Peri-operative morbidity and mortality in a modern series of patients treated with cytoreductive nephrectomy (CN) at five centers.

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Background: For metastatic renal cell cancer (mRCC) patients considering cytoreductive nephrectomy (CN), perioperative morbidity is important to discuss but few contemporary multi-institutional data are available. The objective of this study is to describe factors associated with perioperative outcomes in a modern multi-institutional cohort of patients treated with cytoreductive nephrectomy. **Methods:** Data for perioperative complications was recorded for patients treated with CN at 5 centers from 2005-2019. Postoperative complications within 90 days were categorized using Clavien- Dindo system. Univariate and multivariable analysis was used to evaluate for associations with complications and 90-day mortality. Factors evaluated included receipt of pre-surgical systemic therapy, ECOG performance status (PS), Charlson comorbidity index (CCI), concurrent IVC thrombectomy, age, and surgical approach (open vs. laparoscopic/robotic). **Results:** Perioperative outcomes were evaluated in 937 consecutive patients treated with CN at 5 institutions from 2005-2019. Median age at surgery was 61 years (IQR 53-68) and median tumor diameter was 9.8cm (IQR 7-12).Venous thrombus was present in 406/937 (43.3%) patients overall including 65/406 (16%) patients for whom IVC thrombus extended above the hepatic veins. Open and laparoscopic/robotic approach was used in 715 (76.3%) and 290 (23.4%) patients. The median ECOG PS was 1 (IQR 0-1) and median CCI was 1 (IQR 0-2). Pre-surgical systemic therapy was given to 243 (25.9%) patients prior to CN. The median length of hospital stay was 5 days (IQR 4-7) and 429 (34.6%) received blood transfusion. Median length of stay was 3.0 (IQR 2-4) for laparoscopic/robotic approach and 6 days (IQR 4-8) for patients with IVC thrombectomy. Hospital readmission within 30 days was identified in 112 (9.0%) patients. A total of 93/937 (9.9%) patients had major (≥Clavien 3) complications identified within 90 days postoperatively. On multivariable analysis, IVC thrombectomy was associated with higher risk of major complications OR 1.95 (95% CI 1.2-3.1), p = 0.006. Pre-surgical systemic therapy, ECOG PS, CCI, age and surgical approach were not associated with major complications (p = 0.09-0.85). Perioperative mortality was 12/937 (1.3%) at 30 days and 51/937 (6.7%) at 90 days. After multivariable analysis, pre-surgical systemic therapy, ECOG PS, CCI, age, and IVC thrombectomy were not associated with perioperative mortality (p = 0.1-0.85). **Conclusions:** Cytoreductive nephrectomy is associated with major complications for 10% of patients and 1% mortality at 30 days. Pre-surgical systemic therapy was not associated with increased risk of complications or mortality. Research Sponsor: None.

Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients (pts) with advanced renal cell carcinoma (RCC) (CLEAR study).

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Background: In pts with advanced RCC, second-line treatment with LEN + EVE prolonged progression-free survival (PFS) compared with EVE alone. LEN + PEMBRO, also showed preliminary efficacious evidence in a phase 1/2 RCC study. Here, we describe the investigational study results of first-line LEN + PEMBRO or LEN + EVE versus SUN in pts with advanced RCC. **Methods:** Pts were randomized (1:1:1) to receive LEN 20 mg orally once daily + PEMBRO 200 mg IV every 3 weeks (wks); or LEN 18 mg + EVE 5 mg orally once daily; or SUN 50 mg orally once daily (4 wks on/2 wks off). Eligible pts had advanced RCC with no prior systemic therapy. Randomization was stratified by geographic region and MSKCC prognostic group. The primary endpoint was PFS by Independent Review Committee per RECIST v1.1. Secondary endpoints included overall survival (OS), objective response rate (ORR) and safety. A sequential approach was used to test PFS first, then OS and ORR. PFS and OS were compared across arms by a stratified log-rank test; hazard ratios (HRs) were estimated by a stratified Cox regression model. **Results:** 1069 pts were randomized (Table). After a median follow-up of 27 months (data cutoff August 28, 2020), PFS was significantly improved with LEN + PEMBRO (median 24 months [mos]) vs SUN (median 9 mos; HR 0.39, 95% CI 0.32–0.49) and LEN + EVE (median 15 mos) vs SUN (HR 0.65, 95% CI 0.53–0.80). OS was significantly longer with LEN + PEMBRO vs SUN (HR 0.66, 95% CI 0.49–0.88), whereas OS with LEN + EVE vs SUN was not statistically different (HR 1.15, 95% CI 0.88–1.50). ORR was significantly greater with LEN + PEMBRO (ORR 71%; complete response [CR] 16%) vs SUN (ORR 36%; CR 4%; odds ratio 4.35, 95% CI 3.16–5.97) and LEN + EVE (ORR 54%; CR 10%) vs SUN (odds ratio 2.15, 95% CI 1.57–2.93). Grade ≥3 treatment-related adverse events occurred in 72% of pts in the LEN + PEMBRO arm and 73% of pts in the LEN + EVE arm compared with 59% of pts in the SUN arm. **Conclusions:** LEN + PEMBRO demonstrated significant improvements in PFS, OS and ORR vs SUN. LEN + EVE demonstrated significant improvements in PFS and ORR vs SUN. Safety was manageable and consistent with the known single-agent profiles. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA; and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Median PFS, months (95% CI)	24 (21-28)	15 (11-17)	9 (6-11)
PFS HR vs SUN (95% CI);	0.39 (0.32-0.49);	0.65 (0.53-0.80);	-
***P*-value**	<0.0001	<0.0001	
Median OS, months (95% CI)	NR (34-NE)	NR (NE-NE)	NR (NE-NE)
OS HR vs SUN (95% CI);	0.66 (0.49-0.88);	1.15 (0.88-1.50);	-
***P*-value**	0.0049	0.2975	
24-Month OS rate, % (95% CI)	79 (74-83)	66 (61-71)	70 (65-75)
ORR, % (95% CI)	71 (66-76)	54 (48-59)	36 (31-41)
ORR odds ratio vs SUN (95% CI);	4.35 (3.16-5.97);	2.15 (1.57-2.93);	-
Descriptive *P*-value	<0.0001	<0.0001	
Complete response, %	16	10	4
Median duration of response, months (95% CI)	26 (22-28)	17 (15-21)	15 (9-17)

NE, not estimable; NR, not reached.

Sunitinib versus cabozantinib, crizotinib or savolitinib in metastatic papillary renal cell carcinoma (pRCC): Results from the randomized phase II SWOG 1500 study.

