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SPECIAL CONTENTS

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ABSTRACT 289- Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). *Bex A et al.*

RESULTS: Pts/tumour characteristics are shown in table. Twelve pts (30%) had a PR of the PT from a baseline mean diameter of 10.3 (range 5.6-16.4) cm. Median PT downsizing was 20 (0-43.5) % and median post-treatment vital tumour presence was 50 (1-100) %. At a median follow-up of 23.5 months, recurrence occurred in 13 (32%) pts at a median of 8 (2-23) months and 3 died of disease. Of the 12 pts with PT PR, 11 (92%) are disease-free. Median DFS and OS are not reached. Postoperative adverse events occurred in 8 pts (2 Clavien Dindo grade 3a). There were no treatment-related surgery delays and no PT progression. Post-treatment samples showed upregulation of PD-L1 expression ($p < 0.0001$) and total CD8+ densities ($p < 0.01$) when compared to pre-treatment biopsies. Comparing samples of pts with PR vs no PR in the PT, no clear immune marker differences were observed. Post-treatment samples from pts that recurred were characterized by lower densities of total, intra-epithelial and stromal CD8+, intra-epithelial CD8+CD39+ ($p<0.05$) and total CD8+GZMB+ ($p=0.1$). Pre-treatment biopsies showed no clear differences.

CONCLUSIONS: Neoadjuvant avelumab/axitinib for non-metastatic high-risk RCC leads to PR of the PT in 30% which is associated with DFS. Pts without recurrence had a significant increase in CD8+ densities compared to pts with recurrence suggesting expansion of a pre-existing immune response. Clinical trial information: NCT03341845.

ABSTRACT 290- Pembrolizumab as post nephrectomy adjuvant therapy for patients with renal cell carcinoma: Results from 30-month follow-up of KEYNOTE-564. *Choueiri TK et al.*

RESULTS: 994 pts were randomized 1:1 to pembrolizumab (N = 496) or placebo (N = 498). As of data cutoff date of June 14, 2021, median (range) follow-up, defined as time from randomization to data cutoff, was 30.1 (20.8–47.5) months. In this updated analysis, DFS benefit with pembrolizumab was maintained (HR 0.63, 95% CI 0.50–0.80; nominal $P < 0.0001$) and was consistent across subgroups, including pts with Mo disease with intermediate-high risk of recurrence (HR 0.68, 95% CI 0.52–0.89), Mo high risk of recurrence (HR 0.60, 95% CI 0.33–1.10), or M1 NED (HR 0.28, 95% CI 0.12–0.66). The estimated DFS rate at 24 months was 78.3% with pembrolizumab vs 67.3% with placebo. A total of 66 OS events were observed, 23 in the pembrolizumab arm and 43 in the placebo arm (HR 0.52, 95% CI 0.31–0.86; $P = 0.0048$); the p-value did not cross the statistical hypothesis testing boundary and additional follow-up is planned for this key secondary endpoint. The estimated OS rate at 24 months was 96.2% with pembrolizumab vs 93.8% with placebo. With additional follow-up, no increase in any-grade or grade 3-4 adverse events, or steroid use for immune-mediated adverse events was observed. No deaths related to pembrolizumab occurred.

CONCLUSIONS: At 30 months of follow-up, adjuvant pembrolizumab continued to demonstrate a consistent and clinically meaningful improvement in DFS vs placebo in pts with RCC at high risk of recurrence. No new safety signals were observed with pembrolizumab in the adjuvant setting. Clinical trial information: NCT03142334.

ABSTRACT 308: Characterizing IMDC prognostic groups in contemporary first-line combination therapies for metastatic renal cell carcinoma (mRCC). *Ernst MS et al.*

RESULTS: In total, 692 patients received IPI-NIVO, 244 received IOVE, and 7152 received VEGF-TT. Baseline characteristics for IPI-NIVO, IOVE, and VEGF-TT, respectively, were as follows: median age (interquartile range) 63 (56-69), 64 (57-70), and 63 (56-70); male 72%, 74%, and 72% ($p=0.74$); non-clear cell histology 15%, 10%, and 13% ($p=0.15$); sarcomatoid features 24%, 15%, and 13% ($p<0.0001$); brain metastasis 8%, 4%, and 8% ($p=0.04$); liver metastasis 18%, 14%, and 18% ($p=0.17$); underwent nephrectomy 61%, 79% and 80% ($p<0.0001$). OS and ORR are reported in the table. P-values (log rank) for OS between risk groups were significant for IPI-NIVO ($p<0.0001$), IOVE ($p=0.0005$), and VEGF-TT ($p<0.0001$).

