CONGRESS COVERAGE: ESMO 2020 HIGHLIGHTS – GU MALIGNANCIES

September 2020
On September 23, 2020, following the European Society for Medical Oncology (ESMO) Virtual Congress, Aptitude Health brought together a group of scientists and clinical investigators with expertise in genitourinary (GU) malignancies to attend the Emerging Paradigms in Care Series (EPICS) Congress Coverage meeting.

The goal of the expert panel was to critique and debate new evidence in GU cancers and gain strategic insight into the most impactful abstracts from the ESMO meeting with respect to shaping current research directions and/or changing the scope of practical clinical care.
FACULTY EXPERTS

Chair
Daniel Petrylak, MD

Karim Fizazi, MD, PhD
Leonard Gomella, MD
David Nanus, MD
Oliver Sartor, MD
Cora Sternberg, MD
Scott Tagawa, MD
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Prostate Cancer – Cytotoxic, Hormonal, and Immune-Based Therapies

OLIVER SARTOR, MD
Abstract 611O – Abiraterone acetate plus prednisolone for hormone-naïve prostate cancer (PCa):

> A previous analysis of the STAMPEDE trial, in which 1917 men with M0/M1 hormone-naïve PC were randomized to androgen deprivation therapy (ADT) with or without abiraterone-prednisolone, showed a significant improvement in overall survival (OS) with abiraterone (hazard ratio [HR] = 0.63; \( P < .001 \)). The HR was 0.75 in patients with nonmetastatic disease and 0.61 in those with metastatic disease (James ND, et al. *N Engl J Med*. 2017;377(4):338-351).

The current presentation reported on long-term outcomes in the M1 patient population with 6 years of follow-up:

- The OS advantage has been maintained, with a median OS of 6.6 years in the abiraterone arm compared with 3.8 years in the ADT-alone arm (HR = 0.60; \( P = .00000000003 \)).
- The relative effect of abiraterone was similar in patients with low-burden disease (HR = 0.55; 95% CI: 0.41–0.76) and high-burden disease (HR = 0.54; 95% CI: 0.43–0.69).
- Toxicities at 4 years postrandomization were similar, with 16% of patients in each arm reporting grade 3 or higher adverse events (AEs).
- The addition of abiraterone did not appear to have a negative impact on quality of life (QOL) compared with ADT alone.
Abstract 609O – Results from a phase 1 study of AMG 160, a half-life extended (HLE), PSMA-targeted, bispecific T-cell engager (BiTE®) immune therapy for metastatic castration-resistant prostate cancer (mCRPC). Presenter: Ben Tran

AMG 160 is a BiTE targeting CD3 and prostate-specific membrane antigen (PSMA)

32 patients with mCRPC refractory to prior novel hormonal therapy and 1–2 taxane regimens, with evidence of progressive disease, received treatment with AMG 160

PSA reductions occurred in 15/24 (63%) evaluable patients; reductions >50% occurred in 6/10 (60%) patients at dose levels 5 and 6

Overall, 6/22 (27%) patients had a confirmed PSA responses, all at dose levels ≥3

Cytokine release syndrome (CRS; all grades) occurred in 84% of patients, with 31% of patients experiencing a grade 3 event

Other grade 3 events included hypotension (12.5%) and fatigue (9%); there were no grade 4 AEs
Abstract 615MO – Phase 1b/2 study of VERU-111, novel, oral tubulin inhibitor, in men with metastatic castration resistant prostate cancer (mCRPC) who failed an androgen blocking agent.

Presenter: Mark Markowski

VERU-111 is an oral, alpha/beta tubulin-targeted inhibitor of microtubule polymerization with no affinity for multidrug resistance proteins. 30 men with taxane-naive mCRPC have been enrolled, and antitumor activity was assessed in 8 men treated for ≥4 continuous 21-day cycles.

Diarrhea was the dose-limiting toxicity, but no grade 3 diarrhea was observed at doses <72 mg per day. The most common AEs were mild to moderate nausea, vomiting, diarrhea, and fatigue, with no observed neurotoxicity or neutropenia. Five patients (63%) had PSA declines compared with baseline (two ≥50%). Objective tumor responses were seen in 2 men (soft tissue and bone), and 5 of 8 men (63%) had stable disease (SD). Objective responses and PSA declines lasted >12 weeks.
Abstract 616MO – Efficacy of BN-brachyury (BNVax) + Bintrafusp alfa (BA) + N-803 in Castration-Resistant Prostate Cancer (CRPC): Results from a Preliminary Analysis of the Quick Efficacy Seeking Trial (QuEST). Presenter: Jason M. Redman

- BNVax is a therapeutic poxviral vaccine targeting brachyury, a transcription factor involved in invasion and metastasis.
- BA is a bifunctional fusion protein: an anti-programmed cell death protein 1 ligand 1 (PD-L1) monoclonal antibody fused to the transforming growth factor (TGF)-βRII receptor extracellular domain (a TGF-β trap).
- N-803 is an interleukin-15 superagonist complex.

