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TIP01 - SWOG S1931 (PROBE): Phase III randomized trial of immune checkpoint inhibitor (ICI) combination regimen with or without cytoreductive nephrectomy (CN) in advanced renal cancer [NCT04510597]

Vaishampayan U, Tangen C, Tripathi A, Shuch B, Pal S, Barata P, Tan A, Zuckerman P, Mayerson E, Lara P, Agarwal N, Vogelzang N, Thompson I, Kim H

Patient and Methods: Eligible patients with primary tumor and metastases are treated with one of the FDA approved ICI based combinations: ipililumab and nivolumab, axitinib and pembrolizumab, or axitinib and avelumab. Cabozantinib + nivolumab and lenvatinib + pembrolizumab combinations are being added into the next amendment. Urology evaluation and response assessment is required. Randomization occurs between 10-14 weeks of therapy; 1:1 to receive CN followed by systemic therapy or to continue on systemic therapy.
Statistical Design & Endpoints: The primary endpoint is overall survival. We estimate the median survival from time of randomization for the non-surgical arm will be 25 months. The study hypothesis is that CN will result in improvement in OS outcomes in advanced synchronous RCC post-initial systemic immune checkpoint-based combination therapy. With a sample size of 302 eligible, randomized participants (151 per arm) and a one-sided alpha=0.025, the study has 85% power to detect a 47% improvement in median survival (HR=0.68; 1/0.68 = 1.47)
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TIP09- 89Zr-TLX250 for PET/CT imaging of clear cell kidney cancer

Shuch B, Hayward C, Pantuck A

Trial Design: Zircon is an open label, phase 3 study evaluating the performance of Zirconium-89-labeled girentuximab (89Zr-TLX250) for detecting ccRCC. The trial is open at 34 international sites (NCT03849118). The primary endpoint is the sensitivity/specificity of PET/CT imaging with 89Zr-TLX250 to non-invasively predict resection histology. Secondary endpoints include safety/tolerability, performance in cT1a, positive/negative predictive value, and inter/intra-observer variability. Key inclusion criterion includes a solitary, localized, cT1 lesion scheduled for resection. Exclusion criterion include planned biopsy and concurrent malignancy requiring treatment <4 weeks prior to 89Zr-TLX250 administration. Eligible subjects undergo 89Zr-TLX250 administration followed by PET/CT 3-7 days later. Resection is performed <90 days with local/central pathologic review required and CA9 immunohistochemical staining planned. Monitoring of stage/histology allows for modification of sample size (n=252) which currently has 90% power to detect a sensitivity of 83% in the cT1a group. The U.S. FDA granted Breakthrough Therapy designation for 89Zr-TLX250 which aims to improve the diagnosis and staging of ccRCC.

TIP10 A randomized trial of radium-223 (Ra-223) dichloride and cabozantinib in patients (pts) with advanced renal cell carcinoma (RCC) with bone metastases (RADICAL / Alliance A031801)

McKay RR, JacenHe, Atherton P, Perez-Burbano G, Ajmera A, Baghaie S, Koball J, Zemla T, Chen R, Choudhury A, Lang JM, Cole S, Al Baghdadi T, Kwok Y, Beltran H, George D, Morris M, Choueiri TK

Background: Bone metastases are prevalent in approximately 30% of patients with advanced RCC. Patients with bone metastases have a worse prognosis compared to patients without bone metastases and are at risk of symptomatic skeletal events (SSEs). Cabozantinib, a multitargeted inhibitor of multiple kinases, including vascular endothelial growth factor (VEGF) receptor and MET, has improved survival in pts with metastatic RCC and has enhanced activity in bone. Ra-223, an alpha-emitting radioisotope with natural bone-seeking proclivity, has prolonged survival in men with castration-resistant prostate cancer. We previously conducted a pilot study of Ra-223 with VEGF inhibition and demonstrated safety and declines in bone turnover markers (McKay et al, CCR 2018). We designed a randomized phase 2 study through the National Clinical Trials Network investigating cabozantinib with or without Ra-223 in patients with RCC with bone metastases.
Methods: This is an open-label multicenter study. Eligible patients have metastatic RCC of any histology with ≥1 untreated metastatic bone lesion(s). Patients with non-clear cell RCC are eligible. Patients must have a Karnofsky performance status of ≥60% and be on osteoclast-targeted therapy. Patients are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) Ra-223.
Endpoints: The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, quality of life measures, and correlative analyses including liquid biopsy studies and tumor tissue analysis. Target accrual is 210 patients.

