Clarion perspectives from the

ASCO Genitourinary Cancers Symposium 2018

A Clarion team attended this year's ASCO GU meeting to learn about the current state of the science in renal, bladder, prostate, and other GU cancers, and present the following highlights:

RCC: Immunotherapy combinations to change the standard of care

Advanced renal cell carcinoma (RCC) is undergoing an immuno-oncology (I-O) revolution[1]. A major theme at this year's ASCO GU meeting was that I-O combination regimens are poised to reshape first-line treatment:

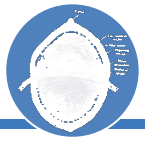
- **Nivolumab + Ipilimumab [BMS]:** Analysis of the risk-benefit profile strengthens the rationale for this combination[4], which had shown superior efficacy vs sunitinib in intermediate/poor-risk patients in the CheckMate-214 trial, as presented previously at ESMO and SITC 2017[2,3].
- **Atezolizumab + bevacizumab [Genentech/Roche]**: The phase 3 IMmotion151 trial was deemed a positive study based on its primary endpoint, mPFS (by investigator assessment) vs sunitinib in PD-L1+ patients, but the results were mixed. On one hand, the regimen induced ORR/CR rates of 33%/ 11% by independent review (36%/15% in PD-L1+ patients). On the other hand, mPFS did not significantly differ from sunitinib in the ITT population. The OS data were not mature, but did show a favorable trend. The regimen was well tolerated, and efficacy was seen across all IMDC risk categories, unlike the nivo + ipi study. Thus in the end, this regimen likely has a role to play.
- **Anti-PD1 + tyrosine kinase inhibitors:** However, the evidence is growing that the combination of anti-PD1 + TKIs may be even more compelling. The studies are still early, but they consistently show that—provided the toxicities are manageable—such combinations have excellent response rates. For example:
  - **Pembrolizumab + axitinib [Merck and Pfizer]** had ORR ~65% and CR ~8% (n=52)[6]
  - **Pembrolizumab + lenvatinib [Merck and Eisai]** had ORR ~63% (n=30), ~83% in 1L (n=12)[7].
  - **Nivo + tivozanib [BMS and Aveo]** had ORR ~64% (n=14)[8].
  - **Nivo ± ipi + cabozantinib [BMS and Exelixis]** had ORR ~54% (n=13)[9].

  Moreover, pembro + axi showed early PFS and OS data[6] which appear superior to historical controls.

As I-O becomes predominant, we face a growing need for treatments that work after failure of first-line I-O. Potential options include the glutaminase inhibitor **CB-839 [Calithera]** + everolimus or + cabozantinib; these combinations seem active even in heavily pre-treated patients[10]. CB-839 is also being studied in combination with immunotherapy (nivo)[11]. The BTK inhibitor **ibrutinib [Abbvie/Pharmacyclics and Janssen]** + nivo has shown responses in 2/11 patients who had received prior I-O[12]. Further studies and results are eagerly awaited.

Sources: 1) Escudier, Keynote; 2) Escudier, ESMO 2017 #LBA5; 3) Motzer, SITC 2017 #O38; 4) #686; 5) #578; 6) #579; 7) Lee, ESMO 2017 #847O; 8) #618; 9) #515; 10) #603; 11) NCT02771626; 12) #600; 13) #580

Bladder Cancer: New insights into predictive biomarkers



Five anti-PD1/PD-L1 immunotherapies have already been approved for treating urothelial carcinoma of the bladder, but only a minority of patients achieve durable responses. It remains unclear how best to use biomarkers to identify the patients who will respond to immunotherapy and those who will benefit more from other treatments, but some progress was reported at this meeting.

- The **atezolizumab** vs chemotherapy phase 3 IMvigor 211 study showed that atezo was not significantly better than chemo in the overall population (based on median OS), but seems to be better than chemo in a subgroup of patients at the tail of the OS curve (2-year OS ~25%)[14]. What biomarkers may define that subgroup? The investigators evaluated a range of potential biomarkers and found the following:
  - **PD-L1 is not predictive on its own and has inconsistent prognostic effects:** mOS was not significantly different for atezo vs chemo in both high and low PD-L1 groups. However, PD-L1 was a positive prognostic marker in this study's chemo arm; the PD-L1-high group had ~3 mo. longer mOS—but, confusingly, PD-L1 was a negative prognostic marker in the Keynote-045 study[15] and in a study of trimodal therapy (surgery + chemo + radiation) [16]. The discrepancy has not yet been explained.
  - **Specific gene signatures were not predictive:** The signatures tested included tGE3, which included the *PD-L1*, *IFNγ*, and *CXCL9* genes, and a DNA damage repair deficiency (DDRD) signature.
  - **Tumor mutational burden (TMB) was predictive and varied independently from PD-L1:** In TMB-high patients, the mOS for atezo vs chemo was 11.3 mo. vs 8.3 mo., whereas the two arms were not

different in TMB-low patients, regardless of PD-L1 levels. The combination of TMB-high and PD-L1+ markers yielded an even starker difference: the mOS for atezo vs chemo was 17.8 mo. vs 10.6 mo. A similar story was recently reported for nivo + ipi in first-line mNSCLC[17]

