ANZUP Annual Scientific Meeting 2022 Conference Review™

Making Education Easy | 10-12 July 2022; Adelaide

In this review:

Abbreviations used in this review:

ccRCC = clear cell renal cell carcinoma; **CT** = computed tomography; **IV** = intravenous; **LHRH** = luteinising hormone-releasing hormone; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MIBC** = muscle-invasive bladder cancer; **NHA** = novel hormonal agent; **NMIBC** = non-MIBC; **PARP** = poly adenosine diphosphate-ribose polymerase; **PSA50** = prostate-specific antigen decline >50%; **TURBT** = transurethral resection of bladder tumour.

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Welcome to this review of the Annual Scientific Meeting of the Australia and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group that was held recently in Adelaide.

This year's theme was 'No Longer on Mute: Patients, Carers and Our Research'. I have selected 10 presentations from the meeting that were particularly interesting.

We hope that you enjoy these selections and we encourage your feedback and comments.

Kind Regards,

Associate Professor Ben Tran

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The influence of lymph node burden and distribution on systemic treatment response of mHSPC in the STAMPEDE trial

Presenter: Noel Clarke, The Christie at Salford Royal, Manchester

Summary & comment: Prof Clarke gave a plenary presentation detailing the impact of cancer burden on outcomes. He reminded us of a study (Tait et al. BJU Int 2014) that demonstrated that outcomes were better for <4 bony metastases versus ≥4 bony metastases, which helped define high volume as used in CHAARTED. He then outlined the importance of lymph node location, burden and treatment outcome in M1 hormone-sensitive prostate cancer from STAMPEDE. Similar to the bony metastases data, he demonstrated that survival outcomes were significantly different for <5 nodal metastases versus ≥5 nodal metastases (Haran et al. BAUS 2020). He also demonstrated the genetic differences observed with both differing distribution and burden of metastases.

International Plenary Session; Jul 11

Renal cancer evolution in time and space

Presenter: Samra Turajlic, Francis Crick Institute, London

Summary & comment: Prof Turajlic discussed the amazing laboratory work performed in renal cell carcinoma. Firstly she outlined the driver mutations and variable clinical behaviour before describing the TRACERx programme (Turajlic et al. Cell 2018). She described that ccRCC evolution can occur in a linear (slow growing), branched (attenuated progression) or punctuated (rapid progression) mode. She also discussed how *BAP1* mutations are commonly present in rapidly progressing tumours while *PBRM1* mutations are commonly present in attenuated progressing tumours.

International Plenary Session; Jul 11

Pembrolizumab with chemoradiotherapy as treatment for muscle-invasive bladder cancer: Interim analysis of efficacy and treatment-related toxicity of the PCR-MIB phase II clinical trial (ANZUP 1502)

Presenter: Ciara Conduit, Peter MacCallum Cancer Centre, Melbourne

Summary: The PCR-MIB trial investigated the efficacy and safety of pembrolizumab when used with standard-of-care curative chemoradiotherapy in patients with MIBC. Dr Conduit presented interim data for complete response rate at 3 months, and treatment-related adverse events. In the trial, 27 patients with non-metastatic cT2-T4aN0M0 MIBC (>50% urothelial carcinoma histology) underwent maximal TURBT followed by whole-bladder radiation therapy over 6.5 weeks, with weekly cisplatin (35 mg/m^2 IV, 6 doses) and pembrolizumab (200mg IV every 3 weeks, 7 doses). Surveillance cystoscopy, urine cytology, and CT of the chest/abdomen/pelvis were performed 12 and 24 weeks after chemoradiotherapy. At 12 weeks, 18 patients had a complete response, 2 had progressive disease, and 7 were non-evaluable. The most common treatment-related adverse events were fatigue, diarrhoea, urinary frequency, haematuria, constipation, and rash.

Comment: PCR-MIB is an ANZUP study led by Andrew Weickhardt aimed at examining the safety and efficacy of pembrolizumab combined with chemoradiotherapy for MIBC. Dr Conduit presented an interim analysis of safety and efficacy data from PCR-MIB. From the 27 patients enrolled, Dr Conduit reported that the complete response rate at 3 months was an impressive 88%. Additionally, the combination was well tolerated with only 26% of grade 3/4 treatment-related adverse events. There was also mention of the phase 3 study KEYNOTE-992 that is currently recruiting.

Session: Best of the Best; Jul 11

Updated data from HIGH TeCH: A phase I/II trial of high dose testosterone in combination with carboplatin in men with metastatic castrate resistant prostate cancer

Presenter: Teesha Downton, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney

Summary: Dr Downton presented updated data from Arm B of the ongoing HIGH TeCH trial (NCT03522064) evaluating bipolar androgen therapy (BAT) combined with carboplatin in men with asymptomatic or minimally symptomatic mCRPC. Men with mCRPC were given IV carboplatin AUC 5 and intramuscular testosterone enanthate 500mg every 28 days, together with ongoing LHRH agonist or antagonist therapy. At data cut-off on 13 Apr 2022, 9 patients (median age 68 years, median 5 previous lines of treatment not including androgen deprivation therapy) who were enrolled in Arm B had received a median 7 cycles (range 2–21) of BAT with carboplatin. Two patients (22%) had a PSA50 response, and 6 (66%) had clinical benefit for >6 months. Median progression free survival to date is 196 days (range 50–604+).

