2022 American Society of Clinical Oncology (ASCO): Meeting highlights

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Introduction

The American Society of Clinical Oncology (ASCO) Annual Meeting, held in Chicago and online on June 3–7, 2022, featured presentations on the latest research in cancer care. This year's program featured over 200 sessions complementing the meeting's theme: *Advancing Equitable Cancer Care Through Innovation*. Following the meeting on June 8, 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. The entire webinar can be viewed on UROpedia Canada, and meeting abstracts can be viewed at the ASCO meeting library.

Prostate cancer

Dr. Nazanin Fallah-Rad presented four abstracts on prostate cancer. Intensification of androgen deprivation therapy (ADT) with an androgen receptor inhibitor (ARI) or chemotherapy is the current standard of care (SOC) for metastatic hormone-sensitive prostate cancer (mHSPC). CHART, a phase 3 trial, compared SHR3680, an ARI, and bicalutamide (Bica), a non-steroidal anti-androgen, in combination with ADT in patients with high-volume mHSPC. Patients were randomized to ADT with SHRS3680 or Bica. SHRS3680 significantly reduced the risk of radiographic progression and death. Although overall survival (OS) data were immature, there was a trend towards improved OS with SHRS3680. This agent was well-tolerated, with less than 1% of patients having to discontinue the drug and less than 6% having an adverse event leading to disruption. Therefore, SHR3680 with ADT appears to be superior to Bica.[1]

OS is the gold standard endpoint in randomized phase 3 trials but often requires a large sample size and long follow-ups. Therefore, there is equipoise for other options, including surrogate endpoints. A study by the STOPCAP M1 consortium evaluated the intermediate clinical endpoints (ICE) as potential surrogates for OS in men with mHSPC. In this study, the surrogate clinical endpoints were radiographic progression-free survival (rPFS), defined as time to progression by computed tomography (CT) or bone scan or death; or clinical progression-free survival (cPFS), defined as time to progression by CT or bone scan, death, treatment switch; or progressive symptoms. Analysis of nine randomized controlled trials (RCTs) concluded that rPFS and cPFS are closely correlated with OS and are therefore valid surrogate endpoints for OS.[2] Although this study had multiple notable limitations, it has the potential to influence clinical trial design.

Theranostic approaches rely on targeted delivery of treatment directly to cancer cells. Lu- prostate-specific membrane antigen (PSMA) is a radiolabelled, small molecule that binds to PSMA on the cell surface and emits beta radiation with a 1 mm path length, effectively targeting malignant cells with little effect on surrounding tissues. VISION, a phase 3 RCT, compared SOC alone and Lu-PSMA with SOC in metastatic castration-resistant prostate cancer (mCRPC) patients who received at least two androgen receptor pathway inhibitors (ARPIs) and 1–2 taxane regimens. Baseline gallium (^{68}Ga) gozetotide (^{68}Ga-PSMA-11) positron emission tomography (PET) imaging was evaluated for its prognostic value in men undergoing treatment with lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617). There was a statistically significant association between PSMA PET parameters and clinical outcomes in whole body and regional analysis, but the association was inconsistent. The mean standard uptake value (SUV_{mean}) was strongly associated with improved outcomes across all endpoints. The absence of PSMA-positive disease in the liver and bone was also associated with improved outcomes. Therefore, the data support the use of PSMA PET for identifying men with mCRPC who will most benefit from PSMA targeted treatment.[3] Another subgroup analysis looked at the effect of prior and concomitant therapies on treatment outcomes. The OS benefits associated with lutetium were

consistent across all prior treatment subgroups. The clinical efficacy of ^{177}Lu-PSMA-617 was observed regardless of prior treatment or SOC, suggesting that disease biology, rather than prior treatment, drives outcomes.[4]

