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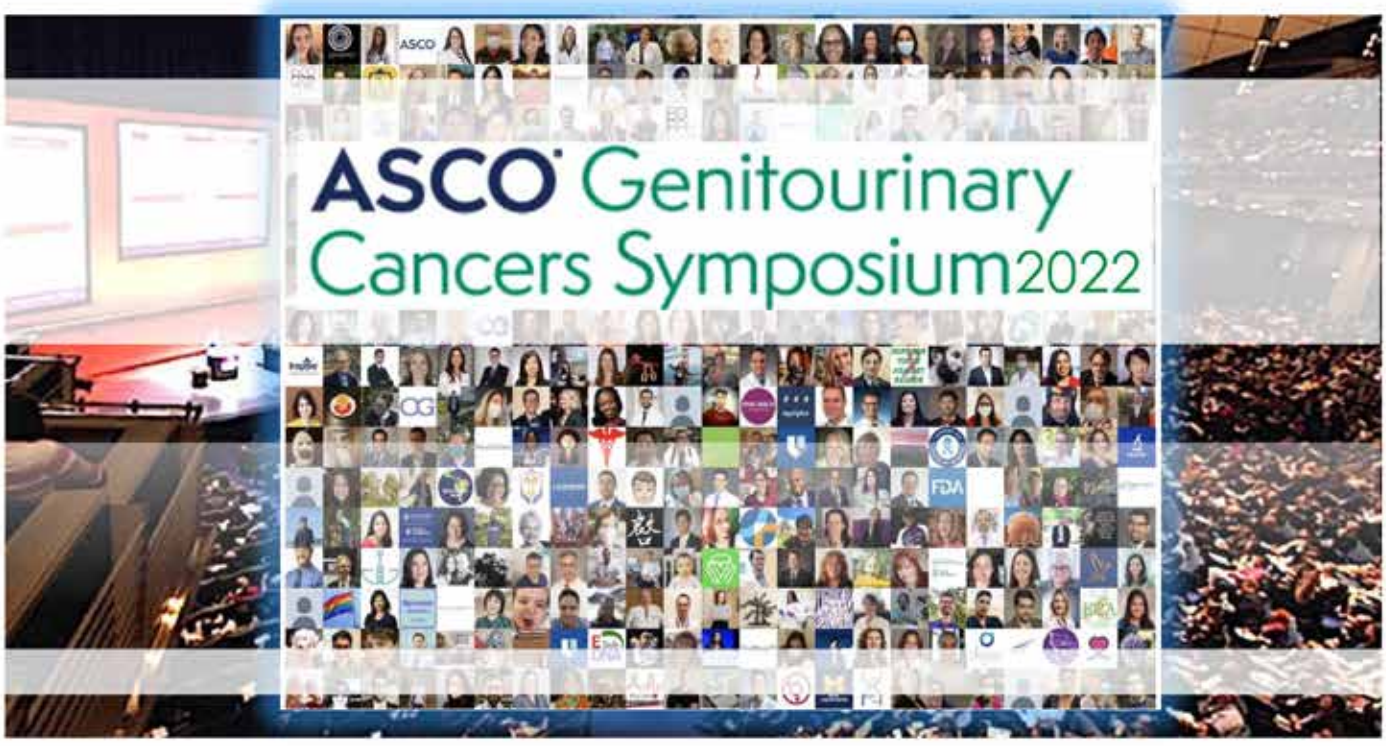

SPECIAL CONTENTS

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ASCO GU22 – Kidney Cancer Highlights

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ABSTRACT
The 2022 ASCO Genitourinary Cancers Symposium took place in San Francisco between February 17-19th. As always, the scientific program contained several exciting abstracts with a focus on prostate cancer, bladder cancer, and kidney cancer. Here we will highlight key abstracts related to kidney cancer/renal cell carcinoma presented at this year's symposium.

Beginning with the poster session, Tannir at al presented long-term follow-up from a post-hoc analysis of the phase 3 CheckMate 214 RCT focusing on the sarcomatoid subgroup (abstract 352). The CheckMate 214 trial explored first-line therapy with ipilimumab + nivolumab and has demonstrated that this combination is superior to sunitinib in intermediate/poor risk mRCC. Sarcomatoid RCC is an aggressive histologic variant that has been associated with a poor prognosis as well as a sensitivity to immune-checkpoint inhibition. With a minimum of 5 year of follow-up, ipilimumab + nivolumab led to improved OS (49 vs 14 months) and PFS (26 vs 5 months) as compared to sunitinib. The objective response rate was 61%, with an impressive 23% complete response rate. Take home message: These results are consistent with other studies demonstrating the efficacy of immune checkpoint inhibitors in this aggressive pathologic subgroup. Patients with metastatic sarcomatoid RCC should be offered immune-based therapy.

Powles *et al* presented a poster outlining the final OS analysis from the phase 3 CheckMate 9ER RCT (abstract 350). In this trial, first-line nivolumab plus cabozantinib was found to be superior to sunitinib in mRCC. This updated analysis was performed after 25.4 months minimum follow-up, with the combination continuing to demonstrate improved OS (37.7 vs 34.3 months) and PFS (16.6 vs 8.3 months) compared to sunitinib. The complete response was also higher with combination therapy (12.4% vs 5.2%). Take home message: These results continue to support the use of nivolumab plus cabozantinib as one potential treatment option in first-line mRCC. Other IO + TKI combinations with OS data include: pembrolizumab + axitinib and pembrolizumab + lenvatinib.

