Welcome to this review of the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

In this review we present a snapshot of the latest research on non-prostate genitourinary cancer, including renal and urothelial carcinomas, presented at this meeting. Selection and review of the research has been carried out independently by Dr Ben Tran who attended the meeting.

Highlights of this review include exciting new findings from the KEYNOTE-426 study which shows efficacy of combination PD-1/PD-L1 checkpoint inhibitors with tyrosine kinase inhibitors of the VEGF pathway, greater than VEGF inhibitors alone, in patients with clear cell renal cancer across all disease risk groups. We also look at an update from the CARMENA trial that analysed the clinical benefit of cytoreductive nephrectomy for de novo mRCC patients in IMDC-risk populations in the setting of targeted therapy. In the area of urothelial cancer, the EV-201 trial shows a meaningful clinical activity with the antibody-drug conjugate enfortumab vedotin in heavily pre-treated patients and a phase II study showed that switch maintenance therapy with pembrolizumab significantly delayed disease progression post-chemotherapy.

The meeting has been published as a Special Issue online supplement to the Journal of Clinical Oncology and can be accessed on the journal’s website: https://ascopubs.org/doi/10.1200/JCO.2019.37.18_suppl. We hope you enjoy these selections, and as always, look forward to hearing your comments and feedback.

Kind Regards,

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Pembrolizumab plus axitinib versus sunitinib as first-line therapy for metastatic renal cell carcinoma: outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study

Speaker: Brian I. Rini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Summary: The KEYNOTE-426 trial established the superiority of combination pembrolizumab plus axitinib (pembro/axi) treatment over sunitinib for first-line therapy in treatment naïve patients with advanced metastatic renal cell carcinoma (mRCC). Results were published in The New England Journal of Medicine in March, 2019. This analysis of KEYNOTE-426 provides outcome results for subgroups of patients with International Metastatic RCC Database Consortium (IMDC) risk score ratings of combined intermediate and poor risk (IPR), and in patients with sarcomatoid (sar) features. In the phase III trial, patients with mRCC who had not received a prior treatment and had a Karnofsky Performance Scale Index >70 were randomised 1:1 to receive pembrolizumab 200mg every 3 weeks plus axitinib 5mg twice daily (n=432) or sunitinib 50mg/day (n=429). The clinical benefit of dual therapy with pembro/axi was observed in increased overall survival rates (OS), reduced risk of disease progression (progression free survival, PFS) and improved objective response rates (ORR). Of the 861 patients enrolled, 592 (68.8%, 294 in the pembro/axi arm and 298 in the sunitinib treatment arm) were classified as IMDC intermediate/poor risk and 105 had sarcomatoid features (51 in the pembro/axi arm and 54 in the sunitinib arm). A significantly increased clinical benefit was observed in both patients with intermediate/poor disease risk and those with sarcomatoid features with pembro/axi dual therapy compared to sunitinib alone. Pembro/axi treatment, compared to sunitinib treatment, reduced the risk of death by 48% in the low risk patients group and 42% in patients with sarcomatoid features (12-month OS IPR group 87.3% vs 71.3%, hazard ratio [HR] 0.52; sar group 83.4% vs 79.5%, HR 0.58) and reduced the risk of disease progression by 33% in the IPR group and 46% in the sarcomatoid group (IPR group DFS 12.6-months vs 8.2-months, HR 0.67; sar group median not reached vs 8.4-months, HR 0.54). More patients, in both subgroups analysed, responded to combination pembro/axi therapy than sunitinib (ORR IPR group 55.8% vs 29.5%; sar group 58.8% vs 31.5%) and more patients achieved a complete response (IPR group 4.8% vs 0.7%; sar group 11.8% vs 0%).