Dr. Andrew Loblaw presented two potentially practice-changing abstracts. TheraP, an RCT, compared ^{177}Lu-PSMA-617 (LuPSMA) and cabazitaxel in mCRPC patients who progressed after docetaxel. Previous studies (VISION[5] and early outcomes of TheraP[6]) demonstrated OS and PFS benefits for lutetium, which was also better tolerated than cabazitaxel. Here, Lu-PSMA demonstrated fewer adverse events, higher response rates, and improved patient-reported outcomes; however, although restricted mean survival time (RMST) was greater with the Lu-PSMA than with cabazitaxel, there was no difference in OS.[7] Updated OS outcomes were reported for ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in mHSPC patients. Patients were stratified based on the volume of metastasis, use of docetaxel, performance status, bone therapies, or comorbidities, and randomized to ADT plus standard non-steroidal anti-androgens (NSAA) or enzalutamide until progression. The interim analysis demonstrated cPFS benefit with enzalutamide in high-volume disease patients regardless of docetaxel use. The updated analysis showed an OS advantage for the overall group, with a 30% reduction in death over time, which is both statistically significant and clinically meaningful. The OS advantage applied to patients taking docetaxel and those with low- and high-volume disease.[8]

A growing number of options will become available for mHSPC patients once approved by Health Canada and the provincial funding agencies. Therapies for patients with mHSPC depend on whether the patient is synchronous or metachronous (de novo or recurrent disease) and disease volume. Enzalutamide and apalutamide appear to provide overall benefits and PFS advantages to all groups. Abiraterone was shown to benefit patients with de novo disease but, at least in some provinces, selection criteria (LATTITUDE: two or more high-risk features) limit its use. Docetaxel requires patients to be chemo-fit and appears to benefit high-volume disease patients, regardless of whether they are synchronous or metachronous. PEACE and ARASENS study data showed that patients could benefit from triple therapy if they are candidates for chemotherapy, but this is mostly for de novo patients.[9] It is also important to consider radiotherapy for patients with de novo, low-volume disease, as it provides PFS and OS benefits for those patients.

Bladder cancer

Dr. Elie Kassouf and Dr. Mira Keyes presented abstracts related to bladder cancer. In the non-muscle-invasive bladder cancer (NMIBC) space, an extended followup of KEYNOTE-057 cohort A evaluated the use of pembrolizumab, an anti-PD-1 antibody, for patients with high-risk (HR) NMIBC unresponsive to bacillus Calmette-Guérin (BCG). Based on this trial, pembrolizumab was approved by Health Canada and the FDA due to its success in achieving a complete response (CR) rate of 41% at three months in patients with carcinoma in situ (CIS). The median duration of CR for responders was 16.2 months.[10]

The QUILT 3032 trial aimed to further improve outcomes with the IL-15RαFc super agonist, N-803, combined with BCG in BCG-unresponsive NMIBC. N-803 plus BCG achieved a CR rate of 71% in CIS patients, with a median CR duration of 26.6 months for responders.[11] For the second cohort, which consisted of high-grade papillary disease (Ta/T1 without CIS), the primary outcome was a median disease-free survival (DFS) of 23.6 months, with 57% DFS at 12 months and 48% at 24 months.

Two other trials were summarized in the BCG-unresponsive NMIBC setting. TRUCE-02, an open-label, single-arm, phase 2 study, evaluated systemic tislelizumab, a monoclonal anti-PD-1 antibody, combined with systemic nab-paclitaxel for the treatment of HR NMIBC. The primary endpoint, CR rate, was 55% at nine months.[12] The combined toxicity of two systemic drugs makes this combination unlikely to undergo further investigation in North America or Europe. Results of the CORE1 trial, however, have generated excitement in the NMIBC field. In this phase 2, single-arm study, the oncolytic virus CG0070 was administered intravesically in combination with systemic pembrolizumab in patients with NMIBC unresponsive to BCG. In this preliminary report, 22 of 24 patients (92%) had a CR, which is a remarkable early result compared to other trials in this space, but it will need to be confirmed as the trial continues to accrue.