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Background: MET signaling is a key molecular driver in pRCC. Given that there is no optimal therapy for metastatic pRCC, we sought to compare an existing standard (sunitinib) to putative MET kinase inhibitors. **Methods:** Eligible patients had pathologically verified pRCC, Zubrod performance status 0-1, and measurable metastatic disease. Patients may have received up to 1 prior systemic therapy excluding VEGF-directed agents. Patients were randomized 1:1:1:1 to receive either sunitinib 50 mg po qd (4 wks on/2 wks off), cabozantinib 60 mg po qd, crizotinib 250 mg po bid, or savolitinib 600 mg po qd. Patients were stratified by prior therapy and pRCC subtype (I vs II vs not otherwise specified [NOS]) based on local review. The primary objective was to compare progression-free survival (PFS) for each experimental arm versus sunitinib. With 41 eligible patients per arm, we estimated 85% power to detect a 75% improvement in median PFS with a 1-sided alpha of 0.10 using intent-to-treat analysis. A pre-planned futility analysis was performed after 50% of PFS events occurred. Secondary endpoints included toxicity, response rate, and overall survival. **Results:** Between 4/2016 and 12/2019, 152 patients were enrolled; 5 were ineligible. Median age was 66 (range:29-89) and 76% were male; 92% had no prior therapy. By local pathologic review, 18%, 54% and 28% of patients were characterized as having type I, type II and NOS histology, respectively. In contrast, the frequency of type I, type II, and NOS by central review was 30%, 45% and 25%, respectively. Accrual to the savolitinib and crizotinib arms was halted early for futility (PFS hazard ratio $>$ 1.0 for both); accrual continued to completion in the sunitinib and cabozantinib arms. Median PFS was significantly higher with cabozantinib relative to sunitinib (Table). Grade 3 or 4 adverse events occurred in 69%, 72%, 37% and 39% of patients receiving sunitinib, cabozantinib, crizotinib and savolitinib, respectively; one grade 5 adverse event was seen with cabozantinib. Overall survival and response data will be presented. **Conclusions:** In this multi-arm randomized trial, only cabozantinib resulted in a statistically significant and clinically meaningful prolongation of PFS in pRCC patients compared to sunitinib. These data support cabozantinib as a reference standard for eligible patients with metastatic pRCC. Clinical trial information: NCT02761057. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Treatment Arm	Number (events/eligible patients)	Median PFS (months)	PFS Hazard Ratio (95% CI)*	1-sided p-value*
Sunitinib	39/46	5.6	Reference	NA
Cabozantinib	31/44	9.2	0.61 (0.37, 0.98)	0.021
Savolitinib**	29/29	3.0	1.25 (0.76, 2.05)	0.81
Crizotinib**	26/28	2.8	1.14 (0.68, 1.90)	0.69

* Cox model, adjusted for stratification factors

** Closed to accrual early due to futility analysis

Phase 2 study of the oral hypoxia-inducible factor 2α (HIF-2α) inhibitor MK-6482 in combination with cabozantinib in patients with advanced clear cell renal cell carcinoma (ccRCC).

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Background: Belzutifan (MK-6482) inhibits HIF-2α and demonstrated antitumor activity and favorable safety as monotherapy in a phase 1 study of patients (pts) with metastatic ccRCC. Current study (NCT03634540) investigates belzutifan plus cabozantinib for pts with advanced ccRCC who were either treatment naive (cohort 1) or previously treated, including immunotherapy and TKIs (cohort 2). This preliminary analysis presents data from cohort 2. **Methods:** Pts had metastatic ccRCC and received no more than 2 prior systemic treatment regimens. Initially, 6 pts in either cohort 1 or 2 were treated with belzutifan 120 mg and cabozantinib 60 mg orally once daily for 21 days and a safety review committee performed an initial evaluation. For purpose of this preliminary analysis, efficacy was evaluated in pts who received ≥1 dose of treatment and had an opportunity of ≥6 mo of follow-up. Primary end point: objective response rate (ORR; RECIST v1.1 by investigator review). Secondary end points: progression free survival (PFS), overall survival (OS), and duration of response (DOR). Safety was evaluated for all cohort participants. **Results:** Evaluation of safety and tolerability of belzutifan 120 mg plus cabozantinib 60 mg was performed in the first 6 pts. Only 1 participant experienced a dose-limiting toxicity of hand-foot syndrome, therefore belzutifan 120 mg plus cabozantinib 60 mg was determined to be the recommended phase 2 dose. 53 pts were included in the safety analysis population. Median age was 64 yrs, 73.6% were male, 54.7% had ECOG PS 1. Twenty-eight (52.8%) received prior first-line and 24 (45.2%) prior second-line therapies. Median (range) time from enrollment to data cutoff was 11.3 mo (5.6-24.0) for pts with ≥6 mo of follow-up (n=41). The confirmed ORR was 22.0% (9 PRs) and 90.2% had any tumor shrinkage. Disease control rate (CR+PR+SD) was 92.7%. Median (range) DOR was not reached (3.7+ to 14.8+ mo); all responses were ongoing. Median (95% CI) PFS was 16.8 mo (9.2-not reached); PFS rate at 6 mo was 78.3%. OS rate at 6 mo was 95.0%. While 52 of 53 (98.1%) pts experienced a treatment-related adverse event (TRAE), 92% of events were grade 1 and 2. Most common (≥30%) TRAEs were anemia (75.5%), fatigue (67.9%), hand-foot syndrome (52.8%), diarrhea (45.3%), hypertension (43.4%), nausea (35.8%), and ALT/AST increase (32-34%). Incidence of grade 3 TRAEs >5% were hypertension (22.4%), anemia (11.3%), fatigue (11.3%), and ALT increase (5.7%). 2 pts experienced grade 3 hypoxia (3.8%). There were no grade 4 TRAEs or deaths. Discontinuations due to TRAEs occurred in 6 pts (11.3%) for belzutifan and 8 pts (15.1%) for cabozantinib. **Conclusions:** In this preliminary analysis, belzutifan in combination with cabozantinib demonstrated promising antitumor activity in previously treated pts with metastatic ccRCC. Safety was consistent with individual profiles of each agent. Clinical trial information: NCT03634540. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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The oral HIF-2 α inhibitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC): Updated follow-up of a phase I/II study.

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Background: Clear cell RCC (ccRCC) accounts for ~70% of kidney cancer cases in the US. Several first-line therapies are approved for ccRCC, but few patients respond completely and most progress within 5-11 mo. A key oncogenic driver in RCC is the transcription factor hypoxia-inducible factor 2α (HIF-2α). MK-6482 is a small molecule HIF-2α inhibitor that blocks the heterodimerization of HIF-2α with HIF-1β, inducing tumor regression in mouse xenograft RCC models. Updated data presented here include additional follow-up from the expansion cohort of patients with ccRCC from the first-in-human phase 1/2 study of MK-6482 in advanced solid tumors (NCT02974738). **Methods:** Patients were aged ≥18 y with advanced ccRCC, received ≥1 prior therapy, and had RECIST v1.1 measurable disease, ECOG status 0 or 1, adequate organ function, and life expectancy ≥6 mo. They received 120 mg of MK-6482 orally once daily. Tumors were assessed at baseline, within 7 days before week 9, and then every 8 weeks; response was assessed using RECIST v1.1. The primary end point was safety. Secondary end points included ORR, duration of response (DOR), and PFS. **Results:** Fifty-five patients with ccRCC were treated with MK-6482 120 mg (52 in expansion and 3 in dose-escalation cohorts). The median number of prior therapies was 3 (range 1-9). Forty-two patients (81%) previously received PD-1/L1 inhibitors and 48 (92%) previously received VEGF inhibitors. Thirteen patients (24%) were classified as favorable risk and 42 (76%) as intermediate or poor risk per IMDC criteria. With a median follow-up of 28 mo, the most common all-grade, all-cause AEs >30% were anemia (76%), fatigue (71%), dyspnea (49%), nausea (36%), cough (31%), and hypoxia (31%). Anemia (27%) and hypoxia (16%) were the most common grade 3 AEs. Two patients (4%) experienced grade 4 AEs, and 4 patients (7%) experienced grade 5 AEs. No grade 4 or 5 AEs were related to treatment. ORR was 25%, with 14 confirmed PRs. Thirty patients (55%) had SD, with a disease control rate (CR+PR+SD) of 80%. Median DOR was not reached; 77% had a response ≥6 mo. By IMDC risk, 4 of 13 patients with favorable risk had PR (ORR = 31%) and 10 of 42 with intermediate or poor risk had PR (ORR = 24%); disease control rate was 92% and 76%, respectively. Median PFS for the total population was 14.5 mo; 51% had a PFS of 12 mo. As of June 1, 2020, 33 patients (60%) discontinued because of PD and 2 (4%) because of AEs; 11 patients (20%) had ongoing treatment. **Conclusions:** MK-6482 remained well tolerated with a favorable safety profile and promising single-agent activity in patients with ccRCC for all IMDC risk groups after further follow-up. A phase III trial in a similar population is underway. Clinical trial information: NCT02974738. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Efficacy of cabozantinib in advanced MiT family translocation renal cell carcinomas (TRCC).