Comment: KEYNOTE-426 is an exciting study that demonstrates the combination of pembrolizumab and axitinib is superior to sunitinib as first line treatment for clear-cell mRCC. Subgroup analysis of this pivotal, phase 3 study demonstrated that the significant OS advantage seen in the original trial is maintained in the combined intermediate/low risk group with HR 0.52 and higher ORR 55.8 versus 29.5%. These benefits were also seen in patients with sarcomatoid features. We look forward to this combination as an option for our mRCC patients here in Australia.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4500)

Abstract
Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy

Speaker: Leonard Joseph Appleman, UPMC Hillman Cancer Center, Pittsburgh, PA

Summary: This 52-week-randomized, double-blind, placebo-controlled multi-center trial of the Eastern Cooperative Oncology Group—American College of Radiology Imaging Network (ECOG-ACRIN) cancer research group (E2810) assessed the efficacy of adjuvant pazopanib for patients with mRCC and no evidence of disease post-metastasectomy on scans. 129 patients were enrolled between August 2012 and July 2017 and randomised to receive 800 mg pazopanib or placebo. Adjuvant pazopanib did not improve disease-free survival (DFS; HR pazopanib vs placebo 0.85; P=0.47) and reduced overall survival compared to placebo (HR 2.65; P=0.03).

Comment: Several studies have been conducted to determine if adjuvant vascular endothelial growth factor (VEGF) targeted tyrosine kinase inhibitor (TKI) therapy following nephrectomy for high risk RCC, can improve OS through reduced risk of recurrence. Thus far, only one study, S-TRAC, has demonstrated an improvement in DFS. No studies have yet demonstrated an improvement in OS. This study, presented here, examines pazopanib in patients who have had a metastasectomy. Like the others, it did not improve DFS compared to placebo. My feeling is that there will never be a role for VEGF-targeted TKI as adjuvant treatment in RCC. Current studies are examining if there might be a role of immune- oncology therapy in this space.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4502)  
Abstract

Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients (pts) with metastatic urothelial cancer (mUC): HCRN GU14-182

Presenter: Matt D. Galsky, Tisch Cancer Institute, New York, NY

Summary: This trial enrolled 107 patients with metastatic urothelial cancer (mUC) who had achieved stable disease after up to 8-cycles of 1st line platinum-based chemotherapy to assess a switch maintenance regimen using the PD-1 blocker pembrolizumab. Patients were randomised to a 24-month program of either intravenous 200 mg pembrolizumab every three weeks (n=55) or placebo (n=52). Each treatment arm had a higher rate of response (ORR 22% vs 12%). The incidence rate of progression with a 36% reduction in the risk of disease worsening with pembrolizumab, compared to placebo, significantly delayed disease progression (HR 0.64; P=0.023; HR 0.64. Maximum Efficacy Robust Test p=0.036; log-rank p = 0.038) and reduced overall survival compared to placebo (HR 2.65; P=0.03).

Comment: Currently, in mUC, platinum based chemotherapy is standard 1st line treatment. Some patients sustain a prolonged response after completing 4-6 cycles and don’t proceed to 2nd line treatment until disease progression. This study explored the use of maintenance pembrolizumab versus placebo in patients who have at least stable disease upon completion of platinum based chemotherapy. In this phase 2 study, as expected with any maintenance therapy, there was a significant PFS improvement with pembrolizumab. It is unclear if this will translate to an overall survival benefit. However, maintenance therapy is a good way to ensure patients receive additional therapy, as local data suggests only 60% of patients who have 1st line treatment, go on to receive 2nd line treatment.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4504)  
Abstract

EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors

Speaker: Daniel Peter Petrylak, Yale School of Medicine, New Haven, CT

Summary: Dr Petrylak presented preliminary results from one cohort of the global EV-201 single-arm, two-cohort, study that is investigating the efficacy of the antibody-drug conjugate enfortumab vedotin (EV) in patients with locally advanced or metastatic urothelial cancer (mUC). This cohort included 128 patients (70% male; median age 69-years) with unresectable or mUC who had received previous treatment with both a platinum chemotherapy and immune checkpoint inhibitor (ICI) 125 of whom received 1.25 mg/kg EV on 3 days of a 28-day cycle. The ORR was 42% with a CR rate of 0%. Responses were observed in all pre-defined subgroups including patients with liver metastases. Cohort 2 will assess EV in platinum-naïve mUC patients who have received ICI treatment but are chemotherapy naïve.