- A total of 22 patients with asymptomatic/minimally symptomatic CRPC have been treated with either BNVax + BA (N = 13) or BNVax + BA + N-803.
- The PSA response rate was 44% with the triplet therapy, and 2 patients had a confirmed partial response (PR).
- There were no dose-limiting toxicities or grade >3 treatment-related AEs (TRAEs).
- Grade 3 TRAEs were 1 pancreatitis, 1 secondary adrenal insufficiency, and 1 hyperglycemia due to new-onset diabetes mellitus.
Abstract 617MO – Repurposing Metformin as anticancer drug: Preliminary results of randomized controlled trial in advanced prostate cancer (MANSMED). Presenter: Reham Alghandour

124 men with high-risk localized or metastatic hormone-sensitive PC were randomized to receive ADT + bicalutamide ± metformin (850 mg twice daily).

With a median follow-up of 18 months, there were 12 deaths in the metformin arm vs 17 deaths in the control arm ($P = .2$).

Median time to castration resistance was longer in the metformin arm (29 mo) compared with the control arm (20 mo; $P = .01$).
The long-term OS data from STAMPEDE in both the higher- and lower-risk populations of patients with metastatic hormone-naive PC treated with abiraterone + ADT are very reassuring, particularly in light of the very similar results in LATITUDE. Although there are some concerns regarding long-term side effects, particularly cardiotoxicity, these appear to be offset by the magnitude of the OS benefit. Several studies have now shown an increase in cardiotoxicity associated with androgen receptor inhibitors. Long-term toxicities need to be better tracked to capture real causes of death (eg, cardiovascular deaths may be related to long-term toxicity). The rates of cardiotoxicity associated with androgen signaling inhibitors may be higher in the community. Clinical trials of these agents typically exclude patients with a history of cardiac disease, while community practitioners may not be as strict. Further, urologists may not be as aware as medical oncologists of these potential side effects with oral androgen receptor blockers, and may not monitor these patients as closely. Experts recommend that urologists who are prescribing these agents partner with primary care physicians or internists to ensure careful monitoring. It would also be helpful for experts to develop guidance on how to best manage a patient with metastatic castration-sensitive PC (CSPC) with a history of cardiac disease or lower left ventricular ejection fraction. There are additional changes associated with long-term androgen deprivation, such as increased adiposity, decreased muscle mass, problems with glucose tolerance, and osteopenia/osteoporosis. Physicians need to be educated about these side effects, and how to help patients implement lifestyle modifications to mitigate them.
There are now a number of options that have been shown to improve OS in patients with CSPC compared with ADT alone, and this may create confusion, particularly for community oncologists. One key outstanding question is the optimal regimen in this setting—should we use ADT + docetaxel + antiandrogen, or ADT + docetaxel, or ADT + antiandrogen? Ongoing trials such as ARASENS and ENZAMET are addressing this question. The number of metastatic lesions does not appear to correlate with benefit from these therapies and should not be used to determine which systemic approach to recommend.

Novel agents—Experts speculated that VERU-111, the novel oral antitubulin agent, is likely to make it to the clinic if it is shown to be efficacious, but current data are still very preliminary. It will be important to determine the degree of cross-resistance of this agent with other taxanes, and whether it has activity in taxane-resistant disease. The data with the triplet BNVax + BA + N-803 are considered provocative, especially since this represents a novel mechanism of action, but experts think it will be challenging to develop this combination as a pharmaceutical-grade therapy.
> Novel agents (contd)

- AMG 160, the PSMA-targeted BiTE, is considered promising, particularly in light of the activity seen in patients treated previously with other PSMA-targeted drugs.

- The high rate of CRS is a concern, and many patients treated on the trial required hospitalization. Efforts are being made to modify treatment in order to lessen toxicities, but it is unclear whether measures such as coadministration of steroids will impact activity.

- Several experts noted that their colleagues in hematology/transplant are learning how to effectively manage CRS, and the use of BiTEs and chimeric antigen receptor T-cell therapies may require a multidisciplinary team approach, at least initially.

- There is also a need to determine the best method for patient selection for PSMA-directed therapies; possibilities include the use of PSMA-positron emission tomography (PET), and/or exclusion of patients with liver metastases.

- Experts would like to see data showing whether response to AMG 160 correlated with PSMA-PET avidity.

- A study is planned to evaluate AMG 160 in combination with pembrolizumab. Amgen is also developing another BITE targeting prostate stem cell antigen.

The data with metformin are also considered provocative, but not yet ready for prime-time use; data from larger trials, such as the ongoing STAMPEDE study, are needed. One important unanswered question is whether metformin has a differential effect in patients with preexisting diabetes and/or high insulin-like growth factor levels.
Targeting Intracellular Signaling and DNA Damage Repair Pathways in Metastatic Prostate Cancer

KARIM FIZAZI, MD, PHD
Abstract 610O – Final overall survival (OS) analysis of PROfound: olaparib vs physician’s choice of enzalutamide or abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations. Presenter: Johann de Bono.

