

# 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium: Meeting highlights

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## Introduction

The 2022 American Society of Clinical Oncology (ASCO) Genitourinary (GU) Cancers Symposium was held in San Francisco and online from February 17–19, 2022. Following the symposium, on February 22, the Canadian Urological Association (CUA) held an online webinar where Canadian experts highlighted key research findings in prostate, bladder, and kidney cancers. In this report, we summarize these exciting advances in GU oncology. The entire webinar can be viewed on the CUA website, and meeting abstracts can be viewed at the ASCO meeting library.

## Prostate cancer

Dr. Tamim Niazi presented two abstracts highlighting pivotal studies in prostate cancer. ARASENS, a global phase 3 trial, assessed the role of darolutamide in patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated with androgen deprivation therapy (ADT) and docetaxel (DOC). Darolutamide is a potent androgen-receptor inhibitor associated with increased overall survival (OS) among patients with non-metastatic castration-resistant prostate cancer (nmCRPC). In the ARASENS study, the addition of darolutamide to ADT and DOC significantly enhanced OS in all subgroups, reducing the overall risk of death by 32.5%. This is despite most patients in the placebo arm having subsequent secondary life-prolonging therapies. Darolutamide was also associated with significant improvements in secondary endpoints, including delaying CRPC and pain progression.<sup>1</sup> These findings suggest that darolutamide, in combination with ADT and DOC, should become a new standard of care for the treatment of mHSPC.

A post-hoc analysis of the TITAN study evaluated outcomes in patients who had received DOC prior to treatment with apalutamide (APA) plus ADT. TITAN, a phase 3 clinical trial, previously demonstrated that the addition of APA, an androgen receptor signalling inhibitor, to ADT improves OS and clinical outcomes in patients with metastatic castration-sensitive prostate cancer (mCSPC).<sup>2</sup> In this post-hoc analysis, clinical outcomes, including OS, radiographic progression-free survival (rPFS), and time to prostate-specific antigen (PSA) progression did not differ in the APA-treated population regardless of prior DOC treatment status. The safety profile of APA was not altered by prior DOC treatment status. Although the analysis was limited, the data suggest that prior use of DOC in patients with mCSPC does not further improve the clinical benefits of APA plus ADT.<sup>3</sup>

With results from the PEACE-1<sup>4</sup> and ARASENS<sup>1</sup> trials, evidence is mounting in favor of triplet therapy (ADT plus DOC plus androgen signalling inhibitors) to become the new standard of care for the treatment of high-volume mHSPC/mCSPC. For low-volume disease, longer-term analysis of the PEACE-1 and ARASENS studies are needed.

Dr. Krista Noonan presented two important first-line mCRPC studies, PROpel and MAGNITUDE, which evaluated the combination of abiraterone and prednisone with a poly ADP-ribose polymerase (PARP) inhibitor. Median OS in mCRPC patients is low (~2–3 years); improving outcomes in the first-line mCRPC setting is critical. In preclinical studies, the combination of PARP inhibitors and agents targeting androgen receptor signalling pathways has demonstrated additive anti-tumor effects. Moreover, prolonged rPFS was demonstrated in mCRPC patients following DOC plus olaparib (a PARP inhibitor) plus abiraterone vs. placebo plus abiraterone, irrespective of homologous recombination repair mutation (HRR) status.<sup>5</sup> PROpel, a phase 3 trial, evaluated the efficacy and safety of olaparib plus abiraterone in patients with mCRPC undergoing first-line treatment after failure of primary ADT. First-line treatment with olaparib plus abiraterone significantly prolonged rPFS

across all subgroups, including patients with and without HRR mutations. OS data is currently immature, but early data indicates a difference is likely in subsequent analysis. Secondary endpoints were supportive of long-term benefits, and treatment was well-tolerated. The most common grade  $\geq 3$  adverse event (AE) reported was anemia: 15.1% vs. 3.3% for olaparib plus abiraterone vs. placebo plus abiraterone; 13.8 vs. 7.8% patients, respectively, discontinued olaparib/placebo because of an AE. These results demonstrate the benefit of olaparib plus abiraterone without the need for HRR stratification in the first-line treatment of mCRPC.<sup>6</sup>