There were several compelling poster abstracts led by the International mRCC Database Consortium (IMDC). The first was presented by Ernst *et al* and explored updated real-world outcomes of patients with mRCC

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treated with first-line immune-based combination therapy (abstract 308). This study demonstrated that the IMDC risk criteria (IMDConline.com) continued to classify patients into favourable, intermediate, and poor risk categories irrespective of the type of therapy received, including combination immunotherapy and targeted therapy. A second abstract was presented by Navani *et al* which examined clinical predictors of response to first-line immune-checkpoint inhibitor combination therapy using the IMDC dataset (abstract 310). Based on a multivariable logistic regression model, the presence of lung metastases, cytoreductive nephrectomy, and better IMDC risk group were associated with a higher probability of response. Take home message: The IMDC model continues to provide prognostic information in a contemporary mRCC population. Clinical factors associated with response to immuno-therapy are promising but require external validation in an independent dataset.

Moving onto the oral presentations, Zibelman *et al* presented the results of a non-randomized phase I/II phase study investigating the combination of axitinib and nivolumab in mRCC (abstract 291). In the first-line setting, this combination resulted in an ORR of 69%, with toxicity comparable to other IO + TKI combinations. Take home message: Although not practice changing, these data appear consistent with other IO + TKI combinations that have previously been tested in large phase 3 RCT's and are approved for use in mRCC, including pembrolizumab + axitinib, nivolumab + cabozantinib, and pembrolizumab + lenvatinib.

In another oral presentation, McKay *et al* presented an elegant study exploring genomic alterations and transcriptional signatures across different metastatic sites in patients with mRCC (abstract 287). They found that several genes were mutated at higher frequencies in select metastatic sites and that molecular subgroups differed by metastatic site. Take home message: This study sheds light on the biologic differences between separate anatomical sites of metastatic disease. Further research is needed to determine whether these molecular differences can act as predictive markers for therapeutic selection.

There were two oral presentations that focused on peri-operative systemic therapy in RCC:

(i) The first was presented by Bex *et al* and examined the use of neoadjuvant avelumab + axitinib prior to nephrectomy in localized RCC (abstract 289). This was a non-randomized phase II trial where high-risk patients (N=40) received 12 weeks neoadjuvant avelumab + axitinib prior to nephrectomy. The primary endpoint was a partial response in the primary tumour. The partial response rate was reported to be 30%, and there were no treatment-related surgical delays. Primary tumor response appeared to be associated with DFS. Take home message: Neo-adjuvant IO + TKI appears safe and leads to primary tumor responses, but it remains unclear if the IO component provides any additional benefit compared to pre-operative TKI alone (prior neo-adj TKI studies have PR rates of around 30%). As such, randomized data in the neo-adjuvant space is needed. The PROSPER phase 3 RCT is exploring peri-operative nivolumab vs. SOC.

(ii) Choueiri *et al* presented an updated analysis of the KEYNOTE-564 trial (abstract 290). This was a large phase 3 RCT exploring adjuvant pembrolizumab for 12 months vs. placebo in patients with intermediate-high or high-risk RCC post-nephrectomy/post-resection of metastatic lesions. In a prior publication of this trial, adjuvant pembrolizumab resulted in significant improvement in disease-free survival. The updated analysis occurred after a median of 30 months of follow-up. With additional follow-up, adjuvant pembrolizumab continued to demonstrate a consistent improvement in DFS (HR 0.63, 95% CI 0.50–0.80; P < 0.0001), with a DFS rate at 24 months of 78.3% with pembrolizumab vs 67.3% with placebo. The OS data remains immature. Take home message: It is reassuring to see a consistent DFS benefit with longer follow-up. Whether these early results are truly practice changing is a matter of debate, as OS improvement remains the gold standard when considering adjuvant therapy. It is important to note that high grade immune-related toxicity was reported in 9% of patients receiving pembrolizumab, including possible long-term toxicity. Therefore, a careful risk/benefit assessment is needed when considering adjuvant therapy in patients who may be cured with surgery alone. Further research into specific high-risk patient subgroups, including biomarkers to better identify these patients, is warranted.

The last oral presentation was presented by Aikens *et al* who provided an update of the HCRN GU16-260 trial (abstract 288). This study explored the role of initial nivolumab monotherapy followed by nivolumab and ipilimumab salvage in treatment naïve mRCC (N=123). The ORR with first-line nivolumab was 34.1%, with a median duration of response of 27.6 months. This included an ORR of 57.1% in the IMDC favourable risk group. Biomarker studies suggested that higher tumor PD-L1 expression enriched for responders. The ORR with the addition of salvage ipilimumab was only 11.4%. Take home points: Nivolumab monotherapy has anti-tumor activity in the first-line setting, with ORR results consistent with other single agent PD-1 inhibitors. Despite this, upfront combination therapy with nivolumab and ipilimumab in intermediate/poor risk patients remains a standard first-line option in mRCC. RCT's comparing single agent ICI therapy to combination therapy are awaited.