Making Education Easy

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Abbreviations used in this review:

ADC = antibody-drug conjugate; **ADT** = androgen deprivation therapy; **ARP(i)** = androgen receptor pathway (inhibitor); **BEP** = bleomycin, etoposide, platinum; **EFS** = event-free survival; **HIF-2α** = hypoxia-inducible factor; **HR** = hazard ratio; **IHC** = immunohistochemistry; **IO** = immuno-oncology; **KIM-1** = kidney injury marker-1; **(m)CRPC** = (metastatic) castration-resistant prostate cancer; **MIBC** = muscle-invasive bladder cancer; **ORR** = overall response rate; **OS** = overall survival; **PARP(i)** = poly-ADP ribose polymerase (inhibitor); **pCR** = pathologic complete response; **QoL** = quality of life; **RCC** = renal cell carcinoma; **RFS** = relapse-free survival; **(r)PFS** = (radiographic) progression-free survival; **RPLND** = retroperitoneal lymphadenectomy; **TKI** = tyrosine kinase inhibitor.

Welcome to our review of the 2025 ASCO (American Society of Clinical Oncology) Genitourinary Cancers Symposium held in San Francisco, USA.

Here I have discussed 10 abstracts which were particularly interesting and relevant for local practice, showcasing some of the latest developments in the field of genitourinary cancer research. We begin with a fascinating post-hoc analysis of the CheckMate 214 trial, which found that higher circulating KIM-1 levels were associated with poorer treatment outcomes in advanced RCC, although patients receiving nivolumab plus ipilimumab who experienced a >30% decrease in KIM-1 at 3 weeks achieved greater response rates and substantially longer OS. This is followed by results from the KEYMAKER-U03 substudy 03B, which showed durable antitumour activity with second-line lenvatinib plus belzutifan in advanced RCC, with a reasonable safety profile. Our final abstract reports on updated results from ENZA-p, which demonstrated that addition of LuPSMA to enzalutamide in poor-risk metastatic, castration-resistant prostate cancer was associated with prolonged OS as well as improvements in pain, fatigue and overall health and quality of life.

Detailed abstracts for the presentations can be located here.

I trust that you will enjoy this review and find it of educational value, and I encourage you to send in your feedback.

Kind Regards,

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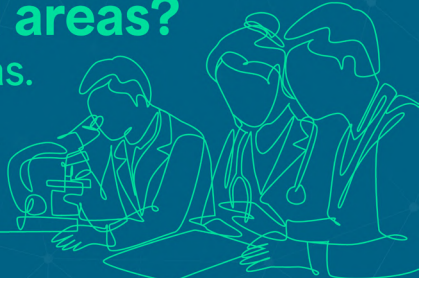
Evaluation of circulating kidney injury marker-1 (KIM-1) as a prognostic and predictive biomarker in advanced renal cell carcinoma (aRCC): Post-hoc analysis of CheckMate 214

Speaker: Wenxin Xu (Dana-Farber Cancer Institute, Harvard Medical School, USA)

Summary: The CheckMate 214 trial showed superior survival and durable responses with nivolumab plus ipilimumab versus sunitinib as first-line treatment in advanced renal cell carcinoma (RCC). This post-hoc analysis explored whether levels of circulating kidney injury marker-1 (KIM-1) were associated with treatment response. Serum KIM-1 levels from 821 patients were analysed at both baseline and 3 weeks after first treatment dose. Patients with higher baseline KIM-1 levels had shorter OS across both treatment arms, irrespective of tumour burden, nephrectomy status or risk group. In the nivolumab plus ipilimumab arm only, patients with a >30% decrease in KIM-1 between baseline and 3 weeks had significantly longer median PFS than those with a <30% decrease (70.8 vs. 4.2 months, respectively), as well as longer median OS (85.4 vs. 26.6 months) and improved ORR (69.3% vs. 13.9%).

Comment: KIM-1 is a detectable circulating protein that may be useful as a prognostic and predictive biomarker in kidney cancer. Previously presented work from IMmotion010 reported that elevated baseline levels post-nephrectomy were associated with shortened duration of RFS and better outcomes with adjuvant immunotherapy. The data here show that in the metastatic setting, elevated levels are associated with poorer outcomes regardless of treatment with sunitinib or IO therapy. However, patients treated with IO with a >30% decrease had a greater response rate and much better OS. Interestingly, patients treated with sunitinib that had a decrease of the same magnitude did not have a correlative improved OS, supporting the theory that oral TKI therapy is a transient suppressive measure for metastatic kidney cancer as compared to durable cancer control with immunotherapy.