MAGNITUDE, a phase 3 trial, assessed the addition of niraparib (NIRA, a PARP inhibitor) to abiraterone acetate and prednisone (AAP) as first-line therapy in mCRPC patients with and without HRR mutations. Although no benefit was observed with NIRA plus AAP in HRR mutation-negative patients, significant improvements in the primary clinical outcome of HRR mutation-positive patients were observed. There was a 47% and 27% improvement in rPFS in patients with *BRCA 1/2* alterations and across all HRR biomarker-positive patients, respectively. NIRA plus AAP had a manageable safety profile, with no new safety signals identified. This study highlights the importance of testing for HRR gene alterations in patients with mCRPC to identify those who will benefit from the addition of NIRA to AAP treatment. This study also supports NIRA plus AAP as a first-line treatment option for mCRPC patients who are HRR mutation-positive.<sup>7</sup>

Dr. Ricardo Rendon presented a number of relevant abstracts, including PRESIDE, a phase 3b study that compared the efficacy of enzalutamide (ENZA) plus DOC and prednisone (PDN) vs. placebo plus DOC and PDN in chemotherapy-naive mCRPC patients who have progressed on ENZA alone. There was a 28% improvement in PFS with ENZA (9.53 months) compared to placebo (8.28 months). ENZA also significantly delayed time to PSA progression (TTPP) and improved PSA response at any time. Treatment-related side effects were similar between ENZA and placebo. However, there was some additional toxicity with ENZA, as deaths were higher in the ENZA group (9.6%) compared to placebo (5.2%). These data suggest that continued treatment with ENZA plus DOC and PDN offers clinical benefit and could be a future treatment option for patients who progress on ENZA alone. However, it is important to note that although there was a statistically significant improvement in PFS, it amounted to a one-month difference while increasing toxicity. Moreover, when analyzing different subgroups, those with soft tissue metastasis (SFT) or SFT and bone metastasis did better than those with bone metastasis; this should be considered when making treatment decisions.<sup>8</sup>

ACDC-RP, a phase 2 trial, assessed the pathological complete response rate (pCRR) with the addition of cabazitaxel to neoadjuvant treatment with leuprolide and abiraterone in high-risk prostate cancer patients prior to radical prostatectomy

(RP). No difference in complete response (CR) or CR plus minimal residual disease (MRD) was found between the two arms. Patients receiving cabazitaxel had lower margins and lower rates of nodal positive disease but also more deep vein thrombosis and pulmonary embolism. There was no difference in biochemical-free survival (BFS) between the two treatment groups. Therefore, adding cabazitaxel to abiraterone plus RP does not significantly improve CR/MRD rates. However, patients who exhibited CR/MRD experienced better BFS rates.

In summary: 1) thromboembolic prophylaxis is recommended for patients in neoadjuvant trials; 2) further evaluation in patients with very high-risk prostate cancer, where chemotherapy might be more effective, is recommended.<sup>9</sup>

## Bladder cancer

The last few years have seen significant advancements in the treatment of patients with metastatic urothelial carcinoma (mUC).

Dr. Nimira Alimohamed presented the recent advances using antibody-drug conjugates (ADC) and targeted therapies. Sacituzimab govitecan (SG) is an ADC composed of an anti-trophoblast cell-surface antigen 2 (Trop-2) antibody coupled to SN-38 (a topoisomerase-I inhibitor).<sup>10</sup> The combination of SG with pembrolizumab as second-line therapy in immune checkpoint inhibitor (CPI)-naive patients with mUC who progressed after platinum-based (PB) regimens, in the TROPHY-U-01 study (cohort 3), resulted in an overall response rate (ORR) of 34%, with a clinical benefit rate of 61%. Median PFS was 5.5 months, with a median followup of 5.8 months. The safety profile was manageable with no new safety signals.<sup>11</sup> These data support further evaluation of SG plus CPI in mUC. Activity was also noted in patients who had progressed on enfortumab vedotin, suggesting that resistance to one ADC does not necessarily mean resistance to another. Trastuzumab deruxtecan is another novel ADC targeting *HER2* expressed in certain mUC patients. In UC patients with high *HER2* expression post-PB therapy, the combination of trastuzumab deruxtecan and nivolumab (anti-PD-1 antibody) resulted in an ORR of 37%, with a median duration of response lasting 13.3 months. However, 32.4% of patients experienced AEs leading to treatment discontinuation.<sup>12</sup>