Previous analysis of the PROfound trial showed significantly prolonged radiographic progression-free survival (rPFS) with olaparib vs physician’s choice of enzalutamide or abiraterone (control arm) in patients with mCRPC with progression on prior therapy and alterations in BRCA1, BRCA2, or ATM (Cohort A), and in the overall population (Cohorts A + B) with alterations in any of 15 prespecified genes with a direct or indirect role in HRR (de Bono J, et al. *N Engl J Med*. 2020;382(22):2091-2102).

In the current final OS analysis:

- Median OS was significantly improved in Cohort A (19.1 mo vs 14.7 mo; HR = 0.69; \( P = .0175 \)); the crossover rate from the control arm was 67%, and statistical analysis suggested a HR of 0.42 after adjusting for crossover.
- In Cohort B, there was no significant difference in OS (median 14.1 mo vs 11.5 mo; HR = 0.96; 95% CI: 0.63-1.49), even after adjusting for crossover (HR = 0.83; 95% CI: 0.11-5.98).
- Exploratory gene-level analysis suggested that patients with BRCA1/2 mutations derived the greatest OS benefit with olaparib, while patients with ATM mutations did not appear to benefit.

- Anemia, nausea, and diarrhea were more frequent in the olaparib arm, but fatigue was similar between arms.
Abstract 614MO – Cabazitaxel (CBZ) activity in men with metastatic castration resistant prostate cancer (mCRPC) with and without DNA damage repair (DDR) defects. Presenter: Mihaela Aldea

This retrospective analysis included 95 men with and 95 men without alterations in DDR-related genes (somatic or germline) treated with cabazitaxel for mCRPC.

- Men with DDR-positive cancers were slightly younger and had more often previously received a poly(ADP-ribose) polymerase (PARP) inhibitor or carboplatin.

- The PSA decline achieved with cabazitaxel was similar in DDR-positive (32%) and DDR-negative (36%) patients (P = .64). Similarly, there was no apparent difference in the rate of PSA decline in patients with BRCA1/2 mutations vs non-BRCA-altered vs DDR-negative status (27% vs 35% vs 36%; P = .62).

- rPFS was also similar between DDR-positive and -negative patients (5.33 mo vs 5.75 mo).

- Median OS favored the DDR-positive patients (15.4 mo vs 11.5 mo), but this could be the result of subsequent post-cabazitaxel treatments with PARP inhibitors or platinums.

- In DDR-positive patients, the frequency of PSA declines ≥50% with cabazitaxel was lower in those previously treated with a PARP inhibitor (17%) compared with those who never received a PARP inhibitor (30%) or who subsequently used a PARP inhibitor (44%), but the absolute number of patients in this analysis was small.
Abstract LBA4 – IPATential150: Phase III study of ipatasertib (ipat) plus abiraterone (abi) vs placebo (pbo) plus

In this trial, 1101 patients with mCRPC were randomized to treatment with abiraterone ± ipatasertib.

- Patients were stratified according to phosphatase and tensin homolog (PTEN) status (PTEN loss was defined as a minimum of 50% of specimen’s tumor area with no detectable PTEN staining by Ventana immunohistochemistry [IHC] assay using the SP218 antibody).

- In patients with PTEN loss defined by IHC, rPFS was significantly longer in the ipatasertib arm (18.5 mo vs 16.5 mo; HR = 0.77; \( P = .0335 \)). However, although there was a trend favoring ipatasertib in the intent-to-treat (ITT) population, the difference did not meet statistical significance at \( \alpha = 0.01 \) level (19.2 mo vs 16.6 mo; HR = 0.84; \( P = .0431 \)).

- In patients with PTEN loss defined by next-generation sequencing (NGS), there appeared to be a greater magnitude of rPFS benefit with ipatasertib (19.1 mo vs 14.2 mo; HR = 0.65; \( P = .0206 \)).

- Time to PSA progression favored ipatasertib in both the PTEN-loss population (HR = 0.69; \( P = .0013 \)) and in the ITT population (HR = 0.73; \( P < .0001 \)).

- No difference in OS was detected in either population.

- Treatment duration was shorter with ipatasertib compared with placebo (11.1 mo vs 14.0 mo), related to the higher rate of treatment discontinuations (21% vs 5%).

- Grade 3/4 AEs that occurred more frequently with ipatasertib included rash, diarrhea, hyperglycemia, aminotransferase increases, and dehydration.
TARGETING INTRACELLULAR SIGNALING AND DNA DAMAGE REPAIR PATHWAYS IN METASTATIC PROSTATE CANCER: DISCUSSION (1/3)

> The OS benefit seen in the PROfound trial with olaparib in HRR-altered mCRPC is viewed as very impressive, particularly considering these patients typically have very aggressive disease. The safety profile is perceived to be acceptable. Experts consider this to be level 1 evidence and believe this should become a standard of care for BRCA1/2 mutated mCRPC.

The crossover statistical analysis suggests that using a PARP inhibitor earlier in the course of treatment may produce greater benefit.

The subgroup analyses suggest that patients with BRCA1/2 mutations derive benefit from the PARP inhibitor, while those with ATM mutations do not.

• Several experts indicated they would choose a taxane over olaparib for patients with an ATM mutation.