Abstract #437
Abstract



KEYMAKER-U03 substudy 03B: Pembrolizumab (pembro) and targeted therapy combinations for advanced clear cell renal cell carcinoma (ccRCC)

Speaker: Laurence Albiges (Gustave Roussy, Paris-Saclay University, Villejuif, France)

Summary: The 03B substudy of the phase 1/2 KEYMAKER-U03 trial is examining different combination therapies in clear cell RCC with disease progression on/after PD-(L)1 inhibition and VEGF-TKI. This presentation shared results from arms B4 (pembrolizumab + belzutifan [HIF-2α inhibitor]; n=62), B5 (lenvatinib [VEGF-TKI] + belzutifan; n=64) and the reference arm (pembrolizumab + lenvatinib; n=73). Follow-up occurred at a median of 16.6 months (B4), 17.6 months (B5) and 19.4 months (reference). Durable antitumour activity was seen in the lenvatinib plus belzutifan arm (B5), with an ORR of 47% (95% CI 34—60), median PFS of 12.5 months (95% CI 5.9—26.3), duration of response of 22.1 months and median OS of 32.3 months (95% CI 22.4—not reached). The safety profile of lenvatinib plus belzutifan was consistent with the known profiles of each agent.

Comment: This umbrella trial of second-line therapy post IO and TKI exposure in patients with metastatic RCC supports the combination of TKI and oral HIF-2α inhibitor as a potential active therapy that shows durable activity and a reasonable safety profile. The current standard of care in Australia is the use of second-line cabozantinib, with response rates from METEOR and other real-world studies being around 15-30%, with PFS rates of 5-8 months. Here, the combination of lenvatinib and the oral HIF inhibitor belzutifan achieved a response rate of 47% and median PFS of 12.5 months, with a duration of response close to 2 years, supporting the ongoing comparison in the LITESPARK-011 phase 3 trial comparing the combination to cabozantinib. Other arms of this study were presented at the meeting with novel immunotherapy combinations, but there was little activity with these combinations in patients previously treated with PD-1 inhibitors, suggesting TKI therapy will be a backbone of any combination.

Abstract #440
Abstract

Prospective COTRIMS (Cologne trial of retroperitoneal lymphadectomy in metastatic seminoma) trial

Speaker: Axel Heidenreich (University Hospital of Cologne, Germany)

Summary: Here, Alex Heidenreich presented the final results from the COTRIMS trial, in which 34 men with stage IIA/B seminoma (mean age 34.2 years; stage IIA n=22; stage IIB n=12) underwent nerve-sparing retroperitoneal lymphadenectomy (RPLND) without adjuvant chemotherapy. Follow-up occurred over a median of 33.4 months. There were low rates of surgery-related complications (11.7% had Clavien Dindo 3a complications), with a mean blood loss of <150mL and a mean hospitalisation time of 4 days (range 3-9). A mean of 19 nodes were dissected, and 88% of patients showed preserved antegrade ejaculation. The mean number of positive lymph nodes was 1.4. Non-seminoma was found in 5.9%, with malignancy in 8.9% and seminoma in 85%. A total of four patients relapsed at 4, 6, 9 and 12 months, respectively, and salvage was achieved in all of these patients with chemotherapy. miR371 showed promise as a predictive biomarker, with 17/18 patients harbouring metastases showing miR371 positivity, and miR371 negativity in 3/3 of those with benign lesions.

Comment: The current standard treatment for patients with stage IIA/B seminoma in Australia is 3 cycles of BEP, with high cure rates of approximately 95% in these favourable-risk patients. Long-term complications of chemotherapy and the 3 months of intensive treatment have led surgeons to consider RPLND as an alternative. The COTRIMS data presented and updated here show that outcomes are reasonably good and offer a decent alternative to chemotherapy, with a low rate of serious complications and a low rate of recurrence (all of which were subsequently treated with salvage BEP). Similar other series from higher-volume international centres support RPLND as a valid approach, albeit one that should only occur at high-volume centres, and with patients understanding that most of them will end up with retrograde ejaculation. Bilateral template surgery may be a way of reducing relapse rates below the 10-30% seen in the current series, but this has a greater risk of increasing ejaculation dysfunction.

