INTRODUCTION
The American Society of Clinical Oncology (ASCO) annual meeting, held in Chicago and online from June 2–6, 2023, showcased the latest research in cancer care, with over 200 sessions centered around the theme, “Partnering with patients: The cornerstone of cancer care and research.” Following the meeting, on June 8, the Canadian Urological Association (CUA) held an online webinar where Canadian experts highlighted key research findings in kidney, prostate, and bladder cancers. This report provides a summary of the significant advances in genitourinary cancers as presented at ASCO 2023. The full webinar can be accessed on UROpedia Canada, and meeting abstracts are available at the ASCO meeting library.

KIDNEY CANCER
Dr. Naveen Basappa presented an update on the advances in the treatment of kidney cancer. The CheckMate 914 trial investigated the use of adjuvant nivolumab plus ipilimumab (NIVO+IPI) in patients with localized renal cell carcinoma (RCC) who were at high risk of relapse after nephrectomy. Surprisingly, the combination treatment did not show any improvement in disease-free survival (DFS) compared to placebo (PBO). 1 To gain a better understanding of the outcomes, exploratory post-hoc analyses were conducted, focusing on specific patient subsets. The results revealed that patients with grade 4 histology, particularly those with sarcomatoid features, showed a potential improvement in DFS with NIVO+IPI. Similarly, patients with over 1% PD-L1 expression seemed to benefit more from NIVO+IPI compared to those with low or no PD-L1 expression. These findings suggest that sarcomatoid features and % PD-L1 expression could serve as a potential biomarker for predicting outcomes in this context. Moreover, NIVO+IPI treatment did not have any detrimental effects on patient quality of life compared to PBO. Another interesting observation was that patients who received more than six cycles of NIVO+IPI tended to have better DFS; however, patients who received six or fewer cycles and discontinued treatment due to adverse events did not experience any DFS benefit. The limited exposure to NIVO+IPI and discontinuation due to adverse events may have contributed to the lack of observed DFS benefit in the trial. Data on overall survival (OS) is still pending. 2 Patient selection is crucial in this treatment setting, and in addition to clinical features, biological characteristics should also be considered.

Long-term followup of KEYNOTE-426 was presented at the meeting. This trial assessed the efficacy of pembrolizumab (PEMBRO), a PD-1 inhibitor, in combination with axitinib (AXI), a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI), as a first-line treatment for advanced clear-cell (cc)RCC. The first interim analysis demonstrated significant improvements in OS, progression-free survival (PFS), and objective response rate (ORR) with PEMBRO+AXI compared to sunitinib (SUN), the control arm in the study. After a minimum followup of five years, the 60-month OS rates were 41.9% for PEMBRO+AXI and 37.1% for SUN (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.71–0.99). Similarly, the 60-month PFS rates were 18.3% and 7.3%, respectively. The median duration of response (DOR) was also longer in the PEMBRO+AXI group. Subsequent anticancer treatments influenced OS, but even after adjusting for this effect, PEMBRO+AXI appeared to show a benefit; however, combination
therapy had a higher incidence of toxicity, adverse events, and treatment discontinuation compared to SUN. Nonetheless, long-term followup data continue to support the use of PEMBRO+AXI as a standard first-line treatment for advanced ccRCC.³

An update was also reported for the CLEAR study, another first-line combination therapy. This trial compared lenvatinib (LEN, a VEGFR TKI) plus PEMBRO (PD-1 inhibitor) to SUN in patients with advanced (a)RCC with a clear-cell component. The primary analysis demonstrated superior PFS, OS, and ORR in the LEN+PEMBRO group compared to SUN. The four-year followup data revealed a response rate of 71.3% in the combination group vs. 36.7% with SUN, with a significantly lower rate of primary progressive disease (5.4%) in the combination group. The median PFS was 23.9 months with the combination and 9.2 months with SUN (HR 0.47, 95% CI 0.38–0.57). While the final median OS was 53.7 months with LEN+PEMBRO and 54.3 months with SUN (HR 0.79, 95% CI 0.63–0.99), there was a consistent OS benefit observed throughout the followup period, indicating an OS advantage for the combination therapy. No significant OS benefit was found with LEN+PEMBRO in the favorable International Metastatic RCC Database Consortium (IMDC) risk group, but the intermediate/poor IMDC risk group showed a positive OS (HR 0.74), with both groups demonstrating a PFS benefit. The final OS analysis, adjusted for subsequent anticancer treatment, revealed a significant benefit with the combination therapy (HR 0.55). Although toxicity was higher in the LEN+PEMBRO group, it was mostly low-grade. These findings reaffirm the primary analysis data and establish LEN+PEMBRO as a viable first-line treatment option for aRCC.