Comment: Enfortumab vedotin is an excelling antibody drug conjugate targeting Nectin-4, that has demonstrated impressive activity in mUC. This study details the response rates in patients who have had platinum based chemotherapy and checkpoint inhibitors. The ORR in this third line setting was impressive at 42%. Additionally, toxicity appears tolerable. Phase III studies are underway examining if enfortumab vedotin provides a survival benefit in mUC.

Reference: J Clin Oncol 2019; 37 (18_suppl.LBA4505)  
Abstract

Randomized trial of adjuvant chemotherapy versus adjuvant radiation therapy for locally advanced bladder cancer after radical cystectomy

Author: Mohamed S. Zaghboul, Children’s Cancer Hospital, Cairo, Egypt

Summary: Brian Baumann presented his group’s results from 2 arms of a 3-arm phase III trial comparing various adjuvant treatments after radical cystectomy in patients with locally-advanced bladder cancer (LABC). The trial, conducted at the National Cancer Institute in Cairo, Egypt, involved treatment of all patients with radical cystectomy followed by adjuvant radiotherapy (45 Gy) in fractions twice daily; n=79 or adjuvant chemotherapy (gemcitabine/cisplatin x 4; n=45). 2-year outcomes showed no clinical superiority of one adjuvant treatment over the other in terms of distant metastasis-free survival (75% vs 79% for radiotherapy vs chemotherapy; P=0.07) or DFS (61% vs 60%; P=0.83). Local-recurrence free survival, however, was significantly improved in the radiotherapy group with a 72% reduction in risk of local relapse (92% vs 69%; P=0.02; HR=0.28) and a post-hoc non-inferiority analysis favoured radiotherapy with a 7% difference in disease-free survival (64% vs 47%).

Comment: This study randomised patients who had a radical cystectomy for locally advanced bladder cancer (at least T3b or positive LN) to postoperative radiotherapy versus adjuvant chemotherapy. As expected, there was superior local control with radiotherapy, and surprisingly no difference in disease-free survival (DFS) or OS. I expected adjuvant chemotherapy to improve OS compared to postoperative radiotherapy, but in this small study of 123 patients there was no significant difference.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4507)  
Abstract

Cytoreductive nephrectomy in metastatic renal cancer

Speaker: Arnaud Miejean, Hôpital Université Georges-Pompidou, Paris, France

Summary: This update from the CARMENA trial provided an analysis of the benefit of cytoreductive nephrectomy in an era of targeted therapy, in IMDC-risk populations with mRCC. The CARMENA study, a phase III clinical trial in 450 patients with mRCC, determined that sunitinib therapy alone is non-inferior to nephrectomy followed by targeted-therapy with sunitinib (Arm A; 50 mg daily) for overall survival in patients with mRCC. It also showed a significantly increased clinical benefit of sunitinib therapy alone (Arm B; 50mg daily). This report provides updated results in patients stratified according to IMDC-defined risk categories, as opposed to MSKCC, and number of risk factors with a longer follow-up. At a follow-up of 61.5-months,10.6-months extended follow-up than the CARMENA trial, nephrectomy performed prior to sunitinib therapy provided no benefit compared to sunitinib alone in patients stratified either by MSKCC criteria (OS 15.6-months vs 19.8-months; HR=0.933) or IMDC criteria (HR 0.957). The same pattern of sunitinib non-inferiority was observed when patients were stratified according to number of metastatic site/s (OS 23.6-months vs 22.7-months; HR 1.08). The only group of patients who derived clinical benefit from nephrectomy prior to sunitinib therapy were those with IMDC-intermediate risk (56% of Arm A and 62% of Arm B patients) with a single risk factor (n=126; Arm A vs Arm B; med OS 30.5-months vs 25.2-months; HR 1.24). This benefit was not maintained in patients with 2 risk factors (n=140; low haemoglobin, high corrected calcium or neutrophil; HR 0.61). Patients in Arm B who received a secondary nephrectomy also showed an increased OS of 48.5-months.