In the context of adjuvant therapy for muscle-invasive urothelial carcinoma, the POUT trial was practice-changing, demonstrating improvements in DFS and metastasis-free survival for upper tract urothelial carcinoma (UTUC).[13] The value of adjuvant chemotherapy for muscle-invasive bladder cancer (MIBC) is less established, but there is emerging trial data for adjuvant use of immune checkpoint inhibitors (ICPi). Three phase 3 trials have been completed, including the Ambassador trial with pembrolizumab, for which results are still awaiting, IMvigor 010 with atezolizumab, and CheckMate 274 with nivolumab. IMvigor 010 failed to meet its primary endpoint and was a negative study; however, in a secondary analysis of a subset of the patients in IMvigor 010, circulating tumor (ct)DNA proved to be both a prognostic and a predictive biomarker.

Treatment with atezolizumab one year post-surgery yielded a DFS and OS benefit in patients who were ctDNA-positive post-surgery but not in patients who were ctDNA-negative. Patients who were ctDNA negative after surgery had a better prognosis than those who were ctDNA positive,

suggesting the prognostic value of this marker. CheckMate 274 previously demonstrated a DFS benefit with one year of nivolumab compared to placebo after radical surgery for MIBC or UTUC.[14] At ASCO 2022, additional exploratory analyses were reported from MIBC patients alone (excluding UTUC) since predefined subgroup analyses in the original report suggested a large effect size in MIBC patients. The DFS benefit was observed for MIBC patients across all subgroups, including patients with tumors that did not express PD-L1 by immunohistochemistry; however, the hazard ratio with respect to DFS was 0.46 for PD-L1+ and 0.70 for PD-L1- tumors, suggesting a greater impact in PD-L1+ patients. There was also an improvement in non-urothelial tract, recurrence-free survival, and distant metastasis-free survival, further supporting the use of this therapy, which has been approved for use in Canada. However, the best candidates for this treatment and whether PD-L1 status should be taken into consideration remains to be determined.[15]

Neoadjuvant therapy is typically used for MIBC. Data from the GETUG-AFU V05 VESPER trial supports the use of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine (dd-MVAC) as perioperative chemotherapy for patients with non-metastatic MIBC. Dd-MVAC treatment improved PFS and pathological complete remission compared to gemcitabine-cisplatin.[16]

The SAKK 076/17 phase 2 trial examined a "sandwich approach" using the ICPi durvalumab with chemotherapy pre-surgery and then continuing the ICPi post-surgery. Here, durvalumab was administered with gemcitabine and cisplatin for T2-T4, N0-1 disease. Event-free survival (EFS) at two years was 76%, and OS was 87%; however, there were some high-grade adverse events.[17]

The AURA trial cohort 2 examined the addition of avelumab alone or with paclitaxel-gemcitabine as a neoadjuvant in platinum-eligible and ineligible patients with non-metastatic MIBC. Avelumab alone resulted in a pathological (p)CR rate of 36% compared to 18% in the chemoimmunotherapy arm.[18] This raises the question of whether any efficacy is gained by adding immunotherapy to chemotherapy. The answer to this is awaiting ongoing phase 3 neoadjuvant trials.

Cell-free DNA (cfDNA) methylation was examined as a predictive biomarker for patients with MIBC in the SWOG S1314 trial. Plasma cfDNA was profiled, and differential methylation between pathological responders and non-responders was analyzed. Machine learning generated an algorithm predictive of treatment response, and pre-chemotherapy plasma cfDNA was used to develop a methylation-based response score (mR-score) predictive of pathological response. Combining the mR-score and circulating bladder DNA fraction successfully predicted pathological response outcomes in 79% of patients based on plasma collected before and after one cycle of chemotherapy. Therefore, cfDNA methylation may be used to predict treatment response in MIBC patients receiving neoadjuvant chemotherapy.[19]