- Other biomarker discussions included **genomic and transcriptomic analyses** to classify urothelial carcinoma into 5 distinct molecular subtypes, each with treatment implications[18], **RNA sequencing** for a molecular grading system that is more prognostic than the conventional approach[19], and measuring **circulating immune biomarkers** such as neutrophil-to-lymphocyte ratio, C-reactive protein[20], or changes in circulating immune cells[21] to guide immunotherapy decisions.

Intriguing early data for novel treatment approaches were also presented at the meeting, including FGFR inhibitor **erdafitinib [Janssen]** for FGFR-mutant or fusion bladder cancer[22,23], the **nivo ± ipi + cabozantinib** combination[24], IL-15 agonist **ALT-803 [Altor]** in combination with BCG therapy[25], and the Nectin-4-targeted antibody-drug conjugate, **enfortumab vedotin [Seattle Genetics]**[26].

Sources: 14) #409; 15) #410; 16) Hoskin, GS4; 17) BMS press release Feb 5, 2018; 18) Lerner, Keynote; 19) #412; 20) #436; 21) #454; 22) #411; 23) #450; 24) #515; 25) #510; 26) #431

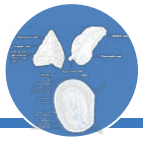
Prostate cancer: Building on a strong foundation

The androgen synthesis inhibitor **abiraterone [J&J]** and the androgen receptor (AR) antagonist **enzalutamide [Pfizer(Medivation)/Astellas]** are mainstays of treatment for metastatic, castration-resistant prostate cancer (mCRPC) due to their excellent efficacy and tolerability, and they are likely to remain dominant for some time. However, innovation and improvement are certainly still possible as the following examples show:

- **Expanding use to non-metastatic (M0) CRPC:** The PROSPER study showed that enzalutamide delays the time to metastasis versus placebo for M0 CRPC[27]. The STRIVE study shows that enza has superior PFS head-to-head versus bicalutamide in M0 CRPC[28].
- **Novel anti-androgen therapies:** Presented alongside PROSPER was a similar study called SPARTAN for M0 CRPC but with a novel AR antagonist, **apalutamide [Janssen]**[29]. SPARTAN formed the basis for apalutamide's recent FDA approval[30]. Other, earlier-stage novel agents include another AR antagonist, **TAS3681 [Taiho]**[31] and a PROTAC-based AR degrader, **ARV-110 [Arvinas]**[32].
- **Post-progression on abi or enza:** Attempts to address this unmet need include:
  - A PARP inhibitor + anti-PD-L1, **olaparib + durvalumab [AstraZeneca]** which had mPFS ~16 months for BRCA-mutant patients; the study was small, but this warrants more research[33].
  - A MEK inhibitor, **trametinib [Novartis]** was active in a patient with BRAF-mutant prostate cancer[34].
  - **Anti-PD1 or PD-L1 immunotherapy** can produce PRs in the majority of microsatellite instability-high (MSI-H) prostate cancer, but a small minority of microsatellite stable (MSS) patients[35,36]. Various studies are exploring I-O combinations and predictive biomarkers to improve the impact[37].
- **Biomarkers:** Not everyone responds well to abi or enza, and there are many studies aiming to better assess risk levels to inform more or less aggressive therapy, e.g., using the Decipher genomic test[38,39,40] or liquid biopsy approaches[41,42].

Sources: 27) #160; 28) #228; 29) #161; 30) Janssen press release Feb 14, 2018; 31) #298; 32) #381; 33) #163; 34) #306; 35) #248; 36) #187; 37) Sharma, GS2; 38) #4; 39) #24; 40) #72; 41) #255; 42) #273

Pheochromocytoma and other rare genitourinary cancers



Clarion proudly supports the SDHB PheoPara Coalition, a foundation dedicated to improving the lives of patients with pheochromocytoma and paraganglioma, with a focus on mutations in *SDHB* (succinate dehydrogenase B)[43]. We were thus pleased to see attention given to pheo, para, and other rare GU tumor types (e.g., adrenocortical carcinoma or ACC) at ASCO GU. A series of talks reviewed the endocrinology, surgery, and pharmacotherapy of pheo and ACC[44,45,46], and two posters assessed germline mutations underlying pheo/para, including *SDHB*[47,48].

Sources: 43) www.sdhbcoalition.org; 44) Else, GS7-1; 45) Quinn, GS7-2; 46) Coleman, GS7-3; 47) #668; 48) #508.

Images adapted from Gray (1918) *Anatomy of the Human Body*

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