Comment: CARMENA was a pivotal study which changed practice for many people, including myself. When it was presented and published last year, I stopped offering patients with de novo mRCC an upfront cytoreductive nephrectomy and instead proceeded directly to systemic therapy. Of course, there are exceptions, such as those with oligometastatic disease, where the best approach remains metastasectomy and nephrectomy. This update examines that patients with better prognosis, i.e. only one IMDC risk factor, might still benefit from upfront cytoreductive nephrectomy. Additionally, it hypothesises that patients who do well enough on systemic treatment to receive a secondary nephrectomy appear to have a much superior survival.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4508)  
Abstract
MINIMUM PRODUCT INFORMATION: Xtandi® (enzalutamide) 40 mg soft capsules. Indications: Treatment of patients with metastatic castration-resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated or who have previously received docetaxel. Contraindications: Patients with known hypersensitivity to enzalutamide or any of the excipients in the formulation; women who are, or may become, pregnant (Category X). Not indicated for use in women. Precautions: Xtandi should only be prescribed by a medical practitioner who is experienced with the treatment of prostate cancer and the use of antineoplastic endocrine therapies. Clinically significant risk of seizure, posterior reversible encephalopathy syndrome, drug interactions. Refer to Xtandi Approved Product Information for additional precautions. Interactions: Strong inhibitors or inducers of CYP2C8, paracetamol, midazolam, warfarin and coumarin-like anticoagulants, omeprazole, colchicine, dabigatran etexilate, digoxin. Groups of medicinal products that can be affected include, but are not limited to: analgesics, antibiotics, antineoplastic agents, anticoagulants, antipsychotics, beta-blockers, calcium channel blockers, corticosteroids, HIV antivirals, hypnotics, immune-modulating agents, steroids metabolised by CYP3A4, Thyroid agents. Adverse effects: Very common (≥10%): asthenic conditions, peripheral oedema, back pain, arthralgia, musculoskeletal pain, diarrhoea, hot flush, headache, upper respiratory tract infection, constipation, hypertension, dizziness, dyspnoea, fall, decreased appetite, weight decreased. Common (≥1% and <10%): muscular weakness, musculoskeletal stiffness, spinal cord compression and cauda equina syndrome, paraesthesia, mental impairment disorders, hypoesthesia, lower respiratory tract and lung infection, insomnia, anxiety, haematuria, polkaura, non-pathologic fractures, pruritus, dry skin, epistaxis, dysgeusia, restless legs syndrome, gynaecomastia. Dosage: The recommended dose is 160 mg (four 40 mg capsules) as a single oral daily dose. Swallow capsules whole with water. Do not chew, dissolve, or open the capsules. If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg) if warranted. The concomitant use of strong CYP2C8 inhibitors should be avoided if possible, but if co-administered, reduce dose to 80 mg once daily. Based on Product Information dated 23 May 2017. Further information on Xtandi is available from Astellas by calling 1800 751 755. mCRPC metastatic castrate resistant prostate cancer QoL Quality of Life References: 1. Xtandi (enzalutamide) Approved Product Information May 2017. 2. Beer TM, et al. N Engl J Med 2014;371:424–433 3. Scher HI, et al. N Engl J Med 2012; 367(13): 1187–97 4. Loriot Y et al. Lancet Oncol. 2015;16(10):S59–21. XTANDI® is a registered trademark of Astellas Pharma Inc. Astellas Pharma Australia Pty Ltd ABN 81 147 915 482, 6 Eden Park Drive, Macquarie Park NSW 2113. AU/XTD/16/0007h(1) Aug 2017
Active surveillance in metastatic renal cell carcinoma: results from the Canadian Kidney Cancer information system

