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INTERNATIONAL KIDNEY CANCER SYMPOSIUM



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A B S T R A C T B O O K

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]

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Background: Kidney cancer presenting with synchronous primary tumor and metastases has demonstrated shorter survival outcome, as compared to the patients relapsing later with metastases after nephrectomy. CARMENA trial demonstrated no change in overall survival with addition of nephrectomy to sunitinib therapy. Immune checkpoint-based combination therapy has now become the standard of care in frontline setting for RCC. The role of nephrectomy or primary resection has not been evaluated in the setting of immune checkpoint based systemic therapy. The PROBE study design attempts to answer the question whether CN has an impact on overall survival outcomes in advanced RCC within the context of immune checkpoint-based combination regimens. The underlying mechanism is that the broader antigen spread and higher neoantigen load enabled by the primary tumor would enhance the efficacy of the immune therapy. CN after initial systemic therapy will potentially enable eradication of the immune resistant clones within the primary.

Patient and Methods: Eligible patients with primary tumor and metastases are treated with one of the FDA approved ICI based combinations: ipilimumab 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)

Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819, U10CA180820

TIP02- First-Line (1L) MK-1308A + lenvatinib or pembrolizumab + belzutifan + lenvatinib versus pembrolizumab + lenvatinib for clear cell renal cell carcinoma (ccRCC): a randomized, open-label phase 3 study

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Background: Pembrolizumab (PD-1 inhibitor) plus lenvatinib (VEGF-TKI) as 1L therapy has demonstrated antitumor activity in patients with advanced ccRCC. Belzutifan (MK-6482; hypoxia-inducible factor 2 α inhibitor) and MK-1308A (coformulation of pembrolizumab and quavonlimab [CTLA-4 inhibitor]) have each shown activity in phase 1 and 2 trials. Belzutifan or quavonlimab with a PD-1/VEGF-TKI backbone combination may provide additional benefit as 1L treatment.

Trial Design: This open-label phase 3 study (NCT04736706) will enroll and randomize 1:1:1 approximately 1431 patients to arm A (belzutifan 120 mg + lenvatinib 20 mg oral QD + pembrolizumab 400 mg IV Q6W), arm B (MK-1308A [quavonlimab 25 mg + pembrolizumab 400 mg] IV Q6W and lenvatinib 20 mg QD), or arm C (pembrolizumab 400 mg IV Q6W + lenvatinib 20 mg QD). Treatment will continue until documented disease progression, withdrawal of consent, or other discontinuation event; pembrolizumab and MK-1308A will be limited to 18 infusions (~2 years). Adults with metastatic ccRCC, measurable disease per RECIST v1.1, KPS score $\geq 70\%$, and no prior systemic therapy for advanced ccRCC will be enrolled.

Endpoints: Dual primary endpoints are progression-free survival per RECIST v1.1 and overall survival for arms A or B versus arm C for patients with International mRCC Database Consortium (IMDC) intermediate/poor status and regardless of IMDC status. Secondary endpoints: objective response rate, duration of response, patient-reported outcomes, and safety.

TIP03- Randomized, open-label, phase 3 study of belzutifan plus lenvatinib versus cabozantinib in patients with advanced renal cell carcinoma (RCC) after anti-PD-1/PD-L1 therapy

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Background: Treatments after first-line anti-PD-1/PD-L1-based therapies are needed for advanced RCC. The transcription factor hypoxia-inducible factor (HIF)-2 α drives oncogenesis in clear cell RCC (ccRCC). First-in-class HIF-2 α inhibitor belzutifan (MK-6482) has shown promising antitumor activity as monotherapy (phase 1) and combined with cabozantinib in heavily pretreated patients with ccRCC (phase 2). This randomized, open-label, active-controlled phase 3 trial (NCT04586231) will evaluate efficacy and safety of belzutifan + lenvatinib versus cabozantinib in patients with advanced ccRCC that progressed after anti-PD-1/PD-L1 therapy.

Trial Design: Approximately 708 patients will be randomized 1:1 to oral belzutifan 120 mg QD + lenvatinib 20 mg QD or to oral cabozantinib 60 mg QD. Stratification factors include International mRCC Database Consortium prognostic scores (0, 1 or 2, or 3–6), prior therapies (1 or 2), and geographic region (North America, Western Europe, or rest of the world). Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Adults with locally advanced or metastatic ccRCC, disease progression on or after anti-PD-1/PD-L1 monotherapy or combination therapy (most recent treatment), ≤ 2 prior systemic regimens (≤ 1 anti-PD-1/PD-L1), measurable disease (RECIST v1.1), and KPS $\geq 70\%$ are eligible.

Endpoints: Dual primary endpoints: progression-free survival (RECIST v1.1, assessed by blinded independent central review [BICR]) and overall survival. Secondary objectives: objective response rate and duration of response (both per RECIST v1.1 by BICR) and safety and tolerability.

TIP04- Treatment of advanced renal cell carcinoma (RCC) after progression on systemic therapy: open-label phase 2 study of two doses of the HIF-2 α inhibitor belzutifan

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Background: Hypoxia-inducible factor (HIF)-2 α drives oncogenesis in clear cell RCC (ccRCC). The genes induced by HIF-2 α regulate several key processes, including angiogenesis, proliferation, invasion, and metastasis. Belzutifan (MK-6482), a first-in-class HIF-2 α inhibitor, showed promising antitumor activity with a favorable safety profile in patients with heavily pretreated ccRCC.

Trial Design: This randomized, open-label, multicenter phase 2 trial (NCT04489771) will evaluate the efficacy and safety of two doses of belzutifan in patients with advanced ccRCC who experienced progression after systemic therapy. Approximately 150 patients will be randomized 1:1 to once-daily oral belzutifan 120 mg or 200 mg. Treatment will continue until progression, unacceptable toxicity, or withdrawal. Adults with locally advanced/metastatic ccRCC (per RECIST v1.1), progression on or after one line of anti-PD-1/PD-L1-based therapy (monotherapy or combination therapy, with the immediately preceding line of treatment being an anti-PD-1/PD-L1 therapy), ≤ 3 prior systemic regimens, and KPS $\geq 70\%$ are eligible. Progression is defined as having received ≥ 2 doses of an anti-PD-1/PD-L1 agent and having demonstrated radiographic disease progression (per investigator). Stratification factors include International mRCC Database Consortium prognostic scores and number of prior TKI-containing therapies.

Endpoints: The primary endpoint is objective response rate per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints are progression-free survival, duration of response, and clinical benefit rate per RECIST v1.1 by BICR, overall survival, pharmacokinetics, and safety.

TIP05- TiNivo-2: a phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following one or two lines of therapy where one line has an immune checkpoint inhibitor

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Background: Tivozanib, a highly selective and potent vascular endothelial growth factor receptor tyrosine kinase inhibitor, has demonstrated single-agent efficacy in advanced renal cell carcinoma (aRCC) along with minimal off-target toxicities and a favorable adverse event (AE) profile. Tivozanib was approved by the FDA on March 10, 2021 for the treatment of patients with aRCC who had progressed on 2 or more prior lines of therapy. Tivozanib was combined with Nivolumab in the TiNivo trial (NCT03136627), showing an objective response rate of 56%, disease control rate of 96%, median PFS of 18.9 months and a favorable safety profile.