CTR11- First-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) in patients with long-term survival of ≥5 years in the CheckMate 214 trial

Tannir NM, Motzer RJ, McDermott DF, Plimack ER, George S, Amin A, Tykodi SS, Srinivas S, Carthon B, Hutson TE, Lee CW, Desilva H, Jiang R, Hammers HJ

Background: First-line NIVO+IPI provided long-term survival benefits versus SUN in patients with advanced renal cell carcinoma (aRCC) after 5 years follow-up in CheckMate 214.
Methods: Patients with clear cell aRCC were randomized to NIVO 3 mg/kg plus IPI 1 mg/kg Q3W×4 then NIVO 3 mg/kg Q2W versus SUN 50 mg QD (4 weeks of 6-week cycles). In this post hoc exploratory analysis, outcomes in patients with overall survival ≥5 years (long-term survivors; LTS) were assessed by IMDC risk (intermediate/poor [I/P-risk] and favorable [FAV-risk]).
Results: Overall, 163/425 I/P-risk and 73/125 FAV-risk patients in the NIVO+IPI arm versus 112/422 I/P-risk and 59/124 FAV-risk patients in the SUN arm were LTS. Baseline characteristics generally did not distinguish LTS from intent-to-treat patients

with NIVO+IPI, except target lesions were smaller and fewer patients had bone metastases. Regardless of risk group in LTS, there were more durable and complete responses with NIVO+IPI versus SUN. Fewer LTS required subsequent systemic therapy with NIVO+IPI versus SUN, and most patients in the SUN arm with subsequent therapy received NIVO monotherapy regardless of risk. More LTS who responded experienced a treatment-free interval with NIVO+IPI versus SUN. Treatment-related adverse events leading to discontinuation did not preclude surviving ≥5 years.
Conclusions: These results highlight the long-term clinical benefits and continued durability of response observed with NIVO+IPI in patients across a spectrum of baseline characteristics and regardless of IMDC risk.

CTR12- Outcomes with first-line nivolumab plus cabozantinib (NIVO+CABO) versus sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC) and treatment-related adverse event (TRAE) timing/management in CheckMate 9ER
Kessler ER, Burotto M, Shah AY, Ryan CW, Shaheen M, Drakaki A, Tomita Y, George S, Motzer RJ, Choueiri TK, Simsek B, Zhang J, Scheffold C, Apolo AB, Bedke J.

Background: First-line NIVO+CABO demonstrated superiority versus SUN in aRCC patients in the phase 3 CheckMate 9ER trial.
Methods: Patients with any IMDC risk and clear cell aRCC were randomized to NIVO 240 mg every 2 weeks + CABO 40 mg once daily versus SUN 50 mg once daily (4/6-week cycles). In this post hoc exploratory analysis, timing/management of grade ≥3 TRAEs and outcomes in patients with these events were assessed to better understand the impact of safety kinetics with NIVO+CABO in first-line aRCC.
Results: Of all treated patients, 310/320 (NIVO+CABO) versus 298/320 (SUN) had any-grade TRAEs and 199 versus 168 had grade ≥3 TRAEs, respectively. Most baseline characteristics in patients with grade ≥3 TRAEs were similar to intent-to-treat patients and generally balanced between arms. Grade ≥3 TRAE time to onset/resolution patterns and management are summarized (Table). Of patients with ≥1 subsequent dose delay/reduction due to any adverse event (72% [NIVO+CABO] vs 70% [SUN]), most continued on therapy. Additionally, progression-free survival (PFS) was improved with NIVO+CABO versus SUN (HR, 0.62 [95% CI, 0.47-0.82]) in patients with grade ≥3 TRAEs (Table).
Conclusions: The safety profile of NIVO+CABO was manageable, most common grade ≥3 TRAEs resolved, and almost all patients assessed here with ≥1 dose delay/reduction continued on therapy. PFS was notably improved with NIVO+CABO in patients with grade ≥3 TRAEs regardless of dose delay/reduction patterns.