In locally advanced and metastatic urothelial cancer (mUC), vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) continued to pave their way. The COSMIC-021 trial examined cabozantinib, a TKI with immunomodulatory properties, in combination with the PD-L1 inhibitor atezolizumab in various mUC disease subgroups (e.g., cisplatin-eligible, cisplatin-ineligible, prior ICPi). There was an overall clinical benefit across all cohorts, but the majority of patients had side effects, and more than 43% experienced grade ≥3 toxicities.[20] The ATLANTIS trial is an adaptive, multi-arm, phase 2 trial platform testing different switch maintenance therapies in patients with mUC who do not progress on first-line chemotherapy. Treatment arms include rucaparib (PARP inhibitor) for patients with a DNA damage repair gene alteration and enzalutamide for patients with androgen receptor pathway alterations. The results were presented at ASCO 2022 for a randomized comparison of cabozantinib vs. placebo in biomarker-negative patients. There was no PFS or OS advantage with cabozantinib and a high percentage of toxicities was observed in patients in the cabozantinib arm.[21]

Tislelizumab, in combination with gemcitabine and cisplatin as neoadjuvant therapy followed by radical cystectomy in MIBC patients, demonstrated promising anti-tumor activity with a high pCR rate (54.5%), pathogenic downstaging rate (77.3%), and good tolerance.[22]

Trials in progress in the bladder preservation space focused on trimodal therapy. A phase 2 trial is evaluating trimodal therapy plus durvalumab vs. trimodal therapy alone in node-positive disease (TanyN1-3M0) with clinical CR as a primary endpoint. Secondary endpoints are OS, metastases-free survival, and rates of salvage cystectomy.[23] Another ongoing trimodal therapy trial from Canada (CCTG BL13) is comparing adjuvant durvalumab after bladder preservation (chemotherapy and radiation therapy) with DFS as a primary endpoint.[24]

In the pathology space, a HER-2 scoring system was assessed to determine which patients may benefit from anti-HER2 antibody-drug conjugate therapy in urothelial carcinoma. The HER-2 test scoring system (modified from breast cancer) was able to determine which patients benefit from anti-HER2-ADC treatment and can therefore be used for this purpose.[25] Another study assessed whether artificial intelligence algorithms could be used to diagnose urothelial carcinoma based on urine cytology. Machines were trained to recognize urine cytology belonging to patients with and without tumors. The algorithm developed was able to accurately classify urine specimens as malignant or benign efficiently and automatically with an accuracy rate of 92%, specificity rate of 86%, and sensitivity rate of 98%.[26] Moreover, digital quantification of T-lymphocyte

infiltration in the tumor-associated stroma was predictive of OS in bladder cancer.[27]

Kidney cancer

Dr. Naveen Basappa presented updates on advanced renal cell carcinoma (RCC). In the first-line treatment space, both the KEYNOTE-426 and CLEAR studies demonstrated OS and PFS benefits in the intent to treat (ITT) population with pembrolizumab plus VEGF-TKI vs. sunitinib (Sun) for advanced clear-cell (cc) RCC. In KEYNOTE-426, a post-hoc exploratory analysis of subsequent therapy use and PFS2 (i.e., the time from randomization to disease progression on second-line of treatment or death from any cause, whichever comes first) was 40.1 months in the axitinib plus pembrolizumab group vs. 27.7 months in the Sun group (hazard ratio [HR] 0.63, confidence interval [CI] 0.53–0.75).[28] Similarly, in an exploratory analysis of the CLEAR study, PFS2 was longer in the lenvatinib plus pembrolizumab arm vs. Sun (PFS2 not reached vs. 28.7 months, HR 0.50, CI 0.39–0.65, $p<0.0001$).[29] In both analyses, the benefits were seen across International mRCC Database Consortium (IMDC) risk groups. Together, these studies suggest that combining a VEGF-TKI with pembrolizumab is a more effective first-line option than Sun for advanced RCC patients.