Trial Design: TiNivo-2 (NCT04987203) is a phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following 1-2 lines of therapy including an immune checkpoint inhibitor. Eligibility criteria include age >18 years, clear cell RCC, ECOG PS 0-1, and disease progression during or following at least 6 weeks of treatment with ICI for RCC. Subjects will be stratified by IMDC risk category and whether ICI was received in most recent line of treatment or not. On both arms, subjects will receive Tivozanib 1.34 mg orally once daily for 21 consecutive days followed by 7 days off. In the combination arm, subjects will also receive Nivolumab 480mg intravenously every 4 weeks. Study assessments include CT scan or MRI of the chest, abdomen, and pelvis every 8 weeks following Cycle 1 Day 1 for 2 years and every 12 weeks thereafter until disease progression is confirmed by independent radiology review.

Endpoints: The primary objective is to compare the progression-free survival (PFS) of tivozanib in combination with nivolumab to tivozanib. A sample size of 326 subjects, with 191 events will provide at least 80% power to detect a 50% improvement in PFS, 12 mos v. 8 mos, as assessed by an IRR. Secondary endpoints include assessment of overall survival (OS), objective response rate (ORR), and duration of response (DoR), as well as safety and tolerability. Exploratory endpoints are to assess the quality of life (FKSI-DRS and EORTC QLQ C-30) and to investigate the pharmacokinetics of tivozanib. TiNivo-2 is actively enrolling and planning to open at 190 sites in the United States, and the European Union.

Funding: Aveo Oncology

TIP06- KEYNOTE-B61: an open-label phase 2 study of first-line (1L) pembrolizumab with lenvatinib for non-clear cell renal cell carcinoma (nccRCC)

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Background: Most RCC cases have clear cell histology (ccRCC) with the remaining being classified as nccRCC. Survival in advanced nccRCC is worse than for ccRCC because these cancers are aggressive, effective systemic treatment options are lacking, and there is no standard of care. Current treatment guidelines recommend clinical trials as the preferred strategy. Monotherapy with the PD-1 inhibitor pembrolizumab has shown efficacy with an acceptable safety profile as 1L treatment. In the phase 3 KEYNOTE 581/CLEAR study, the VEGF-TKI lenvatinib + pembrolizumab combination showed antitumor activity in patients with metastatic ccRCC as 1L therapy, suggesting that this combination might be effective for nccRCC.

Trial Design: The phase 2, open-label, single-arm KEYNOTE-B61 study (NCT04704219) will evaluate pembrolizumab 400 mg Q6W + lenvatinib 20 mg QD as 1L treatment for nccRCC; approximately 152 patients will be enrolled. Treatment will continue for up to 2 years (pembrolizumab) or beyond (lenvatinib) until disease progression, unacceptable toxicity, or withdrawal of consent. Patients who discontinue one treatment may continue the other treatment as monotherapy. Adults with histologically confirmed nccRCC, locally advanced/metastatic measurable disease per RECIST v1.1 by blinded independent central review (BICR), no prior systemic therapy for nccRCC, and KPS \geq 70% will be enrolled.

Endpoints: The primary endpoint is objective response rate per RECIST v1.1 by BICR. Secondary efficacy endpoints are clinical benefit rate, disease control rate, duration of response, progression-free survival, overall survival, and safety.

TIP07- Investigational immune and targeted combination therapies for patients with advanced clear cell renal cell carcinoma (ccRCC): a phase 1b/2 umbrella study

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Background: New treatments for first and subsequent lines of therapy for ccRCC are needed. This umbrella platform study is an adaptive, open-label, rolling-arm, multicenter, phase 1b/2 trial in advanced ccRCC evaluating combinations of investigational agents targeting CTLA-4 (quavonlimab [MK-1308]), HIF-2 α (belzutifan [MK-6482]), LAG-3 (favezelimab [MK-4280]), ILT4 (MK-4830), PD-1 (pembrolizumab), and VEGF-TKI (lenvatinib). Substudy 03A (NCT04626479) will evaluate first-line therapy combinations and substudy 03B (NCT04626518) will evaluate therapies in patients with progression on or after PD-1/PD-L1 inhibitors and VEGF-TKIs.

Trial Design: Adults with histologically confirmed ccRCC and KPS \geq 70% are eligible. Both sub-studies comprise a safety lead-in phase for experimental combinations with investigational agents to establish a recommended phase 2 dose, followed by an efficacy phase. Experimental arms will enroll ~80 (03A) and ~50 (03B) patients. Patients will be randomly assigned 2:1 (03A) or 1:1 (03B) to an experimental arm or to a reference arm (pembrolizumab + lenvatinib). Experimental arms in 03A are MK-1308A (quavonlimab and pembrolizumab) + lenvatinib, MK-4280A (favezelimab and pembrolizumab) + lenvatinib, and belzutifan + lenvatinib + pembrolizumab. Experimental arms in 03B are MK-1308A, MK-4280A, pembrolizumab + belzutifan, lenvatinib + belzutifan, and pembrolizumab + MK-4830.

Endpoints: Primary endpoints are safety and tolerability (safety lead-in phase) and safety and ORR per RECIST v1.1 by blinded independent central review (BICR; efficacy phase). Secondary endpoints during the efficacy phase are DOR, PFS (RECIST v1.1 by BICR), CBR, and OS.

TIP08- OPTimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC)

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Background: The standard first-line IO combinations for metastatic clear cell renal cell carcinoma (mccRCC) include an anti-PD-1 antibody plus either (1) an anti-CTLA-4 antibody (IO/IO), or (2) an anti-VEGF TKI (IO/TKI). Currently, there is no level-1 evidence to guide physician's choice between an IO/IO versus IO/TKI combination.

Methods: A correlative study of the phase III IMmotion 151 trial assigned 823 clear cell kidney cancer tumors into seven gene expression clusters based on RNA-sequencing data (Motzer et al., Cancer Cell 2020). The proposed phase II, multicenter study uses the established seven clusters as a predictive biomarker to assign mccRCC patients to either an IO/IO (ipilimumab/nivolumab) or an IO/TKI regimen. This evaluates the hypothesis that patients with clusters enriched in immunogenic/proliferative pathways (clusters 4/5/7) will have improved outcomes with ipilimumab/nivolumab compared to unselected historical controls, while patients with clusters enriched in angiogenic pathways (cluster 1/2) will have improved outcomes with IO/TKI compared to unselected historical controls. The trial design includes two parallel single arms enrolling: 27 patients with cluster 4/5/7 tumors on ipilimumab/nivolumab arm (primary endpoint: objective response rate (ORR); H0: ORR < 40%, HA: ORR > 60%) and 34 patients with cluster 1/2 tumors on the IO/TKI arm (primary endpoint: ORR; H0: ORR < 55%, HA: ORR > 75%).

TIP09- 89Zr-TLX250 for PET/CT imaging of clear cell kidney cancer

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Background: Small renal masses make up the majority of new kidney cancer diagnoses. Overtreatment contributes to significant morbidity/mortality. There are no accurate, non-invasive ways to predict tumor subtype. Clear cell renal cell carcinoma (ccRCC) accounts for ~65% of localized disease and the majority of deaths. VHL loss in ccRCC upregulates surface marker carbonic anhydrase 9 (CA9) in 95% of tumors with minimal normal tissue expression making it a promising imaging agent. Identification of ccRCC may limit biopsies and/or appropriately select patients for treatment.

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)

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

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 $\geq 60\%$ 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

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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 \times 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.

CLINICAL TRIALS WITH RESULTS

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

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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.

CLINICAL TRIALS WITH RESULTS

CTR13- A prospective randomized pilot trial of stereotactic body radiation therapy vs. radiofrequency ablation for the management of small renal masses

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Background: The potential of ablative technologies in replacing surgery for the treatment of small renal masses (SRMs) ≤ 4 cm is unclear. Our objective was to evaluate the feasibility and toxicity of stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) for SRMs to determine the utility of a future full-scale multicenter trial.

