2023 American Society of Clinical Oncology Genitourinary (ASCO-GU) Cancers Symposium
Meeting highlights

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INTRODUCTION

The 2023 American Society of Clinical Oncology (ASCO) Genitourinary (GU) Cancers Symposium, held in San Francisco and online on February 16–18, focused on the latest innovations and study findings in the diagnosis and treatment of GU malignancies. Following the symposium on February 21, the Canadian Urological Association (CUA) held an online webinar where Canadian experts highlighted key research in bladder, kidney, and prostate cancers. Here, we summarize the latest advances presented at ASCO-GU 2023. The entire webinar can be viewed on UROpedia Canada, and meeting abstracts can be viewed at the ASCO meeting library.

BLADDER CANCER

Many new technological and therapeutic advances with the potential to shape the future of bladder cancer management were presented at this year's ASCO-GU. The most exciting developments were in localized urothelial cancers.

Dr. Armen Aprikian presented four studies that have the potential to be practice-changing in the future. A prospective study evaluated the utility of cell-free urinary tumor DNA (utDNA) to detect minimal residual disease (MRD) in non-muscle-invasive bladder cancer (NIMBC) at the time of repeat transurethral resection of bladder tumor (rTURBT).[1] Using utDNA, tumor-specific alterations were detected in 10/11 patients undergoing rTURBT, and patients that had a tumor present exhibited a higher utDNA fraction. Therefore, utDNA shows promise as a biomarker for detecting MRD, with the potential to aid in risk stratification and personalized medicine in the future.

The advent of real-time adaptive radiation treatments tailored to the individual patient is showing promising early results. A prospective, randomized phase 2 trial of image-guided adaptive radiotherapy, with or without dose escalation, suggested potentially better local control, with low toxicity for image-guided (chemo) radiotherapy compared to historical controls in muscle-invasive bladder cancer (MIBC) patients.[2]

RETAIN, a phase 2 study, used a rigorous assessment of residual disease and molecular tumor phenotyping, post-neoadjuvant chemotherapy, to select MIBC patients for active surveillance in lieu of cystectomy.[3] Although the results were not statistically significant (24 months metastasis-free survival for intent to treat [ITT] was 72.8%), there was a trend, thus warranting further investigation into the use of molecular analysis in patient selection for cystectomy or chemoradiation avoidance.

Finally, Keynote-057, a phase 2 study, tested long-term immunotherapy with pembrolizumab in high-risk NMIBC unresponsive to bacillus Calmette-Guérin (BCG), where the standard of care (SOC) is radical cystectomy.[4] Results from cohort A (carcinoma in situ [CIS] ± papillary tumors) showed a clinical complete response rate (cCRR) of 41% at three months, which led to FDA approval. Results from cohort B (papillary tumors without CIS) suggest disease-free survival (DFS) of 35% at three years with acceptable toxicity. Therefore, pembrolizumab monotherapy may benefit patients with high-risk papillary NMIBC unresponsive to BCG.

Dr. Normand Blais presented updates on the major trials in bladder cancer and highlighted some promising studies using neoadjuvant chemo-immunotherapy combinations. Two trials investigating chemo-immuno-

therapy combinations in the neoadjuvant setting were presented.

HCRN GU 16-257 evaluated the combination of nivolumab and cisplatin-gemcitabine for muscle-invasive urothelial carcinoma (MIUC).[5] Repeat cystoscopies were performed following four induction cycles, and patients were classified as "clinical CR" or "no clinical CR." Cystectomy was then offered to patients in the "no clinical CR" group, as well as those in the "clinical CR" group who preferred cystectomy. A clinical CR was obtained in 33/72 patients, and 32/33 chose observation, in addition to eight further cycles of nivolumab. Approximately 70% of the patients in clinical CR remained cystectomy-free. Nine patients eventually presented a relapse needing salvage surgery, and only two patients developed metastatic disease. Therefore, a significant number of patients with MIUC may be treated using this strategy without upfront cystectomy.

Another study, HCRN GU14-188, evaluated two cohorts of patients undergoing four months of neoadjuvant chemotherapy with immunotherapy.[6] Cohort A received pembrolizumab with cisplatin and gemcitabine, whereas cohort B were cisplatin-ineligible patients who received pembrolizumab with gemcitabine. Cystectomy was performed in all eligible patients (88% of the total), and the pathological CR rate was 44% in cohort A and 45% in cohort B. Progression-free survival (PFS) at 18 months favored cohort A at 82% vs. 65% for cohort B. Pathological CR rates remain in the 30–50% range with neoadjuvant chemotherapy alone or chemotherapy combined with immune-oncology (IO).