CONCLUSIONS: These findings provide real-world survival and response benchmarks for contemporary first-line mRCC treatments and could be helpful for patient counselling. In addition, these findings mirror the efficacy of combination therapies established in clinical trials against VEGF-TT monotherapy. IMDC criteria continue to risk stratify patients in these novel combination therapies.

ABSTRACT 334 - Pathologic outcomes at cytoreductive nephrectomy (CN) following immunotherapy (IO) for patients with advanced renal cell carcinoma (RCC). *Panian J et al.*

RESULTS: We identified53 patients with advanced RCC across 9 institutions who were eligible for the study. For the line of IO therapy immediately preceding CN, 49% received nivolumab+ipilimumab, 30% received IO monotherapy, and 21% received combination IO/VEGF therapy. The median duration of therapy prior to surgery was 11.3 months (range 0.38-47.8). 28% of patients discontinued treatment after CN for observation. Best overall response prior to CN was stable disease in 25% of patients, partial response in 60%, and progressive disease in 4% with 11% unknown. Following receipt of IO-based treatment, 38% of patients exhibited downstaging from the baseline clinical T stage to the CN pathological T stage (Table). 11% of patients had no residual disease at CN. For pathologic outcomes, 85% of patients had negative margins, 75% had necrosis present, and the median tumor size at CN was 6.5 cm. The median PFS was 11.3 months and median OS was 25.7 months for the overall cohort.

CONCLUSIONS: IO-based strategies demonstrate efficacy in the renal primary in patients with advanced RCC. T stage downstaging was demonstrated in 38% of patients with 11% having a complete pathologic response in the renal primary following IO administration. Biomarker studies on baseline and CN tissue will further elucidate molecular predictors of response and resistance to IO therapy.

ABSTRACT 350: Final overall survival analysis and organ-specific target lesion assessments with two-year follow-up in CheckMate 9ER: Nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. *Powles T et al.*

RESULTS: After 25.4 months minimum follow-up (median, 32.9 months) for OS in ITT pts, a total of 271 OS events occurred, and N+C continued to demonstrate OS improvement vs SUN (N = 323 vs 328; median 37.7 vs 34.3 months; HR 0.70 [95% CI 0.55–0.90]). PFS (median 16.6 vs 8.3 months; HR 0.56 [95% CI 0.46–0.68]) and ORR (55.7% [95% CI 50.1–61.2] vs 28.4% [95% CI 23.5–33.6]) benefits were maintained with N+C vs SUN, and 12.4% (N+C) vs 5.2% (SUN) of pts had a complete response. Median duration of response was 23.1 months with N+C vs 15.1 months with SUN. A higher percentage of pts experienced any reduction and ≥30% reduction from baseline with N+C vs SUN in target lesions at all organ sites assessed (Table). Among all treated pts, 97.2% (N+C; N = 320) vs 93.1% (SUN; N = 320) had a treatment-related adverse event (TRAE) of any grade (65.0% vs 54.1% had a grade ≥ 3 TRAE). Conclusions: N+C continued to provide survival improvement vs SUN among ITT pts in the final OS analysis, additionally PFS and ORR benefits with N+C were sustained with minimum 2-year follow-up. A higher proportion of pts experienced tumor shrinkage benefit with N+C vs SUN across all 4 organ sites assessed. No new safety signals emerged with extended follow-up in either arm. These results highlight N+C as a first-line treatment for pts with aRCC. Clinical trial information: NCT03141177.