Methods: Patients scheduled for renal cell carcinoma (RCC) treatment at a single academic center were approached for this pilot trial, with the aim of recruiting 24 patients. Participants were assigned 1:1 to SBRT or RFA using RedCAP for randomization. The 13-month protocol includes imaging at 3, 6, 9, and 12 months post-procedure. Biopsies were completed prior to the procedure and at 12 months. Multiple clinical parameters were collected.

Results: Beginning in December 2019, 24 patients were recruited and randomized (SBRT=11; RFA=13). Nine had SBRT, 8 RFA, 5 have not yet had treatment, and 2 became ineligible. Patient characteristics are in Table 1. Two patients (both SBRT) had a 12-month biopsy showing no evidence of recurrence or metastases, while two patients (1 RFA, 1 SBRT) had 9-month CT showing no recurrence. Data are not yet available for the remaining patients. An early grade 2 flare-up occurred in one SBRT patient.

Conclusions: Recruitment and randomization of patients with SRMs is feasible on a timeline that allows for regular follow-ups and imaging. Thus far, both treatments have been shown to have an excellent short-term safety profile.

CLINICAL TRIALS WITH RESULTS

CTR14 - Characterization and management of adverse reactions (ARs) in patients with advanced renal cell carcinoma (aRCC) receiving lenvatinib + pembrolizumab (CLEAR study)

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Background: In the CLEAR study, lenvatinib + pembrolizumab significantly improved efficacy outcomes versus sunitinib in first-line treatment of aRCC. Herein, we characterize key ARs grouped by preferred terms per FDA definitions from the US prescribing information in patients with aRCC treated with lenvatinib + pembrolizumab; we also discuss respective AR management strategies.

Methodology: In the CLEAR study, patients were randomized (1:1:1) to lenvatinib 20mg QD PO + pembrolizumab 200mg IV Q3W (n=355); lenvatinib 18mg QD PO + everolimus 5mg QD PO (n=357); or sunitinib 50mg QD PO (4 weeks on/2 weeks off) (n=357). Key ARs in patients treated with lenvatinib + pembrolizumab are characterized herein.

Results: Median times (weeks) to first onset of key ARs (any grade, incidence >30%) with lenvatinib + pembrolizumab were: decreased appetite (14.6), diarrhea (20.0), fatigue (4.4), hypertension (3.0), hypothyroidism (14.3), musculoskeletal pain (6.4), nausea (14.4), rash (11.4), and stomatitis (6.6). Key ARs resulting in dose modifications/discontinuations among patients who received at least 1 dose of any study drug are shown in the Table. The time to onset of grade ≥ 3 ARs and AR management strategies will be reported.

Conclusions: In general, ARs due to lenvatinib + pembrolizumab were consistent with known safety profiles. As will be presented, clinicians play a critical role in prompt identification and AR-directed management of patients with aRCC; such management may potentially reduce treatment interruption(s) and/or lenvatinib dose reduction.

CTR15- First results of 68Ga-EMP-100 PET for imaging c-MET expression in metastatic renal cell carcinoma

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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 SUV_{mean} and SUV_{max} measurements.

Results: Overall, 87 tumor lesions were delineated: Of these, 79.3% were visually rated c-MET positive (median SUV_{max} of 4.4 / SUV_{mean} 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

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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 BBζ 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.

N17- Deconstructing the clear cell renal cell carcinoma using single nuclei multiomics

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Clear cell renal cell carcinoma - ccRCC accounts for about 80% of kidney tumors and often carries a worse prognosis than other renal cell carcinomas. We hypothesize that sub-phenotypes of ccRCC exhibit unique cellular programs across the heterogeneous tumor microenvironment interactions, resulting in differing survival outcomes. We employed a multiomics approach that utilized both single nuclei RNA sequencing and single nuclei ATAC sequencing to address this hypothesis. The multiomics method retains high sequencing quality across samples and offers the benefit of additional chromatin state information relative to single-cell RNA sequencing alone. We incorporated CellRanger, Seurat, Monocle3, and Garnett to analyze the multiomics sequencing results from six ccRCC patient samples with differing survival profiles: two short-term (1-5 years - 9,623 total nuclei) and four long-term (>5 years - 13,615 total nuclei). Curated gene lists from literature were used to assign a kidney, immune, or tumor cell type to each UMAP cluster. These cell classifications, along with the patient survival status, allowed us to identify differential transcripts, enriched chromatin factors, and ontology pathways associated with the more aggressive sub-populations of ccRCC cells. Interestingly, certain proximal tubule cells and vascular endothelial cells clustered near the more aggressive tumor cells, recapitulating the biological origin of these tumors. The identification of molecular programs germane to specific sub-populations of ccRCC cells allowed us to identify more aggressive sub-populations of ccRCC. Such classification will ultimately allow for the development of additional biological targets for treatment and prognosis.

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N18- Navigating multiomics in clear cell renal cell carcinoma-ccRCC: Network analyses on DNA methylation-5mC, DNA hydroxymethylation-5hmC, messenger RNA-mRNA, and microRNA-miRNA expression

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Background: Although significant technological advances in recent years have allowed the extensive molecular characterization of ccRCC, critical gaps remain in understanding the underlying genetic and epigenetic regulatory mechanisms in ccRCC. Here, we aim to investigate the associations of 5mC and 5hmC with mRNA and miRNA expression in ccRCC.

Methods: This pilot study selected eight ccRCC samples from the Dartmouth Renal Tumor Biobank based on tumor grade (Grades 1-2: n = 3; Grades 3-4: n = 5), towards a full study target of 200 samples. Tandem bisulfite (BS) and oxidative-bisulfite (oxBS) conversion on DNA followed by hybridization to Infinium MethylationEPIC BeadChip were used to measure 5mC and 5hmC. mRNA and miRNA expression were measured using whole RNA-seq and small RNA-seq technologies. The Enhancer Linking by Methylation/Expression Relationships (ELMER) package was used to construct the genetic-epigenetic regulatory networks from epigenome and transcriptome profiles. Metascape was used for enrichment analyses.

Results: Gene enhancer associated 5hmC was enriched for angiogenesis, and 5mC was enriched for fatty acid and choline metabolism regulatory networks. Promoter regions associated 5hmC was enriched for hypoxia and apoptosis regulation, and 5mC was enriched for mitotic cell cycle regulation.

Conclusion: Gene regulatory networks differ by cytosine modification type 5hmC/5mC in ccRCC progression. More extensive mapping of 5mC, 5hmC, mRNA, and miRNA regulatory networks in ccRCC promises a better understanding of the tumor progression and potential discoveries of enhanced biological targets.

N19 - COVID-19 vaccination in patients with renal cell carcinoma receiving immune checkpoint inhibitors

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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.

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 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 COVID-19 infections, vaccination is important to mitigate this risk.

N20- Radiation prior to combination-immunotherapy in patients with metastatic renal cell carcinoma (mRCC) and bone metastases.

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Background: Retrospective studies and post-hoc analyses have shown that patients with metastatic renal cell carcinoma (mRCC) and bone metastasis have worse outcomes. A synergistic interaction between radiation (XRT) and Immunotherapy (IO) has been postulated. We performed a retrospective review of patients with bone metastasis treated with IO-combination, with and without prior XRT.

Methods: Patients with mRCC and bone metastasis treated at Vanderbilt-Ingram Cancer Center with IO doublets were identified. Data cutoff was August 31, 2021. Patients who received XRT within six months of IO were included as having prior-XRT. Descriptive analyses of PFS, OS, and ORR were performed.