The association between depth of response (DepOR) and clinical outcomes in patients with previously untreated advanced RCC was examined by CheckMate 9ER. More patients on nivolumab plus cabozantinib achieved deeper responses (≥60% tumor reduction) and had a lower progressive disease rate (5% vs. 15%) than those on Sun. Regardless of treatment, deeper responses were associated with better outcomes. DepOR may be a useful early indicator of durable efficacy and improved prognosis among patients treated with nivolumab plus cabozantinib.[30]

Immunotherapy and VEGF-TKI combination therapies are now well-established for the management of advanced RCC, and several effective options are available. New and emerging therapeutic strategies were presented at ASCO 2022. For example, administration of belzutifan, a HIF-2α inhibitor, was examined in a phase 1 study (LITESPARK-001; MK-6482-001) for advanced solid tumors, including a cohort of patients with ccRCC. Belzutifan was relatively safe, but a high percentage of patients experienced anemia and some experienced hypoxia. At the three-year followup, the overall response rate (ORR) was 25%, with a disease control rate of 80%. Patients who received both prior immunotherapy (IO) and a VEGF-TKI or directed therapy had a response rate of 21%, with a disease control rate of 74%. In patients who received either an IO or a VEGF-TKI (but not both), the response rate was 38%, and the disease control rate was 94%. Median PFS was 14.5 months in all patients.[31] This data is very promising and justifies further evaluation of this drug. Indeed, there are now two phase 3 studies evaluating belzutifan vs. everolimus, and belzutifan plus lenvatinib vs. cabozantinib.

Clostridium butyricum MIYAIRI 588 (CBM 588) is a live biotherapeutic product (probiotic) that produces butyrate and other short-chain fatty acids and is believed to have immunomodulatory activity. One study characterized the microbial resistome in metastatic (m)RCC patients treated with CBM588 and investigated the interplay between antibiotic use and ICPi activity. Patients who received CBM 588 in combination with immunotherapy and antibiotics did better than those who did not. CBM588 decreased antibiotic resistance genes associated with multiple commonly used classes of antibiotics, facilitating the ability of antibiotics to clear resistant bacteria. CBM588 enhanced the efficacy of ICPis in patients receiving antibiotics.[32]

Overexpression of the receptor tyrosine kinase AXL strongly correlates with ccRCC patient prognosis and survival. Batiraxcept is a recombinant fusion protein that binds GAS6, thus potently and specifically inhibiting AXL, thereby reducing invasion and migration of human cancers. A phase 1b/2 study examined the use of batiraxcept (AVB-S6-500) in combination with cabozantinib in patients with advanced or metastatic ccRCC who received front-line treatment. Batiraxcept suppressed serum GAS6 to below the level of quantitation, showing a clear pharmacokinetic/pharmacodynamic relationship. Anti-tumor activity was encouraging, with most patients showing tumor decrease relative to baseline. The sAXL/GAS6 biomarker enriches the response rate (ORR of 67% vs. 50%) and increases PFS (91% vs. 73%) and DOR (80%) at seven months.[33]

Dr. Anand Swaminath presented some key findings from radiation studies performed in other cancers and discussed how they could be applied to patients within the RCC space. A phase 2 breast cancer trial (NRG BR002) evaluated radiation therapy in oligometastatic breast cancer patients. Patients were treated with either stereotactic ablative radiotherapy (SABR) or surgery in combination with systemic therapy. Most patients who received ablative radiotherapy showed no PFS benefit;[34] however, breast cancer and RCC are different diseases, and data from one cannot be easily extrapolated to the other.

The most commonly cited study for oligometastatic disease, as it pertains to ablative radiotherapy, is the SABR-COMET trial,[35] which showed a significant PFS benefit with SABR in patients with various metastatic cancers; however, that was a multihistology trial, and only a few patients in that study had RCC. Therefore, a randomized study should be conducted to better evaluate the benefit of radiation in patients with RCC. A prospective study examined the concept of sequential radiotherapy in lieu of systemic therapy and determined that PFS and systemic therapy-free survival were high with SABR.[36] Patients had multiple courses of

radiation during their cancer trajectory before they needed systemic treatment, and some did not require any systemic treatment after subsequent lines of SABR.

There are multiple first-line therapy options in RCC, including active surveillance for low-volume, indolent disease with favorable OS. Patient selection in RCC is key; some patients may not need systemic therapy with SABR, but there are no randomized trials comparing systemic therapy alone (or active surveillance) vs. a metastasis-directed therapy approach. Micrometastatic disease appears to drive failure rates, as opposed to controlled local disease. Indeed, in the NRG BR002 trial, out-of-field progression rates were similar to COMET-SABR, but PFS was not driven by local disease control. Therefore, there is a need for biomarkers to help identify patients that would benefit most and those most at risk of failure.