When considering the KEYNOTE-426 and CLEAR studies together, it becomes apparent that the combination therapy of immune checkpoint inhibitors (IO) with TKIs surpasses the efficacy of standard TKI therapy alone (SUN) in terms of PFS, ORR, and OS; however, the durability of OS benefits seems to diminish over time. In the CheckMate-214 study, IO+IO therapy (nivolumab + ipilimumab) appeared to provide better-maintained OS and ORR benefits over time.¹ This raised some discussion of a controversial nature at the meeting as to which treatment should be considered over the other. In the absence of a clinical trial directly comparing these combinations, there was no definitive answer. Regardless, all these options demonstrated superior efficacy compared to standard SUN and should be considered when discussing therapeutic strategies in patients with aRCC.

The phase 3 CONTACT-03 study aimed to assess the impact of adding the PD-L1 inhibitor atezolizumab (ATEZO) to cabozantinib (CABO) compared to CABO alone in patients with aRCC who experienced disease progression during or following IO-based therapy. The study explored the potential benefits of rechallenging PD-1/L1 inhibitors after initial disease progression on a checkpoint inhibitor; however, the addition of ATEZO to CABO did not result in PFS or OS benefits compared to CABO alone. The ORR was similar in both treatment arms, and the DOR was 12.7 months with ATEZO+CABO and 14.8 months with CABO alone. The occurrence of grade 3/4 adverse events (AEs) was higher in the combination group, leading to a greater number of patients discontinuing treatment with ATEZO+CABO compared to CABO alone. Consequently, the addition of ATEZO to CABO did not improve clinical outcomes and instead resulted in increased toxicity in aRCC patients who had progressed during or after IO treatment. Therefore, it is not recommended to use anti-PD-L1 therapy post-treatment with anti-PD-1/L1 therapy.⁶

In summary, the combination of IO and TKI therapies has shown significant benefits in terms of PFS, ORR, and OS; however, the long-term sustainability of OS benefits may vary among different combination therapies. Additionally, in patients who have progressed on or after prior IO treatment, the addition of PD-L1 inhibitors does not improve outcomes and may lead to increased toxicity.

**PROSTATE CANCER**

Dr. Urban Emmenegger presented four abstracts that addressed various aspects of prostate cancer care, including the management of localized prostate cancer and metastatic castration-sensitive prostate cancer (mCSPC), the use of poly ADP-ribose polymerase inhibitors (PARPi), and the significance of BRCA2 aberrations in prostate cancer.

High-risk localized prostate cancer (HRLPC) is a major contributor to prostate cancer-related mortality. The current standard of care for HRLPC involves...
In PCa, there is prognostic hierarchy, with non-BRCA mutation patients having the best outcomes, followed by HRR mutation patients, and BRCA mutation patients showing the most adverse prognosis.
efit the most. OS data is immature. Moreover, the combination did come with added, albeit manageable, toxicity, leading to frequent PARPi dose reductions, interruptions, or discontinuations. All three reported phase 3 ARSi+PARPi studies (TALAPRO-2, PROpel, and MAGNITUDE) demonstrated rPFS benefits in mCRPC patients, with BRCA1/2 having the greatest benefit, followed by patients with non-BRCA HRR mutations, and finally all-comers.

The final abstract examined the role of somatic/germ line HRR mutations in the outcomes of mCRPC patients undergoing non-PARPi therapies as part of the CAPTURE study. Germline BRCA2 defects are associated with poor outcomes in prostate cancer; however, the role of somatic BRCA2 alterations and defects in other HRR genes is less well-documented, despite HRR defects being detected in around 20–30% of patients. This study revealed a prognostic hierarchy, with non-BRCA mutation patients having the best outcomes, followed by HRR mutation (but non-BRCA) patients, and finally, BRCA mutation patients showing the most adverse prognosis. Different BRCA alterations (germline vs. somatic, mono-allelic vs. biallelic, BRCA2 vs. BRCA1) were associated with similar rPFS, PFS, and OS. In BRCA-mutated cancers, first-line ARSi provided similar benefits compared to first-line docetaxel.

Overall, the presented abstracts shed light on different aspects of prostate cancer treatment, including treatment intensification/de-intensification strategies in HRLPC, the role of prostate irradiation in low-volume mCSPC, the use of PARPi monotherapy and combination therapy, and the impact of somatic/germ line HRR mutations on treatment outcomes.