Results: 28 patients were identified: 12 patients with prior XRT and 16 patients without prior XRT. Baseline characteristics were balanced between the groups with median age of 56, 82% of patients with clear cell histology type, 25% received prior systemic therapy, and 81% having intermediate/poor risk per IMDC. Notably, 42% (5/12) of patients in the no-XRT had prior nephrectomy compared to 81% (13/16) in the XRT group. The ORR among the no-XRT group was 19% (3/16) compared with 17% (2/12) in the prior-XRT group; Odds ratio was 0.87 (0.12-6.21; $p=0.89$). The mPFS was 3.5 mo (95% CI: 1.5-11.0) in the no-XRT group vs 2.8 mo (1.4-14.7) in the prior-XRT group. The mOS was 18.8 mo (4.7-42.5) in the no-XRT group, and the mOS was not reached (7.4-NR) in the prior-XRT group.

Conclusion: In our single-center retrospective analysis, no major difference in clinical outcomes were observed in patients by receipt of prior XRT.

N21- Adverse events (AE) management among advanced renal cell carcinoma (aRCC) patients receiving first-line (1L) axitinib + checkpoint inhibitor (CPI) therapy

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Background: Real-world safety outcomes data is lacking for aRCC patients receiving axitinib+CPI. This study assesses AEs and management strategies used among US aRCC patients treated with 1L axitinib+CPI.

Methods: A retrospective physician-administered chart review included adult aRCC patients treated with 1L axitinib+CPI (avelumab or pembrolizumab) with documented frequently-reported axitinib-related AEs of fatigue, diarrhea, nausea, hypertension, or palmar-plantar erythrodysesthesia (PPE). Patient characteristics, AEs experienced, and AE management strategies (no action vs axitinib modifications [dose reduction and/or treatment interruption]) were described.

Results: Among 481 patients (median age 63 years, 67% male, 74% White) abstracted by 201 oncologists (67% community-based, 37% academic-based), 131 and 350 patients received axitinib+avelumab and axitinib+pembrolizumab, respectively; 83% patients remained on 1L at chart abstraction. Among patients with IMDC risk scores, 11%, 52%, and 37% had favorable, intermediate, and poor risk, respectively. Any AE incidence varied by type: 48% fatigue, 38% diarrhea, 29% nausea, 22% hypertension, 11% PPE. Median time from 1L initiation to AE onset was 1 month. Of 251 AEs managed with axitinib modifications, 60% dose reduced and 49% stopped temporarily. The Table shows frequency of and time to AE resolution/improvement by management strategy across AEs.

Conclusions: Patients whose AEs were managed with axitinib treatment modifications had higher AE resolution/improvement rates and shorter time to resolution/improvement compared to no action. This real-world study highlights the importance of proactive therapy management strategies to enable optimal axitinib+CPI treatment.

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

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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.

N23- Real-world clinical characteristics and treatment patterns of patients with advanced renal cell carcinoma treated with first-line avelumab + axitinib in the United States

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Background: In May 2019, the FDA approved first-line avelumab+axitinib (A+Ax) to treat patients with advanced renal cell carcinoma (aRCC), widening first-line treatment options. We examined treatment patterns and durations in patients with aRCC with differing International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) statuses, who received first-line A+Ax.

Methods: Data were drawn from a point-in-time survey administered to oncologists (Onc), nephrologists (Neph) and urologists (Uro) in the US between Oct2020 and Feb2021. Physicians completed record forms for their next 8 consecutively consulting adult patients with aRCC. A patient subset that received first-line A+Ax for ≥ 3 months formed the primary analysis set. Descriptive analyses were used and missing data excluded.

Results: Physicians (n=27; community, 52%; academic, 48%; Onc, 74%; Uro, 15%; Neph, 11%) provided data on the patient subset of 158 patients with 143 patients receiving first-line A+Ax. Of these, mean age was 64.8 years, 68% were male, 60% had a performance status of 0-1, 4% had a IMDC poor-risk score and mean ongoing duration to date was 5.2 months.

Conclusions: This real-world study provides an early perspective on aRCC patients treated with A+Ax in first-line. Because of the unique study methodology, all first-line patients were receiving ongoing treatment, thus explaining the limited duration of therapy. A+Ax was being used across all IMDC risk groups but few poor-risk patients received it. Additional follow-up may enhance understanding of treatment patterns and sequencing.

N24- Disease control rate (DCR) with tivozanib (TIVO) vs sorafenib (SOR) in relapsed/refractory (R/R) advanced RCC

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Background: The TIVO-3 trial supported FDA-approval of TIVO in R/R advanced RCC, demonstrating improved PFS over SOR. The likelihood of measurable RCC tumor response diminishes after ≥ 2 lines of therapy, and the clinical relevance of prolonged SD is increasingly important. DCR is a landmark measure of tumor response and SD, but results vary by required duration of SD. We assessed probability of disease control and magnitude of benefit with TIVO vs SOR over time.

Methods: Exploratory analysis of DCR (CR+PR+SD) was calculated using investigator-assessed response at wks-8, -16 and -24 for TIVO and SOR.

Results: Include the ITT population, with inevaluable/missing scans considered PD. Odds ratios, CIs and P-values are reported for each timepoint using logistic regression. DCR across prespecified subgroups were analyzed descriptively. Results: 350 patients were randomized to TIVO (n=175) or SOR (n=175). DCR at wk-8, -16 and -24 was consistently higher with TIVO than SOR (Table 1). The absolute difference increased from 13% to 20% between wk-8 to wk-16, and was maintained at wk-24. Odds of disease control with TIVO were $>2x$ that of SOR. Similar degree and time-dependent increases in DCR were seen with TIVO across all subgroups at each timepoint, with the exception of IMDC poor at wk-8 only, which did not differ regardless of treatment received.

Conclusions: DCR with TIVO is superior to SOR in advanced RCC, and the incremental benefit is greater at timepoints beyond 8-wks SD. Table 1. DCR at 8-, 16- and 24-wks in TIVO-3

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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)

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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.

N26- Gene expression profiling (GEP) of non-clear cell renal cell carcinoma (nccRCC) identifies a unique spectrum of transcriptional signatures with potential clinical relevance

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Background: Tumor GEP has identified RCC subgroups with distinct transcriptional profiles that are predictive of response to anti-angiogenic and immune checkpoint blocking (ICB) drugs. While prior work has characterized GEP among patients with ccRCC, characterization of nccRCC tumors to identify predictive markers of response remains an unmet need. In this multi-institutional real-world analysis, we examined the transcriptional profiles among the spectrum of RCC histologies including ccRCC and nccRCC tumors.

Methods: Next-generation sequencing was performed for samples submitted to a commercial CLIA-certified lab (Caris Life Sciences). Central pathology review confirmed diagnoses of nccRCC samples. Molecular subgroups were defined according to Motzer et al., 2020, with subgroups determined by a weighted average of gene expression levels.

Results: RCC samples (n=467; median age: 62 years; 70.6% men) were profiled, including papillary (9.6%), chromophobe (4.6%), medullary (1.2%), collecting duct (0.9%), and mixed (6.2%) nccRCC histologies (n=148). Specimen sources included kidney (51.7%), lung (11.4%), bone (6.8%), lymph nodes (5.2%), liver (4.2%) and other metastatic sites (20.7%). While most ccRCC samples were classified as 'Angiogenic' or 'Angio/stromal' (50.4%), these molecular subgroups comprised <10% of nccRCC samples, which were predominately classified as 'proliferative' (48.6%). ccRCC and nccRCC samples classified as 'T-effector/proliferative' were more commonly associated with immunotherapy-response related markers (MSI-High/TMB-High/PD-L1+) and increased immune cell infiltration compared to other subgroups.