A transcriptomic profiling study identified genomic markers associated with SABR benefits in oligoprogressive mRCC. The duration of treatment prior (DOT-P) and subsequent (DOT-S) to SABR was evaluated. SABR allowed the extension of systemic therapy by a median of 19.7 months (DOT-S). PBRM1, VHL, and SETD2 were identified as genomic markers predictive of a better response to SABR; however, whether these genomic expression changes meaningfully correlate with clinical outcomes remains to be determined.[37] Transcriptomic analysis found an enrichment of reactive oxygen species (ROS) pathways in patients who had a poor response to radiation. ROS is associated with a poor prognosis and poor response to radiation in multiple cancers. Therefore, there is a need for well-designed, randomized trials testing SABR in oligometastatic RCC. Trials using novel imaging techniques and biomarkers will help better evaluate the burden of mRCC and identify patients who may benefit from this treatment approach.

Conclusions

The latest cancer research findings were on display at this year's ASCO, highlighting advances in cancer diagnostics, treatment, and research.

In prostate cancer, novel ARIs and theranostic approaches, such as Lu-PSMA, continue to pave the way toward more targeted therapeutics. As evidence on the efficacy of triple therapy for mHSPC emerges, we are faced with challenges in determining which patients are most suitable for this approach. With the completion of more RCTs for patients with mHSPC, intermediate clinical endpoints are becoming more robust and promise to facilitate and expedite future RCT design by acting as surrogate measures of the gold standard endpoint, OS.

In bladder cancer, immunotherapy and targeted therapies, including VEGF-TKIs, continue to reshape the disease landscape in the neoadjuvant, adjuvant, and metastatic spaces. Novel biomarkers, such as cfDNA methylation, continue to emerge as both prognostic and predictive of treatment response. The treatment of BCG-unresponsive NMIBC is evolving rapidly, with multiple clinical trials demonstrating the efficacy of novel drugs alone and in combination.

Immunotherapy and VEGF-TKIs are well-established, in various combinations, in the management of mRCC. The depth of early response to these treatments is associated with better outcomes. The efficacy of radiotherapy, although promising, requires further evaluation. Therefore, there is a strong impetus towards combining multiple precise, targeted biomarker-based therapies, as those will likely continue to extend both the health and lifespan of patients.

Competing interests: Dr. Black has been a consultant for AbbVie, Astellas, AstraZeneca, BMS, Bayer, EMD Serono, Ferring, Janssen, MDxHealth, Merck, Minogue, Nonagen, Nanology, Protara, QED, Roche, Sanofi, Sesen, STIMIT, Therelase, UroGen, and Verity; a speaker for Bayer, BioSyent, Pfizer, Sanofi, and TerSera; has participated in clinical trial supported by Roche; and owns a patent for Veracyte. Dr. Fallah-Rad has received honoraria from Astellas, Bayer, Ipsen, Janssen, Johnson and Johnson, and Nektar Therapeutics. Dr. Loblaw has received grants/research support from TerSera and Tolmar; honoraria/travel expenses from AbbVie, Astellas, Bayer, Janssen, Knight, Sanofi, and TerSera; and has been an advisory board member/consultant for AbbVie, Astellas, Bayer, Janssen, Sanofi, and TerSera. Dr. Kassouf has been a speaker for AstraZeneca, BMS, GSK, Merck, Novartis, Pfizer, and Sanofi; and a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, BMS, GSK, Janssen, Kite, Merck, Novartis, Pfizer, and Sanofi. Dr. Basappa received a travel grant for ASCO 2022 from Eisai; has received honoraria from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, Merck, Pfizer, Roche, and Seagen. Dr. Swaminath has been an advisory board member for AstraZeneca; and is a speaker for AstraZeneca, BMS, and Eisai.

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