Several randomized trials have completed accrual and will better define the optimal use of immunotherapy in this setting. Integration of radiation therapy as an alternative to cystectomy is also being actively pursued.

In the adjuvant space, a 36-month followup update of the CheckMate-274 trial, examining nivolumab compared to placebo in high-risk post-cystectomy patients with urothelial cancers, continued to show DFS benefits;[7] however, a longer followup will be required before overall survival (OS) benefits can be assessed. Adjuvant IO trials in high-risk MIUC presented variable results, with IMvigor010 (atezolizumab) demonstrating negative DFS and OS data, CheckMate-274 (nivolumab) demonstrating DFS improvement with OS data still outstanding, and AMBASSADOR (pembrolizumab), for which data is eagerly anticipated.

In the advanced setting, the final analysis of IMvigor 130, which compared atezolizumab with or without chemotherapy to chemotherapy alone, resulted in a non-significant improvement in OS and will not impact the current standard of care.[8] The standard approach remains the use of immunotherapy in sequence with chemotherapy, either as a maintenance strategy in responding patients or as a second-line option in patients progressing on chemotherapy. Many new and exciting treatments are exploring the novel antibody-drug conjugate technology where a tumor-targeted monoclonal antibody is coupled with a cytotoxic drug payload. One of these compounds, enfortumab vedotin (EV) has already been approved for advanced and refractory urothelial carcinoma and studies in the first-line advanced and neoadjuvant settings are showing promising results.[9] Interestingly, some studies suggest that EV is more efficacious but is also associated with more immune-related adverse events when used directly after immune checkpoint inhibitor (ICI) treatment compared to after chemotherapy. Indeed, Koshkin et al demonstrated a 58% response rate to EV after ICIs and 37% after chemotherapy (p=0.02).[10]

Sacituzumab govitecan (SG) is a TROP-2-directed antibody with a govitecan (topoisomerase-1 inhibitor) payload. The TROPHY trial series is investigating SG in different cohorts of patients. In cohort 1, patients that progressed after platinum and ICI-based therapy reported a response rate (RR) of 27%, with a median duration of response of 7.2 months, a median PFS of 5.4 months, and a median OS of 10.9 months with SG.[11] The TROPHY-U-01 cohort 2, including patients that were cisplatin-ineligible, had similar outcomes as cohort 1, with a RR of 32% and a median OS of 13.5 months.[12] These data have led to the approval of SG by the FDA, although this indication is yet to be approved in Canada. An important question for current practice is whether SG retains activity after EV or whether the reverse strategy of SG followed by EV may be best. A small, real-world experience

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study suggested that EV followed by SG leads to a RR of 23% and a PFS of 2.5 months.[13] There is currently no data on the opposite sequence. Therefore, ideal combinations and sequences, as well as biomarkers for patient selection, are important aspects that need further investigation in this space.

KIDNEY CANCER

There were many thought-provoking and practice-informing presentations on kidney cancer at ASCO-GU.

Dr. Rodney Breau focused on abstracts emphasizing patients with clinically localized tumors. Post-surgery recurrence remains a major area of interest, as adjuvant immunotherapy trials forge on. Two systematic reviews summarized the current landscape of immunotherapy trials.[14,15]

Of the four phase-3 trials (CheckMate 914, IMmotion 010, KEYNOTE 564, and PROSPER), only KEYNOTE 564 showed an improvement in recurrence-free survival (RFS) in the immunotherapy arm (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.50–0.79). The pooled analysis revealed that most of the inconsistencies were due to variability between trials, and the pooled decrease in recurrence risk was 15% (pooled HR 0.85, 95% CI 0.69–1.04). The four adjuvant trials are not mature enough to assess OS.

To predict the impact of adjuvant immunotherapy on OS in high-risk clear-cell renal cell carcinoma (ccRCC), Garg et al performed an analysis on the United States National Cancer Database.[16] Patient populations in line with recent phase 3 trials (clinically localized high-risk ccRCC post-nephrectomy) were included in the study. They identified 768 patients who received adjuvant therapy in the form of tyrosine kinase inhibitor (TKI) or IO. There was no difference in OS between IO and TKI-treated patients. Given that phase 3 randomized controlled trials of adjuvant TKIs are mature and show no survival benefit compared to placebo, the authors concluded that IO adjuvant therapy might not improve survival.