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Background: MiT family translocation renal cell carcinomas (TRCC) represent a rare and aggressive subgroup of RCC harboring high expression of c-MET. While response rates of VEGF receptor-tyrosine kinase inhibitor and immune checkpoint inhibitors are limited, efficacy of cabozantinib (a TKI that inhibits VEGFR, MET, and AXL) in this subgroup is unclear. **Methods:** We performed a multicentre, retrospective, international cohort study of patients with TRCC treated with cabozantinib regardless the line of treatment at 7 centers (3 in France and 4 in the US). The main objectives were to estimate response rate according to RECIST criteria, and to analyze progression-free survival (PFS) and overall survival (OS). **Results:** Among 31 metastatic patients treated in the participating centers, 24 were evaluable for response and were included in this study (21 with TFE3 and 3 with TFEB translocations). Median age at diagnosis was 43.5 years (range, 22–70). Most frequent metastatic sites at diagnosis were lungs (62.5%), retroperitoneal lymph nodes (45.8%) and bone (37.5%). Patient's IMDC risk group at diagnosis was favourable (20,8%), intermediate (62,5%) and poor (16,7%). Seven (29%) patients received cabozantinib at first line, 9 (37.5%) at second line and 8 (33%) at third line and beyond. The proportion of patients who achieved an objective response was 16.6%, including 1 complete response and 3 partial responses. For 11 (45.8%) patients, stable disease was the best response. With a median follow-up of 14 months (IQR 5-23), median PFS was 8.4 months (range, 1-34+) and median OS was 17 months (range, 2-43). No PFS difference was detected overall or in any subgroup except in patients with bone metastasis which harbored a median PFS of 3.6 months as compared to 9.1 months for those without (p=0.03). **Conclusions:** This real-world study provides evidence supporting activity of cabozantinib in TRCC, with more durable responses to therapy than those observed with of VEGF receptor-tyrosine kinase inhibitor and immune checkpoint inhibitors. International collaborations and prospective studies are necessary to identifies efficacious therapies for this rare disease that lacks evidence-based treatment options. Research Sponsor: None.

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NAXIVA: A phase II neoadjuvant study of axitinib for reducing extent of venous tumor thrombus in clear cell renal cell cancer (RCC) with venous invasion.

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Background: Venous tumor thrombus (VTT) extension occurs in 4-15% cases of renal cell cancer (RCC). The Mayo classification distinguishes 4 levels of VTT extension between the renal vein and supradiaphragmatic inferior vena cava (IVC). Although surgery is performed with curative intent, mortality is high (5-15%) with complications increasing with the level of the VTT. 5-year survival rates are poor; ~40-65% in non-metastatic RCC. It is hypothesised that neoadjuvant targeted therapy could downstage the VTT reducing the extent of surgery, leading to reduced surgical morbidity and mortality, and increased survival. However, level I or II evidence is lacking. NAXIVA provides the first level II evidence in this patient group, assessing the response of VTT to axitinib. Extensive translational sampling will provide in depth interrogation of VTT (using genomics, proteomics, immunophenotyping and metabolomics) to examine the role of the tumor microenvironment of VTT and response to axitinib. **Methods:** NAXIVA was a single arm, single agent, multicenter phase 2 feasibility study of axitinib in patients with both metastatic and non-metastatic clear cell RCC prior to nephrectomy and thrombectomy. A Simon two stage minimax design was adopted and the trial designed for adequate power to distinguish a $<$5% from a $>$25% improvement in the Mayo VTT level. 21 patients were recruited over a 24 month period between 15/Dec/2017 and 06/Jan/2020 at 5 sites across the UK. Patients were treated with 8 weeks of axitinib (starting dose 5mg bd, increasing to 10mg bd as tolerated) prior to planned surgery. The primary endpoint was the percentage of evaluable patients with an improvement in VTT according to the Mayo classification (assessed using MRI abdomen scans at screening and week 9, prior to surgery. Secondary endpoints were percentage change in surgical approach, percentage change in VTT height, response rate (by RECIST) and evaluation of surgical morbidity assessed by Clavien-Dindo classification. **Results:** The percentage of evaluable patients with an improvement in VTT according to the Mayo classification was 26.58% [80% CI: 15.76%, 39.74%] (6 of 21 evaluable patients). 35.29% (6 of 17 patients who progressed to surgery) had a change in surgical approach to a less invasive option. There was a median percentage reduction in VTT height of 21.49% (SD=27.60%). The response rate (by RECIST) in the evaluable population was 61.90% SD, 14.29% PR, 9.52% PD. In terms of surgical morbidity 11.76% (2 of 17 patients who progressed to surgery) experienced a Clavien-Dindo 3 or greater complication (0 CD3, 1 CD4, 1 CD5). **Conclusions:** NAXIVA provides unique prospective data on the feasibility of neoadjuvant axitinib administration to down stage IVC VTT and reduce the extent of surgery. Work is ongoing to establish predictors of response. Clinical trial information: NCT03494816. Research Sponsor: Pfizer.

Outcomes of first-line (1L) immuno-oncology (IO) combination therapies in metastatic renal cell carcinoma (mRCC): Results from the International mRCC Database Consortium (IMDC).

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Background: Ipilimumab and nivolumab (IPI-NIVO) and IO/vascular endothelial growth factor (VEGF) inhibitor combinations (IOVE) are now standard of care 1L treatment options for mRCC. However, there is limited head-to-head comparative evidence between these strategies. **Methods:** Using the IMDC dataset, patients treated with a 1L IOVE combination (pembrolizumab axitinib, avelumab axitinib and nivolumab cabozantinib) were compared with those treated with IPI-NIVO. The outcomes of interest were overall response rate (ORR), treatment duration (TD), time to next treatment (TTNT), and overall survival (OS). A preplanned subgroup analysis of the IMDC intermediate/poor risk population was conducted. Hazard ratios were adjusted for IMDC risk factors. **Results:** 723 patients were included for analysis (N=571 for IPI-NIVO and N=152 for IOVE). The median age was 60 in both groups. The proportion of patients with IMDC favorable, intermediate and poor risk disease in IPI-NIVO vs. IOVE groups were 9% vs. 33%, 58% vs. 53%, 33% vs. 14%, respectively. In the intermediate/poor risk groups (Table), ORR and median TD were lower and shorter in IPI-NIVO vs IOVE while no difference in median TTNT and OS was detected. The HR for death adjusting for IMDC criteria for IPI-NIVO vs. IOVE was 0.92 (95% CI 0.61-1.40, p=0.71). IMDC risk groups and the presence or absence of sarcomatoid histology, brain, liver or bone metastases were not associated with differences in OS between these treatments (all p>0.2). Patients that had dose delays or steroid use (defined as >40mg of prednisone equivalent/day) for immune related adverse events (irAEs) were associated with longer median TTNT (21.6 vs. 9.5 mons, p=0.02) and OS (NR vs. 44.4 mons, p=0.01) despite similar treatment durations (7.6 vs. 8.9 mons, p=0.77) compared to those without dose delays or steroid use. **Conclusions:** We were unable to detect any differences in OS between IPI-NIVO and IOVE regimens in the IMDC intermediate/poor risk groups and amongst various subgroups. Patients who experienced irAEs requiring dose delay or steroids had longer overall survival. Research Sponsor: None.