Approximately one in four mUC patients exhibit a DNA repair deficiency (DRD) phenotype. However, to date, no DRD-targeted agents have been approved for mUC treatment. ATLANTIS is a phase 2, randomized trial using maintenance PARP inhibition following chemotherapy for the treatment of mUC in patients with a DRD mutation. Patients with stage 4 UC who had not progressed after PB were randomized to rucaparib vs. placebo. Rucaparib was well-tolerated, and the median PFS in the rucaparib arm was 35.3 weeks compared to 15.1 weeks in the placebo arm.<sup>13</sup> Further investigations in biomarker-selected populations are

warranted. Notably, the JAVELIN Bladder 100 study previously demonstrated a significant improvement in OS with avelumab as maintenance immunotherapy in all patients with mUC who had not progressed on first-line PB chemotherapy, and this has become the current standard of care.<sup>14</sup>

An unmet need in Canada continues to be in patients who are ineligible for PB chemotherapy. There is currently no access to novel therapies in these settings, and some patients will receive best supportive care (BSC) alone. BAYOU, a phase 2 study, investigated durvalumab plus olaparib vs. durvalumab plus placebo in the first-line treatment of PB-ineligible patients with unresectable, stage 4 UC. Patients were stratified according to their HRR status. Durvalumab plus olaparib did not improve PFS or OS in HRR-negative patients. However, findings suggested a potential role for PARP inhibition in UC patients harboring HRR mutations. No new safety signals were observed.<sup>15</sup> This study supports further investigation of PARP inhibitors in patients with mUC with HRR mutations. Both the ATLANTIS and BAYOU studies support genomic testing in mUC patients.

Dr. Wassim Kassouf highlighted advances in the non-metastatic setting unrelated to radiation. A phase 2/3 clinical trial investigated the IL-15R $\alpha$ Fc superagonist N-803 (anktiva) in bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC). The combination of BCG and N-803 enables the innate immune system to mount a more robust and prolonged response, which was previously demonstrated to induce a CR in NMIBC patients. The study consisted of a single arm with two cohorts; both received N-803 and BCG. In cohort A (carcinoma in situ [CIS]), the CR rate was 71%, with a 62% probability of maintaining CR for  $\geq 12$  months. For cohort B (papillary), disease-free survival (DFS) was 57% and 48% at 12 and 24 months, respectively. These findings demonstrate a numerically higher response rate than other currently approved treatments. The combination of N-803 and BCG was safe and well-tolerated.<sup>16</sup> Pending FDA approval, this combination will provide an alternative option for patients with BCG-unresponsive disease.

Cisplatin-ineligible muscle-invasive bladder cancer (MIBC) patients make up approximately 50% of the disease population and do not currently have effective neoadjuvant chemotherapy (NAC) options prior to undergoing radical cystectomy (RC) and pelvic lymph node dissection (PLND). Enfortumab vedotin (EV), an ADC directed at Nectin-4, which is highly expressed in UC, has demonstrated benefits in UC patients with locally advanced or metastatic cancer in phase 2 and 3 trials. In cohort H of the EV-103 phase 1b/2 trial, patients received neoadjuvant EV prior to RC and PLND. Pathological complete response (pCR) rate was 36.4% and pathological downstaging (pDS), no longer having muscle-invasive disease, took place in 50% of EV-treated patients. Safety data indicated that 18.2% of patients had

grade  $\geq 3$  EV treatment-related AEs, which is in line with EV AEs in other clinical settings. Three deaths occurred during the study, which may be higher than expected and requires further examination. This supports the ongoing phase 2/3 programs evaluating EV in MIBC.<sup>17</sup>

The VESPER trial compared dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) vs. gemcitabine and cisplatin (GC) in the perioperative space in patients treated with RC. dd-MVAC demonstrated a higher CR rate and appeared to be more effective than GC in the neoadjuvant group. Further analysis on the histological variants of UC did not reveal a significant difference in CR or PFS after NAC. Only the nested variant was associated with a decreased pathological response.<sup>18</sup> Therefore, neoadjuvant cisplatin-based chemotherapy should be offered to patients with MIBC regardless of the presence of variant histology.