Conclusions: In our analysis of real-world RCC samples, we demonstrate differential GEP patterns among ccRCC and nccRCC tumors. nccRCC was strongly associated with the 'Proliferative' subtype and weakly associated with 'Angiogenic' subtypes compared to ccRCC. These observations provide a new understanding for personalized treatment of nccRCC and warrant further evaluation in prospective trials.

N27- Spectral dual-layer detector CT: a new independent prognostic tool in metastatic renal cell carcinoma

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Background: Spectral Dual-Layer Detector CT (DL-CT) can separate X-ray photons, enabling generation of conventional CT and DL-CT series. The prognostic ability of DL-CT in patients with mRCC remains to be assessed.

Methods: Patients with mRCC were included in a prospective cohort-study, ClinicalTrials.gov identifier: NCT03616951. Baseline DL-CT scans were reconstructed to DL-CT series and conventional CT series used for quantification of iodine concentration (IC) and Hounsfield Units (HU) in the entire volume of all RECIST v1.1-defined target lesions using histogram analyses, and defined as IC(combined) and HU(combined). Data were adjusted for treatments (checkpoint immunotherapy or tyrosine kinase inhibitors) and IMDC risk factors and associated with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) using logistic regression and Cox regression, respectively.

Results: A total of 115 patients were included, of which 17% were in the favorable, 52% in the intermediate and 31% in the poor IMDC prognostic group. Median baseline IC(combined) and HU(combined) were 2.26 mg/ml (range, 0.04-9.46) and 86.00 (range, 15.00-224.00). After multivariate adjustment, high baseline IC(combined) was associated with favorable OS (HR=0.37; 95%CI: 0.22-0.63; P<0.001), favorable PFS (HR=0.51; 95%CI: 0.32-0.80; P=0.004) and higher ORR (OR=4.35; 95%CI: 1.84-10.27; P=0.001). High baseline HU(combined) was associated with favorable OS (HR=0.42; 95%CI: 0.24-0.72; P=0.001) and higher ORR (OR=2.52; 95%CI: 1.12-5.69; P=0.03). The estimated c-index for IMDC features was 0.650, and increased to 0.687 and 0.692 when high HU(combined) and IC(combined), respectively, were added.

Conclusions: IC(combined) and HU(combined) are new, independent, prognostic imaging biomarkers in patients with mRCC, and may add to the prognostic accuracy of IMDC.

N28- Direct imaging characteristics of myeloid derived suppressor cell (MDSC) populations in renal cell carcinoma patients (RCC) by ethnicity – an exploratory analysis

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Background: MDSC are a key mediator of resistance to immune checkpoint blockade. Previous studies in RCC have investigated peripheral MDSC via flowcytometry. Multiplexed immunohistochemistry (mIHC) allows direct visualization of MDSC in tissue, thus enabling spatial analysis of these populations. We hypothesized ethnic differences may influence spatial patterns of MDSC.

Methods: In this pilot study, RCC samples (n=10) were obtained from tissue biorepository and stained by the Ultimapper I/O MDSC 5 Plex kit for CD11b, CD14, CD15, HLA-DR, and a nuclear counterstain. Granulocytic (PMN)-MDSC [CD11b+, CD15+, HLADR-Low], and monocytic(M)-MDSC [CD11b+,CD14+,HLA-DR-Low] were identified. An Image analysis algorithm (QuPath) was trained by a qualified pathologist to identify specific MDSC Cell populations. Spatial characteristics of these MDSC were then compared in an exploratory fashion.

Results: PMN-MDSC were the most predominant population of tumor infiltrating MDSC (74%). MDSC comprised 0.56% (95%CI 0.1%-0.9%) of tumor cells, and 0.31% (95%CI 0.1-0.11%) of stromal cells and did not differ by race (p=0.85). When comparing the proportions of tumor infiltrating MDSC with total MDSC, trends were noted in Caucasian versus African American tumor samples [(5% vs 33%), p=0.07], in addition to differences in the Ratios of MDSC populations in tumor vs stroma [Caucasian (47%) vs African American (196%), p=0.08].

Conclusions: RCC tumor samples appear to be primarily infiltrated by Granulocytic MDSC, ethnicity may potentially influence the spatial distribution of MDSC and should be investigated in further studies.

N29- Expression of aberrant splice variants are strongly associated with clinical Outcome in clear cell RCC

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Background: Alternative mRNA splicing is recognized as a key driver of proteomic diversity for humans. In cancer, this splicing process can be altered resulting in generation of aberrant splice variants that can contribute to tumor pathogenesis either directly through novel mRNA isoforms or indirectly as pre-mRNA that impact transcription. However, our understanding of the clinical significance of splice variants in clear cell renal cell carcinoma (ccRCC) is currently limited. Given the lack of actionable genomic mutations in clear cell RCC, aberrant splicing may provide a novel avenue towards biomarkers, drivers and therapeutic targets.

Methods: We analyzed RNA-seq data of ccRCC primary tumors obtained from our high-risk institutional Total Cancer Care cohort (TCC; n=111) and The Cancer Genome Atlas (TCGA; n=491) to elucidate the expression of RNA splice variants identified to be highly frequent in and specific to ccRCC. Specificity of the variants to ccRCC was confirmed by screening non-RCC tumors in our TCC cohort (n=4365) in addition to adjacent normal kidney tissue in the TCGA (n=71) cohort. Variant expression (defined by presence or absence) was then correlated with clinical data, including overall (OS) and cancer-specific survival (CSS).

Results: In our TCC cohort, good (median OS 151 months; CSS not reached), intermediate (median OS 116 months; CSS 140 months) and poor (median 64 months; CSS 102 months) survival outcomes were stratified based on the absence of 0-1, 2-3 or 4-5 ccRCC-specific splice variants (PDZD2, COBLL1, FAM107B, EGFR and PTPN12), respectively (p.logrank = 0.008). This was then validated using the larger TCGA cohort with similar findings (p.logrank = 0.003). Thus, loss of these specific ccRCC splice variants appears to be associated with inferior OS and CSS outcomes, independent of pathologic stage. We also find that the presence of RNASET2 splice variant expression is significantly associated with worse outcomes in the TCGA cohort (p.logrank < 0.001).

Conclusions: The absence of ccRCC-specific splice variants is strongly associated with poor overall and cancer-specific survival. Uniquely, the presence of RNASET2 splice variants is associated with worse survival, suggesting a potential role in driving progression.

N30- Molecular profiling of metastatic renal cell carcinoma (mRCC) treated with ipilimumab-nivolumab (ipi-nivo)

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Background: Molecular biomarkers for mRCC predicting for immunotherapy responses are lacking. T-effector and myeloid profiles have been associated with immunotherapy responses, and low expression of a 5-gene panel (FOXP3, CCR4, KLRK1, ITK, and TIGIT) was previously associated with nivolumab resistance.

Methods: Patients with ipi-nivo treated mRCC and archival tumor specimens were identified at Duke Cancer Institute and Cleveland Clinic Cancer Center. FFPE samples were evaluated by RNA sequencing and IHC. Radiographic objective response rate (ORR) was assessed with RECIST 1.1 criteria. Inflammation (strong, mod, weak), cell proliferation (CP: high, moderate, poor), PD-L1, CTLA-4 status, and 5-gene panel expression were correlated with clinical outcomes.

Results: 62 tumors were analyzed. Inflammation (27 strong, 19 moderate, 16 weak) did not correlate with ORR (OR 0.37, 95% CI 0.08-1.73, p=0.21 for strong vs weak; OR 0.44, 95% CI 0.13-4.12, p=0.34 for moderate vs weak). CP groups (3 high, 15 moderate, 44 poor) showed moderate CP had lower prognosis than poor CP (HR for OS 3.75, 95% CI 1.05-13.43, p=0.04). High vs low 5-gene panel did not correlate with ipi-nivo response (OR 1.44, 95% CI 0.41-5.04, p=0.57). Moderate CP vs poor CP with low CTLA4/high PD-L1 showed poorer OS (HR 20.82, 95% CI 2.13-203, p=0.01) and shorter PFS (HR 8.58, 95% CI 1.86-39.6, p=0.01).