Furthermore, a survey of over 1000 kidney cancer patients by the Kidney Cancer Research Alliance (KCCure) revealed that most patients overestimated their risk of recurrence.[17] In contrast, in the subgroup of patients who had received, or were receiving, adjuvant therapy (n=74), patients grossly overestimated the reduced risk of recurrence, with 25% believing that adjuvant therapy would reduce their risk of recurrence by over 50%. Much remains to be learned about the benefits and harms of adjuvant therapy for patients with high-risk clinically localized RCC. Evidence needs to be presented carefully and clearly to patients so that they can make informed decisions that align treatment choices with their values and preferences.

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Von Hippel Lindau (VHL) disease continues to pose challenges for patients and care providers. The LITESPARK 004 phase 2 clinical trial evaluated belzutifan (a HIF-2α inhibitor) treatment in patients with VHL disease.[18] In this updated analysis, the mean annual financial cost of VHL-related surgery and surgery-related complications was estimated to be $57 259/year before starting belzutifan compared to $2536/year after starting belzutifan. Of note, Merck was the sponsor of this study, and the cost of belzutifan was not incorporated in this cost analysis. Also, belzutifan had a 15% risk of grade 3 treatment-related toxicity, mainly anemia and hypoxia.

ZIRCON, a phase 3 trial, evaluated the diagnostic performance of ^{89}Zr-DFO-girentuximab positron emission tomography (PET)/computed tomography (CT) imaging for ccRCC.[19] Girentuximab (cG250) is a monoclonal antibody against carbonic anhydrase IX (CA IX). CA IX is a glycoprotein expressed on the surface of most ccRCC tumors but is infrequently expressed in normal tissue. ^{89}Zr-DFO-girentuximab has a zirconium payload that is detectable on PET/CT. In this trial, 288 patients with cT1a/b renal tumors and planned partial or radical nephrectomy were included. Diagnostic performance was assessed by comparing the PET/CT results to the pathology from surgery. Approximately 70% of patients had ccRCC, 15% had papillary RCC, 8% had chromophobe RCC, and the remaining were benign and malignant tumors. Notably, there were no imaging-related significant adverse events. ^{89}Zr-DFO-girentuximab PET/CT's sensitivity and specificity were 85% and 87%, respectively.

These results were robust for patients with smaller tumors (cT1a) and were consistent across three blinded central reviewers. Applied clinically, a patient with a small renal mass has an approximate 70% probability of ccRCC. If that patient has a positive ^{89}Zr-DFO-girentuximab PET/CT, the likelihood of ccRCC increases to approximately 93%. If

the ^{89}Zr-DFO-girentuximab PET/CT is negative, the probability of ccRCC decreases to approximately 25%. The information from ^{89}Zr-DFO-girentuximab PET/CT may be helpful in counselling patients about the decision to biopsy a small renal mass or the decision to treat without biopsy. The main limitation to ^{89}Zr-DFO-girentuximab PET/CT is that non-clear-cell RCC may be "cold" on ^{89}Zr-DFO-girentuximab PET/CT, so a negative test is far from definitive.

Dr. Christian Kollmannsberger reviewed the treatment landscape for metastatic RCC, which has dramatically changed over the past 6–8 years. Indeed, immunotherapy-based combinations have largely replaced single-agent vascular-endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI). With dual immunotherapy regimens now the SOC, early results of the first triple combination of cabozantinib/nivolumab/ipilimumab have started to emerge. In addition, integrating local therapy options, such as stereotactic body radiation (SBRT), radio-frequency ablation, or surgery appears to be of great value in managing the primary tumor, oligo-metastases, or oligo-progression.

COSMIC-313 is the first randomized phase 3 study to investigate a triple regimen of VEGFR-TKI (cabozantinib) with dual PD-1/CTLA-4 (nivolumab/ipilimumab) checkpoint blockade in first-line advanced RCC.[20] Initial results demonstrated a significant PFS benefit for International Metastatic RCC Database Consortium (IMDC) intermediate/poor-risk patients. Overall, PFS remained significant in the partial ITT (PITT) (first 550 randomized patients) and the ITT population, resulting in a 25% reduction in the risk of progression and death. A 32% reduction in the risk of progression or death was observed with the triplet regimen compared with the control in the intermediate-risk group (HR 0.68, 95% CI 0.54–0.86) but no statistically significant difference was observed in the poor-risk group (HR 0.93, 95% CI 0.64–1.35). The objective response rate was also higher with the triplet than the control only in intermediate-risk patients. Treatment-related AEs led to treatment discontinuation in a greater proportion of intermediate-risk (51% vs. 26%) compared with poor-risk patients (29% vs. 20%). More data with longer followup is needed before triplet therapy can be conclusively assessed as first-line therapy in metastatic RCC. Thus far, the benefit appears modest.