The final results of a multicenter, prospective, phase 2 trial of GC NAC in patients with high-grade upper tract UC (UTUC) noted a CR, defined as pT0N0, in 19% of treated patients. Downstaging to non-muscle-invasive UTUC was approximately 63%. This supports neoadjuvant cisplatin-based chemotherapy prior to nephroureterectomy for UTUC patients, especially for those who may not be eligible for cisplatin-based therapy post-surgery.<sup>19</sup>

Dr. Alejandro Berlin, summarized the current state of knowledge on optimizing bladder preservation with the goal of fostering better adoption of this modality for patients with MIBC.

Diffusion-weighted image (DWI) is a magnetic resonance (MR) based functional imaging technique that could be used to discern tumor cells and normal tissue through cellular density reflected quantitatively in an apparent diffusion coefficient value (ADCV). Following successful treatment, ADCV increases, reflecting a decrease in tumor cellularity. Monitoring ADCV change throughout treatment has the potential to identify early non-responders who may benefit from a change in treatment approach. However, sensitivity remains a challenge, as demonstrated by a suboptimal negative predictive value (approximately 50–60%).<sup>20</sup> A phase 1 study exploring dose-escalated adaptive bladder radiotherapy, where radiotherapy regimen is adapted to dynamic changes in bladder shape and size, reached a maximum tolerated dose (70 Gy) with relatively low toxicity.<sup>21,22</sup> Combining the two concepts and adapting radiotherapy to both dynamic changes in bladder shape and size in addition to changes in ADCV can more effectively target dense tumor areas with higher doses of radiotherapy and reduce the overall volume of healthy tissue exposed to radiotherapy.<sup>23</sup>

A multicenter study comparing tightly matched RC and trimodality therapy (TMT) for MIBC demonstrated that five years post-treatment, metastasis-free survival was 73% in the RC group compared to 78% in the TMT group. Five-year OS was 66% with RC compared to 78% with TMT. Salvage RC was performed in 13% of patients post-TMT, and



NMIBC recurrence was observed in 20.5% of TMT patients. Oncological outcomes seem to be equivalent between TMT and RC; TMT should, therefore, be offered as an effective alternative for select patients.<sup>24</sup>

In another study, RC plus NAC and TMT were associated with similar OS in cystectomy-eligible patients. However, differences in OS were observed in cystectomy-ineligible patients. Hence, studies aiming to compare effectiveness based on population registries should be interpreted with caution, as biases and pertinent information, such as eligibility for cystectomy, may be lacking or unreliable.<sup>25</sup> A long-term comparison of costs associated with TMT vs. RC revealed higher costs for TMT than RC at two years (\$372 839 vs. \$191 363) and five years (\$424 570 vs. \$253 651). Outpatient expenditures largely drove the excess spending associated with TMT vs. RC. Interestingly, patients who received no definitive treatment(s) also incurred substantial costs of \$73 780 and \$88 275 at two and five years, respectively.<sup>26</sup>

Although chemoradiation therapy (CRT) and RC provide comparable outcomes, toxicity concerns, particularly in elderly, frail patients, limit their use in this population. In a retrospective study, 40% of patients who underwent definitive CRT for UC were alive, and 31% had died with no evidence of disease at last followup. While the estimated five-year OS was 48%, the estimated five-year disease-specific mortality rate was 31%, and 80% of patients achieved CR. CRT had a favorable toxicity profile and encouraging cancer control outcomes in this unselected, mostly elderly and frail patient cohort.<sup>27</sup>

Taken together, current evidence supports TMT as an established option with an excellent therapeutic index for patients with MIBC. Patient selection is not a handicap to TMT but a feature, as with any therapeutic intervention. A patient-centric collaborative approach among specialists should be implemented before making treatment decisions.