Clinical outcome of IMDC intermediate/poor risk patients treated with IPI-NIVO vs. IOVE.

Clinical Outcome	IPI-NIVO % (n/n) or median (mons) (95% CI)	IOVE % (n/n) or median (mons) (95% CI)	P value
ORR	37 (143/382)	59 (43/73)	< 0.01
Best response			
CR	4 (16/382)	4 (3/73)	
PR	33 (127/382)	55 (40/73)	
SD	32 (120/382)	26 (19/73)	
PD	31 (119/382)	15 (11//73)	
Median TD	4.6 (3.8-6.0)	15.0 (10.9-21.4)	< 0.01
Median TTNT	10.1 (8.3-12.0)	18.6 (13.9-24.8)	0.08
Median OS	40.2 (22.6-53.5)	39.7 (30.4-55.9)	0.17
Adjusted Hazard Ratios* (IOVE vs. IPI-NIVO)			
TD	0.54 (0.39-0.73)		<0.01
TTNT	0.76 (0.55-1.07)		0.11
OS	0.92 (0.61-1.40)		0.71

*Hazard ratio <1 means longer for IOVE

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

277 **Rapid Abstract Session**

Stereotactic radiotherapy and pembrolizumab for oligometastatic renal tumors: The RAPPORT trial.

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Background: Pembrolizumab monotherapy, whilst not standard of care, has demonstrated efficacy in clear cell renal cell carcinoma (ccRCC). The first-line KEYNOTE-427 study demonstrated an overall response rate (ORR) of 34%, and a median progression-free survival (PFS) of 7.1 mo (McDermott D et al. J Clin Oncol 2020; 38:S15; 5069-5069). Stereotactic ablative body radiotherapy (SABR) is an option for oligometastatic ccRCC, but patients often develop distant progression or relapse within irradiated sites. The RAPPORT study (NCT02855203) was a multi-institutional single arm, phase I/II study evaluating safety and efficacy of SABR and pembrolizumab. **Methods:** Patients with up to 2 lines of prior systemic therapy with 1-5 oligometastases from ccRCC were eligible. A single fraction of 20Gy SABR to all metastatic sites was given (or 10 fractions of 3 Gy of conventional radiotherapy [CRT] if SABR was not feasible), followed by pembrolizumab 200mg administered Q3W for 8 cycles. The primary objective was safety (CTCAEv4.03), with secondary key objectives of efficacy (RECIST1.1) by disease control rate (DCR), defined as complete response (CR), partial response (PR) or stable disease for at least 6 months, ORR, PFS and overall survival (OS). **Results:** Thirty patients were enrolled and received protocol treatment. The median follow-up was was 2.3 years. The median age was 62 (range 47-80) years, 23 patients (77%) were male. Twenty-three patients (77%) were treatment naïve, 1 patient (3%) had a prior interleukin-2 therapy and 6 patients (20%) had a prior tyrosine kinase inhibitor. Nine patients (30%) had prior metastasectomy. Eighty-three oligometastases were treated (median of 3 per patient), of which 64 (77%) received SABR, and 19 (23%) received CRT. There were 8 adrenal, 11 bone, 43 lung, 12 lymph node and 9 soft tissue metastases irradiated. Four patients (13% [95%CI: 4-31%]) had one or more grade 3 treatment-related AE: Pneumonitis (n=2), dyspnoea (n=1) and elevated ALP/ALT (n=1). There were no grade 4 or 5 AEs. All eight cycles of pembrolizumab were completed by 24 (80%) patients. DCR was 83% (95%CI: 65-94%). ORRs are tabulated below. Median PFS was 15.6 mo. Estimated 1 and 2-year OS was 90% (95%CI: 72-97%) and 74% (95%CI: 53-87%), respectively, while PFS was 60% (95%CI: 40-75%) and 45% (95%CI: 27-62%), respectively. Freedom from local progression at 2-years was 92% (95%CI: 80-97%). **Conclusions:** The combination of SABR and pembrolizumab in oligometastatic renal cell carcinoma is well tolerated with excellent local control. Durable responses and encouraging PFS were observed with this approach, which warrants further investigation. Clinical trial information: NCT02855203. Research Sponsor: Bob Parker Fund for Kidney Cancer Research, Pharmaceutical/Biotech Company.

Best overall response
CR 12 (40%)
PR 7 (23%)
SD 7 (23%)
PD 4 (13%)
CR/PR (ORR) 19 (63% [44, 80])

TIVO-3: Tivozanib in patients with advanced renal cell carcinoma (aRCC) who have progressed after treatment with axitinib.

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Background: Tivozanib (T) is a potent and highly selective VEGF receptor (R) tyrosine kinase inhibitor in clinical development for RCC. Axitinib is also a potent and selective VEGF-R inhibitor now commonly part of front-line aRCC treatment. The activity of T after axitinib has not been previously defined. The activity of T after prior therapy types including axitinib is of clinical relevance. **Methods:** The pivotal TIVO-3 study enrolled subjects with mRCC who failed 2 or 3 prior systemic regimens, one of which included a VEGFR TKI, stratified by IMDC risk category and type of prior therapy (two TKIs; TKI plus checkpoint; TKI + other) then randomized in a 1:1 ratio to T or S. The primary objective of the overall trial was to compare progression free survival (PFS) by blinded independent radiological review. Patients with prior axitinib received as monotherapy in the second or third line setting and other predefined subgroups were reviewed for outcome with T. **Results:** Patients treated with T after prior axitinib had a PFS of 5.5 months and an ORR of 13% compared to 3.7 months and 8% for patients treated with S. Other subgroups are presented in the table below. Clinical trial information: NCT02627963. **Conclusions:** Tivozanib improved PFS vs. sorafenib in patients who have progressed after multiple VEGFR-TKIs, including patients with prior second or third line axitinib treatment. These results suggest differential activity from tivozanib and axitinib despite both being potent and selective VEGF-R inhibitors. Research Sponsor: AVEO Oncology.

		PFS HR	95% CI	T mPFS(m)	T ORR	S mPFS(m)	S ORR
ITT	350	0.73	0·56-0·94	5.6	18%	3.9	8%
Prior TKI and IO subgroup	91	0.55	0.32, 0.94	7.3	24%	5.1	7%
Prior two TKI subgroup	159	0.58	0.40, 0.84	5.5	15%	3.7	8%
Prior axitinib in third line subgroup	93	0.71	.044, 1.14	5.5	16%	3.9	6%
Prior axitinib in fourth line subgroup	79	0.64	0.38, 1.08	5.5	11%	3.6	10%
Prior axitinib in third or fourth line subgroup	172	0.66	0.46, 0.93	5.5	13%	3.7	8%

279 **Poster Session**

Patterns and predictors of oral anticancer agent utilization in diverse metastatic renal cell carcinoma patients.

