutka focused on 3 key aspects, starting with efforts aimed at improving the risk-stratification of patients with BCa, an intrinsically high-risk surgical population that presents with frailty and comorbidities. In this context, prehabilitation represents a rapidly emerging field of research that aims to improve patient status in order to improve eligibility for surgery and surgical recovery through multidomain interventions aimed at improving patients' function, nutrition, and social and emotional supports. However, while several studies on prehabilitation exercise have suggested improvements in patient QoL, an impact on surgical outcomes has yet to be demonstrated[19]. Making prehabilitation plans more accessible and personalized to patients through technology may increase their impact[20]. Overcoming limitations in patient-reported QoL outcome measures is also key. While several general oncology and cancer-specific tools exist, they have limitations, particularly with regards to the length as well as the content of the assessment. Efforts in developing QoL assessment tools that are relevant to patients are underway[21]. Finally, Dr. Psutka advocated in favour of moving towards the adoption of multidisciplinary survivorship clinics that integrate palliative, oncological, and surgical care to improve survivorship.

During the Q&A, Dr. Psutka was asked about the current status of survivorship programmes in different centres. While there are formalized programmes, those are not widespread nor fully adopted, resulting in important variation across centres. The main issue with this approach is that programmes may end up being less comprehensive and some key established aspects, such as mental health, may be missed. She emphasized the importance of establishing a survivorship team, with clearly delineated responsibilities and checklists for improved programme delivery.

The following presentation was by Dr. Philippe E. Spiess (United States), who examined the five practice-changing advances on the horizon for kidney cancer. Renal cell carcinoma (RCC) carries a large disease burden worldwide. Incidence rates are higher in countries where there are higher rates of obesity,

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smoking, and hypertension, such as in European and North American countries, which is also reflected in the mortality rates[22]. A lot of ongoing research is focused on multi-omic tumour profiling and the discovery of novel targets for treatment in the advanced setting[23].

As the first advance, Dr. Spiess examined emerging data on the role of radiation therapy to manage localized or locally advanced primary RCC. Tumour ablation with radiation therapy may be an attractive management approach, particularly in patients who are not eligible or who defer surgery. In a small retrospective study from 6 leading international tertiary referral centres treating RCC with inferior vena cava (IVC) tumour thrombus, 15 patients received stereotactic radiation therapy. Median OS was 34 months with radiographic response in 58% of patients. Only grade 1 and grade 2 adverse events were reported, suggesting good tolerability to treatment[24]. These data suggest that in a select subset of patients who are symptomatic and ineligible for surgery, locoregional control with radiation therapy may be considered, even in the presence of significant IVC thrombus. This approach may be particularly relevant as an alternative to surgery in patients with high-burden metastatic RCC and poor risk, according to the International Metastatic RCC Database Consortium (IMDC) criteria, who present with symptomatic primary tumours.

Next, Dr. Spiess discussed the use of radiomics in predicting RCC tumour biology. A recently published radiomic analysis of computed tomography (CT) scans obtained prior to nephrectomy in a prospective registry of 684 patients revealed good performance of predictive modelling[25]. There was high congruity between the virtual diagnosis and final pathology to differentiate benign and malignant tumours (area under the curve = 0.84)[25]. Combining radiomic data with clinical factors further improved sensitivity and specificity, as wells as positive and negative predictive values and accuracy. While these results are promising, Dr. Spiess emphasized that radiomics is not yet ready for clinical application. This still requires robust clinical optimization and validation. The combination of genomics with radiomics and further collaboration across centres will likely contribute to this end.

Also on the horizon for RCC is the clinical application of liquid biopsies. This minimally invasive approach offers a quick and comprehensive approach to tumour profiling. Specimens can be easily obtained with minimal pain or risk for the patient[26]. Biomarkers derived from liquid biopsies may lead to tools to understand tumour biology, screen and diagnose patients, and guide treatment decision-making, prognosis, and surveillance in RCC. Specific combinations of urinary cell–free and exosomal micro RNAs (miRNAs), urinary miRNA-15a, and specific panels of urinary metabolites (assessed by metabolomics) appear promising, as summarized in a recent systematic review[27]. However, this is still a challenging field of research. Some potentially promising liquid biopsy biomarkers, such as aquaporin 1 and perilipin-2, have been reported[28], but further robust validation of these potential biomarkers is lacking. More recently, 16 aberrant splice variants enriched in clear cell RCC were identified from transcriptomic data from the Cancer Cell Line Encyclopedia. Many of these variants are associated with disease biology and/or clinical outcomes, suggesting potential applicability to clinical practice[29]. The first predictive biomarkers are likely to be discovered in patients with metastatic RCC because of the number of trials conducted in these patients. In an exploratory subgroup analysis in the phase 3 IMmotion151 trial, biomarker analyses identified patients who may benefit from treatment with atezolizumab plus bevacizumab, despite the negative OS results of the trial in the intention-to-treat population[30].