Lastly, there is a general trend towards increasingly precise therapy for UC treatment. Incorporating genomic testing in UC will help enhance access to additional novel therapeutic approaches. An integrative analysis of urine cell-free DNA was used to detect residual disease in localized bladder cancer patients. Patient blood and urine samples were collected prior to RC. Patients who had residual disease detected in their surgical sample (no pCR) had significantly higher copy number alterations (CNA)-derived tumor fractions in urine compared to patients with pCR and healthy adults. Further analysis with urine cancer personalized profiling by deep sequencing (uCAPP-Seq) revealed that non-silent, single-nucleotide, variant-based urine tumor DNA (utDNA) detection correlated with the absence of pCR. Moreover, utDNA-positive patients exhibited significantly worse PFS compared to utDNA-negative patients. These results suggest that integrative multiomics on urine derived from MIBC patients has potential clinical impact for monitoring and selecting patients for bladder-sparing approaches.<sup>28</sup>

## Kidney cancer

Dr. William Chu shared a radiation oncology perspective on renal cell carcinoma (RCC). Surgery is the gold standard treatment for small renal masses (SRMs) in localized RCC. Partial nephrectomy achieves cancer-specific survival (CSS) of over 95% at five years and >90% at 10 years. A well-recognized, non-surgical, ablative approach is radiofrequency ablation (RFA), which involves thermal damage leading to coagulative necrosis. RFA is an excellent ablative option for SRMs (<3 cm in size), with a large body of evidence supporting its ability to achieve local disease control and CSS in a large majority of patients.<sup>29,30</sup> Stereotactic body radiotherapy (SBRT) is the precise delivery of ultra-high doses of conformal radiation with steep dose gradients to minimize dose to adjacent normal tissues. SBRT presents multiple advantages over RFA. It is a non-invasive, outpatient treatment that is not limited by tumor size or location. RFA is also well-tolerated and relatively low-cost. RADSTER, a prospective, randomized, parallel-controlled pilot trial comparing SBRT and RFA for the management of SRMs demonstrated that recruitment and randomization of patients with SRMs in an SBRT vs. RFA prospective trial are feasible. Thus far, SBRT and RFA have had excellent short-term safety profiles, with low recurrence rates. This sets the groundwork for a larger, multicenter trial comparing SBRT and RFA to evaluate the overall cost-effectiveness and efficacy of SBRT and RFA in RCC tumor ablation.<sup>31</sup>

In the advanced/metastatic RCC space, a small, retrospective study evaluated the efficacy and toxicity of SBRT in prolonging systemic therapy in oligoprogressive metastatic RCC (mRCC). A ratio between the duration of systemic therapy prior to oligoprogression (DOTp) and post-SBRT completion (DOTs) was calculated to determine the impact of SBRT on systemic treatment prolongation. Results demonstrated the median DOTs/DOTp ratio to be 1:3, suggesting that adding SBRT to systemic therapy during oligoprogression more than doubles time on systemic therapy. SBRT was well-tolerated and may prolong lines of therapy, thereby decreasing additional toxicities associated with exposure to new regimens.<sup>32</sup> Moreover, in a more extensive prospective study, the use of SBRT delayed the need to change systemic tyrosine kinase inhibitor (TKI) therapy by a median of >1 year, with low toxicity rates.<sup>33</sup> There are ongoing trials to evaluate the synergy between SBRT and standard double immunotherapy. CYTOSHRINK is a Canadian-led, randomized, phase 2 trial of cytoreductive stereotactic hypofractionated radiotherapy with combination ipilimumab/nivolumab for metastatic kidney cancer. Results from this trial are not available yet but can be practice-changing.<sup>34</sup>