• The subset of patients with rare mutations in Cohort B is too small to draw any conclusions. While it appeared this subset did not derive benefit from olaparib, it is impossible to determine whether any individual genes were predictive of benefit. In particular, there have been suggestions in other trials that PALB2 alterations may also predict benefit from PARP inhibitors, and this warrants further study.

• Several experts noted that the control of abiraterone or enzalutamide in patients who progressed on the alternate agent may not have been optimal, and that a more active control, such as a taxane or a platinum, might have been more appropriate.
The data with ipatasertib + abiraterone in the IPATential150 trial are considered positive, but some experts noted that the magnitude of benefit is smaller than expected in the group with PTEN loss by IHC. For this reason, they suggested this combination may not be ready for prime time use in the clinic. Longer follow-up and OS results are needed, particularly in light of the rate of treatment discontinuations due to AEs in the ipatasertib arm.

The NGS data are considered more impressive than the IHC data, and questions were raised about the potential subjectivity of IHC scoring, as well as the cutoff of 50% used in the trial. NGS may be a more accurate and consistent method for determining PTEN status. However, it was noted that the NGS analysis represents a small subgroup within a subgroup, and it is not known whether there may have been imbalances in terms of demographics or stratification factors.

Experts suggested that a prospective study using NGS assessment of PTEN loss as the standard for patient selection would be helpful and might produce more convincing results.
TARGETING INTRACELLULAR SIGNALING AND DNA DAMAGE REPAIR PATHWAYS IN METASTATIC PROSTATE CANCER: DISCUSSION (3/3)

Experts found reassuring the retrospective data suggesting that cabazitaxel is effective regardless of DDR status. This makes cabazitaxel an attractive option for patients when DDR status cannot be assessed, or for patients with \( \text{BRCA1/2} \)-mutated mCRPC who do not have access to olaparib.

Carboplatin, or a combination of carboplatin + cabazitaxel, are also considered options for this latter group of patients. There is some concern that the efficacy of cabazitaxel may be lower in patients previously treated with PARP inhibitors, but it was noted that this subset included only 18 patients and is thus too small to draw any conclusions. However, this phenomenon should be investigated further in larger patient populations.

Additional randomized trials are needed to determine the optimal treatment for patients with DDR-positive mCRPC.
Renal Cell Carcinoma

DAVID NANUS, MD
Abstract 696O – Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma:

- 651 patients with advanced/metastatic clear cell renal cell carcinoma (ccRCC) were randomized to first-line treatment with either nivolumab + cabozantinib or sunitinib.

- 22.6% favorable risk, 57.6% intermediate risk, 19.7% poor risk; 24.9% PD-L1 positive.

- Median PFS was significantly longer in the nivolumab + cabozantinib arm (16.6 mo vs 8.3 mo; HR = 0.51; P < .0001).

- Median OS was also significantly improved with combination immunotherapy (IO)-tyrosine kinase inhibitor (TKI) therapy (median not reached in either arm; HR = 0.60; P = .0010).

- Subset analysis suggested greater benefit with combination therapy in patients with intermediate or poor-risk disease.

- AEs that were higher in the nivolumab + cabozantinib arm included diarrhea and increased liver enzymes.

- Nineteen percent of patients treated with the IO-TKI combination required corticosteroids to manage immune-related AEs (all grades).
> Abstract 702O – Cabozantinib (C) in combination with atezolizumab (A) as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): results from the COSMIC-021 study. Presenter: Sumanta Pal

- A total of 70 patients with advanced/metastatic ccRCC received first-line therapy with atezolizumab + cabozantinib (either 40 mg or 60 mg once daily)

- Objective response rates (ORRs) were 53% and 58% in the 2 cohorts, with disease control rates of 94% and 92%, respectively

- Median PFS was 19.5 months in the 40 mg cohort and 15.1 months in the 60 mg cohort

- Baseline PD-L1–positive status and higher levels of CD8-positive T cells were associated with greater tumor lesion reduction and overall response
Abstract LBA25 – Results from the phase 2 BIOmarker driven trial with Nivolumab (N) and Ipilimumab or VEGFR tyrosine Kinase inhibitor (TKI) in naïve metastatic Kidney cancer (m-ccRCC) patients (pts): the BIONIKK trial. Presenter: Yann Vano

- Molecular profiling was performed using a 35-gene signature to classify patients into 4 categories: immune high, immune low, proangiogenic, and normal like

- Patients in the immune high (n = 31) and low (n = 62) subgroups were randomized to receive either nivolumab alone or nivolumab + ipilimumab

- Patients in the proangiogenic (n = 55) and normal like (n = 6) subgroups were randomized to receive nivolumab + ipilimumab or TKI monotherapy

- The primary endpoint was ORR

- In the immune low cohort, the ORR was higher with nivolumab + ipilimumab compared with nivolumab alone (39% vs 21%)

- In the immune high cohort, the ORR was similar between the combination arm and nivolumab monotherapy (53% vs 50%)

- In the proangiogenic group, the ORR was similar between TKI monotherapy compared with the IO doublet (54% vs 48%)

- In the normal like group, there was 1 PR to IO combination therapy and no responses to TKI therapy
Abstract 700O – Kidney ccRCC Immune Classification (KIC) enhances the predictive value of T

The current study reported on the results of a translational analysis of patients enrolled in the NIVOREN GETUG-AFU 26 trial, which evaluated nivolumab in patients with metastatic ccRCC in a real-world setting. Angio and Teff gene signatures were associated with outcomes in patients treated with nivolumab; an angio-low/Teff-high signature was associated with the highest ORR (47%) and longest PFS (10.1 mo), while an angio-low/Teff-low signature was associated with the lowest ORR (5%) and shortest PFS (2.6 mo).