CTR15- First results of 68Ga-EMP-100 PET for imaging c-MET expression in metastatic renal cell carcinoma
Mittlmeier L, Todica A, Gildehaus FJ, Unterrainer M, Beyer L, *Brendel M, Albert NL, Ledderose ST, Vettermann FJ, Schott M, Rodler S, Marcon J , Ilhan H, Cyran CC, Stief CG, Bartenstein P and Staehler M*

Background: c-MET as receptor tyrosin kinase is upregulated in renal cell carcinoma and has been shown to be correlated with patients' survival in metastatic renal cell carcinoma (mRCC). Prediction of treatment response to tyrosin kinase receptor inhibitors targeting c-MET such as cabozantinib is important to improve disease management in mRCC. 68Ga-EMP-100 is a novel PET ligand that directly targets c-MET expression. Here we present first-in human data of 68Ga-EMP-100 in mRCC comparing uptake characteristics on an intra- and interindividual level.
Methods: 12 patients with mRCC prior or at assessment of further therapy options underwent 68Ga-EMP-100 PET/CT imaging. Uptake of mRCC lesions were compared by SUVmean and SUVmax measurements.
Results: Overall, 87 tumor lesions were delineated: Of these, 79.3% were visually rated c-MET positive (median SUVmax of 4.4 / SUVmean 2.5). Comparing tumor sites, the highest uptake was at the primary tumor followed by bone, lymph node and visceral metastases. The highest number of PET-negative metastatic sites were in lung and liver.
Conclusions:68Ga-EMP-100 which targets c-MET expression shows increased uptake in mRCC patients with high inter- and intraindividual differences. Our pilot study shows that 68Ga-EMP-100 could be a promising molecular imaging tool for mRCC patients undergoing tyrosin kinase inhibitor therapies.

N16- Anti-CAIX BBζ CAR4/8 T cells exhibit superior efficacy in a clear cell renal cell carcinoma (ccRCC) mouse model
Wang Y, Buck A, Grimaud M, Culhane AC, Kodangattil S, Razimbaud C, Bonal D, Nguyen QD, Zhu Z, Wei K, O'Donnell ML, Huang Y, Signoretti S, Choueiri TK, Freeman GJ, Zhu Q, Marasco WA

Improving CAR-T cell therapy for solid tumors requires a better understanding of CAR design and cellular composition. Here, we compared second-generation (BBζ, 28ζ) with third-generation (28BBζ) carbonic anhydrase IX (CAIX) targeted CAR constructs and investigated the anti-tumor effect of CAR-T cells with different CD4/CD8 proportions in vitro and in vivo. The results demonstrated that BBζ exhibited superior efficacy compared to 28ζ and 28BBζ CAR-T cells in a ccRCC skrc-59 cell bearing NSG-SGM3 mouse model. The mice treated with a single dose of BBζ CAR4/8 showed complete tumor remission and remained tumor-free 72 days after CAR-T cells infusion. Profiling tumor infiltrating T cells via scRNAseq, we found that BB CAR8 upregulated expression of HLA II and cytotoxicity associated genes, while downregulating inhibitory immune checkpoint receptor genes and diminishing differentiation of Tregs, leading to excellent therapeutic efficacy in vivo. Increased memory phenotype, elevated tumor infiltration, and decreased exhaustion genes were observed in the CD4/8 UNT cells compared to CD8 alone, suggesting that CD4/8 is the preferred cellular composition for CAR-T cell therapy with long-term persistence. In summary, these findings support that BBζ CAR4/8 T cells are a highly potent, clinically translatable cell therapy for ccRCC.

N19 - COVID-19 vaccination in patients with renal cell carcinoma receiving immune checkpoint inhibitors
Dzimitrowicz H, Hwang J, Shah R, Ashcraft K, George DJ, Salama A, Zhang T

Background: Patients on cancer treatment were excluded from COVID-19 vaccine trials; thus safety of COVID-19 vaccination in patients with RCC receiving ICIs is not well described.

follow up at Duke Cancer Center. We retrospectively reviewed encounters over 3 months post-vaccination. Primary outcome was adverse events attributed to vaccination; other outcomes included subsequent immune related adverse events (IRAE) and COVID-19 infection. Results: 36 study patients (vax+ with ICI) and 36 control patients (vax+) were identified. Baseline characteristics are in Table 1. 22.2% of study patients (N=8/36) reported vaccination-related symptoms: chills (8.3%; N=3), headache (5.6%; N=2), fatigue (5.6%; N=2), and one with fever, nausea, vomiting, diarrhea, myalgias, injection site pain, and rash. One control patient developed PVCs. Two study patients (5.6%) developed new/worsening IRAE requiring systemic steroids and/or treatment hold (colitis and adrenal insufficiency). One study patient (2.8%) and 0 patients developed COVID-19 infection after one and two vaccine doses, respectively. Conclusions: In a population of patients with RCC receiving ICI, COVID-19 vaccination appears to be well tolerated and safe. The higher rate of post-vaccination symptoms reported in ICI+ patients may be related to more frequent visits vs controls. In solid tumor populations at higher risk for severe COVID19 infections, vaccination is important to mitigate this risk.