The randomized phase 3 study, Checkmate 9ER, compared nivolumab plus cabozantinib vs. sunitinib as first-line therapy in patients with metastatic RCC.[21] Results to date have reported a PFS and OS benefit in favor of the combination regimen, which is now a standard regimen in the first-line setting. Three-year followup results for Checkmate 9ER and stratification by the IMDC risk group revealed that PFS and OS remain significant in favor of the combination across IMDC intermediate/poor-risk subgroups. Overall response rates also remained significant in favor of the combination in all IMDC subgroups. Toxicity was acceptable and manageable. Therefore, after a median followup of 44 months, nivolumab plus cabozantinib maintained clinically meaningful benefits for long-term survival and response compared to sunitinib, thus continuing to support the combination as a first-line treatment for patients with advanced or metastatic RCC.

CaboPoint is an ongoing, phase 2, open-label study that aims to evaluate the efficacy and safety of cabozantinib in adults with unresectable, locally advanced, or metastatic RCC with a clear-cell component whose disease progressed after first-line checkpoint-inhibitor (CPI)-based therapy.[22]

Two cohorts of patients were examined, cohort A with patients progressing after a CPI/CPI combination, and cohort B progressing after a CPI/TKI combination. A total of 88 patients were included, 60 pretreated with CPI/CPI and 28 treated with CPI/TKI. After a median followup of three months, response rates were 29.5%, 31.7%, and 25.0% for overall, cohort A, and cohort B, respectively. Cabozantinib demonstrated a robust overall response rate in patients with metastatic RCC after CPI-based combination therapy, irrespective of the first-line regimen, and appears to be a good second-line option irrespective of prior combination therapy.

A small institutional study examined whether active treatment of residual disease after immunotherapy-based first-line treatment can improve the CRR in metastatic RCC.[23] A total of 80 ccRCC patients were included; first-line treatment consisted of CPI/CPI, CPI/TKI, and other CPI-based therapy. Nine (11%) and 26 (45%) patients achieved a complete and partial response to first-line therapy, respectively, while 23 (29%) patients demonstrated stable disease. Ten patients underwent local treatment for residual disease, one patient with stable disease and nine with partial remission as the best response, which increased the CRR from 11% to 24%. After a median followup of 23 months, the median duration of response has not been reached. Systemic therapy was discontinued in all patients after local therapy, and only two patients progressed. Therefore, the addition of local therapy for residual disease in responding patients is feasible and has the potential to meaningfully increase the CRR. Different

local treatment options can be used, including surgery, radiofrequency ablation, and SBRT. Treatment discontinuation may be possible in these patients. These cases should be discussed in multidisciplinary tumor boards to optimize outcomes.

PROSTATE CANCER

Dr. Tamim Niazi presented two abstracts on localized or locally advanced prostate cancer.

Moderate hypo-fractionated radiation therapy of 60 Gy in 20 fractions was previously demonstrated to be non-inferior to 74 Gy in 37 fractions at five years.[24] The 10-year efficacy and comorbidity outcomes of CHHip, a phase 3 randomized trial of conventional vs. moderate hypo-fractionated high-dose intensity-modulated radiotherapy for prostate cancer were evaluated.[25] Over 3200 prostate cancer patients with predominantly intermediate-risk disease were randomized to either 74 Gy in 37 fractions, 60 Gy in 20 fractions, or 57 Gy in 19 fractions. Patients also received 3–6 months of androgen deprivation therapy (ADT). With a median followup of over 12 years, the 10-year biomedical or clinical failure (BCF) rates were 76%, 79.8%, and 73.4%, respectively, for 74 Gy, 60 Gy, and 57 Gy. For the 60Gy in 20 fractions, non-inferiority was confirmed with borderline significance for superiority. Long-term efficacy was confirmed with very low toxicity.

Many centers across Canada have already adopted this fractionation for low- and intermediate-risk prostate cancer patients treated with external beam radiation therapy (EBRT). This confirms the adequacy of short-course radiation therapy for these patient groups. This fractionation should not be used for high-risk patients, as their SOC includes long-term ADT and pelvic radiation therapy. For high-risk prostate cancer patients destined for EBRT, the recently presented Canadian fractionation study at ASTRO 2022, consisting of 68 Gy in 25 fractions with 45 Gy in 25 fractions to the pelvis and long-term ADT, is more adequate.