The Kidney ccRCC Immune Classification (KIC) gene profile characterizes tumors into 5 subgroups based on stromal and immune components. A KIC immune-high/stromal-low signature was associated with the highest ORR with nivolumab, with ORRs of 48% and 36% in the discovery and validation cohorts, respectively.
Abstract 701O – Assessment of circulating cell-free tumor DNA (ctDNA) in 847 patients (pts) with metastatic renal cell carcinoma (mRCC) and concordance with tissue-based testing. Presenter: Zeynep B. Zengin

This retrospective analysis included 847 patients with mRCC who had undergone ctDNA mutation testing using the Guardant360 gene panel; mutational analysis was also performed on 47 patients, using either whole-exome sequencing (Ashion Analytics) or targeted NGS (Foundation Medicine).

The most frequently altered genes in ctDNA were TP53 (37%), VHL (22%), and EGFR (6%). When restricted to only the genes included in the ctDNA assay, a total of 154 genomic alterations were found across both assays. Of these, 39% of genomic alterations were exclusive to ctDNA, 44% were exclusive to tissue, and 17% were found on both platforms.

Concordance between assays was higher when the time between obtaining samples from tumor and plasma was ≤6 months compared with >6 months.

- 61 patients with VHL disease-associated mRCC received treatment with MK-6482, and 56 patients remain on treatment
- The ORR was 36%, and an additional 62% of patients experienced disease stabilization
- Median duration of response has not been reached (range, 11.9–62.3 wk)
- The PFS rate at 52 weeks was 98%
- Anemia was the most common AE (84% grade 1/2, 7% grade 3). There were no grade 4/5 AEs
- Clinical activity was also observed in other non-RCC lesions
The combination of cabozantinib + nivolumab is likely to gain regulatory approval as a first-line therapy for mRCC on the basis of results from the CheckMate 9ER trial.

With multiple effective regimens available, experts expect to tailor first-line treatment to individual patients on the basis of toxicity profiles and comorbidities, need for rapid response, and independent data monitoring committee (IDMC) risk category.

Experts favor an IO-TKI combination for patients in need of a rapid response. However, an IO-IO combination is perceived to produce a higher rate of complete responses (CR), with longer OS; this approach may be preferred.
Atezolizumab in combination with cabozantinib is also perceived to have strong antitumor activity in the first-line setting for metastatic ccRCC, and experts predict this regimen will also eventually gain approval, pending results of the CONTACT-03 trial. It was noted that the ORRs in the 2 cohorts are very similar to those seen with cabozantinib + nivolumab, and similar between the 2 dose levels of cabozantinib, which may be helpful for tolerability. Experts noted that the combination of atezolizumab + cabozantinib has also shown impressive activity in mCRPC, with a substantially higher response rate than that seen with either agent alone. This combination also appears to be much more active than atezolizumab + bevacizumab, highlighting the importance of determining the best partner. The results in both metastatic ccRCC and mCRPC also suggest cabozantinib may have an immunomodulatory effect. The study design of CONTACT-03 is considered very interesting, since the trial will evaluate this combination in patients who have progressed on a prior immune checkpoint inhibitor (CPI). This could provide an important second-line option if cabozantinib is shown to resensitize tumors to IO. More research into mechanisms of resistance to immune CPI therapy is needed. Experts believe that for VHL-related ccRCC, the data with MK-6482 are strong enough to support approval, and no phase III will be necessary. It is unclear whether this agent will move forward in non-VHL-related RCC.
RENAL CELL CARCINOMA: DISCUSSION (3/3)

> Molecular biomarkers, including transcriptomics and IHC, are showing promise for identifying patients for IO and/or TKI therapy. Although these assays are not yet ready for clinical use, experts predict that eventually a biomarker assay will be developed and validated for use in the clinic for making therapeutic decisions for individual patients.

The BIONIKK trial is considered a well-done academic study that demonstrates the potential for using biomarkers to identify a subset of patients who respond particularly well to single-agent immune CPI therapy. However, patient numbers were very small, and thus this study is considered hypothesis generating, rather than practice changing. In addition, experts would like to have seen the randomization include an IO-TKI combination.