Dr. Anil Kapoor presented advances in the surgical aspects of kidney cancer. Currently, the five-year recurrence rate in patients with high-risk RCC following nephrectomy can be up to 60%. The NeoAvAx study examined the efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients with localized RCC who are at high risk of relapse

after nephrectomy. Prior phase 2 trials of neoadjuvant axitinib, a TKI, demonstrated partial primary tumor response rates of 22–46%. NeoAvAx, a phase 2 trial, investigated 12 weeks of combination neoadjuvant avelumab (an immune checkpoint inhibitor [IO])/axitinib (a TKI) prior to nephrectomy in patients with high-risk non-metastatic clear-cell RCC. Thirty percent of patients demonstrated a partial response (PR) of their primary tumor, with a median tumor downsizing of 20%. Of the patients with PR, 83% were disease-free post-surgery. At a median followup of 23.5 months, recurrence occurred in 32.5% of patients, and three died of disease. The secondary endpoint for this trial was surgical morbidity, which is a concern with neoadjuvant immunotherapy and TKI prior to surgery; 53% of surgeries had normal tissue planes, 22% moderately adhesive, and 25% severely desmoplastic. Biomarker analysis indicated that patients with low CD8+ levels had a higher risk of recurrence.<sup>35</sup>

In a phase 2 study of patients with locally advanced non-metastatic clear-cell RCC, treatment with neoadjuvant cabozantinib, a TKI, resulted in tumor reduction in all participating patients. The median tumor size reduction was 23%. Side effects were as expected, and there were no complications related to cabozantinib treatment.<sup>36</sup> Data on the impact of presurgical neoadjuvant IO therapy on primary tumor size and complexity in correlation with surgical quality and short-term oncological outcomes were also presented. Bifecta, which is a negative surgical margin and no complications for 30 days, was achieved in 78.6% of patients, and tumors were downsized but not as dramatically as demonstrated with TKI treatments.<sup>37</sup> These trials suggest that neoadjuvant TKI may produce a better tumor response than neoadjuvant IO, resulting in more resectable tumors.

Data on adjuvant therapy after surgical resection of high-risk RCC was also presented. A study was done using the Canadian Kidney Cancer information system (CKCis) database to compare outcomes in patients with high-risk clear-cell non-metastatic RCC that participated in adjuvant therapy trials vs. those that did not. Patients who participated in adjuvant therapy trials fared better than those who did not. At five years, OS and RFS were significantly higher in the adjuvant therapy trial group, suggesting that adjuvant therapy may be beneficial.<sup>38</sup> In terms of cost-effectiveness, a Markov model study found adjuvant pembrolizumab post-nephrectomy to be cost-effective at five years only for the highest-risk subsets of patients. On a population level, it was found to be cost-effective only at the 15-year mark.<sup>39</sup>

Although multiple abstracts focused on neoadjuvant therapy before non-metastatic kidney cancer surgery, more data is needed on surgical risk with preoperative IO/TKI treatments. Adjuvant therapy after high-risk kidney cancer surgery has a strong DFS signal, but OS signal data is still outstanding. Moreover, the patients that would benefit the most from adjuvant pembrolizumab still need to be clarified.

Indeed, systemic therapy for RCC has undergone substantial changes over the past years, in particular with the introduction of immunotherapy. Questions regarding the use of novel IO/IO or IO/TKI regimens in the adjuvant setting in specific RCC subgroups and optimal treatment management are yet to be conclusively answered. Dr. Christian Kollmannsberger presented three abstracts on systemic therapy for RCC. Keynote-564, a phase 3 study, investigated the use of pembrolizumab (an IO) as a post-nephrectomy adjuvant therapy in high-risk, localized, completely resected RCC or M1 NED. Initial results demonstrated a DFS benefit for pembrolizumab. At a longer median followup of 30 months, pembrolizumab continued to demonstrate a significant DFS benefit. The benefit was seen across all relevant subgroups, including intermediate-high, high, and M1 NED patients. A total of 18.6% of patients in the pembrolizumab arm had grade 3–4 toxicity, which led to treatment discontinuation in 18.2%. Therefore, adjuvant pembrolizumab is a management option for intermediate-high, high-risk, and M1 NED patients;<sup>40</sup> however, when discussing adjuvant pembrolizumab with patients, the overall treatment burden, including benefit, current lack of OS benefit, toxicity, the potential for permanent toxicity, and financial cost, have to be considered.

