ASCO GU 2021: Key Highlights
(February 11–13, 2021)

ASCO GU 2021 featured diagnostic and clinical advances across the spectrum of genitourinary malignancies. We've selected congress highlights most likely to shape treatment paradigms across prostate cancer, bladder cancer and renal cell carcinoma.

PROSTATE CANCER

PSMA-targeted radioligand theranostics will expand prostate cancer treatment options

Prostate-specific membrane antigen (PSMA) is a promising target for imaging diagnostics and targeted radionuclide therapies (theranostics). The FDA has already approved Ga 68 PSMA-11 as a radiologic diagnostic agent in the US (December 2020), and the Phase III (VISION) trial of PSMA-targeted 177Lu-labeled PSMA-617 in progressive, 3L mCRPC patients is ongoing. 177-Lu PMSA-617 may have therapeutic potential in 2L, docetaxel-treated mCRPC as well, based on a higher PSA50-RR (PSA≥50% response) vs. cabazitaxel (66% vs. 37%) reported in the Phase II TheraP (ANZUP 1603) trial.[1]

Encouraging Phase II evidence emerges as pivotal PD-1 inhibitor development in prostate cancer continues

Phase II KEYNOTE 365 results (Cohort B) of pembrolizumab + docetaxel + prednisone in chemo-naïve, enzalutamide or abiraterone pre-treated mCRPC patients reported an rPFS of 8.5 months and mOS of 20.2 months. This regimen continues to be evaluated in the Phase III KEYNOTE 921 trial.[2] Similarly, the final analysis of the Phase II CHECKMATE 9KD trial reported that nivolumab + docetaxel + prednisone provided for a 40% PSA50-RR, an 8.5 month rPFS, and an mOS of 16.2 months (chemo-naïve mCRPC) in the ADT-treated subgroup, as further evaluation of the combination is ongoing in the Phase III CHECKMATE 7DX study.[3]

Role of PD-L1 is also being explored in a Phase III trial of atezolizumab + cabozantinib (CONTACT 02) in mCRPC patients who progressed on prior hormonal therapy in either M0-CRPC/`mCSPC/M1-CRPC setting.[4] The trial leverages the synergistic activity demonstrated in the Phase Ib COSMIC 021 trial.

Promising therapeutic innovations underscore key open questions.

Key Questions:

- *What sequencing strategies might be considered across the treatment continuum?*
- *Which patients are best suited for radionucleotide therapy? Is re-treatment with radionuclide therapy an option to be explored?*
- *What will be the impact on treatment paradigms with the potential entry of checkpoint inhibitors?*

Liquid biopsies may enhance genomic profiling in prostate cancer

In the largest liquid biopsy trial to date (n=3,334), tumor genomic changes detected through the ctDNA-based genomic profiling were compared with those identified in tissue-based analysis in mCRPC patients, including AR resistance mechanisms. In concordance analysis, tissue-based BRCA1/2 mutation detection was consistent with that identified using ctDNA, although ctDNA harboured some BRCA1/2 alterations not identified by tissue testing, and more acquired resistance alterations were detected using ctDNA analysis. Comprehensive genomic profiling (CGP) by ctDNA, as an alternative to tissue-based CGP, may become an established SoC as more data emerges.[5]

Molecular signatures may predict for sensitivity to apalutamide and other androgen signaling inhibitors

Exploratory analysis of the Phase III SPARTAN study in non-metastatic CPRC reported that long-term responders to apalutamide had molecular signatures with increased T cell activity (T cell activation, stimulation, cytokine response, and interferon production), decreased T cell exclusion, low proliferative capacity and increased hormonal dependence. In the future, these molecular determinants may help inform selecting patients who may derive the most benefit from apalutamide and other androgen signaling inhibitors. This provocative observation warrants confirmation in larger studies.[6]

BLADDER CANCER

Changing treatment dynamics and management of early-stage bladder cancer with IOs and ADCs

Adjuvant immunotherapy doubles post cystectomy DFS for MIBC patients

Cisplatin-based neoadjuvant chemotherapy is the SoC when cystectomy is planned for MIBC for patients eligible to receive cisplatin. To date, the role of adjuvant treatment for patients who did not receive neoadjuvant chemotherapy and for those with residual disease after neoadjuvant cisplatin-based therapy has been inconclusive. The Phase III CHECKMATE-274 trial reported that adjuvant nivolumab doubled mDFS (21 months vs. 10.9 months) in MIBC patients versus observation alone, regardless of whether or not they had received neoadjuvant cisplatin-based chemotherapy. Nivolumab is the first immunotherapy in the adjuvant setting that has shown a statistically significant and clinically meaningful improvement in DFS following cystectomy.[7]

Perioperative strategies may further expand treatment options in MIBC

Enfortumab vedotin, a Nectin-4 targeting ADC already approved in the metastatic setting, is being evaluated as both a monotherapy and in combination with pembrolizumab in the Phase III EV-303 trial perioperative (neo-adjuvant and adjuvant) regimens for MIBC in cisplatin ineligible patients undergoing cystectomy. The results of this trial are eagerly awaited, as it may establish a new regimen for cisplatin ineligible MIBC patients. In addition, sacituzumab govitecan, a TROP-2 targeting ADC, is in Phase II development in cisplatin ineligible patients undergoing radical cystectomy in two sequential cohorts: SURE-01 will study sacituzumab govitecan as a neo-adjuvant monotherapy and SURE-02 will study sacituzumab govitecan in combination with pembrolizumab as neo-adjuvant therapy, followed by pembrolizumab as post-cystectomy adjuvant therapy.[8]