Abstract #618
Abstract

Additional efficacy and safety outcomes and an exploratory analysis of the impact of pathological complete response (pCR) on long-term outcomes from NIAGARA

Speaker: Matthew Galsky (Mount Sinai, New York, USA)

Summary: These researchers reported additional outcomes from the NIAGARA trial which assessed the additive benefit of perioperative durvalumab to neoadjuvant chemotherapy in MIBC, as well as an exploratory analysis into the impact of pathologic complete response (pCR). Patients randomised to the durvalumab plus neoadjuvant chemotherapy arm (n=533) showed significant reductions in risks of distant metastases or death than those who received neoadjuvant chemotherapy alone (n=530; HR 0.67; 95% CI 0.54—0.83; p<0.001) and greater reductions in the risk of death from bladder cancer (HR 0.69; 95% CI 0.52—0.91; p=0.008). A greater proportion of patients in the durvalumab arm achieved a pCR at radical cystectomy versus neoadjuvant chemotherapy alone (37% vs. 28%), and pCR patients in the durvalumab arm had improved EFS and OS than those who did not achieve a pCR. Those treated with durvalumab plus chemotherapy demonstrated greater EFS and OS benefits versus neoadjuvant chemotherapy alone, in both the pCR group (EFS HR 0.58; OS HR 0.72) and the non-pCR group (EFS HR 0.77; OS HR 0.84).

Comment: Neoadjuvant chemotherapy with durvalumab led to improvements in OS and metastases-free survival compared to standard cisplatin-based chemotherapy. Interestingly, this was true even in patients who achieved a complete response to neoadjuvant chemotherapy alone. This supports the use of chemotherapy-IO in patients for neoadjuvant therapy, rather than the alternative of using neoadjuvant chemotherapy alone and using IO as adjuvant therapy such as nivolumab for those patients who have inadequate downstaging (CheckMate 274 approach).

Abstract #659
Abstract

Neoadjuvant treatment with disitamab vedotin plus perioperative toripalimab in patients with muscle-invasive bladder cancer (MIBC) with HER2 expression: Updated efficacy and safety results from the phase II RC48-C017 trial

Speaker: Xinan Sheng (Peking University Cancer Hospital & Institute, Beijing, China)

Summary: This presentation shared the updated efficacy and safety results from the single-centre, phase 2 RC48-C017 trial, in which patients with HER2-expressing MIBC received neoadjuvant disitamab vedotin (HER2-targeted monoclonal antibody) plus perioperative toripalimab (anti-PD-1 inhibitor). At the time of data cut-off, 47 patients had been enrolled and treated (10.6% with baseline HER2 IHC 1+; 57.4% with IHC 2+; 31.9% with IHC 3+). A total of 33 patients (70.2%) underwent radical cystectomy and pelvic lymph node dissection. The pCR rate (primary endpoint) was 77.8% in PD-L1-positive patients and 62.5% in PD-L1-negative patients. The 1-year overall EFS rate was 89.5% (95% CI 69.8—96.7%), and OS data were not yet mature. No new safety signals were reported.

Comment: ADCs such as enfortumab vedotin (a nectin-4 ADC) and disitamab vedotin (HER2-targeted ADC) are highly active in metastatic urothelial cancer, especially when combined with immunotherapy. Thus, we eagerly await phase 3 trials of combination ADC and IO therapy for neoadjuvant downstaging of MIBC, with the potential advantages of not only a higher pCR rate, but the ability to use these drugs in patients who were previously deemed ineligible for cisplatin due to hearing or renal impairment. This Chinese study is tantalising and encouraging, as it reports a very high pCR rate for those patients who were HER2 1+ or above; but, note that 14 patients who received disitamab vedotin and IO therapy did not undergo cystectomy (?wanted bladder preservation), and therefore the direct comparison to other phase 2 series is difficult due to different methodologies in accounting for these drop-outs.

Abstract #665
Abstract

Which patients with metastatic hormone-sensitive prostate cancer (mHSPC) benefit more from androgen receptor pathway inhibitors (ARPIs)?