ABSTRACT 359: Impact of cytoreductive nephrectomy (CN) on survival in metastatic renal cell cancer (mRCC) treated with immune checkpoint inhibitors (ICI). Add to Collection *Perimbeti S et al.*

Results: A total of 4,369 patients were identified- 36.4% (n=1589) had undergone CN. Among patients who got CN, 85.3% were treated with upfront surgery while 13.8% received prior systemic therapy (P = 0.001). The study population was predominantly Caucasian (89.2%) and male (70.6%). Patients who underwent CN were younger (median age 61 vs. 65 years, P = <0.001). Large primary tumors and clinically node-negative status were associated with higher odds of CN (T4 disease - odds ratio (OR) for 1.49, 95% CI 1.13-3.44, P = 0.03; cN0 disease - OR 1.56, 95% CI 1.23-4.56, P = 0.04). OS after 1 year was significantly higher in patients who underwent CN (66.8% vs 33.2%. P <0.001). On multivariate analysis, CN was independently predictive of improved OS with a hazard ratio (HR) of 0.53 and 95% CI 0.41-0.68, P <0.001. Conclusions: In this large retrospective analysis, CN was associated with improved OS among patients with mRCC receiving ICI-based therapies. Our findings suggest that despite recent advances in systemic therapies for mRCC, CN retains an important role in carefully selected patients.

ABSTRACT 360: Quantifying absolute benefit of adjuvant treatments in renal cell carcinoma: A systematic review and network-meta-analysis. *Sipra QUAR et al.*

Results: This NMA included six RCTs with a total of 7525 participants and five unique treatment options. Mixed treatment comparisons showed significant DFS and OS benefit with pembrolizumab (rank 1) when compared against sunitinib (DFS HR 0.74 [0.55-0.99]; OS HR 0.51 [0.27-0.94]). However, there were no significant differences with pembrolizumab compared to pazopanib (DFS HR 0.81 [0.60- 1.09]; OS HR 0.54[0.29-1.01]) and axitinib (DFS HR 0.78 [0.54-1.14]; OS HR 0.52 [0.24-1.16]). The safety profiles were comparable. Absolute benefit of TKIs in adjuvant setting was minimal whereas this benefit increased with higher T and N patients in patients treated with pembrolizumab (Table). Similarly, the treatment benefit increased with higher Leibovich's risk scores at 5, 10 and 15 years of follow up. Conclusions: The current analysis suggests that a risk adapted approach may be useful when considering adjuvant pembrolizumab in RCC patients.

ABSTRACT 370: HIF-pathway genes prognostic for progression-free and overall survival in metastatic clear cell renal cell carcinoma (mccRCC). *Tamukong P et al.*

RESULTS: A total of 28 HIF-related genes (involved either in canonical or non-canonical HIF regulation) were assessed in univariate PH. Nine of these genes were associated with OS (i.e., HIF2A, VEGFC, VEGFD, TGFA, VHL, CCND1, EGFR, EGLN3 and HSP90AA1); and 6 of them were also associated with PFS (i.e., HIF2A, TGFA, VHL, CCND1 and EGLN3, and HSP90AA1). The HIF isotypes HIF1A and HIF3A were not prognostic, likewise VEGFA and VEGFB. Prolyl hydroxylase domain (PHD) proteins efficiently hydroxylate HIFa in normoxic conditions. PHD isotypes EGLN (1-3) were evaluated and only EGLN3 was associated with OS and PFS. HIF is also regulated by non-canonical pathways that function independent of oxygen concentration. HSP90AA1 was the only non-canonical pathway gene that was prognostic, and it predicted both OS and PFS.
CONCLUSIONS: VHL, HIF2A (but not HIF1A and HIF3A), EGLN3 (but not EGLN1 and EGLN2) and some of the HIF-response genes were prognostic of both OS and PFS. HSP90AA1 was prognostic for OS and PFS, suggesting that the non-canonical HIF pathway also plays a role in disease progression. Future studies should consider these HIF pathway genes as potential drug targets, and as predictors of response to treatments targeting the hypoxia pathway and angiogenesis.