Six months of gonadotropin-releasing hormone (GnRH) with salvage radiotherapy (SRT) is still the SOC for most prostate cancer patients failing radical prostatectomy. FORMULA-509 was designed to evaluate whether adding six months of abiraterone/prednisone (AAP) and apalutamide (Apa) could improve outcomes.[26] Patients with detectable prostate-specific antigen (PSA) ≥0.1 and one or more unfavorable features (Gleason 8–10, PSA 0.5, pT3/T4, pN1 or radiographic N1, PSA doubling time of 10 months, negative margins, persistent PSA, gross local/regional disease, or decipher high risk) participated in this study. All patients received SRT plus six months of GnRH agonist and were randomized to concurrent bicalutamide or AAP + Apa. The primary endpoint was PSA PFS, and the secondary endpoint was metastasis-free survival (MFS) determined by conventional imaging. At a median followup of 34 months, there was no significant difference for the systemic treatment enhancement for PFS (HR 0.71); however, for patients with PSA ≥0.5, the PFS was significantly better (HR 0.50, p=0.03). No statistically significant benefit was detected in preplanned analyses of pN1 vs. PN0. This was the first systemic treatment enhancement in the salvage setting, and although the overall cohort did not have significant benefits, the prespecified subgroup of PSA >0.5 benefited. A single high-risk feature to intensity is most likely insufficient, and long-term data are needed. This will not impact the SOC for Canadian patients, at least not for now.

Dr. Neil Fleshner presented two abstracts.

The ARASENS study compared the addition of darolutamide (DARO) to ADT and docetaxel (DOC) in patients with metastatic hormone-sensitive prostate cancer (mHSPC).[27] DARO reduced the risk of death by 32.5% compared to placebo (HR 0.68, 95% CI 0.57–0.80, p<0.0001). Stratified results demonstrated that the combination of DARO, ADT, and DOC provided OS and secondary endpoint benefits regardless of the volume and risk of disease, although low-volume disease OS benefit did not reach statistical significance. Overall, treatment-related adverse events were consistent across subgroups. The authors concluded that DARO should be added as a new SOC for this patient population; however, this may not benefit all mHSPC patients, especially those with low-volume disease.

The second study presented evaluated long-term data on testosterone recovery in patients with intermediate- and high-risk prostate cancer treated with radiotherapy and different durations of ADT.[28] Data from two randomized studies (PCS II and PCS IV) was included. Only patients that were considered cured were included in the analysis. Eighty percent of patients had normal testosterone levels at base-

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line (9–25 nmol/L), whereas 20% had abnormal (<9 nmol/L) levels. With a median followup of 14 years overall, 76.7%, 54.6%, and 45.1% of patients recovered normal testosterone on 6-, 18-, or 36-month ADT schedules, respectively (p<0.001). The median time to recovery was 1.53, 3.07, and 5.06 years, respectively. Older age, longer ADT, diabetes, and poor disease features were associated with a lower testosterone recovery. Moreover, a normal testosterone level at baseline was associated with a higher testosterone recovery post-ADT. These data are important to discuss with patients during counselling.

Dr. Samantha Gray presented three studies on poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of metastatic castrate-resistant prostate cancer (mCRPC).

PROpel is a phase 3 trial comparing abiraterone (abi) and olaparib (ola) vs. abi and placebo (pbo) as first-line therapy for mCRPC.[29] The study's primary endpoint was previously reported with an improvement in median rPFS of 16.6 months (abi alone) vs. 24.4 months with the combination of ola and abi. In this final analysis, the combination of abi and ola was associated with a median OS of 42.1 months vs. 34.7 months for abi alone (HR 0.81, p=0.037) in the ITT population. The benefit of the combination treatment was seen across subgroups, and no new safety signals were observed. The median OS of 42.1 months is the longest reported in a phase 3 trial in first-line mCRPC. Consistent with rPFS results, a trend toward OS benefit was observed in homologous recombination repair mutation (HRRm), non-HRRm, BRCAm, and non-BRCAm subgroups, with the greatest benefit in the BRCAm subgroup.

TALAPRO-2 is a phase 3 study comparing talazoparib (tala) with enzalutamide (enza) vs. pbo with enza as first-line treatment in patients with mCRPC.[30] The primary endpoint of the study, regardless of HRR status, was radiographic (r) PFS. Median rPFS by blinded central review was not reached in the combination arm (tala and enza) compared to 21.9 months in the pbo and enza arm (HR 0.63, p<0.001). The rPFS was significantly improved in the HRR-deficient group (HR 0.45, p<0.001), which received the combination of tala and enza, and the HR was more pronounced than in the HRR-non-deficient or unknown groups (HR 0.70, p=0.004). The OS data is still immature, but the other secondary endpoints (overall response rates, time to PSA progression, time to cytotoxic chemotherapy) all favored the combination arm. The most common grade 3–4 treatment-emergent adverse events were anemia, low neutrophil, and low platelet counts. In fact, 46% of men in the combination group had grade 3–4 anemia vs. 4% in the pbo and enza group. The authors concluded that this study supports the combination of talazoparib and enzalutamide for all mCRPC patients.