Speaker: David Fisher (MRC Clinical Trials Unit at UCL, London, UK)

Summary: In this STOPCAP Collaboration meta-analysis, researchers analysed individual patient data to explore which patients with metastatic hormone-sensitive prostate cancer benefit most from ARPIs versus docetaxel plus ADT doublet. Across the LATITUDE, STAMPEDE A versus G, SWOG-1216, ENZAMET and STAMPEDE A versus J trials (total n=5472), the addition of an ARPI to ADT was associated with an improvement in OS (HR 0.69; 95% CI 0.64—0.74), and four of these trials with PFS data (excluding SWOG-1216) also showed improved PFS (HR 0.49; 95% CI 0.45—0.53). The PFS benefit seen with ARPIs was greater among patients who were younger (p=0.034), those with higher BMI (p=0.048) and those less burdened with metastases (p=0.034).

Comment: This meta-analysis did not have data from some of the darolutamide and apalutamide trials, and was over-weighted with abiraterone trials. The outcomes with the addition of ARPIs seem good across all subgroups, although the talking point is the reduced benefit of adding abiraterone to ADT in the elderly (defined as those aged over 75 years), compared to using ADT alone. Perhaps this is due to the use of abiraterone in patients with concurrent cardiovascular or diabetic disease, where other real-world databases have highlighted toxicity issues. Clinicians will need to be mindful of the trade-offs of using the alternative of the '-amides', such as apalutamide and enzalutamide in the elderly, which have higher rates of fatigue and falls, as well as the potential to reduce cognition.

Abstract #20
Abstract

Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial

Speaker: Neeraj Agarwal (University of Utah, USA)

Summary: During this session, Neeraj Agarwal discussed the final OS findings from the TALAPRO-2 trial, in which the preliminary data showed improved rPFS with talazoparib plus enzalutamide versus placebo in patients with metastatic castration-resistant prostate cancer (mCRPC). At an extended follow-up of 52.5 and 53.0 months in the talazoparib plus enzalutamide and placebo arms, respectively, 52% and 60% of patients had died (median OS 45.8 vs. 37.0 months, respectively; HR 0.796; p=0.0155). The updated rPFS results were consistent with the primary analysis, with improved rPFS in the talazoparib plus enzalutamide arm (33.1 vs. 19.5 months; HR 0.667; p<0.0001). No novel safety signals were observed.

Comment: While TALAPRO-2 met predefined endpoints to show improved OS (8 months) and rPFS in patients unselected for *HRR* gene alterations in the mCRPC setting, I think most clinicians still have some scepticism about combining PARPis with ARP inhibition in this population, and wonder about real-world applicability. Firstly, we see less patients with CRPC who have not received an ARPi already. Secondly, data from single-agent PARPis in this population show only benefit of PARP inhibition in small *HRR*-defined populations (*BRCA2*>*BRCA1*>*PALB2*>>>other mutations). Thirdly, concerns about longer duration of exposure to gastrointestinal and bone marrow toxicity reduce enthusiasm.

Abstract #LBA18
Abstract

Radical prostatectomy (RP) versus radiotherapy (RT) in high-risk prostate cancer (HR-PCa)

Speaker: Soumyajit Roy (Rush University Medical Centre, Chicago, USA)

Summary: Soumyajit Roy's team compared the use of radical prostatectomy versus radiotherapy in high-risk prostate cancer, through an emulated randomised comparison with individual patient data across two phase 3 RCTs (NRG/RTOG 0521 and CALGB 90203). The analysis included 1290 patients (radical prostatectomy n=733; radiotherapy n=557), with a median follow-up of 6.4 years. Before inverse probability of treatment weighting, those who underwent radical prostatectomy had lower baseline PSA and were significantly younger than radiotherapy patients. Overall, 18% and 14% of radical prostatectomy patients received adjuvant and salvage therapy, respectively. Patients in the radiotherapy group had a significantly lower cumulative incidence of distant metastasis (primary endpoint) at 8 years than radical prostatectomy patients (16% vs. 23%; HR 0.48; 95% CI 0.34—0.69; p<0.001); however, there was no significant between-group difference in 8-year mortality rates after distant metastasis (8% vs. 10%; p=0.72). Patients in the radiotherapy group had a significantly increased mortality risk without distant metastasis (HR 2.09; 95% CI 1.01—4.34; p=0.048).