A larger randomized trial, possibly of just one of the molecular subgroups, such as the immune signature-high or the proangiogenic signature, would be interesting.

ctDNA testing and tumor testing are considered complementary methods for assessing biomarkers—while ctDNA assays may not be as sensitive, tumor biopsies may miss some intratumoral heterogeneity as well as genetic changes over time, and older tissue blocks may undergo some sample degradation. Both strategies are considered valuable and necessary. Experts predict ctDNA will increasingly be used for monitoring patients and selecting therapies, but these assays will need to be optimized for each particular tumor type.
Bladder Cancer – Immunotherapies

CORA STERNBERG, MD
Abstract 697O – A phase 3, randomized, open-label study of first-line durvalumab (D) with or without tremelimumab (T) vs standard of care chemotherapy in patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE). Presenter: Thomas Powles

- A total of 1032 patients with previously untreated, unresectable, stage IV urothelial carcinoma (UC) were randomized to receive either durvalumab, durvalumab + tremelimumab, or gemcitabine + cisplatin or carboplatin.

- The trial failed to show a statistically significant OS advantage with regard to either of the co-primary endpoints.

- Durvalumab monotherapy vs chemotherapy in the PD-L1–high population (median OS: 14.4 mo vs 12.1 mo; HR = 0.89; P = .3039)

- Durvalumab + tremelimumab vs chemotherapy in the ITT population (median OS: 15.1 mo vs 12.1 mo; HR = 0.85; P = .0751)

- There did appear to be a benefit with durvalumab + tremelimumab compared with chemotherapy in the PD-L1–high population, a secondary endpoint (median OS: 17.9 mo vs 12.1 mo; HR = 0.74; 95% CI: 0.59 – 0.93).

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
Abstract LBA23 – Pembrolizumab (P) combined with chemotherapy (C) vs C alone as first-line (1L) therapy for advanced urothelial carcinoma (UC): KEYNOTE-361. Presenter: Ajjai Alva

A total of 1010 patients with unresectable/mUC were randomized to first-line therapy with either platinum-based chemotherapy ± pembrolizumab or pembrolizumab alone.

Median PFS favored chemotherapy + pembrolizumab compared with chemotherapy alone in the ITT population, but did not reach the prespecified boundary for statistical significance (8.3 mo vs 7.1 mo; HR = 0.78; \( P = .0033 \))

Similarly, there was a trend toward improved OS in the ITT population with chemotherapy + pembrolizumab, but it did not reach statistical significance (median OS: 17.0 mo vs 14.3 mo; HR = 0.86; \( P = .0407 \))

There was no difference in OS in the population of patients with a combined positive score ≥10 with pembrolizumab alone compared with chemotherapy alone (median OS: 16.1 mo vs 15.2 mo; HR = 1.01; 95% CI: 0.77–1.32)
Abstract 704MO – Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone with 1L chemotherapy (CTx) for advanced urothelial carcinoma (UC): Subgroup analyses from JAVELIN Bladder 100. Presenter: Petros Grivas

700 patients with mUC who had a response or SD after 4–6 cycles of a first-line platinum-containing regimen were randomized 1:1 to receive maintenance avelumab + BSC or BSC alone. The initial analysis showed that avelumab + BSC significantly prolonged OS compared with BSC alone in all randomized patients (21.4 mo vs 14.3 mo; HR = 0.69; \(P= .0005\)) and in patients with PD-L1-positive tumors (median not reached vs 17.1 mo; HR = 0.56; \(P= .0003\)) (Powles T, et al. N Engl J Med. 2020;383(13):1218–1230).

The current subgroup analyses showed an OS benefit with avelumab + BSC across prespecified subgroups, including patients with objective response (CR/PR; 23.8 [19.0 mo vs 15.0 mo]; HR = 0.69; 95% CI: 0.53–0.89) or SD (19.9 mo vs 14.0 mo; HR = 0.70; 95% CI: 0.46–1.05) as best response to first-line chemotherapy. OS benefit was also similar whether patients had received cisplatin (HR = 0.69) or carboplatin (HR = 0.66) as part of their first-line regimen.
Abstract 699O – Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma (UC): association between clinical outcomes and exploratory biomarkers. Presenter: Thomas Powles

Tumor analyses included PD-L1 (Ventana SP263 assay) and CD8 IHC, whole-exome sequencing (including FCGR2A and FCGR3A genotypes), whole-transcriptome sequencing, and T-cell receptor sequencing. Analyses of peripheral blood included baseline C-reactive protein level and neutrophil:lymphocyte ratio, as well as T-cell receptor sequencing before and on treatment.

None of the established biomarkers assessed, including PD-L1 on tumor or immune cells or tumor mutational burden, either alone or in combination, optimally predicted OS benefit with avelumab. Other biomarkers were identified as potentially predictive, which could be explored in future research. Potential biomarkers include alleles encoding high-affinity FcγRIIA and FcγRIIIA variants, as well as gene signatures associated with immune cell types and tumor growth-promoting pathways.
Abstract LBA27 – Phase II multicenter, randomized study to evaluate efficacy and safety of

avelumab with gemcitabine/carboplatin (CG) vs CG alone in patients with unresectable or metastatic urothelial carcinoma (mUC) who are ineligible to receive cisplatin-based therapy.