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Background: Availability of targeted oral anti-cancer agents (OAA) has transformed care delivery for metastatic renal cell carcinoma (RCC) patients. Our objective was to identify patterns and predictors of OAA use within the 12 months after metastatic RCC was detected to understand the extent of real-world adoption of these treatment advances. **Methods:** We used a novel, North Carolina, registry-linked multi-payer claims data resource to examine patterns of use of sorafenib, sunitinib, pazopanib, everolimus, axitinib, cabozantinib, and levantinib in a cohort of metastatic RCC patients diagnosed over 10 years (2006-2015, with claims through 2016). Patients were required to have 12 months of pre- and post-metastatic-index-date continuous enrollment. Log-Poisson models estimated unadjusted and adjusted risk ratios (RRs) and 95% confidence limits (CLs) for associations between patient characteristics and OAA use. In sensitivity analyses, we used a competing risk framework to estimate adjusted risk differences (RD) in OAA use. **Results:** Our population-based study of 713 patients demonstrated relatively low (37%) OAA use at any time during the 12 months post-metastatic-index date among publicly and privately insured patients, with shifting patterns of use consistent with regulatory approvals over time. Lower OAA use was observed among patients who were older, frailer, and with greater comorbidity burden. Other patient-level characteristics, such as sex, race, rurality and type of insurance were not significant predictors of OAA use. **Conclusions:** These data underscore the importance of distinguishing clinically appropriate from potentially poor-quality care and warrant additional studies to understand in more depth the system, provider and patient level drivers of these patterns. Research Sponsor: U.S. National Institutes of Health.

Oral anticancer agent (OAA) adherence and survival in elderly patients with metastatic renal cell carcinoma (mRCC).

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Background: Multiple effective oral anticancer agents (OAAs) are now approved for the treatment of patients with advanced or metastatic renal cell carcinoma (mRCC) based on improvement in overall and progression-free survival in randomized clinical trials. However, real-world adherence and outcomes associated with OAA use in the general mRCC patient population have not been previously investigated. **Methods:** Retrospective analysis of SEER-Medicare patients with mRCC who received treatment with an OAA between 2007 and 2015. Adherence was assessed as proportion of days covered (PDC) within 3 months of OAA initiation with PDC $>$ 50% categorized as adherent. The impact of initial OAA adherence on overall and disease-specific survival was analyzed landmarked at 3 months after OAA initiation. **Results:** A total of 905 patients met study criteria, of which 577 (63.8%) were categorized as adherent to initial OAA treatment. Multivariable analysis adjusting for clinical and demographic factors revealed that living within an impoverished neighborhood was associated with a 20% lower likelihood of adherence (OR 0.80, CI 0.68 – 0.93). No association was observed between adherence and race, ethnicity, marital status, or number of comorbidities. In survival analyses OAA adherence was associated with a significant reduction in both overall (HR 0.71, CI 0.58 – 0.87) and RCC-specific mortality (HR 0.68, CI 0.57 – 0.86). Receipt of sunitinib was associated with a significant reduction in overall and disease specific mortality compared with sorafenib. Post-hoc analysis of patients taking pazopanib as their initial OAA (N = 252) demonstrated reduced all-cause mortality if they received the minimum effective dose of 800 mg daily (HR 0.50, CI 0.35 – 0.72) and decreased adherence associated with initial higher out-of-pocket payments (χ^2 test, p = 0.003). **Conclusions:** Socioeconomic factors predict poor adherence to OAA therapy in Medicare beneficiaries with metastatic RCC, which is in turn associated with poor overall and disease-specific survival. Efforts to improve outcomes and mitigate disparities in the general mRCC population should incorporate considerations of OAA adherence and economic factors. Sunitinib and pazopanib appear associated with favorable survival and remain the most commonly used OAAs in this over 65 year old patient population. Research Sponsor: U.S. National Institutes of Health.

281 **Poster Session**

The association between the Affordable Care Act on insurance status, cancer stage, and overall survival in patients with renal cell carcinoma.

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Background: We aimed to determine whether insurance expansions implemented through the Patient Protection and Affordable Care Act (ACA) were associated with changes in insurance coverage status, stage at diagnosis, and overall survival for patients with renal cell carcinoma (RCC). **Methods:** We identified patients 40 to 64 years old diagnosed with RCC between 2010 and 2016 in the National Cancer Database. States were categorized as participating on time in Medicaid expansion or not participating. We stratified patients into advanced cancer (stage III + IV) and localized cancer (stage I + II) groups. We stratified patients into low, middle, and high income groups. Stage trend and insurance trend analysis were performed to based on income status amongst patients living in expansion and non-expansion states. Absolute percentage change (APC) was calculated for insurance status and stage migration. Cox Regression Multivariable Analysis was conducted to assess risk of all-cause mortality (ACM) for patients before and after the implementation of the ACA, adjusting for insurance status, income, education, age, race, ethnicity, comorbidity, and living in an expansion state. **Results:** We identified 78,099 patients who met inclusion criteria. Following implementation of ACA, APC of patients with insurance increased in both Medicaid and non-expansion states by 4.0% and 2.10% ($p<0.01$), respectively. The largest increases occurred in expansion states, with low income patients acquiring Medicaid (APC +11.0% $p<0.01$), middle income patients acquiring Medicaid (APC +8.20% $p<0.01$), and high-income patients acquiring Medicaid (APC +4.0% $p<0.01$). In our stage trend analysis, there was a higher proportion of patients with localized stage disease after the implementation of the ACA in low income (APC +4.0% $p<0.01$) and middle-income patients (APC +1.6% p=0.02.) who live in expansions states, as well as middle income patients in non-expansions states (APC 1.4% p=0.02). Cox Regression MVA revealed that before ACA implementation, low income and middle income were associated with higher risk of mortality (HR 1.29 95%CI 1.18-1.40 $p<0.01$) and (HR 1.18 95% CI 1.10-1.26, $p<0.01$, but was not following ACA implementation (p=0.20) and (p=0.05) respectively. **Conclusions:** Following the implementation of the ACA the proportion of patients with newly diagnosed RCC with health insurance increased with the largest effects seen in Medicaid expansions states. In addition, higher proportions of patients were diagnosed with localized disease in Medicaid expansion states amongst low- and middle-income patients. Furthermore, income status ceased being a risk factor for mortality following ACA implementation. Our findings suggest that ACA implementation has been associated with downward stage migration in low/middle-income patients and attenuation of income status as a risk for mortality in RCC. Research Sponsor: Stephen Weissman Kidney Cancer Research Fund.

Radiomic features of renal cell carcinoma primary and metastatic sites as predictors of *TERT* and *BAP1* mutations.

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Background: *TERT* and *BAP1* mutations are associated with poor clinical outcome in patients (pts) with metastatic renal cell carcinoma (mRCC) (Dizman *et al* JITC 2020; Joseph *et al* J Urol 2016). In this study we explore radiogenomics as a non-invasive method to identify these alterations. **Methods:** Pts with mRCC who had genomic testing in the course of routine clinical care were included in the current analysis. Pts were assessed with the GEM Extra assay, a CAP-accredited, CLIA-certified test encompassing paired tumor-normal whole exome sequencing (WES) and tumor whole transcriptome sequencing (TGen; Phoenix, AZ). Pts underwent CT imaging; radiomic analysis was performed on the segmented metastatic and primary lesions. Features were independently correlated with *TERT* and *BAP1* mutation status to generate Pearson correlation values (PCVs). **Results:** 92 pts (65:27 M: F) were included in the analysis; of these, the majority of pts (84%) had clear cell histology. Alterations in the *TERT* gene were seen in 12 pts. In these pts 1,325 radiomic features of the primary tissue were examined and 251 features correlated with a PCV $\geq$ |0.2|. Of these, 42 features were correlated with a PCV $\geq$ |0.3|. Highest correlation with *TERT* mutation was seen with Gray Level Cooccurrence Matrix (GLCM) and First Order Features (FOF). 9 pts had *BAP1* mutation with 5 detected in primary tumor and 4 in metastatic sites. Analysis of primary tumor imaging yielded no significant associations between radiomic features and *BAP1* mutation. However, out of approximately 1,500 radiomic features noted in metastatic sites, 111 features correlated with *BAP1* mutation with a PCV $\geq$ 0.2. Of these, 15 features correlated with a PCV $\geq$ 0.3. The radiomic features with the highest correlation with *BAP1*mt were Gray Level Dependence Matrix (GLDM) and GLCM. **Conclusions:** By identifying a correlation between radiomic features of *TERT* mutation in primary tumors and *BAP1* mutation in metastatic sites, our work may ultimately yield a non-invasive method of discerning mutational status in patents with mRCC. Efforts are ongoing to validate our findings within The Cancer Imaging Archive. Research Sponsor: None.