ABSTRACT 372: Association of intra-tumoral microbiome and response to immune checkpoint inhibitors (ICIs) in patients with mRCC. *Meza et al.*

RESULTS: Among the 28 pts (22:6, M:F) included in this analysis, 24 (86%) had clear cell histology and 20 (71%) were IMDC intermediate/poor risk. 11 pts (39%) received ICIs as first line treatment and 17 (61%) as second line. Clinical response was seen in 50% of pts included in the study and the most common rendered treatment was nivolumab (17 pts). In the overall cohort, Cutibacterium acne, Moraxella osloensis, and Pasteurella multocida had the highest relative abundances. Additionally, significant differences in relative abundances of specific bacteria were found between ICI responders and non-responders. Among these, Stenotrophomonas maltophilia (p = 0.037) and Corynebacterium sp. zg-917(p = 0.035) had significantly higher relative abundances in pts who responded to ICIs. Conclusions: This is the first study evaluating the association between intra-tumoral microbiome and response to ICIs in pts with mRCC. Among bacteria associated with response, several have particular relevance – for instance, Corynebacterium spp. have been studied for decades as a possible adjunct to immunotherapeutic agents such as BCG. Efforts are ongoing to validate these findings in a larger cohort.

ABSTRACT 375: Association between biomarkers and clinical outcomes of lenvatinib + pembrolizumab in advanced renal cell carcinoma (RCC): Results from Study 111/KEYNOTE-146. Lee CH et al.

RESULTS: Of 147 treated pts, RNA sequencing and WES data were available for 80 (54%) and 60 (41%), respectively. TcellinfGEP was not associated with ORR (P=0.827) or PFS (P=0.741), nor were the other 11 signatures before or after adjustment for TcellinfGEP. ORR for DNA variants reported in the table. Conclusions: In this exploratory analysis of pts with metastatic RCC enrolled in Study 111/KEYNOTE-146 treated with lenva + pembro, responses were observed regardless of biomarker status. There were no statistically significant associations between gene signatures and clinical outcomes. Clinical benefit was observed regardless of VHL, PBRM1, BAP1, or SETD2 mutation status. Analyses in larger randomized datasets will provide additional information on the role of biomarkers in RCC. Clinical trial information: NCT02501096.

ABSTRACT 384: CD70 is a promising CAR-T cell target in patients with advanced renal cell carcinoma. Ye H et al.

METHODS: Four Tissue Microarrays (TMAs) were constructed using 395 tumors from 374 patients with RCC, 4 to 8 cores per tumor. There were 359 primary tumors, 36 metastatic tumors, and 344 matched normal. The primary RCC included 309 CCRCC including 11 with sarcomatoid differentiation, 38 papillary RCC (pRCC) including 1 with sarcomatoid differentiation, 8 chromophobe RCC (ChRCC), and 4 collecting duct RCC (CDC). The metastatic RCC were composed of 31 CCRCC including 3 with sarcomatoid differentiation and 5 PRCC. CD70 expression was evaluated using immunohistochemistry (IHC) and Definiens image analysis.
RESULTS: CD70 staining was detected in tumor cells in primary and metastatic RCC, with minimal staining in normal renal parenchyma. When the positive cutoff was defined as ≥1% of tumor cells demonstrating CD70 staining, the positive rate in CCRCC, pRCC, ChRCC, CDC, and SarRCC was 98%, 32%, 0%, 11%, and 46%, respectively. When the positive cutoff was defined as ≥ 25% of tumor cells stained positive for CD70, the positive rate in CCRCC, pRCC, ChRCC, CDC, and SarRCC was 41%, 10%, 0%, 0%, and 23%, respectively. Finally, when the positive cutoff was defined as ≥50%, the positive rate in CCRCC, pRCC, ChRCC, CDC, and SarRCC was 22%, 2%, 0%, 0%, and 8%, respectively. Metastatic RCC showed a higher % of tumor cells expressing CD70 compared to primary RCC for patients with CCRCC (mean 15% vs 9%) or SarRCC (12% vs 9%).
CONCLUSIONS: Clear cell and sarcomatoid RCC are the RCC subtypes that demonstrate the highest CD70 expression. CD70 expression is further increased in metastatic lesions compared to the primary tumors. Anti-CD70 CAR-T cell therapy may benefit a significant fraction of patients with advanced CCRCC and sarcomatoid RCC.