Dr. Spiess then discussed developments in modelling cost-effectiveness of systemic therapy for metastatic RCC. According to the national United States billing data, the cost of kidney cancer care is estimated to be between 2 billion and 6 billion US dollars annually[31]. With multiple first-line combination therapies currently recommended for metastatic RCC[32], cost of therapy is an important consideration in selection of treatment. Chan et al.[33] conducted an adjusted, lifetime cost-effectiveness analysis incorporating the cost of drugs, the cost of treatment of adverse events, and varying costs incurred based on national United States sources and published literature. Between nivolumab-ipilimumab, pembrolizumab-axitinib, and sunitinib for patients with metastatic RCC,

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nivolumab-ipilimumab was the most cost-effective option[33]. These data highlight that while therapeutic efficacy remains the most important factor in making treatment decisions for patients with metastatic RCC, additional considerations may come into play when multiple suitable treatment options are available.

Lastly, Dr. Spiess examined the new era of triple agent combination therapies for metastatic RCC. He focused specifically on early data recently reported for COSMIC-313, a phase 3 trial investigating cabozantinib in combination with nivolumab plus ipilimumab in previously untreated advanced RCC of intermediate or poor IMDC risk[34]. The trial met its primary endpoint of progression-free survival (PFS; hazard ratio [HR] = 0.73 [95% CI 0.57 to 0.94]; *P* = 0.013). Median PFS was not reached in the triple agent arm but was 11.3 months in the nivolumab + ipilimumab + placebo arm. Prespecified subgroup analysis revealed benefit with triple agent combination in the intermediated IMDC risk subgroup (HR = 0.63 [95% CI 0.47 to 0.85]), but not in the poor risk subgroup (HR = 1.04 [95% CI 0.65 to 1.69]). Grade 3/4 adverse events related to treatment occurred more frequently in the triple agent arm (73% vs. 41%)[34]. This trial may represent the beginning of a new era of systemic therapy combinations in metastatic RCC, pioneering the study of triplet treatment. While promising, these data are preliminary and require final analysis before any definitive conclusions can be made.

Dr. Spiess is also the president of the Global Society of Rare Genitourinary Tumors (GSRGT). During the Q&A, he highlighted promising advances in that space. These include an unpublished report of combination treatment (epidermal growth factor receptor [EGFR] inhibitor + immunotherapy + platinum-based chemotherapy) from a phase 2 trial in advanced penile cancer. The complete response rate from this study is encouraging. Conservative surgery for penile cancer is also an area of increased investigation. But most importantly, Dr. Spiess emphasized the ongoing challenges in rare genitourinary cancers worldwide, particularly related to access to evidence-based care.

Concluding this session was a presentation by Dr. Rafael Sanchez-Salas (Canada) on the five practice-changing advances on the horizon for prostate cancer (PCa). He posited that the evolution of PCa management is centred on three pillars: 1) diagnosis and patient stratification, 2) treatment intensification, and 3) enhancement of patient QoL and satisfaction along with treatment efficacy.

Dr. Sanchez-Salas first focused on advances in imaging and biopsy for PCa diagnosis. The goals of imaging are to allow the identification of significant PCa in time for curative treatment, avoid overdiagnosis and overtreatment, and improve surveillance[35]. In recent years, novel imaging modalities have started to make their way into clinical practice with demonstrated benefits in clinical trials compared to conventional imaging. mpMRI is the most studied imaging modality. It improves biopsy detection rates as demonstrated in the 4M[36], PROMIS[37], PRECISION[38], and MRI-FIRST[39] trials. Micro-ultrasound is a novel visualization tool that may help to detect small lesions undetected by magnetic resonance imaging (MRI) [40] and can be combined with mpMRI for improved biopsy targeting[41]. Micro-ultrasound also allows more refined visualization of prostatic tissue than conventional ultrasound[42] and has a favourable learning curve of 20 to 40 cases[43]. More recently, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT imaging has demonstrated superior accuracy compared to conventional imaging with lower radiation exposure, as seen in the proPSMA trial[44]. Additionally, imaging-guided biopsies are shifting from a transrectal to a transperineal approach, which may provide higher sensitivity under mpMRI guidance[45] with lower risk of sepsis, even in the absence antibiotic prophylaxis[46].