**BLADDER CANCER**

Dr. Srikala Sridhar presented updates on muscle-invasive bladder cancer (MIBC) and metastatic urothelial carcinoma (mUC). The SWOG S1011 phase 3 surgical trial evaluated the benefit of standard vs. extended pelvic lymph node dissection (PLND) performed at the time of radical cystectomy for MIBC. Extended (e) PLND resulted in a higher median number of lymph nodes removed compared to standard (s)PLND (39 vs. 24 nodes) but there was no significant difference in the rate of node metastasis between the two groups. ePLND patients had more cases of N3 disease and experienced increased grade 3–4 AEs compared to sPLND. Moreover, perioperative mortality was higher in the ePLND group, with 19 deaths (6.5%) within 90 days of radical cystectomy compared to nine deaths (2.4%) in the sPLND group. ePLND offered no improvement in DFS or OS compared to sPLND.

The conclusion of this trial was that sPLND should be favored in MBC patients.

In mUC, approximately 15–20% of patients have fibroblast growth factor receptor (FGFR) alterations. This is often associated with reduced T-cell infiltration, which may affect the tumor’s response to immune checkpoint inhibitors. Several FGFR inhibitors have been studied, and erdafitinib, a pan-FGFR inhibitor, has been approved by Health Canada and the FDA for the treatment of patients with platinum-refractory mUC with specific FGFR 2/3 alterations. A previous phase 2 trial reported an ORR of 40% with a PFS of 5.5 months and an OS of 13.8 months with erdafitinib in this patient group. The corresponding THOR phase 3 trial was presented at ASCO. It compared erdafitinib with second-line chemotherapy in patients with advanced or metastatic urothelial cancer and select FGFR 2/3 alterations, who had progressed following 1–2 lines of prior treatment (mostly chemotherapy and/or immunotherapy). The interim analysis at a median followup of 15.9 months, showed that erdafitinib significantly improved OS (12.1 months vs. 7.8 months) and reduced the risk of death by 36% compared to chemotherapy. Additionally, erdafitinib significantly improved median PFS (5.6 months vs. 2.7 months) and ORR (46% vs. 12%) compared to chemotherapy. Based on these positive results, the Independent Data Monitoring Committee (IDMC) recommended to stop the study early, unblind the trial, and allow patients on chemotherapy to cross over to erdafitinib. In terms of toxicity, erdafitinib showed a manageable and anticipated safety profile, with relatively low occurrences of grade 3–4 AEs; however, eye disorders were reported in 42% of patients, and 17% experienced central serous retinopathy, which requires careful monitoring and management.

First-line therapy for cisplatin-ineligible mUC patients remains an area of significant unmet need. Patients with FGFR alterations have shown reduced responses to checkpoint inhibition, but preclinical studies indicate that treatment with erdafitinib may lead to tumor infiltration with CD4+ and CD8+ T cells, providing the rationale to combine erdafitinib and an immune checkpoint inhibitor. The Norse phase 2 study explored the combination of erdafitinib (FGFR inhibitor) and cetrelimab (PD-1 inhibitor) to enhance efficacy, reverse resistance, address heterogeneity, and target the tumor microenvironment. Cisplatin- ineligible patients with FGFR 2/3 alterations who had received no prior treatment were randomized to receive erdafitinib alone or erdafitinib+cetrelimab. The combination showed a higher ORR of 54.5%...
The combination of erdafitinib and cetrelimab has clinically meaningful activity and is promising for cisplatin-ineligible mUC patients with FGFR 2/3 alterations.

of bringing new drugs to patients in Canada is critical to meet the unmet needs in gentialtary cancers.

REFERENCES


CONCLUSIONS

The latest research findings presented at ASCO 2023 showcase significant developments in the treatment of patients with kidney, prostate, and bladder cancers, highlighting the importance of personalized treatment approaches, biomarker identification, and careful patient selection. Combination therapies, particularly those involving immune checkpoint inhibitors, show promise in improving outcomes for specific patient subsets; however, further research is necessary to refine patient stratification, identify novel biomarkers, and explore treatment combinations for enhanced clinical outcomes. Additionally, expediting the process...


15. Siefker-Radtke AO, Powles T, Moreno V, et al. Erdafitinib (ERDA) vs. ERDA plus cetuximab (ERDA+CET) for patients (pts) with metastatic urothelial carcinoma (mUC) and fibroblast growth factor receptor alterations (FGFRs): Final results from the phase 2 Norse study. J Clin Oncol 2023;41:4504-4504. https://doi.org/10.1200/JCO.2023.41.16_suppl.4504


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