Delaying surgery for clinical T1b-T2bNOM0 renal cell carcinoma: Oncologic implications in the COVID-19 era and beyond.

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Background: During COVID-19, many operating rooms were reserved exclusively for emergent cases. As a result, many elective surgeries for renal cell carcinoma (RCC) were deferred, with an unknown impact on outcomes. Since surveillance is commonplace for small renal masses, we focused on larger, organ-confined, RCCs. Our primary endpoint was pT3a upstaging and our secondary endpoint was overall survival (OS). **Methods:** We retrospectively abstracted cT1b-cT2bNOM0 RCC patients from the National Cancer Database (NCDB), stratifying them by clinical stage and time from diagnosis to surgery. We selected only those patients who underwent surgery. Patients were grouped by having surgery within <1 month, 1-3 months, or >3 months after diagnosis. Logistic regression models measured pT3a upstaging risk. Kaplan Meier curves and Cox proportional hazards models assessed OS. **Results:** 29,746 patients underwent partial or radical nephrectomy. Delaying surgery >3 months after diagnosis did not confer pT3a upstaging risk among cT1b (OR=0.90; 95%CI: 0.77–1.05, p = 0.170), cT2a (OR=0.90; 95%CI: 0.69–1.19, p=0.454), or cT2b (OR=0.96; 95%CI:0.62–1.51, p=0.873) masses (Table). In all clinical stage strata, non-clear cell RCCs were significantly less likely to be upstaged (p<0.001). A sensitivity analysis, performed for delays of <1, 1-3, 3-6, and >6 months, also showed no increase in upstaging risk. **Conclusions:** Delaying surgery up to, and even beyond, 3 months does not significantly increase risk of tumor progression in clinically localized RCC. However, if deciding to delay surgery due to COVID-19, tumor histology, growth kinetics, patient comorbidities, and hospital capacity/resources, should be considered. Research Sponsor: U.S. National Institutes of Health.

Upstaging of RCC by duration of surgical delay.

cT1b

		Univariable		*Multivariable**	
Variables		**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Time to surgery from Diagnosis (months)	1	Ref	-	Ref	-
	1-3	1.05 [0.95, 1.16]	0.371	0.96 [0.86, 1.07]	0.447
	>3	1.06 [0.92, 1.23]	0.422	0.90 [0.77, 1.05]	0.170

cT2a

		Univariable		*Multivariable**	
Variables		**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Time to surgery from Diagnosis (months)	1	Ref	-	Ref	-
	1-3	1.01 [0.87, 1.16]	0.983	0.93 [0.8, 1.09]	0.379
	>3	0.98 [0.75, 1.27]	0.866	0.90 [0.69, 1.19]	0.454

cT2b

		Univariable		*Multivariable**	
Variables		**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Time to surgery from Diagnosis (months)	1	Ref	-	Ref	-
	1-3	0.83 [0.68, 1.01]	0.066	0.87 [0.7, 1.07]	0.186
	>3	0.93 [0.62, 1.42]	0.752	0.96 [0.62, 1.51]	0.873

RCC = renal cell carcinoma; OR = odds ratio; 95% CI = 95% confidence interval; *Adjusted for age, sex, Charlson-Deyo index, race, insurance, income, education, facility type, facility location, distance to facility, histology

Evaluation of treatment patterns and outcomes in patients diagnosed with genitourinary (GU) cancers with linked claims plus prior authorization data.

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Background: Integration of clinical and claims data allows for the examination of outcomes and characteristics which is essential for real world evidence generation and clinical decision making. We describe utilization of clinical data collected from an oncology Prior Authorization (PA) program integrated with claims data to evaluate treatment patterns, resource utilization, and total costs of care during therapy for patients with newly diagnosed metastatic and non-metastatic renal (R), bladder (B), and testicular (T) cancers. **Methods:** Commercially insured patients with a GU cancer diagnosis, from 2/2016 to 12/2019 with both clinical information from a PA tool (based on NCCN guidelines) and claims from the Optum Research Database were identified. Demographics, clinical information (metastatic status and line of therapy), treatment duration, resource utilization, and all-cause costs were collected, and uploaded to a dynamic web-based Tableau dashboard. Analysis was conducted for non-metastatic and metastatic settings based on the first observed treatment episode. Drug additions or switches incremented line of therapy; single drug discontinuations did not. All cost data were adjusted to 2019 values. **Results:** A total of 3,736 patients were included; 13% were censored (i.e. on treatment at the end of the study period). 916 patients (25%) were metastatic and 2,820 (75%) were in their adjuvant/neoadjuvant (A/N) line. 60% of the population was ≥55 years old and 85% were male. The top regimen in A/N line for each cancer type were: nivolumab (R), BCG(B), bleomycin + carboplatin/cisplatin+ etoposide (T). The top regimen in metastatic cancer were: nivolumab (R), carboplatin/cisplatin + gemcitabine (B), bleomycin + carboplatin/cisplatin + etoposide (T). The median duration of A/N line ranged from 50(B) to 119(R) days while the median duration for metastatic line range from 71(T) to 82(R) days. The highest rate of inpatient admissions was observed in patients with R (31%). Of the three cancers, R was the most expensive in the A/N and metastatic settings with mean (standard deviation) costs of $192,308 ($269,358) and $136,293 ($146,632), respectively. **Conclusions:** Combination of clinical and claims data provide valuable information on real world outcomes in routine clinical care and may support treatment selection decisions at the point of care. Research Sponsor: United Health.

285 Poster Session and Poster Highlights Session; Displayed in Poster Session

Patient-reported outcomes of patients with advanced renal cell carcinoma (aRCC) treated with first-line nivolumab plus cabozantinib versus sunitinib: The CheckMate 9ER trial.

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Background: In the phase III, open-label CheckMate 9ER trial (NCT03141177), patients with aRCC were randomized 1:1 (stratified by International Metastatic Renal Cell Carcinoma Database Consortium risk score, tumor programmed death ligand 1 expression, geographic region) to nivolumab 240 mg IV Q2W + cabozantinib 40 mg PO QD (N+C; n = 323) or sunitinib (S) 50 mg PO (4 weeks of 6-week cycles; n = 328) for first-line treatment until disease progression or unacceptable toxicity (max N treatment, 2 years). N+C met primary and secondary efficacy endpoints by significantly improving progression-free survival, overall survival, and objective response rate versus S in aRCC patients with a clear cell component. Here, we present in-depth health-related quality of life (HRQoL) patient-reported outcome (PRO) results, including overall between-group comparisons of treatment groups and time to confirmed deterioration (TCD). **Methods:** PROs in all randomized patients were an exploratory endpoint assessed using the Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19) and EQ-5D-3L instruments. PRO assessments at baseline, common on-treatment scheduled visits, and common follow-up visits for both arms were analyzed. Changes from baseline were assessed using mixed-model repeated measures (MMRM), adjusting for baseline scores and stratification factors. TCD was calculated from Kaplan–Meier estimates and Cox proportional hazards models. **Results:** Median follow-up for overall survival was 18.1 months. PRO completion rates were $>$ 90% at baseline, and $\geq$ 80% at all on-treatment assessments ($\geq$ 10 patients) through week 91 in both arms. The overall least squares mean difference in change from baseline favored N+C over S in FKSI-19 (all domains) and in EQ-5D-3L. Patients treated with N+C experienced less treatment burden, with decreased risk of confirmed deterioration across most measurements versus S, including FKSI-19 total, disease-related symptoms (DRS), DRS-physical (DRS-P), DRS-emotional (DRS-E), functional well-being (FWB), and EQ-5D-3L visual analog scale (VAS) scores (Table). **Conclusions:** Patients reported statistically significant HRQoL benefits with N+C versus S. Treatment with N+C significantly reduced the risk of deterioration in HRQoL scores, including in disease-related symptoms of kidney cancer. These results suggest that the superior efficacy of N+C over S comes with the additional benefit of improved HRQoL. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

MMRM analyses and TCD; N+C versus S.