The long-term efficacy and safety of nivolumab (an IO) plus ipilimumab (an IO) vs. sunitinib (TKI) was evaluated for the first-line treatment of patients with advanced sarcomatoid renal cell carcinoma (sRCC) in a subgroup analysis of the phase 3 CheckMate 214 trial. The prognosis of patients with sRCC is poor and targeted therapies provide limited benefit. Nivolumab plus ipilimumab demonstrated unprecedented activity in sRCC. The overall response rate was 60.8%, with an impressive 23% CR rate and 37.8% PR rate. Median PFS and OS were 26.5 and 48 months for nivolumab plus ipilimumab vs. 5.5 and 14.3 months for sunitinib, respectively, after a minimum followup of five years. No new toxicity issues emerged. The unprecedented efficacy results demonstrated in previous analyses are maintained long-term. Given the excellent outcomes, nivolumab plus ipilimumab should be considered the standard first-line therapy for sRCC and set the bar for comparison to other regimens.<sup>41</sup>

TKIs remain a mainstay of mRCC therapy in the first-line setting. Several small, non-randomized studies have examined the role of dose-schedule individualization for TKIs and reported improved results. SURF, a randomized phase 2 study, is the largest prospective study to date. Patients were started on first-line sunitinib and, in case of a required dose adjustment, randomized to either 37.5 mg for four weeks on/two weeks off or 50 mg for two weeks on/one week off. The study demonstrated superior PFS and OS outcomes for the two weeks on/one week off schedule. More patients remained on the two weeks on/one week off schedule at six months than in the dose-reduced four weeks on/two weeks off schedule. Serious AEs and permanent discontinuation due to toxicity

were reduced with the two weeks on/one week off schedule. This study underscores the importance of dose-schedule individualization for TKIs to fully realize their potential. This also applies to the use of TKIs in combination regimens with IO.<sup>42</sup>

## Conclusions

This year's ASCO GU symposium showcased the latest prostate, bladder, and kidney cancer research findings, unveiling the most cutting-edge diagnostics and treatments. More precise, custom-tailored therapies, informed by disease biomarkers and genetics, along with improved ongoing imaging and disease monitoring, are likely to impact disease pathogenesis and continue to shape the GU cancer landscape. Novel treatment agents and therapeutic innovations that enhance a patient-centric therapeutic approach should continue to be pursued to improve overall outcomes, survival, and quality of life for patients with GU cancers.

**Competing interests:** Dr. Kapoor has received advisory honoraria from Abbvie, Astellas, AstraZeneca, BMS, Eisai, Ipsen, Janssen, and Merck; is a speakers' bureau member for Eisai, Ipsen, and Merck; holds investments in Point Biopharma and Verity; has participated in clinical trials for CCTG, Eisai, Janssen, and Merck; and holds a leadership/board position with Kidney Cancer Canada. Dr. Niazi has received honoraria/research funding from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Knight Therapeutics, Merck, Sanofi, TerSera, and Tolmar. Dr. Noonan has been a consultant for Astellas, AstraZeneca, EMD Serono, Janssen, and Pfizer. Dr. Rendon has been an advisory board member for Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Sanofi, and TerSera; a speakers' bureau member for Amgen, Astellas, Bayer, Ferring, and Janssen; has received grants/honoraria from Amgen, Astellas, Bayer, and Janssen; and has participated in clinical trials supported by Abbvie, Amgen, Astellas, AstraZeneca, Ferring, Janssen, Myovant, Pfizer, and Sanofi. Dr. Alimohamed has had advisory/consultancy roles with EMD Serono, Merck, Pfizer, and Seagen. Dr. Kassouf has had advisory/consultancy roles with Abbvie, Astellas, BMD, EMD Serono, Ferring, Janssen, Merck, Roche, and Sesen Bio; and has participated in clinical trials supported by BMS, Janssen, Roche, Sesen Bio, and Theralase. Dr. Kollmannsberger has been a consultant for Astellas, Bayer, BMS, Eisai, Ipsen, Merck, Pfizer, and Sanofi; has received honoraria for presentations from Bayer, BMS, Eisai, Ipsen, Janssen, and Pfizer; and has served on scientific advisory boards for Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, and Sanofi. Dr. So has been an advisory board member for Abbvie, Astellas, Bayer, Janssen, Merck, and TerSera. The remaining authors do not report any competing personal or financial interests related to this work.

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