Neoadjuvant gemcitabine and split dose cisplatin in combination with pembrolizumab (Phase II, LCCC1520) in cisplatin eligible MIBC patients undergoing cystectomy reported a pCR of 56%, irrespective of PD-L1 expression levels and 67% in PD-L1 positive patients. Data reported in this trial supports the use of this combination in the ongoing Phase III study KEYNOTE 866.[9]

Key Questions:

- *How will the anticipated entry of IOs and ADCs into the MIBC setting impact their use in metastatic patients?*
- *What treatment sequencing strategies will emerge?*
- *Will PD-1 expression levels inform PD-1 inhibitors use in the non-metastatic setting?*
- *How will cisplatin eligibility impact PD-1 inhibitors adoption in the MIBC setting?*

Checkpoint inhibitors may have a role in patients who are ineligible for or refuse cystectomy

Patients with locally advanced, node positive (Stage III) bladder cancer who are cisplatin ineligible and who are unfit for surgery have few treatment options. However, an encouraging preliminary read out of the DUART trial of durvalumab + RT followed by durvalumab reported a CR of 54.5% and a DCR of 72.9% in patients with T2-4 N0-2 M0 disease that was unresectable (35%), who were unfit for surgery (50%) and/or who were cisplatin ineligible (89%). One-year landmark PFS (70%) and OS (84%) was also reported.[10] A larger, Phase II durvalumab based bladder sparing chemoradiation study in this setting is being conducted by ECOG-ACRIN and NRG group (EA8185/ The INSPIRE) for which results are awaited.

RENAL CELL CARCINOMA

TKI based combination regimens with checkpoint inhibitors or novel MoAs continue to be studied as therapeutic innovations in RCC.

Adding checkpoint inhibitors to TKIs improves RCC treatment outcomes

Nivolumab in combination with cabozantinib was approved by the FDA in January 2021 in first-line RCC. The pivotal CHECKMATE 9ER trial met its primary end point, doubling mPFS vs. sunitinib (17 months vs. 8.3 months). With a median follow-up of 16 months, an mOS of 29.5 months was reported for the sunitinib arm, and was not reached for the combination. In addition, nearly twice as many patients responded to the combination of nivolumab and cabozantinib than to sunitinib (ORR: 55% vs. 28%).[11] Patients treated with nivolumab plus cabozantinib combination also reported improved quality of life compared to those who received sunitinib.[12]

Lenvatinib + pembrolizumab (Phase III CLEAR) showed significant improvement in ORR (71% vs. 36%), mDoR (26 months vs. 15 months), and mPFS (24 months vs. 9.2 months), in first-line advanced RCC vs. sunitinib. Patient follow-up is still too immature to report mOS outcomes. The results support the potential use of the combination for the first-line treatment of advanced RCC.[13]

Key Questions:

- *What patient characteristics or disease parameters will be drivers of choice between the expanding number of frontline options in RCC?*
- *How will treatments be sequenced along the RCC treatment continuum?*

Oral hypoxia-inducible factor 2α (HIF-2α) inhibitor MK-6482 (belzutifan) in combination with cabozantinib is being evaluated in a Phase II in treatment-naïve and VEGF/PD-1/L1-treated advanced clear cell RCC trial. Preliminary efficacy among evaluable patients in the IO-treated cohort (n=41) reported an ORR of 22% (all PRs), mPFS of 16.8 months, and a 12 month OS rate of 81% .[14] Study follow-up is continuing in both cohorts. A Phase III trial evaluating belzutifan in patients with previously treated ccRCC (NCT04195750) is ongoing.

TKI combinations mark their presence in hard-to-treat RCC histologies

Approximately 10% of patients with renal cell carcinoma have sarcomatoid features in their tumors. Post hoc analysis of the Phase III CHECKMATE-214 1L study of the dual checkpoint inhibitor nivolumab + ipilimumab regimen vs. sunitinib reported an ORR of 61% vs. 23.1%, a mPFS of 26.5 vs. 5.1 months, and an mOS for sunitinib of 14.2 months. mOS for the combination has not been reached with a median patient follow-up of 25.5 months.

Agents continue to target aggressive RCC histologies with high unmet need

- In the subset analysis of Phase III CHECKMATE 9ER in patients with sarcomatoid histology, 1L nivolumab + cabozantinib showed an mOS of 19.7 months, mPFS of 10 months, and ORR: 56%.[15]
- Cabozantinib improved PFS in patients with previously treated, metastatic papillary RCC compared to sunitinib (mPFS: 9 months vs. 5.6 months).[16]
- Cabozantinib demonstrated intracranial responses of 61%, mTTF of 9.9 months, and mOS of 14.7 months in mRCC with uncontrolled brain mets at baseline. No neurological toxicity was reported.[17]

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SmartAnalyst is helping the clients interpret the data presented at ASCO GU 2021 (February 11–13, 2021) focusing on key developments in genitourinary cancers and excellent research that impacts efficacy outcomes.

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