	Difference in mean change, *P* value	TCD HR (95% CI)
FKSI-19 domains		
Total	2.90, $<$ 0.0001	0.64 (0.50-0.81)
DRS	1.55, $<$ 0.0001	0.62 (0.46-0.82)
DRS-P	1.98, $<$ 0.0001	0.53 (0.40-0.69)
DRS-E	0.15, 0.0494	0.65 (0.47-0.90)
FWB	0.42, 0.0349	0.67 (0.50-0.90)
TSE	0.31, 0.0125	0.90 (0.68-1.19)
EQ-5D-3L VAS	3.26, 0.0011	0.71 (0.55-0.94)

TSE, treatment side effects.

Real-world treatment patterns and sequencing for metastatic renal cell carcinoma (mRCC): Results from the Flatiron database.

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Background: RCC accounts for ~80%–90% of all kidney cancers worldwide. The mRCC treatment landscape is rapidly changing with the approval of new therapies; data describing real-world (RW) treatment patterns and sequencing are limited. This study investigates the characteristics, treatment patterns, and sequencing for mRCC patients in the RW (December 2015–May 2020) and post-dual immuno-oncology therapy (IO-IO) approval in the United States (April 2018–May 2020). **Methods:** Adults diagnosed with mRCC between December 2015 and May 2020 were selected from the Flatiron electronic medical record database for this retrospective study. The study cohort was required to have ≥ 1 month of medical data from the initial mRCC diagnosis date (index date). We used descriptive statistics to analyze baseline patient characteristics, treatment patterns, and sequencing. **Results:** Of 3,524 patients with mRCC (overall cohort, December 2015–May 2020), most were male (68.5%) and had clear cell histology (68.2%). The median age at metastatic diagnosis was 68 years (range, 23–85) and the median follow-up from index date was 328 days. Based on IMDC risk score, 75.8% of patients were categorized as intermediate/poor risk and 23.2% as favorable risk (1% missing). Systemic therapy for RCC was initiated in 79.1% (N = 2788) of patients. The most common treatments for first-line (1L) therapy were tyrosine kinase inhibitor (TKI) monotherapy (mono; 56.4%), IO-IO (19.1%), IO-TKI (9.5%), IO mono (6.9%), and others (8.1%). Second-line (2L) therapy was received by 1303 patients; treatment sequences are presented in the table below. Among patients who received IO-based therapy in the 1L (N = 990), 11% were retreated with IO on any subsequent line. When stratified by clear cell and non-clear cell histology, similar treatment patterns and sequences were observed. Among patients who initiated 1L treatment post-April 2018 (N = 1395), the most common treatments for 1L therapy were IO-IO (36.9%) and TKI mono (32.7%). Among patients who received 2L treatment after initiating 1L post-April 2018 (N = 486), TKI mono followed by IO mono, and IO-IO followed by TKI mono were the most prescribed sequences (Table). **Conclusions:** Following approval of IO-based therapies for 1L, RW treatment patterns for mRCC are evolving; IO-IO has become the most common 1L therapy received by all patients initiating treatment for mRCC. Research Sponsor: Bristol Myers Squibb.

1L to 2L treatment sequences reaching > 2% in patients who received 2L.

Treatment sequence (1L to 2L)	Patients who received 2L December 2015–May 2020, n (%) (N = 1303)	Patients who received 2L after receiving 1L post April 2018, n (%) (N = 486)
TKI mono to IO mono	523 (40.1)	111 (22.8)
TKI mono to TKI mono	175 (13.4)	34 (7.0)
IO-IO to TKI mono	112 (8.6)	106 (21.8)
TKI mono to IO-IO	69 (5.3)	34 (7.0)
TKI mono to IO-TKI	55 (4.2)	26 (5.3)
IO-IO to IO-TKI	29 (2.2)	28 (5.8)
IO-TKI to TKI mono	26 (2.0)	24 (4.9)
Others	314 (24.1)	123 (25.3)

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The impact of hypertension on response rates in patients with renal cell carcinoma.

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Background: There are many clinical trials that demonstrate the benefits of immunotherapies and targeted therapies in patients (pts) with advanced or metastatic RCC (mRCC). Most of these studies specifically exclude many real-world pts with comorbidities such as autoimmune disease, heart failure, and hypertension. Data on treatment efficacy and adverse events in patients with a history of uncontrolled hypertension is lacking, as there have been few studies analyzing more recently approved RCC drug regimens in real-world practice. **Methods:** We retrospectively collected data from pts with mRCC treated with immunotherapy and/or targeted therapies. Patient characteristics, performance status, treatment type, reason for treatment discontinuation, treatment response/progression per RECIST v1.1, survival, and presence of clinical trial exclusion criteria such as hypertension, heart failure, presence of autoimmune disease, renal or liver failure, and International Metastatic RCC Database Consortium (IMDC) Risk score were collected. **Results:** A total of 198 pts were included. The majority of patients received Tyrosine Kinase Inhibitors (TKIs) (42.42% pazopanib (n = 84), 21.71% sunitinib (n = 43), 13.64% cabozantinib (n = 27)), whereas 10.61% were on combination of axitinib + pembrolizumab (n = 21) and 11.62% received ipilimumab + nivolumab (n = 23), and. 71.72% of patients who qualified for systemic therapy had a history of uncontrolled hypertension, whereas 28.28 % of total patients had no history of uncontrolled hypertension. The median time on first-line treatment was 5.17 months. A history of hypertension did not significantly affect Overall Survival (OS), 15.90 months median OS for those with hypertension vs 27.80 median OS for those with no hypertension (p = 0.38). Median OS for all patients was 22.80 months. There was also no difference in response rate between those with a history of hypertension vs those with no history of uncontrolled hypertension (p = 0.65) or in Progression Free Survival (PFS) (p = 0.97) Data on how many patients developed exacerbations of hypertension on therapy will be available at time of presentation. **Conclusions:** Uncontrolled hypertension typically excludes patients from clinical trial enrollment. We found no difference in median OS in those with a history of hypertension compared to those with normal blood pressures. Further large-scale studies are needed to further determine outcomes in patients with hypertension on systemic therapy for mRCC. Research Sponsor: None.

Treatment sequence after first-line nivolumab plus ipilimumab or sunitinib monotherapy in patients with metastatic renal cell carcinoma (mRCC) using real-world data.