Speaker: Igor Kushnir, Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Summary: This Canadian group presented a retrospective cohort analysis of outcomes of asymptomatic patients with low-volume mRCC disease treated with active surveillance compared to immediate systemic treatment. Patient data (n=1711) was extracted from the Canadian Kidney Cancer information system, a database of combined information from 14 academic centers, with immediate treatment defined as within 6-months from diagnosis. 5-year OS for surveillance (n=663) vs immediate treatment (n=848) cohorts was 70.2-months vs 32.1-months (P<0.0001). Age and IMC risk criteria-adjusted OS was significantly higher in a subset of patients who received systemic therapy ≥6-months after diagnosis compared to those in B who received treatment <6-months from diagnosis (HR 0.46; P=0.0001).

Comment: In Australia, for several years, we had very few options for patients with mRCC. For that reason, active surveillance was not an unusual approach for some mRCC patients, particularly those with slow growing disease. A retrospective study published by Daphne Day from Monash health suggested that this watchful waiting / active surveillance approach, did not impair outcomes. This study presented here, analyses a larger Canadian cohort of 863 active-surveillance patients, and once again confirms that active surveillance in mRCC patients can be performed safely.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4516)

Clinical outcomes according to PD-L1 status and age in the prospective international SAUL study of atezolizumab for locally advanced or metastatic urothelial carcinoma or non-UC of the urinary tract

Speaker: Cora N. Sternberg, Weil Cornell Medicine, New York, NY

Summary: The phase III, prospective, single-arm, International SAUL trial enrolled 1004 patients with advanced cancer of the urinary tract to assess the safety and outcomes of second-line treatment with atezolizumab (atezo). A broad range of patients were recruited from 32 countries and comprised some with complex comorbid disease including renal impairment, autoimmune disease and HIV-positive status. All had progressed after 1-3 prior therapies for inoperable, locally advanced or metastatic disease with 95% of tumours urothelial carcinoma (5% non-urothelial) located 1-3 prior therapies for inoperable, locally advanced or metastatic disease with 95% of tumours urothelial carcinoma (5% non-urothelial) located predominately in the bladder (75%), the renal pelvis (12%) and ureter (10%). All patients received atezo 1200 mg every 3-weeks. Preliminary SAUL results, published in European Urology, established the tolerability of atezo, efficacy including OS, similar to that seen in other atezo trials with more stringent inclusion criteria such as IMVigor211. At the 2019 ASCO Meeting, Sternberg presented the pre-specified subgroup analysis results for atezo treatment according to PD-L1 (IC 0/1 and IC 2/3, assessed by VENTANA SP142) status. Median OS overall, IC 0/1 (n=666) and IC 2/3 (n=268) groups were 8.7-months, 7.9-months and 11.8-months. ORR rates were 13%, 10% and 21%, respectively. Higher PD-L1 expression (IC 2/3 group) associated with more favourable OS and ORR.

Comment: This study is essentially a real world approach to treating mUC with atezolizumab. Patients with poor Eastern Cooperative Oncology Group performance status (0-2), renal impairment, brain metastases, stable autoimmune disease, and concomitant steroids were included. They demonstrated in this large cohort that atezo was effective and well tolerated across all subgroups. Additionally, patients who were PD-L1 positive had improved OS and ORR.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4519)

Efficacy of immune checkpoint inhibitors and genomic characterization of sarcomatoid and/or rhabdoid metastatic renal cell carcinoma (mRCC)