Presenter: Begona Perez Valderrama

- 85 patients with cisplatin-ineligible mUC were randomized to receive either 2 cycles of avelumab followed by 6 cycles of CG followed by maintenance avelumab vs 6 cycles of CG alone

- Median PFS was 6.9 months in the avelumab-CG arm compared with 7.4 months with CG alone ($P = .1356$)

- Early progression was higher in the induction avelumab arm (31% vs 9.3%), independent of prognostic factors

- Median OS was 10.5 months with avelumab-CG vs 13.2 months with CG alone ($P = .2642$)

- ORR was 57% vs 53.5% with avelumab-CG vs CG alone, respectively
Abstract 698O – Patient-reported outcomes (PROs) from IMvigor130: a global, randomised, partially blinded Phase III study of atezolizumab (atezo) + platinum-based chemotherapy (PBC) vs placebo (PBO) + PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC). Presenter: Aristotelis Bamias

1213 patients with previously untreated mUC were randomized to receive first-line therapy with atezolizumab ± platinum-based chemotherapy or chemotherapy alone. Previous analysis showed a significant improvement in median PFS with atezolizumab + chemotherapy compared with chemotherapy alone in the ITT population (8.2 mo vs 6.3 mo; HR = 0.82; \( P = .007 \)) (Galsky MD, et al. Lancet. 2020;395(10236):1547-1557). Patients in both arms similarly reported nominal changes (either maintaining pretreatment levels, or improvement) in most symptom and function/QOL domains, suggesting overall positive impacts.

Analyses of PROs show the addition of atezolizumab to gemcitabine-platinum resulted in PFS improvement without compromising patients' function or QOL.
Abstract 705MO – Sitravatinib (sitra) in combination with nivolumab (nivo) demonstrates clinical activity in checkpoint inhibitor (CPI) naïve, platinum-experienced patients (pts) with advanced or metastatic urothelial carcinoma (UC). Presenter: Pavlos Msaouel

- 39 patients with platinum-pretreated, CPI-naive mUC were treated with sitravatinib, a novel TKI targeting TAM, VEGFR2, and KIT, in combination with nivolumab; 30 patients were evaluable for efficacy with a median follow-up of 8.7 months.

- The ORR was 37% (3% CR, 34% PR), and 37% of patients experienced SD. The median duration of response was 5.6 months.

- Median PFS was 4.0 months, and median OS was 9.2 months.
Experts were surprised by the negative results of the KEYNOTE-361 trial evaluating pembrolizumab + first-line chemotherapy for mUC. At the current time, experts do not see a role for IO first-line for patients with mUC who are eligible for platinum-based chemotherapy, although it was noted that the IMvigor130 trial was positive. In general, they favor chemotherapy first-line followed by switch maintenance with an immune CPI for this patient population.

For patients with cisplatin-ineligible, PD-L1-high mUC, experts would favor gemcitabine + carboplatin, rather than an immune CPI, in the first-line setting. They noted that there is a subgroup of patients with rapidly progressive disease, with potentially IO-refractory tumors, who need chemotherapy upfront. If these patients receive an immune CPI first-line, their disease may progress so rapidly that they never get a chance for chemotherapy.

The inclusion of the subgroup of patients with rapidly progressive disease that is refractory at the outset to both chemotherapy and IO may be a contributing factor in the modest results observed in first-line trials of chemotherapy + immunotherapy. This may also explain why a maintenance IO strategy has been more effective to date in mUC; in the JAVELIN Bladder 100 trial, patients who progressed on first-line chemotherapy were ineligible for the trial, thereby using clinical criteria to eliminate patients with the most aggressive disease.
More effort is needed to identify biomarkers to differentiate patients with platinum-eligible mUC who may benefit from first-line IO from those who require chemotherapy upfront, and a breakthrough in patient selection will be necessary for IO to move into the first-line setting for mUC. The current eligibility cutoff of PD-L1 expression (1%) may be too low for first-line trials. Experts suggested reanalyzing results using a much higher cutoff, such as 50%, to determine whether a subset of patients sensitive to IO can be identified. On the basis of the exploratory analysis of JAVELIN Bladder 100 showing that none of the established biomarkers predicted for OS benefit with maintenance avelumab, alone or in combination, it is likely that additional biomarkers and/or molecular signatures will be needed to better select patients with mUC for IO. Subgroup analysis of JAVELIN Bladder 100 suggests that patients derived similar benefit from maintenance avelumab whether they achieved a CR, PR, or SD to first-line chemotherapy, and regardless of which platinum they received in combination with gemcitabine. Future first-line trials will need to consider that platinum-based therapy followed by maintenance with an immune CPI is the standard of care for most patients. Experts believe a major objective will be to further increase response rates to first-line therapy. It may be a challenge to add agents to a gemcitabine-platinum backbone while balancing toxicities, and an alternative strategy may be to add active agents to the switch maintenance regimen.
The results of the DANUBE trial, which did not meet either of the co-primary endpoints, are considered disappointing. This trial highlights the importance of endpoint selection, since the combination of durvalumab + tremelimumab did show an OS advantage in the PD-L1-high population, but this was a secondary endpoint. Experts believe the trial would need to be repeated in order to move forward with the IO combination in the PD-L1-high patient population.

PROs from the IMvigor130 trial suggest the combination of atezolizumab + platinum-based chemotherapy did not compromise patient function or QOL.