N22- Nivolumab plus cabozantinib (N+C) versus sunitinib (S) in patients with advanced renal cell carcinoma (aRCC) and bone metastasis: subgroup analysis of the Phase 3 CheckMate 9ER trial

Apolo A, Powles T, Bourlon MT, Suarez C4, Porta C, George S, Choueiri TK, Motzer R, Scheffold C, Zhang J, Mangeshkar M, Shah AY, Escudier B,

Background: In the phase 3 CheckMate 9ER trial (NCT03141177), N+C significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in first-line aRCC. This exploratory analysis evaluated outcomes by baseline bone metastasis status per investigator.
Methods: 651 patients with clear cell aRCC were randomized 1:1 to N (240 mg Q2W) plus C (40 mg QD) or S (50 mg QD for 4 weeks of 6-week cycles). Data cut-off was Sep 10, 2020. PFS and ORR were per blinded independent central review per RECIST v1.1.
Results: 151 patients had bone metastasis at baseline. PFS was longer with N+C vs S in patients with or without bone metastasis and the HR favored N+C vs S (Table). The OS HR also favored N+C vs S. ORR was higher, and duration of objective response (OR) was longer in N+C vs S in both groups. Both subgroups had longer duration of treatment for N+C vs S. All-causality Grade 3-4 adverse events for N+C vs S were 78% vs 67% and 71% vs 68%, in patients with and without bone metastasis, respectively; treatment-related Grade 3-4 adverse events were 71% vs 42% and 59% vs 55%.
Conclusions: Treatment with N+C vs S improved PFS, OS, and ORR in patients with first-line aRCC irrespective of bone metastasis at baseline, consistent with outcomes in all randomized patients.

N25 - Cost per survivor (CPS) and cost per life-month (CPLM) of nivolumab plus ipilimumab (NIVO+IPI) versus pembrolizumab plus axitinib (PEMBRO+AXI) for previously untreated advanced renal cell carcinoma (aRCC)

Huo S, Del Tejo V, Du EX, Wu A, Chin A, Betts KA

Background: NIVO+IPI and PEMBRO+AXI demonstrated survival benefits versus sunitinib (SUN) for previously untreated aRCC in the CheckMate 214 and KEYNOTE-426 trials, respectively. In the absence of head-to-head trial, their comparative costs have not been assessed. This study compared the CPS and CPLM of the two treatments.
Methods: Overall survival (OS) rates were derived from a matching-adjusted indirect comparison of NIVO+IPI (CheckMate 214, median follow-up: 55 months) versus PEMBRO+AXI (KEYNOTE-426, median follow-up: 43 months). Treatment costs (2020 USD) included costs of drug acquisition, administration, and grade 3/4 adverse events. The monthly incremental CPS for NIVO+IPI or PEMBRO+AXI relative to SUN was calculated as the difference in monthly costs divided by the difference in OS rates at 12, 24, 36, and 48 months. The incremental CPLM was estimated similarly using restricted mean survival time.
Results: The monthly incremental CPS relative to SUN for NIVO+IPI decreased over time and were consistently lower than that for PEMBRO+AXI (at 48 months: $18,881 vs. $136,342) (Figure 1). Similarly, NIVO+IPI had consistently lower incremental CPLM (relative to SUN) compared with PEMBRO+AXI throughout follow-up with a difference in incremental CPLM of $63,611 over 48 months.
Conclusions: NIVO+IPI had consistently lower incremental CPS and CPLM (relative to SUN) compared with PEMBRO+AXI over time, indicating greater cost efficiency for NIVO+IPI as first-line aRCC treatment.

N33- Outcomes of cytoreductive nephrectomy followed by active surveillance in metastatic renal cell carcinoma

Khaleel S, Silagy A, Duzgol C, Kotecha R, Rappold P, Weiss K, Dinatale R, Patil S, Coleman J, Russo P, Voss M, Hakimi A.