Speaker: Ziad Bakouny, Dana-Farber Cancer Institute, Boston, MA

Summary: Bakouny et al. retrospectively analysed patients with sarcomatoid and/or rhabdoid (S/R) mRCC tumors to identify genetic characteristics and compare efficacies of treatment with immune checkpoint inhibitors (IC) and non-IC therapy. Treatment data was available on 125 S/R mRCC patients (68 S, 23R and 14 S/R with clear cell carcinoma) and sequencing data on 48. Fisher’s test comparison of an NGS panel of between 275-447 genes showed a significantly increased frequency of genetic alterations in BAP1 in S/R tumors compared to non-S/R (25% vs 4.3%; q=0.096). Multivariate analysis comparing S/R patients treated with IC (n=59) vs non-IC (n=66) showed significantly improved clinical outcomes in the IC treatment group with increased rates of 24-month OS (48.8% vs 29.7%) and ORR (43.2% vs 27.8%).

Comment: There has always been a question mark over how best to treat patients with sarcomatoid or rhabdoid mRCC. Both these histologies can occur as a component of both clear cell and non-clear cell RCC. This study examined the genomics of these tumours and demonstrated some genomic alterations in BAP1, NF2, TP53 and SETD2 were more frequent, while tumour mutation burden was not significantly different. Additionally, this retrospective study confirmed previous findings that immune checkpoint inhibition was associated with significantly improved outcomes in these tumours.

Reference: J Clin Oncol 2019; 37 (15_suppl. 4514)

Biomarker analyses from the JAVELIN Renal 101: avelumab + axitinib versus sunitinib in advanced renal cell carcinoma

Speaker: Toni K. Choueiri, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA

Summary: This analysis of the JAVELIN Renal 101 study examined molecular and genetic features of clear cell RCC tumors to investigate therapy-specific outcomes. The JAVELIN Renal 101 study, published in the New England Journal of Medicine, found a significant benefit in terms of PFS and ORR in de novo advanced RCC patients treated with a frontline combination of the PD-L1 checkpoint inhibitor avelumab plus the tyrosine kinase inhibitor axitinib (A+Ax) compared to sunitinib. The greatest predictor of benefit from the A+Ax combination therapy was PD-L1 expression (>7% immune cells) which provided the highest PFS in the A+Ax group and the lowest PFS in the sunitinib group (HR 0.63). In terms of gene expression signatures, mutations in CDH3, PTEN, or DNMT1 resulted in treatment-specific changes in PFS compared to the wildtype. Sunitinib treatment resulted in improved PFS in patients with high-angiogenesis expression signatures whereas patients with low angiogenesis subgroups or a high number of effector T cells and inflamed T cells had longer PFS with A+Ax therapy.

Comment: This translational study using the JAVELIN Renal 101 cohort (phase 3 study randomising mRCC to A+Ax versus sunitinib) conducted PD-L1 expression using SP263, CD8 expression, RNAseq and whole exome sequencing. Patients with PD-L1 ≥1% had no difference in PFS when receiving A+Ax, but had a significantly poorer PFS when treated with sunitinib. Patients with higher CD8 density had significantly improved PFS when receiving A+Ax but trended towards poorer PFS when receiving sunitinib. RNAseq was used to develop a 26-gene signature which was significant associated with improved PFS when treated with A+Ax, but no difference in PFS when treated with sunitinib. This exciting work moves the field forward towards a more personalized approach when treating mRCC.

Reference: J Clin Oncol 2019; 37 (15_suppl. 101)

Dr Ben Tran is a consultant medical oncologist in Melbourne, Australia with appointments at Peter MacCallum Centre and Walter and Eliza Hall Institute of Medical Research. He is actively involved in clinical trials and translational research, with special interests in genitourinary cancers, drug development and personalised medicine. Ben is currently the chair of the GU tumour group within Cancer Trials Australia (CTA), and is the deputy chair of the germ cell subgroup within the Australian and New Zealand Urological and Prostate Trials (ANZUP) Group.

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