Sitravatinib + nivolumab represents a rational approach to augmenting the efficacy of immune CPIs in platinum-refractory mUC. Toxicities are perceived to be challenging with this regimen, but experts think that if they can be managed, it is likely this combination will have a future in mUC.
Bladder Cancer – ADCs

SCOTT TAGAWA, MD
Abstract LBA24 – TROPHY-U-01 Cohort 1 Final Results: A Phase 2 Study of Sacituzumab Govitecan (SG) in Metastatic Urothelial Cancer (mUC) That Has progressed After Platinum (PLT) and Checkpoint Inhibitors (CPI). Presenter: Yohann Loriot

- 113 patients with mUC that had progressed after prior platinum and immune CPI therapies received treatment with the Trop-2-targeted antibody-drug conjugate (ADC) sacituzumab govitecan; patients had received a median of 3 prior therapies
- The ORR was 27% (5% CR, 22% PR), with a median duration of response of 5.9 months
- 76% of patients experienced some reduction in tumor size
- Median PFS was 5.4 months and median OS was 10.5 months
- Neutropenia was the most common grade 3/4 AE (34%), and 3 patients discontinued due to neutropenia or its complications; 30% of patients required growth factor support
- Diarrhea and nausea were the most common all-grade AEs (65% and 58%, respectively)
- The phase III TROPiCS trial is comparing sacituzumab vs treatment of physician’s choice in patients with unresectable/mUC after progression on platinum-based and PD-L1/PD-1 therapy in the metastatic setting (or platinum-based and/or PD-L1 therapy in the [neo]adjuvant setting if progression within 12 mo).

- 125 patients with mUC previously treated with platinum-based and immune CPI therapies received treatment with enfortumab vedotin (EV) as part of the single-arm EV-201 trial. Median follow-up is now 22.3 months.

- Median OS is 12.4 months, with 50% of patients alive at 12 months and 34% alive at 18 months.

- 6 patients remain on therapy; median time on treatment was 4.6 months.

- The most common TRAEs included alopecia (49.6%), fatigue (49.6%), and decreased appetite (44%).

- TRAEs of interest included any skin reactions (51.2% all-grade, 12.8% grade ≥3), any peripheral neuropathy (50.4% all-grade, 3.2% grade ≥3), and any hyperglycemia (11.2% all-grade, 5.6% grade ≥3).
Abstract 771P – Efficacy of enfortumab vedotin in populations of interest among patients with advanced urothelial cancer. Presenter: Vadim Koshkin

This retrospective study included 83 patients treated with EV at 8 US institutions:

- 57% received treatment on a clinical trial, and 43% received EV as standard-of-care therapy
- 26% of patients had variant histologies
- 29% had baseline neuropathy, 16% had baseline diabetes, and 59% had baseline glomerular filtration rates ≤60 mL/min
- 77% were evaluable for response

- 39% of patients had a best response of CR/PR and 13% had SD
- The ORR was 22% in patients receiving treatment outside of a clinical trial, and 66% on a clinical trial (which included trials of combination therapies)
- The ORR was 48% in tumors with urothelial histology and 45% in variant histologies
- The ORR was 14% in tumors with FGFR3 alterations

- The most common AEs were fatigue (18%), rash/skin changes (14%), and neuropathy (12%). One-fourth of the patients experienced a grade ≥3 AE, and there was one grade 5 AE
Data with EV and sacituzumab govitecan suggest remarkable consistency across early phase and later-phase clinical trials with regard to ORRs and survival duration. When both ADCs are available, experts expect the initial choice of agent will be driven by toxicity profiles and patient comorbidities. For patients with diabetes or significant neuropathy, they would favor sacituzumab govitecan. For patients who have trouble with diarrhea or neutropenia, they would favor EV. However, experts expect a substantial fraction of patients will ultimately receive both drugs, noting that patients with mUC are now living longer and able to receive multiple lines of therapy. EV and sacituzumab govitecan are not expected to be cross-resistant, and importantly, their main toxicities are non-overlapping.

A key clinical question concerns the management of patients with an \(FGFR3\) alteration, and whether these patients should receive an \(FGFR3\)-targeted agent or an ADC first. Although the ORR with EV appeared lower in patients with \(FGFR3\) alterations in the retrospective analysis, it is not clear whether these patients had already received an \(FGFR3\) inhibitor and were receiving the ADC as a later-line therapy, or whether this reflects an intrinsic resistance. The question of optimal sequencing will need to be addressed in a clinical trial.
Experts found reassuring the retrospective data regarding patients treated with EV in a real-world setting, although numbers are small. Results suggest a similar level of efficacy and toxicity in patients with preexisting comorbidities. One expert noted that some patients with bone metastases treated with EV have experienced rapid relief of bone pain.

ADCs clearly have a role in the treatment of mUC and are expected to move into earlier lines of treatment. Experts believe that because ADCs can have different targets, with different payloads having non-overlapping mechanisms of action, there is room for multiple ADCs in the treatment armamentarium. Some experts speculated that the targets of these ADCs (Nectin-4, Trop-2) might also be useful as targets for radiopharmaceutical compounds.
Key Highlights and Strategic Takeaways
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