Background: Cytoreductive nephrectomy (CRN) for management of metastatic renal cell carcinoma (mRCC) has been recently debated. We retrospectively evaluated systemic therapy (ST)-naïve mRCC patients undergoing CRN followed by active surveillance (CRN+AS), subclassified into favorable- and unfavorable-risk based on prognostic criteria proposed by Rini et al for length of AS after CRN (2016). We assessed intervention-free survival (IFS), overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS).
Methods: We searched our institutional mRCC database for ST-naïve patients undergoing CRN+AS between 1989-2020. Categorical and continuous outcomes were assessed using Chi-squared and Welch T-test, respectively. Cox regression and Kaplan-Meier method were used to assess survival outcomes.
Results: Of 517 ST-naïve patients who underwent CRN, 414; (80%) had residual disease, followed by AS vs ST in 97 (23.4%) vs 295 (76.6%) patients. Median IFS was 22.2 months in the CRN+AS cohort, with 58 patients undergoing further ST/surgery. Median PFS, OS and CSS were 7.7, 52.3, and 56.5 months, respectively. Favorable Rini-risk was significantly associated with longer IFS (HR 0.60; 95% CI: 0.38–0.95, p=0.026) and CSS (HR 0.51; 95% CI: 0.27–0.99, p=0.041), but not OS or PFS, in CN+AS patients (Figure 1).

Conclusions: In this retrospective study, mRCC patients selected for primary CRN+AS had median IFS of 22.2 months, supporting CRN+AS in well-selected patients, avoiding the morbidity of primary or adjuvant ST. Prognostic criteria proposed by Rini et al for CRN+AS patients may aid in patient selection and management.

Methods: We identified patients with RCC who received at least 1 dose of an FDA-authorized COVID-19 vaccine (vax+), on or off ICI, between 12/1/2020 and 4/1/2021, with at least 3 months

E42- Characterizing the immune response in patients with renal cell carcinoma (RCC) following COVID-19 vaccination

Malhotra J, Salgia S, Zengin Z, Meza L, Ely J, Hsu J, Kelley E, Mead H, Chehrazi-Raffle A, Govindarajan A, Muddasani R, Dizman N, Chawla N, Dorff T, Lyou Y, Karczewska E, Trent J, Salgia R, Altin J, Pal SK

Background: There are limited data evaluating COVID-19 vaccine efficacy and response among RCC patients.
Methods: Patients with genitourinary cancer (prostate, kidney, and bladder) who had not received any COVID-19 vaccine were included. Blood was collected prior to vaccination, as well as at 2, 6, and 12 months following administration of one vaccine dose. Patients receiving systemic treatments provided additional blood at three consecutive therapy cycles. An ELISA assay was used to assess the blood specimens for antibody titers and the result was reported as an immune status ratio (ISR).
Results: Of the 80 patients that submitted both baseline and 2-month specimen, 33 had RCC. A majority of these patients were receiving systemic therapy (n=31, 93.9%), with immune checkpoint inhibitors as the most common (n=19, 61.2%) followed by targeted agents (n=11, 35.5%). The median age was 64 (interquartile range [IQR], 57.5-72.0), with a majority of male (n=22, 66.7%) and white (n=28, 84.8%) patients. BNT162b2 (Pfizer) was the most commonly administered vaccine (n=20, 60.6%). In the 33 patients included in this analysis, the median baseline ISR was 0.14 (IQR, 0.12-0.24) compared to 7.33 (IQR, 7.08-7.34) at 2 months (P<0.001). Results demonstrated a seroconversion rate of 90.9% by the 2-month timepoint, and no significant difference in ISR change between baseline and month 2 based on systemic treatment rendered.
Conclusions: Our data demonstrates sufficient immune response in RCC patients who have received a commercially available COVID-19 vaccine and encourages continued vaccination in these patients.

E43- Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: results of a phase 2 trial.