Comment: Dr Downton detailed the use of BAT which involves rapid cycling between supra- and sub-physiological levels of testosterone. While some activity has been seen, it has been limited. Dr Downton reported the combination of carboplatin and BAT, with the rationale that high-dose testosterone can cause transient DNA damage that can be leveraged by carboplatin. She reported results from the 15 patients enrolled onto the combination. While these were very heavily pretreated patients, 2 PSA50 responses were observed, with 1 patient sustaining clinical benefit for >2 years. This response rate is consistent with carboplatin given on its own and it remains unclear if there is synergistic benefit of combining carboplatin with BAT.

Session: Best of the Best; Jul 11

Impact of concomitant medications (conmeds) and comorbidities on novel hormonal agents (NHAs) in metastatic castration resistant prostate cancer (mCRPC)

Presenter: Ying Yan Zhong, Peter MacCallum Cancer Centre, Melbourne

Summary: This real-world study used the electronic Prostate Cancer Australian Database (ePAD) to evaluate the impact of concomitant medications and comorbidities on the use and effects of NHAs (abiraterone or enzalutamide) in 235 patients with mCRPC. 64% of patients prescribed abiraterone had potential drug interactions compared to 71% prescribed enzalutamide. Category C (monitor), D (modify) and X (avoid) drug interactions were present in 54%, 3% and 5% of patients taking abiraterone and in 70%, 33% and 0% of patients taking enzalutamide. Comorbidities with potential to interact occurred in 73% of patients prescribed abiraterone and in 23% prescribed enzalutamide. In patients prescribed enzalutamide, clinically significant drug interactions were associated with shorter median treatment duration (8 vs 22 months) and lower PSA50 response rates (51% vs 74%; p=0.04). No differences were seen amongst abiraterone recipients.

Comment: Dr Zhong's research addresses the potential for comorbidity and concomitant medication interaction with NHAs used for mCRPC. She reported data from ePAD where 73% of patients suitable for NHAs had comorbidities that might interact with abiraterone, while 23% had comorbidities that might interact with enzalutamide. Additionally, in the same group of patients, 8% of patients had conmeds that should be avoided/modified when combined with abiraterone, while 33% had conmeds that should be avoided/modified when combined with enzalutamide. It is clear the comorbidities and drug-drug interactions play a significant role in the mCRPC patient population and should be considered carefully when prescribing abiraterone or enzalutamide.

Session: Best of the Best; Jul 11

WATIP: A pilot study of water irrigation post TURBT for preventing recurrence of NMIBC

Presenter: Mo Li, Eastern Health, Melbourne

Summary: The WATIP trial assessed the feasibility and safety of water irrigation after TURBT. Between May 2019 and Nov 2021, 30 patients (median age 67 years, 83% male) were enrolled and underwent TURBT with water irrigation. Median tumour size was 16mm, and 76.7% of patients had NMIBC on histology. The median postoperative irrigation time was 3h. The only adverse event reported was clot retention (n=1). There was no significant difference in pre- and post-TURBT serum sodium or haemoglobin levels, and postoperative serum lactate dehydrogenase levels were all within normal range.

Comment: Dr Li reported the results of water irrigation following TURBT to prevent recurrence of NMIBC. She outlined that while intravesical mitomycin C should be administered immediately post TURBT to reduce recurrences, its use is limited due to logistical issues in accessing chemotherapy in this setting. Dr Li suggested that 3h of water irrigation might be a suitable alternative given its lytic effects on cancer cells. 30 patients were recruited with 29 receiving at least 3h of water irrigation. There were no safety issues identified. There were 6 recurrences at 3 months (29%) and 8 recurrences at 12 months (42%). Dr Li concluded that further study is required to determine if water irrigation can reduce the risk of NMIBC recurrence.

Session: Best of the Best; Jul 11

Evaluating PARP inhibitor combination therapies with high-throughput screens of prostate cancer organoids

Presenter: Mitchell Lawrence, Monash University, Melbourne

Summary: A scalable pipeline for automated seeding, treatment, and analysis of prostate cancer organoids was developed and used to analyse new PARP inhibitor combination therapies. Patient-derived xenografts (PDXs) were used to establish organoid cultures of castrate-sensitive and castrate-resistant prostate cancer, as well as adenocarcinoma and neuroendocrine pathologies. Organoids were robotically embedded in 384-well plates, and their growth, size and composition were measured. To validate the high-throughput assay, the investigators verified that changes in metabolic and live-cell imaging-based end-points were consistent with the in vivo sensitivity of each tumour to the PARP inhibitor talazoparib. In-depth analyses of morphological and compositional differences between and within organoid cultures revealed significant decreases in uniformity and density of PARP inhibitor-sensitive organoids. Combining talazoparib with CX-5461 (a small molecule that activates the DNA damage response) synergistically decreased organoid viability and significantly reduced the growth of homologous recombination proficient PDXs in vivo. A phase 1 trial of talazoparib and CX5461 will commence in 2022.