Conclusions: Predictive biomarkers remain elusive for mRCC. Gene expression profiles predicting response may vary by treatment. Multifaceted composite biomarkers may help in patient selection, but prospective studies are needed.

N31- Evaluation of provider preferences in first-Line metastatic renal cell carcinoma

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Background: Dual immunotherapy (ipilimumab/nivolumab, IO/IO) and immunotherapy/ tyrosine kinase inhibitor (IO/TKI) combinations (e.g. pembrolizumab/ axitinib) are approved for the first-line treatment of intermediate/poor risk metastatic renal cell carcinoma (RCC). We sought to understand how oncologists decide between IO/IO vs. IO/TKI.

Methods: We sent a 10-question electronic survey centered on a patient scenario to 294 academic/disease-focused and general oncologists in the US.

Results: We received 105 responses (36% response rate): 61% (64) of providers chose IO/IO, 39% (41) chose IO/TKI. 78% (82) of oncologists were academic or disease-focused, 22% (23) were general. Academic/disease-focused oncologists were significantly more likely to choose IO/IO (68%, 56/82) than general oncologists (35%, 8/23), $p = 0.004$ (Figure 1). Among those who chose IO/IO, the perceived main issue with IO/TKI was: long-term toxicities - 31% (20), short-term toxicities - 28% (18), less effective - 28% (18), and less convenient - 8% (5). Among those who chose IO/TKI, the perceived main issue with IO/IO was: short-term toxicities - 43% (17), less effective - 28% (11), long-term toxicities - 15% (6), and risk of death - 10% (4). 88% (92) of providers would be comfortable enrolling patients into a phase III trial comparing IO/IO vs. IO/TKI.

Conclusions: There was a significant association between type of practice and choice of therapy; academic/disease-focused oncologists were more likely to choose IO/IO. The majority of oncologists would be comfortable enrolling patients into a phase III trial comparing IO/IO vs. IO/TKI, demonstrating equipoise regarding this question.

N32- Assessing human kidney cancer metabolism with intraoperative isotope tracing

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Background: Tumor metabolic phenotypes reflect multiple factors including organ-specific metabolic preferences and local nutrient availability. However, it remains unclear to what extent genetics and the local environment dictate nutrient utilization in human tumors.

Methods: We utilized a multidisciplinary clinical approach to intraoperatively infuse ¹³C-substrates in over 70 patients with different subtypes of kidney cancer.

Results: We demonstrate that glucose utilization patterns vary across kidney cancer subtypes, highlighting the fact that the kidney environment alone cannot account for all aspects of cellular metabolism in kidney cancers. Previous studies determined that glucose oxidation is suppressed in clear cell renal cell carcinoma (ccRCC), the most common and deadly form of kidney cancer. Here, by assessing freshly-cultivated, surgically-resected tissues from tumors and adjacent kidney, we determine that suppressed glucose oxidation in human ccRCC is a tumor-intrinsic property. Infusions of acetate in intact patient tumors and isolated patient mitochondria underscore low TCA cycle turnover in primary ccRCCs. We also show that isolated mitochondria from these tumors display reduced respiration relative to mitochondria from the kidney, indicating that human ccRCC involves metabolic reprogramming at the level of the electron transport chain. Surprisingly, preliminary analysis of some ccRCC metastases show increased glucose oxidation and mitochondrial respiration relative to primary ccRCCs, suggesting a possible divergent metabolic program that affects kidney cancer progression and metastasis.

Conclusions: Altogether, our findings indicate genetically-defined metabolic heterogeneity among human kidney cancer subtypes, and reveal an unexpected possible metabolic adaptation during ccRCC metastasis in patients.

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

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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 CRN+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.

N34- BAP1 suppresses tumor growth via interferon beta and ISGF3 in clear cell renal cell carcinoma

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Background: BAP1 is mutated in about 15% of clear cell Renal Cell Carcinoma (ccRCC). Kidney cancer patients carrying BAP1 mutations have very bad prognosis. The mechanism of BAP1's tumor suppression is unclear and seems cell type/context specific. There is no treatments specific to BAP1-deficient cancers/ccRCC. Previously, our lab has shown that BAP1 is required to maintain ISGF3 activity in VHL-/- ccRCC cancer cells, and in general ISGF3 is potently tumor suppressive. We set out to investigate how BAP1 regulates ISGF3, and whether ISGF3 activation by a STING agonist can retard BAP1-deficient tumor growth.

Methods: ccRCC cancer cells were manipulated to suppress or re-express BAP1, VHL, or HIF2alpha to examine their impact on interferon beta (IFN- β), ISGF3 targets and STING. Xenograft analyses were performed to assess whether genetic change or treatment compound can alter tumor growth. BAP1 C91G point mutant was used to assess the importance of its deubiquitinase activity on ISGF3 regulation.

Results: 1. VHL and HIF2 α regulate IFN- β expression in ccRCC cells, and IFN- β activates ISGF3 and suppresses tumor growth; 2. BAP1 promotes ISGF3 activity in a deubiquitinase-dependent manner; 3. BAP1 up-regulates IFN- β expression to stimulate ISGF3 activity; 4. BAP1 stimulates ISGF3 activity through up-regulating STING expression; 5. BAP1 is a bona fide ccRCC tumor suppressor; 6. A STING agonist increases ISGF3 activity and slows the growth of BAP1-deficient tumors.

Conclusions: In VHL-deficient ccRCC cancer cells, HIF up-regulated IFN- β to trigger a tumor-suppressive pathway-up-regulation of ISGF3. BAP1 loss-of-function would lead to reduced STING expression and IFN- β , thus crippling the tumor-suppressive pathway. In BAP1-deficient xenograft tumors, a STING agonist could re-activate ISGF3 and slow tumor growth.

N35- Machine learning predicts BAP1/PBRM1 from digital histology in clear cell renal cell carcinoma: TRACERx Renal

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Background: Histological analysis is the cornerstone of diagnosis for clear cell renal cell carcinoma (ccRCC). Genomic profiling provides prognostic information that could inform clinical management. This requires multi-region sampling for next-generation sequencing to capture molecular intratumoural heterogeneity, which is cost-prohibitive in clinical practice. However, extensive sampling is routine for histology. Predicting genetic alterations from histology presents a cost-effective, implementable solution. Machine learning (ML) can predict genetic mutations from histology in other cancer types, unachieved in kidney cancer. We aim to develop an ML model to predict genomic alterations from histology in ccRCC. This could improve relapse risk stratification in the stage III setting enabling personalised patient management.

Methods: Multi-region research samples of ccRCC are collected within the prospective TRACERx Renal study (NCT03226886). We train a convolutional neural network with 606 tumour regions across 50 patient cases to predict the mutational status of specific genes from H&E sections. Each tumour region is bisected providing directly concordant specimens for histological and genomic analysis.

Results: In our pilot study, we accurately predicted the mutational status of two ccRCC driver genes from digital H&E images. Region level hold-out prediction accuracy was high for both genes (Accuracy: PBRM1: 0.926 and BAP1: 0.967, F1-score: PBRM1: 0.920 and BAP1: 0.867).

Conclusions: Our results provide proof-of-principle that genomic alterations can be predicted from histology in ccRCC. We will train for other driver events (including gene mutations and copy number alterations). Our aim is to predict evolutionary modes from histology, which we have shown to correlate with relapse risks.