TRITON-3 is a phase 3 study comparing rucaparib to physician's choice of docetaxel (DOC), abiraterone (abi), or enzalutamide (enza) in patients with chemotherapy-naive mCRPC with BRCA 1/2 (BRCA) or ATM alterations.[31] The study met its primary endpoint of improved rPFS in previously reported results. Updated interim analysis demonstrated an rPFS of 11.2 months with rucaparib vs. 6.4 months with physician's choice in the BRCA group (HR 0.50). rPFS in the ITT group was 10.2 months with rucaparib vs. 6.4 months with physician's choice (HR 0.61). OS maturity was 54% in the BRCA subgroup and 59% in the ITT population. The most frequent treatment-emergent adverse event in the rucaparib, DOC, and abi/enza groups was asthenia/fatigue. At least one blood transfusion was required in 29% of patients in the rucaparib group vs. 2% of patients in the physicians' choice group. The authors concluded that rucaparib significantly improved rPFS compared to either DOC or abi/enza and that the interim OS results also suggest a trend towards improvement with rucaparib in patients with mCRPC and BRCA alterations. Safety was felt to be consistent with prior reports.

PARP inhibition remains an important treatment pathway for patients with mCRPC. Patients with HRRm, especially BRCA mutations, derive the most benefit. These drugs are not without toxicity and the risks and benefits need to be assessed prior to prescribing to patients.

CONCLUSIONS

This year's ASCO-GU meeting highlighted the most cutting-edge advances in bladder, kidney, and prostate cancer, foreshadowing a future full of exciting opportunities in the GU space; however, many treatment specifics, such as sequence, duration, patient selection, and cost are challenges that remain to be addressed in the future.

In bladder cancer, utDNA shows promise as a biomarker with the potential to aid in risk stratification and personalized medicine. Real-time adaptive radiation therapy showed early promise, while adjuvant IO treatments continue to demonstrate variable results. Neoadjuvant chemo-immunotherapy combinations and novel antibody-drug conjugates continue to show potential in this space.

In kidney cancer, immunotherapy trials continue to demonstrate disparate results, with only KEYNOTE

564 demonstrating RFS benefits, while OS results are still outstanding. In metastatic RCC, immunotherapy-based combinations and the integration of local therapy are promising, while triple regiments of VEGFR-TKI and dual immunotherapy showed only modest benefits.

In prostate cancer, hypo-fractionated radiotherapy has shown long-term efficacy in treating low- and intermediate-risk prostate cancer patients. While PARP inhibitors continue to offer benefits in the treatment of mCRPC, treatment toxicity can not be ignored. Patient stratification based on BRCA and HRD status can ensure appropriate patient selection.

COMPETING INTERESTS: Dr. Aprikian has been a medical advisor (with honoraria) for AstraZeneca, Bayer, Merck, Pfizer, Roche, TerSera, and Tolmar; and owns stocks in Nanostics. Dr. Blais has been a medical advisor (with honoraria) for AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Ipsen, Merck, Novartis, Pfizer, Roche, Sanofi, Servier, and Takeda; and has received research grants from Astras-Zeneca (Étude CLEAR). 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, Merck, and Pfizer; and has been a scientific advisor for Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, and Sanofi. Dr. Niazi has received research/educational funds from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Janssen, Sanofi, TerSera, and Tolmar; and has received honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Knight Therapeutics, Merck, Paladin, Sanofi, TerSera, Tolmar, and Watson. Dr. Fleshner has received grants/sponsorship support from Astellas, Bayer, Janssen; honorarium/consulting fees/speaker fees from Abbvie, Astellas, Bayer, Janssen, and Sanofi; and is the co-founder of Point Biopharma and Verity. Dr. Gray has received honorarium/advisory board/speaker fees from Bayer, BMS, EMD-Serono, Esai, Ipsen, and Merck; and research funding (institutional) from Astellas and BMS. Dr. Breau does not report any competing personal or financial interests related to this work.