Comment: Given a lack of head-to-head trials of surgery or radiation, we are limited to meta-analyses like this to compare the alternative therapeutic approaches to treating patients with high-risk prostate cancer. The trials included in this are all from a PSMA-PET-free era, so some of these patients in the trial will have been enrolled with low-volume metastatic disease. Patients receiving radiotherapy and ADT had a lower incidence of distant metastatic disease compared to surgery alone, although this difference was less when accounting for surgical patients who underwent post-operative radiotherapy. The data support informed decision-making with high-risk prostate patients, and the need to counsel patients who ultimately choose surgery that there is a high likelihood of needing at least radiotherapy, and possibly even a period of ADT with the radiation, to improve their OS and reduce the chance of distant metastatic disease.

Abstract #309
Abstract

Independent commentary by Associate Professor Andrew Weickhardt

Andrew is a medical oncologist at the Olivia Newton-John Cancer and Wellness Centre in Melbourne. He has an interest in using immunotherapy and personalised treatments for patients with genitourinary cancer. He is actively involved in translational research investigating biomarkers of response and resistance to these treatments and is involved in several phase 1 trials of new drugs in development.

Gene signature predictor of dose-response to prostate radiation: validation of PORTOS in phase III trials

Speaker: Shuang Zhao (University of Wisconsin-Madison, USA)

Summary: The aim of this study was to determine whether the PORTOS gene expression scoring system could identify patients with prostate cancer who would and would not benefit from radiotherapy dose escalation in the phase 3 NRG/RTOG 0126 (n=215) and SAKK 09/10 (n=226) trials. Researchers evaluated the efficacy of PORTOS as a predictive biomarker for biochemical failure (via Phoenix criteria) with dose escalation in RTOG 0126, and clinical PFS in SAKK 09.10. Patients in the RTOG 0126 trial with higher PORTOS scores showed a significant benefit with radiotherapy dose escalation (middle PORTOS tertile HR 0.45; p=0.02; higher PORTOS tertile HR 0.30; p=0.009), whereas those in the lowest tertile showed no difference in biochemical failure (p=0.73). PORTOS scores also identified patients who benefitted from dose escalation in the SAKK 09/10 trial, with only patients in the higher PORTOS score group experiencing a benefit in clinical PFS (HR 0.19; p=0.01).

Comment: Dose escalation might only be beneficial for patients undergoing prostate radiotherapy in those with a high PORTOS gene signature score. The combination of two large trials was used to generate this biomarker work. Improved outcomes were limited to patients with this higher RNA-based gene signature, and the clinical use of the assay could reduce exposure to some of the toxicity issues associated with higher radiotherapy doses.

Abstract #308
Abstract

Overall survival and quality of life with [^{177}Lu] Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in poor-risk, metastatic, castration-resistant prostate cancer in ENZA-p (ANZUP 1901)

Speaker: Louise Emmett (St Vincent's Hospital & UNSW, Sydney, Australia)

Summary: At a follow-up of 20 months, the interim analysis of ENZA-p demonstrated that patients with poor-risk, metastatic, castration-resistant prostate cancer experienced prolonged PFS and improved depth of PSA response with [^{177}Lu] Lu-PSMA-617 (LuPSMA) plus enzalutamide versus enzalutamide alone. Here, Louise Emmett shared the updated OS and health-related QoL outcomes from a median follow-up of 34 months. Patients administered LuPSMA plus enzalutamide achieved significantly longer median OS than those who received enzalutamide alone (34 vs. 26 months; HR 0.55; 95% CI 0.36—0.84; p=0.005), with significantly improved deterioration-free survival for physical function (38% vs. 17%; p<0.001) and overall health and QoL (40% vs. 13%; p<0.001). Patients in the LuPSMA plus enzalutamide arm also experienced improved pain scores versus enzalutamide alone (difference 7.2; 95% CI 1.6—13; p=0.01) and improved scores for pain (difference 5.9; 95% CI 1.1—10.7; p=0.02). There was a higher frequency of self-rated xerostomia with LuPSMA plus enzalutamide (74% vs. 57%; p=0.04).

Comment: The addition of lutetium therapy to enzalutamide in patients with risk factors for poor outcomes with enzalutamide alone in metastatic castrate-resistant prostate cancer led to an 8-month improvement in OS. Additionally, QoL and pain outcomes were better in those patients who received lutetium. The trial incorporated an adaptive dosing methodology that was novel in comparison to other lutetium-PSMA trials, with patients receiving only two cycles if they had a substantial PSA drop and reduction in PSMA expression after their first two treatments. This may not only reduce bone marrow toxicity, but also cost of therapy, and should be explored in the hormone-sensitive population of patients in future trials.

Abstract #17
Abstract