N36- Adverse radiologic and pathologic features impact survival outcomes for small renal masses following nephrectomy

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Background: The influence of finding adverse pathologic T3 features in small renal masses (SRMs, ≤ 4 cm) following partial or radical nephrectomy (PN, RN) remains unclear, particularly given the poor sensitivity of preoperative imaging for adverse features of cT3 disease in SRMs. We retrospectively reviewed SRMs that underwent PN/RN at our institution, comparing SRMs with/without adverse preoperative radiologic +/- pathologic features (cT3/pT3, cT1a/pT3) to lower-stage SRMs (cT1a/non-pT3).

Methods: We searched our institutional database for SRMs that underwent PN/RN between 2010-2020, excluding cases with known advanced (pT4, M1) disease preoperatively. Continuous and categorical variables were compared using ANOVA and Kruskal-Wallis (K-W) tests, respectively. Cox proportional hazard regression (CPHR) analysis was used to model potential predictors of survival outcomes.

Results: Of 2146 cases, 8.4% were deemed pT3 post-operatively (3.8% cT3/pT3; 4.6% cT1a/pT3). Median follow-up was 3.3 years (IQR 1.5–6.1). pT3-SRMs had higher rates of positive margins, overall and cancer-specific mortality, and metastases than their non-pT3 counterparts, particularly in the cT3/pT3 subgroup (K-W $p < 0.05$; Table 1). On CPHR analysis, only the cT3/pT3 subgroup was significantly associated with higher risk for overall and cancer-specific death ($p < 0.05$), but not incidence of metastases, adjusting for age, BMI, mass size, histology, and Charlson comorbidity index.

Conclusions: While rare, adverse pathologic upstaging portends worse outcomes for SRMs, particularly in the presence of concurrent adverse radiologic features. SRM subtrification by these features may aid in surgical and potentially multimodal treatment planning.

E37- Characterization of the tumor immune microenvironment in clear cell renal cell carcinoma (ccRCC): prognostic and therapeutic implications of an M0-macrophage enriched subtype

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Background: Appropriate selection criteria for those who may benefit from ICB therapy is limited. Here, we elucidate the immune composition of multiple ccRCC cohorts, develop an immune content score, and test its prognostic and predictive capabilities.

Methods: We analyzed TCGA-Kidney Renal Clear Cell Carcinoma (KIRC) patients with localized disease (discovery dataset n=382) and patients from the Clinical Proteomics Tumor Analysis Consortium (CPTAC) cohort (validation dataset n=94). CIBERSORT immune cell deconvolution and unsupervised hierarchical clustering divided the cohort based on similar immune infiltration. Survival and hallmark gene set enrichment (GSEA) analyses were performed by cluster. Finally, the immune cells associated with worse PFS were used to create an immune score, which was then tested on an independent cohort of nivolumab treated patients in CheckMate 010/025 (n=133).

Results: An M0 macrophage predominant cluster emerged in both the TCGA (n=25) and CPTAC (n=9). This cluster demonstrated decreased PFS and OS as well as an enrichment of cell cycle progression, angiogenesis and epithelial-mesenchymal transition hallmark gene sets. In addition, these tumors displayed a prevalence of cancer associated fibroblasts (CAFs), myeloid derived suppressor cells (MDSCs), and greater T-cell exclusion (Table). Those with a high-risk score had a lower ORR to nivolumab (6% high-risk, 28% low-risk; p=0.04).

Conclusion: We developed a signature that can improve prognostication of ccRCC patients and identify those most suitable for immunotherapy in the adjuvant and/or advanced disease setting.

E38- Disease free survival (DFS) as a predictor of overall survival (OS) in localized RCC following first nephrectomy

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Background: Association between DFS and OS was assessed in patients (pts) with newly diagnosed, completely resected, intermediate-high (pT2N0Grade4/pT3N0) or high-risk (pT4N0/pTanyN1) RCC post-nephrectomy.

Methods: This retrospective observational study used the SEER-Medicare database (2007–2016). Survival analysis and regression models compared OS from time of recurrence in pts with recurrence vs OS from comparable time point in pts without. Association between DFS and OS was examined using correlation analysis (Kendall's τ rank correlation) and comparing post-nephrectomy OS among pts with and without recurrence at multiple landmark time-points.

Results: 643 post-nephrectomy RCC pts met the inclusion criteria. The median post-nephrectomy OS and DFS was 8.61 and 4.44 yrs, respectively. Pts with recurrence had significantly shorter OS than those without [median: 2.53 yrs vs not reached; adjusted HR (95% CI):6.00(4.24–8.48)]. Kendall's τ rank correlation model demonstrated a statistically significant correlation between DFS and OS (Kendall's $\tau = 0.70$; 95% CI:0.65–0.74; $P < 0.001$). Compared to pts without, pts with recurrence by each landmark time point had significantly shorter OS [1 yr post-nephrectomy median OS: 2.35 vs 9.66 yrs, and the OS 1, 3, and 5 after the 1 yr landmark was 69.9 vs 96.5%, 41.8 vs 83.8%, and 37.0 vs 70.1%, respectively; all P s < 0.001], 2.6–3.5 times increased death risk and \$6,320 higher all-cause healthcare cost.

Conclusion: In SEER-Medicare data, post-nephrectomy recurrence was associated with significantly shorter OS among pts with intermediate-high or high-risk RCC, resulting in a strong positive association between DFS and OS.

E39- Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) in advanced renal cell carcinoma (aRCC)

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Background: Conditional survival estimates provide critical prognostic information for aRCC patients as landmark survival milestones are reached. Efficacy, safety, and conditional survival outcomes were assessed in CheckMate 214 with 5 years minimum follow-up (median follow-up, 67.7 months).

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). Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were assessed in IMDC intermediate/poor-risk, intent-to-treat, and favorable-risk populations. Conditional survival—the probability of remaining alive, progression-free, or in response 2 years beyond landmark timepoints of 2 and 3 years—was analyzed.

Results: Superior OS, PFS, ORR, and complete response benefits with NIVO+IPI versus SUN were maintained in intent-to-treat and intermediate/poor-risk patients and are summarized together with outcomes in favorable-risk patients (Table). The probability of remaining alive, progression-free, or in response for an additional 2 years beyond the 3 year landmark was higher with NIVO+IPI versus SUN regardless of IMDC risk (Table). No new safety signals emerged with longer follow-up.

Conclusions: Durable efficacy benefits were observed with NIVO+IPI versus SUN in aRCC patients with long-term follow-up, and most patients who were alive or in response with NIVO+IPI at 3 years remained so at 5 years.

Previously presented at the ESMO Virtual Congress 2021: September 16-21. Abstract 2291.

E40- First-line nivolumab plus cabozantinib (NIVO+CABO) versus sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC) by prior nephrectomy status in the CheckMate 9ER trial

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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 intravenously every 2 weeks plus CABO 40 mg orally once daily versus SUN 50 mg orally once daily (4 weeks of 6-week cycles). In this post hoc exploratory analysis, efficacy was evaluated in subgroups with and without prior nephrectomy.

Results: Overall, 222 (NIVO+CABO) versus 233 (SUN) patients had prior nephrectomy and 101 versus 95 had no prior nephrectomy, respectively. Of patients with prior nephrectomy, 24.3% (NIVO+CABO) and 30.9% (SUN) underwent nephrectomy within 3 months of enrollment. Baseline characteristics were generally balanced between arms within subgroups. NIVO+CABO improved progression-free survival (PFS), and response outcomes versus SUN regardless of nephrectomy status (Table). Of evaluable patients without prior nephrectomy, median reduction in target kidney lesions was 30% (NIVO+CABO; n=53) versus 16% (SUN; n=51). Overall survival (OS) benefits were observed with NIVO+CABO versus SUN in patients with prior nephrectomy; longer follow-up is needed to characterize OS outcomes between arms in patients without prior nephrectomy.