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REFERENCES

1. Rose KM, Murthy P, Gould B, et al. Cell-free urinary tumor DNA to detect minimal residual disease prior to repeat-transurethral resection of bladder tumor in non-muscle-invasive bladder cancer: A prospective study. *J Clin Oncol* 2023;41:LBA445-LBA445. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA445
2. Huddart RA, Hafeez S, Omar A, et al. Randomised phase 2 trial of adaptive image guided radiotherapy in muscle-invasive bladder cancer: Late toxicity and cancer outcomes. *J Clin Oncol* 2023;41:446. https://doi.org/10.1200/JCO.2023.41.6_suppl.446
3. Geynisman DM, Abbosh P, Ross EA, et al. A phase 2 trial of risk-enabled therapy after initiating neoadjuvant chemotherapy for bladder cancer (RETAIN). *J Clin Oncol* 2023;41:438. https://doi.org/10.1200/JCO.2023.41.6_suppl.438
4. Necchi A, Roumiguié M, Esen AA, et al. Pembrolizumab (pembro) monotherapy for patients (pts) with high-risk non-muscle-invasive bladder cancer (HR NMIBC) unresponsive to bacillus Calmette-Guérin (BCG): Results from cohort B of the phase 2 KEYNOTE-057 trial. *J Clin Oncol* 2023;41:LBA442-42. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA442
5. Galsky MD, Witjes AA, Gschwend JE, et al. Extended followup results from the CheckMate 274 trial. *J Clin Oncol* 2023;41: LBA443-43. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA443
6. Bamias A, Davis ID, Galsky MD, et al. Final overall survival (OS) analysis of atezolizumab (atezo) monotherapy vs chemotherapy (chemo) in untreated locally advanced or metastatic urothelial carcinoma (mUC) from the phase 3 IMvigor130 study. *J Clin Oncol* 2023;41:LBA441-LBA441. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA441
7. Galsky MD, Daneshmand S, Lewis SC, et al. Co-primary endpoint analysis of HCRN GU 16-257: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing in patients with muscle-invasive bladder cancer (MIBC). *J Clin Oncol* 2023;41:447. https://doi.org/10.1200/JCO.2023.41.6_suppl.447
8. Brown J, Kaimakliotis HZ, Kelly WK, et al. HCRN GU14-188: Phase 1b/2 study of neoadjuvant pembrolizumab and chemotherapy for T2-4aNOMO urothelial cancer. *J Clin Oncol* 2023;41:448. https://doi.org/10.1200/JCO.2023.41.6_suppl.448
9. Rosenberg JE. LBA73 - Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC). *Ann Oncol* 2022;2022:S808-69. https://doi.org/10.1016/j.annonc.2022.08.079
10. Koshkin VS, Henderson N, Kilari D, et al. Enfortumab vedotin (EV) outcomes with and without immediate prior immune checkpoint inhibitor (ICI) in patients (pts) with advanced urothelial carcinoma (aUC). *J Clin Oncol* 2023;41:514. https://doi.org/10.1200/JCO.2023.41.6_suppl.514
11. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A phase 2 open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol* 2021;39:2474-85. https://doi.org/10.1200/JCO.20.03489
12. Petrylak DP, Tagawa ST, Jain RK, et al. Primary analysis of TROPHY-U-01 cohort 2, a phase 2 study of sacituzumab govitecan (SG) in platinum (PT)-ineligible patients (pts) with metastatic urothelial cancer (mUC) that progressed after prior checkpoint inhibitor (CPI) therapy. *J Clin Oncol* 2023;41:520. https://doi.org/10.1200/JCO.2023.41.6_suppl.520
13. Vlachou E, Hahn NM, Dabb A, et al. Evaluation of clinical benefit of sacituzumab govitecan (SG) following enfortumab vedotin (EV) in advanced urothelial cancer (UC): Real-world experience. *J Clin Oncol* 2023;41:523. https://doi.org/10.1200/JCO.2023.41.6_suppl.523
14. Sipra QUAR, Riaz IB, Naqvi SAA, et al. Adjuvant immunotherapy in renal cell carcinoma: A living systematic review and network meta-analysis (NMA). *J Clin Oncol* 2023;41:694. https://doi.org/10.1200/JCO.2023.41.6_suppl.694
15. Huang E, Riveros C, Ranganathan S, et al. Adjuvant immunotherapy in renal cell carcinoma: A systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol* 2023;41:671. https://doi.org/10.1200/JCO.2023.41.6_suppl.671
16. Garg H, Bhandari M, Noel O, et al. Adjuvant immunotherapy for patients with renal cell carcinoma at increased risk of recurrence following resection: A National Cancer Database analysis. *J Clin Oncol* 2023;41:649. https://doi.org/10.1200/JCO.2023.41.6_suppl.649
17. Battle D, Msaouel P, Pal SM, et al. Patient perceptions of benefits and risks of adjuvant therapy in renal cell carcinoma. *J Clin Oncol* 2023;41:663. https://doi.org/10.1200/JCO.2023.41.6_suppl.663
18. Wang L, Bensimon AG, Sundaram M, et al. Burden of surgeries and surgical complications in patients with Von Hippel Lindau (VHL) disease before and after treatment with belzutifan. *J Clin Oncol* 2023;41:733. https://doi.org/10.1200/JCO.2023.41.6_suppl.733
19. Shuch BM, Pantuck AJ, Bernhard JC, et al. Results from phase 3 study of 89Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma (ZIRCON). *J Clin Oncol* 2023;41:LBA602-LBA602. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA602
20. Powles T, Motzer RJ, Albiges L, et al. Outcomes by IMDC risk in the COSMIC-313 phase 3 trial evaluating cabozantinib (C) plus nivolumab (N) and ipilimumab (I) in first-line advanced RCC (aRCC) of IMDC intermediate or poor risk. *J Clin Oncol* 2023;41:605. https://doi.org/10.1200/JCO.2023.41.6_suppl.605
21. Burotto M, Powles T, Escudier B, et al. Nivolumab plus cabozantinib vs. sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year followup from the phase 3 CheckMate 9ER trial. *J Clin Oncol* 2023;41:603. https://doi.org/10.1200/JCO.2023.41.6_suppl.603
22. Albiges L, Powles T, Sharma A, et al. CaboPoint: Interim results from a phase 2 study of cabozantinib after checkpoint inhibitor (CPI) therapy in patients with advanced renal cell carcinoma (RCC). *J Clin Oncol* 2023;41:606. https://doi.org/10.1200/JCO.2023.41.6_suppl.606
23. Moinard-Butot F, Oriel M, Tricard T, et al. Effect of treatment of residual disease after immunotherapy-based combinations on complete response rate in metastatic renal cell carcinoma. *J Clin Oncol* 2023;41:601. https://doi.org/10.1200/JCO.2023.41.6_suppl.601
24. Dearnaley D, Syndikus I, Mossop H, et al. Conventional vs. hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomized, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17:1047-60. https://doi.org/10.1016/S1470-2045(16)30102-4