Comment: Dr Lawrence detailed the serially transplantable PDX in vivo mouse models and corresponding in vitro organoid cultures that have been used to test the efficacy of combination treatments. He reported that talazoparib synergises with the RNA polymerase I (Pol I) transcription inhibitor pidnarulex (CX-5461) in *DDR* proficient castration-resistant prostate cancer. This has led to a clinical trial which is soon to open, truly achieving bench to bedside research.

Session: ANZUP Young Translational Innovators; Jul 12

Molecular characterisation of metastatic neuroendocrine prostate cancer

Presenter: Andrisha-Jade Inderjeeth, Peter MacCallum Cancer Centre, Melbourne

Summary: This study determined expression patterns of neuroendocrine prostate cancer markers in metastatic sites of patients with de-novo-neuroendocrine or neuroendocrine-transformed prostate cancer. Rapid-autopsy samples collected from 10 metastatic sites of a de-novo patient and 11 sites of a neuroendocrine-transformed patient were stained for DLL3, INSM1, p53, RB1 and PTEN using immunohistochemistry. All samples had DLL3 expression. INSM1 was also present in all sites of both patients, although levels were higher in the de-novo patient than in the neuroendocrine-transformed patient (mean 63.5% vs 34% cells positive). All sites had loss of AR, p53 and RB1. PTEN was intact in 2 sites of the de-novo patient (liver and nodal) and 2 brain lesions of the neuroendocrine-transformed patient, but was lost in the remaining samples.

Comment: Dr Inderjeeth explained the work performed to better understand neuroendocrine prostate cancer. She described that these tumours often lack AR and RB1 and P53 loss. This patient population is more likely to benefit from platinum-based chemotherapy rather than the usual systemic therapies used for prostate cancer. Dr Inderjeeth described a translational cohort study that confirmed that loss of RB1, PTEN and AR are commonly observed in neuroendocrine prostate cancer, but this is not observed across all metastatic sites. However, DLL3 is expressed across all metastatic sites in neuroendocrine prostate cancer patients.

Session: ANZUP Young Translational Innovators; Jul 12

Multiregion, longitudinal tumour sampling reveals determinants of anti-PD-1 response in clear cell renal cell carcinoma

Presenter: Lewis Au, Francis Crick Institute, London

Summary & comment: Dr Au presented excellent work in ccRCC, describing possible biomarkers of immuno-oncology (IO) response. Firstly he outlined possible issues that have led to difficulties in reproducing results using gene expression signatures, including intratumour heterogeneity. He described results from the ADAPTeR study (Au et al. Cancer Cell 2021) where 15 patients were recruited, including 10 non-responders and 5 responders. Whole exome sequencing confirmed that genetic features do not correlate with response. RNAseq data, when averaged for multiple biopsies, were able to reproduce data from existing gene expression signatures that predict for response to IO. Dr Au then examined T-cell receptor (TCR) clonality and demonstrated that responders to IO are more likely to have expanded clustered TCR clones that are maintained during treatment, representing a response to persistent antigen stimulation.

Session: ANZUP Young Translational Innovators; Jul 12

Combining PARP inhibition and androgen receptor antagonists in 1st line mCRPC

Presenter: Noel Clarke, The Christie at Salford Royal, Manchester

Summary & comment: Prof Clarke provided an excellent overview of the data supporting the combination of olaparib with abiraterone in mCRPC, in particular, those without DNA repair defects. He described the phase 2 clinical trial titled Study 8 and the positive results seen which led to the phase 3 study PROpel that has been published in NEJM Evidence 2022. He detailed the 34% reduction in radiographic progression-free survival in all-comers, regardless of presence of DNA repair defects. He then presented the results from the phase 3 study MAGNITUDE of niraparib and abiraterone. This study demonstrated that while there was a benefit with those with DNA repair defects, there was no benefit in those without them. He described possible explanations for these differences, including differences in study design (earlier use of abiraterone), and dose of PARP inhibitor used (lower dose of niraparib used in combination with abiraterone compared to niraparib as a single agent).

Session: Plenary – Moving Forward in Prostate Cancer; Jul 12

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Independent commentary by Associate Professor Ben Tran

Ben is a medical oncologist in Melbourne, Australia with appointments at Peter MacCallum Centre and Walter and Eliza Hall Institute. He is actively involved in clinical trials and translational research, with special interests in genitourinary cancers, drug development and real-world evidence. Ben is currently the chair of the Phase 1 group within Cancer Trials Australia (CTA), and is also the Chair of the germ cell subcommittee within the Australian and New Zealand Urological and Prostate Cancer Trials (ANZUP) Group.

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