Next, Dr. Sanchez-Salas discussed the increased use of PSMA PET/CT for PCa risk stratification, due to the increased sensitivity and specificity of PSMA PET tracers in detecting micrometastases compared to conventional imaging[47,48]. Clinical practice guidelines have started to recommend the use of PSMA PET/CT for PCa staging[49]. While mpMRI has an established role in the staging and treatment planning of high-risk PCa, the use of quantitative PSMA shows promise for extraprostatic disease assessment, with similar detection as mpMRI but with higher interreader

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agreement[50]. PSMA PET staging is being progressively implemented in clinical practice, particularly for higher grade disease. In a recent population-based study conducted in Australia, patients undergoing staging with PSMA PET vs. conventional imaging alone were observed to have a higher proportion of cN1 disease but not cM1 disease[51].

Important advances are also underway in treatment intensification with radiation therapy, which is expanding in PCa. Results of the randomized, multicentre, phase 3 FLAME trial have demonstrated that a focal radiation boost to the intraprostatic lesion improves biochemical disease-free survival (DFS) in patients with localized intermediate and high-risk PCa, with no significant toxicity or impact on QoL[52]. In the randomized, single-centre, phase 3 POP-RT trial, prophylactic whole-pelvic radiotherapy resulted in significantly improved biochemical failure-free survival and DFS compared with prostate-only radiotherapy, with minimal toxicity[53]. The role of neoadjuvant treatment prior to radical prostatectomy is also under evaluation. A recent observational analysis suggested that neoadjuvant therapy with an androgen receptor pathway inhibitor (ARPI) may improve the time to biochemical failure in patients with high-risk PCa[54]. Results of the phase 3 PROTEUS trial examining neoadjuvant therapy with the ARPI apalutamide are eagerly awaited[55].

The development of genomic classifiers is also key to further informing management decisions in PCa. Approximately 20% to 30% of patients with metastatic PCa have genetic alterations associated with the homologous recombination repair (HRR) pathway[56,57]. Alterations in the *BRCA2* gene are the most prevalent and often of germline origin[58]. In the European Association of Urology guidelines, consideration of germline testing is recommended in men with metastatic PCa (weak recommendation)[49]. Germline and somatic alterations play an important role in the management of PCa. As seen in the PROfound trial, patients harbouring HRR alterations and treated with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib experienced a 66% reduction in risk of progression or death[59]. Dr. Sanchez-Salas highlighted that, in the future, genetic testing will likely expand from the metastatic setting and be incorporated into the initial diagnosis of high-risk localized PCa.

The last advance on the horizon is the investigation of triplet combination therapy in advanced PCa. In this context, the open-label phase 3 PEACE-1 trial investigating treatment with androgen deprivation therapy (ADT) and docetaxel combined with abiraterone plus prednisone and/or radiation therapy in patients with metastatic castration-sensitive PCa (mCSPC) is notable. Triplet combination with ADT + docetaxel + abiraterone resulted in longer radiographic PFS (HR = 0.54 [99.9% CI 0.41 to 0.71]; $P < 0.0001$) and OS (HR = 0.82 [95.1% CI 0.69 to 0.98]; $P = 0.030$) than ADT + docetaxel without abiraterone[60]. Important benefit was seen in patients with high-volume mCSPC. In the phase 3 ARASENS trial, a triplet combination with ADT + docetaxel + darolutamide also improved OS (HR = 0.68 [95% CI 0.57 to 0.80]; $P < 0.001$) compared to dual therapy with ADT + docetaxel + placebo[61]. Improvements in all secondary endpoints, relating to disease progression and QoL, were also observed.

During the Q&A, Dr. Sanchez-Salas discussed clinical trial developments in micro-ultrasound imaging and the use of this technology to counterbalance the challenges of mpMRI implementation in several countries. Of note is the phase 3 OPTIMUM trial, which is evaluating micro-ultrasound vs. fusion mpMRI to simplify and reduce the costs of the prostate biopsy pathway[62]. Dr. Sanchez-Salas highlighted that novel imaging approaches should not be seen as competitors, but instead as powerful tools to optimize PCa management.

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Abbreviations Used in the Text

ADT	androgen deprivation therapy
AI	artificial intelligence
ARPI	androgen receptor pathway inhibitor
BCa	bladder cancer
CI	confidence interval
CT	computed tomography
DFS	disease-free survival
EGFR	epidermal growth factor receptor
GSRGT	Global Society of Rare Genitourinary Tumors
HR	hazard ratio
HRR	homologous recombination repair
IMDC	International Metastatic RCC Database Consortium
IVC	inferior vena cava
mCSPC	metastatic castration-sensitive prostate cancer
MIBC	muscle-invasive bladder cancer
miRNA	micro RNA
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
NMIBC	non–muscle-invasive bladder cancer
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PCa	prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PSMA	prostate-specific membrane antigen
QoL	quality of life
RCC	renal cell carcinoma

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