25. Syndikus I, Griffin C, Philipps L, et al. 10-year efficacy and comorbidity outcomes of a phase 3 randomized trial of conventional vs. hypofractionated high-dose intensity modulated radiotherapy for prostate cancer (CHHiP; CRUK/06/016). *J Clin Oncol* 2023;41:304. https://doi.org/10.1200/JCO.2023.41.6_suppl.304
26. Nguyen PL, Kollmeier M, Rathkopf DE, et al. FORMULA-509: A multicenter randomized trial of postoperative salvage radiotherapy (SRT) and 6 months of GnRH agonist with or without abiraterone acetate/prednisone (AAP) and apalutamide (Apa) post-radical prostatectomy (RP). *J Clin Oncol* 2023;41:303. https://doi.org/10.1200/JCO.2023.41.6_suppl.303
27. Hussain MHA, Tombal BF, Saad F, et al. Efficacy and safety of darolutamide (DARO) in combination with androgen-deprivation therapy (ADT) and docetaxel (DOC) by disease volume and disease risk in the phase 3 ARASENS study. *J Clin Oncol* 2023;41:15-15. https://doi.org/10.1200/JCO.2023.41.6_suppl.15
28. Nabid A, Carrier N, Martin AG, et al. Testosterone recovery in patients with prostate cancer treated with radiotherapy and different ADT duration: Long-term data from two randomized trials. *J Clin Oncol* 2023;41:300-300. https://doi.org/10.1200/JCO.2023.41.6_suppl.300
29. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Final overall survival (OS) in PROpel: Abiraterone (abi) and olaparib (ola) vs. abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2023;41:LBA16-LBA16. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA16
30. Agarwal N, Azad A, Carles J, et al. TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2023;41:LBA17-LBA17. https://doi.org/10.1200/JCO.2023.41.6_suppl.LBA17
31. Bryce AH, Piulats JM, Reaume MN, et al. Rucaparib for metastatic castration-resistant prostate cancer (mCRPC): TRITON3 interim overall survival and efficacy of rucaparib vs. docetaxel or second-generation androgen pathway inhibitor therapy. *J Clin Oncol* 2023;41:18. https://doi.org/10.1200/JCO.2023.41.6_suppl.18

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