Lee CH, Voss MH, Carlo MI, Chen YB, Zucker M, Knezevic A, Lefkowitz RA, Shapnik N, Dadoun C, Reznik E, Shah NJ, Owens CN, McHugh DJ, Aggen DH, Laccetti AL, Kotecha R, Feldman DR, Motzer RJ

Background: Cabozantinib plus nivolumab (CaboNivo) improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) over sunitinib in a phase 3 trial for metastatic clear cell renal cell carcinoma (RCC). (Choueiri, abstract 6960, ESMO 2020) We report the results of a phase 2 trial of CaboNivo in patients (pts) with non-clear cell RCC.
Methods: Pts had advanced non-clear cell RCC, 0 or 1 prior systemic therapies excluding prior immune checkpoint inhibitors, and measurable disease by RECIST. Cabo 40 mg/day plus Nivo 240 mg every 2 weeks or 480 mg every 4 weeks was given across two cohorts. Cohort 1: papillary, unclassified, or translocation associated RCC; Cohort 2: chromophobe RCC. The primary endpoint was ORR by RECIST; secondary endpoints included PFS, OS, and safety. Cohort 1 was a single stage design that met its primary endpoint and was expanded to produce more precise estimates of ORR. Cohort 2 was a Simon two-stage design that closed early for lack of efficacy. Correlative analyses by next generation sequencing were performed and to be presented.
Results: A total of 40 pts were treated in Cohort 1, and 7 pts were treated in Cohort 2 (data cutoff: Jan 20, 2021). Median follow up time was 13.1 months (range 2.2 – 28.6). In Cohort 1, 26 (65%) pts were previously untreated, and 14 (35%) pts had 1 prior line: 10 (25%) received prior VEGF-targeted therapy and 8 (20%) received prior mTOR-targeted therapy. ORR for Cohort 1 was 48% (95% CI 31.5–63.9; Table). Median PFS was 12.5 months (95% CI 6.3–16.4) and median OS was 28 months (95% CI 16.3–NE). No responses were seen among 7 patients in Cohort 2 with chromophobe histology (Table). Grade 3/4 treatment emergent adverse events were consistent with that reported in the phase 3 trial; Grade 3/4 AST and ALT were 11% and 13%, respectively. Cabozantinib and nivolumab were discontinued due to toxicity in 13% and 17% of pts, respectively.
Conclusions: CaboNivo had an acceptable safety profile and showed promising efficacy in metastatic non-clear cell RCC pts with papillary, unclassified, or translocation associated histologies whereas activity in patients with chromophobe RCC was limited.

LB47 Molecular dissection of clear cell renal cell carcinoma reveals prognostic significance of epithelial-mesenchymal transition gene expression signature

Nallandhighal S, Vince R, Karim R, Groves S, Stangl-Kremser J, Russell C, Hu K, Pham T, Cani AK, CJ, Zaslavsky A, Mehra R, Cieslik M, Morgan TM, Palapattu GS, Udager AM, Salami S

Background: There is an ongoing need to develop prognostic biomarkers to improve the management of clear cell carcinoma (ccRCC).
Methods: We retrospectively identified two complementary discovery cohorts of patients with ccRCC who underwent: 1) radical nephrectomy (RNx) with inferior vena cava (IVC) tumor thrombectomy (Patients=5, Samples=24); and 2) RNx for localized disease and developed recurrence vs. no recurrence (n=36). Using TCGA ccRCC cohort for validation (n=386), Kaplan-Meier (KM) survival analysis and multivariable cox-proportional hazard testing were utilized to investigate the prognostic impact of cell cycle proliferation (CCP) and a novel 22-gene epithelial mesenchymal transition (EMT) score on progression free survival (PFS) and disease specific survival (DSS).
Results: In the discovery cohorts, we observed over-expression of WT1 and CCP genes in the tumor thrombus vs. the primary tumor, as well as in patients with recurrence vs. those without recurrence. Hallmark pathway analysis demonstrated enrichment of EMT and CCP related pathways in patients with high WT1 expression in the TCGA (validation) ccRCC cohort. CCP and EMT scores were derived in the validation cohort which was stratified into four risk groups using Youden-Index cut points: CCPlow/EMTlow; CCPlow/EMThigh; CCPhigh/EMTlow; and CCPhigh/EMThigh. CCPhigh/EMThigh risk group was associated with the worst PFS and DSS (both p<0.001). In a multivariable analysis, CCPhigh/EMThigh was independently associated with poor PFS and DSS (HR=4.6 and 10.3, respectively; p<0.001).
Conclusions: We demonstrate the synergistic prognostic impact of EMT in tumors with high CCP score. Our novel EMT score has the potential to improve risk stratification and provide potential novel therapeutic targets.