Conclusions: NIVO+CABO provided improved efficacy benefits versus SUN in patients with and without prior nephrectomy. These results continue to support NIVO+CABO as a first-line treatment option for patients with aRCC.

Previously presented at the ESMO Virtual Congress 2021: September 16-21. Abstract 590.

E41- A phase 3 trial of lenvatinib plus pembrolizumab (LEN+PEMBRO) versus sunitinib as a first-line treatment for patients with advanced renal cell carcinoma (aRCC): overall survival follow-up analysis (CLEAR study)

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Background: In the phase 3 CLEAR study, OS was improved with LEN+PEMBRO versus sunitinib (HR, 0.66; 95% CI, 0.49-0.88; P=0.005) (data cutoff: August 28, 2020; median OS follow-up: 26.6 months). We report an OS follow-up analysis of LEN+PEMBRO versus sunitinib.

Methods: Patients (n=1069) with treatment-naïve clear cell aRCC were randomized 1:1:1 to LEN (20 mg/day orally) + PEMBRO (200 mg IV Q3W); LEN (18 mg/day orally) + everolimus (5 mg/day orally); or sunitinib (50 mg/day orally; 4 weeks on/2 weeks off). Randomization was stratified by geographic region and MSKCC prognostic risk group. In this analysis (data cutoff date: March 31, 2021), OS was compared using a stratified log-rank test. The HR and 95% CIs were estimated using a stratified Cox regression model.

Results: At data cutoff, 225 (63.4%) patients in the LEN+PEMBRO group (n=355) and 197 (55.2%) patients in the sunitinib group (n=357) were alive and remained in the study. OS favored LEN+PEMBRO versus sunitinib (Table). Median duration of follow-up for OS was similar between the 2 arms (LEN+PEMBRO, 33.7 months [95% CI, 32.8-34.4]; sunitinib, 33.4 months [95% CI, 32.5-34.1]). OS by MSKCC and IMDC risk groups is reported (Table).

Conclusions: The OS benefit with LEN+PEMBRO versus sunitinib in patients with aRCC was maintained at longer follow-up. Moreover, OS favored LEN+PEMBRO in patients with MSKCC or IMDC intermediate or poor risk.

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

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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.

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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.

E44- Initial management of indeterminate renal masses in a statewide collaborative: a MUSIC-KIDNEY analysis

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Background: The widespread use of imaging has led to the increasing detection of incidental renal lesions. While some lesions are accurately classified as suspicious or benign, lesions without clear distinguishing characteristics are often labeled as indeterminate. We assess the use of follow up imaging and biopsy in the initial management of indeterminate renal lesions (IRL).

Methods: The MUSIC -KIDNEY small renal mass registry commenced data collection in September 2017 by recording clinical, radiographic, pathologic, and follow-up data at 13 diverse practices. Data regarding radiological impressions and clinical management was queried to better understand the initial management of IRL.

Results: 21.0% (444/2109) patients(pts) were recorded as having an IRL at initial imaging, of which 36% had non-contrast imaging. 23.6% (105/444) of pts with IRL underwent subsequent imaging, of which 58.1% were re-classified as solid enhancing lesions, 21.0% as benign, with only 21.0% IRL remaining. In total, 53/444 patients underwent biopsy to guide their management with 37 revealing malignant pathology, 9 benign, and only 7 remaining indeterminate. Surveillance (287/444) was the most common approach for these lesions; however, 30% of patients that underwent surgery as initial treatment did not have any subsequent imaging performed

Conclusions: About 80% of patients with IRL can be reclassified with subsequent dedicated imaging. Initial contrast axial imaging, the addition of further imaging and consideration of biopsy more fully characterizes an IRL, often affecting subsequent management. A significant portion of patients went to treatment without imaging or biopsy, and this presents an important QI opportunity to reassure patients and reduce unnecessary procedures.

E45- Documentation of nephrometry scores for cT1a renal masses correlates with avoidance of radical nephrectomy across the MUSIC-KIDNEY statewide QI collaborative

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Background: Tumor complexity (TC) assessment with nephrometry scoring has been shown to help with identification of case complexity and contribute to preoperative planning. Our objective was to assess documentation of TC and its association with performance of radical nephrectomy (RN) for tumors <4cm (cT1aRM).

Methods: The MUSIC-KIDNEY program commenced data collection in September 2017. An educational session was conducted in Nov 2018 regarding documentation of RENAL Nephrometry scoring by the Urologist in clinic. Correlation coefficient was calculated for the rates of nephrometry documentation for cT1RM and percent of RN performed by urologists.

Results: Total of 1527 cT1RM patients were seen by 32 urologists with documentation of TC performed in 40%. Management of cT1RM was 52% surveillance, 31% PN/TA, and 15% RN. RN rates for T1b were 65% (154/236) and for T1a were 18% (74/401) ($p < 0.001$). Rates of RN for cT1aRM ranged from 4%-45% among 19 urologists. 42% of RN for cT1aRM had no documentation of TC. The lowest 5 surgeons documented TC for only 4.4% and performed RN for 25%, while the top 5 surgeons documented TC for 74% and performed RN on only 15%. At surgeon level, the correlation coefficient between rates of RENAL documentation and the rates of RN was -0.24.

Conclusions: There are multiple factors that impact the decision to perform a RN for a cT1aRM. TC assessment with nephrometry scoring throughout our collaborative is an ongoing focus for QI, particularly as it appears to correlate with reduced rates of RN for cT1aRM.

E46- Building a roadmap for surveillance of renal masses: results from MUSIC consensus panel

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Background: Current guidelines are limited for the selection of patients pursuing surveillance for renal masses. The MUSIC-KIDNEY group has seen significant variability in evaluation and management strategies. We aim to establish a consensus roadmap for patients entering renal mass surveillance.

Methods: A consensus panel (CP) following the modified Delphi method was organized within MUSIC. Participants indicated their agreement with statements relating to surveillance via an online tool. Factors not achieving agreement were iteratively developed during three rounds of questionnaires. Level of agreement necessary to achieve consensus was set at 80%.

Results: Twenty-six MUSIC urologists formed the CP. 58% felt current surveillance guidelines were useful. Life expectancy (LE) was noted to be the primary driver for patient selection (Figure 1). Consensus for initial evaluation: All patients should undergo axial imaging, tumor complexity assessment, renal function and chest imaging only for tumors >3 cm. Consensus for follow up: 1st imaging (axial) should be between 3-6 months, with subsequent imaging timing varying per tumor size, chest imaging should be reserved for tumors >5 cm, tumor growth rate was an appropriate trigger to intervention, duration of surveillance should be >5 years for healthy patients and at least 3 years for comorbid patients.

Conclusions: We were able to highlight several areas for further discussion where consensus was not achieved. Future directions are to bring MUSIC-KIDNEY data to the attention of other national and international kidney cancer groups for further expert-based opinions and construction of tools such as a LE calculator to aid decision making for a broader range of patients.

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

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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.

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TIP02	First-Line (1L) MK-1308A + Lenvatinib or Pembrolizumab + Belzutifan + Lenvatinib Versus Pembrolizumab + Lenvatinib for Clear Cell Renal Cell Carcinoma (ccRCC): A Randomized, Open-Label Phase 3 Study	Martin H. Voss
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N17	Deconstructing the clear cell renal cell carcinoma using single nuclei multiomics	Michael P. Mariani
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