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Background: The introduction of second-line (2L) nivolumab (NIVO) in 2015 (CheckMate 025) and first-line (1L) NIVO plus ipilimumab (NIVO+IPI) in 2018 (CheckMate 214) revolutionized the management of mRCC in the US. This study sought to leverage real-world (RW) data by applying CheckMate 214 inclusion criteria to develop a RW comparator for the trial to assess treatment patterns and sequences in RW patients (pts) with mRCC after receiving 1L NIVO+IPI or sunitinib (SUN). **Methods:** This retrospective study identified pts with clear cell mRCC from the Flatiron Health EHR-derived de-identified database who received 1L NIVO+IPI or SUN monotherapy on or after December 2015. Pts must have met the strict selection criteria from CheckMate 214 for this analysis. Evaluation of 1L, 2L, and third-line (3L) therapies was stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk (favorable [FAV] and intermediate/poor [I/P]). **Results:** Of 401 mRCC pts included in the study, 197 (49.1%) received NIVO+IPI and 204 (50.9%) received SUN as 1L therapy (Table). The median follow-up time was 10.1 months in NIVO+IPI pts and 20.2 months in SUN pts ($P < 0.0001$). Among 66 (33.5%) NIVO+IPI pts who received 2L line therapy, the 2 most common therapies were cabozantinib (CABO; 50.0%), and pazopanib (PAZO; 12.1%). Among 119 (58.3%) SUN pts who received 2L therapy, the most common therapies were NIVO (48.7%), and PAZO (8.4%). The 2 most common 3L therapies were axitinib (AXI; 18.2%) or everolimus plus lenvatinib (EVE+LEN; 18.2%) for NIVO+IPI pts, and CABO (26.7%) or NIVO (15.0%) for SUN pts. The treatment sequence is similar between patients with FAV and I/P risk. **Conclusions:** In the RW setting, the treatment sequences after NIVO+IPI and SUN were largely similar across the IMDC risk groups. CABO was the most common therapy in 2L after NIVO+IPI in RW pts, and NIVO was the most common 2L therapy after SUN monotherapy, which was consistent with the sequence in the trial. Research Sponsor: Bristol Myers Squibb.

Selected 2L and 3L therapies, showing top 2 by frequency for each 1L therapy.

	All pts: 1L NIVO+IPI (N = 197)	All pts: 1L SUN (N = 204)	I/P risk: 1L NIVO+IPI (N = 164)	I/P risk: 1L SUN (N = 154)	FAV risk: 1L NIVO+IPI (N = 33)	FAV risk: 1L SUN (N = 48)
Pts with 2L therapy, n (%)	66 (33.5)	119 (58.3)	55 (33.5)	92 (59.7)	11 (33.3)	26 (54.2)
CABO	33 (50.0)	8 (6.7)	28 (50.9)	4 (4.3)	5 (45.5)	4 (15.4)
PAZO	8 (12.1)	10 (8.4)	6 (10.9)	6 (6.5)	2 (18.2)	4 (15.4)
NIVO	1 (1.5)	58 (48.7)	0	46 (50.0)	1 (9.1)	11 (42.3)
Pts with 3L therapy, n (%)	22 (11.2)	60 (29.4)	19 (11.6)	46 (29.9)	3 (9.1)	13 (27.1)
AXI	4 (18.2)	5 (8.3)	2 (10.5)	3 (6.5)	2 (66.7)	2 (15.4)
EVE+LEN	4 (18.2)	5 (8.3)	4 (21.1)	5 (10.9)	0	0
CABO	2 (9.1)	16 (26.7)	2 (10.5)	13 (28.3)	0	3 (23.1)
NIVO	1 (4.5)	9 (15.0)	1 (5.3)	7 (15.2)	0	2 (15.4)

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Outcomes and prognostic factors in metastatic renal cell carcinoma patients with brain metastases.

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Background: The study aimed to evaluate the outcomes and prognostic factors in patients with brain metastatic renal cell carcinoma (bmRCC). **Methods:** The data of 322 patients with renal cell carcinoma, between 2012 and 2020, were retrospectively reviewed. The clinicopathological features and treatments of the patients with bmRCC were recorded. Overall survival (OS) and prognostic factors were evaluated with Kaplan-Meier analysis and Cox-regression analysis. **Results:** Forty (12.4%) of the patients had bmRCC. The median follow-up period was 7.3 months (range, 0.2-55.5). The male/female ratio was 2.3, and the median age at diagnosis was 62 years (range, 25-84). Seventeen (42.5%) of the patients were de-novo metastatic, and nine (22.5%) of the patients had brain metastases at presentation. The most common extracranial metastatic sites of the disease were lung (72.5%), bone (47.5%), lymph node (27.5%), and liver (12.5%). Twenty-four (60%) patients previously had received various therapies (tyrosine kinase inhibitor, checkpoint inhibitors, or palliative radiotherapy). After brain metastases developed, 92% of the patients received brain radiotherapy (whole-brain radiotherapy or stereotactic radiosurgery), and twenty-five (62.5%) patients received different therapies. Nine patient received sunitinib, nine patient pazopanib, five patient nivolumab, and two patient axitinib. A total of 32 (80%) patients died during the study period. The median OS was 8.8 months (range, 2.9-14.6) for all patients with bmRCC. Six months- and one-years overall survival ratios were 60% and 40%, respectively. In univariate analysis, the number of brain metastasis ($p = 0.352$), the localization of brain metastasis ($p = 0.790$), the longest size of brain metastasis ($p = 0.454$), the number of extracranial metastatic sites ($p = 0.812$), de-novo metastatic disease ($p = 0.177$), primary tumor localization (left or right) ($p = 0.903$), and tumor grade ($p = 0.093$) were not statistically significant factors on OS. However, age ($p = 0.02$), a history of nephrectomy ($p < 0.001$), receiving brain radiotherapy ($p = 0.005$), and type of treatment ($p = 0.044$) was statistically significant. Only, the effect of brain radiotherapy on OS ($p = 0.011$) was confirmed in multivariate analysis. **Conclusions:** The prognostic data of patients with bmRCC is limited. In this study, we observed that the prognosis of patients with bmRCC was poor. Despite a small number of patients, we detected that the effect of tyrosine kinase inhibitors and nivolumab was comparable, and receiving brain radiotherapy was a prognostic factor for OS.
Research Sponsor: None.

Use of nivolumab (N) and cabozantinib (C) for treatment of the metastatic renal cell carcinoma (mRCC) in the Veneto region: Results of AMOUR study.

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Background: Second (2L) or third-line (3L) treatment options for mRCC have dramatically changed in the last years. The standard of care as per Italian Regulatory Agencies approvals is N or C. To date, there are no criteria for the choice between N and C, which both demonstrated OS gain in the pivotal trials. **Methods:** We planned a retrospective, real world analysis of the use of N and C as 2L and 3L treatment in 17 Oncology Units of Veneto Region. All consecutive patients (pts) with mRCC treated in advanced setting in 2017-2018 were included. **Results:** We identified 170 pts, 73% males, median age 68.4 years. All pts started a 2L treatment while only 59% received a 3L treatment. In our cohort, patients with NLR $>$ 3 at treatment start had a shorter OS (43 vs 90 months (mos), p $<$ 0.0001); IMDC classification maintained its prognostic role. In 2L, N was administrated in 108 pts (63%), C in 29 pts (17%); in 3L N was administrated in 42 pts (25%), C in 49 pts (29%). Reported oncologists' reasons for 2L choice were: change of mechanism of action compared to first line (28%), response to previous TKI (21.2%), intolerance to TKI (17.6%), previous toxicity (12.9%), tumor burden (11.2%), age of the patient (4.1%). Median OS and PFS in 2L were 28.4 and 6.6 mos for N, 16.8 and 6.6 mos for 2L C. Median OS and PFS in 3L were 27 and 5.2 mos for N, 16.6 and 7.5 mos for C. 46 pts received the sequence of drugs N $>$ C, 12 the opposite sequence C $>$ N. Median OS for N $>$ C vs C $>$ N were 96.6 vs 36 mos (p $>$ 0.0001); median PFS for both the sequences were similar at 5.7 mos (p = ns). The cost per patient of the sequence N $>$ C is 51.606 € while for the sequence C $>$ N is 31.480,00 €. Between the two sequences a cost effectiveness per month of survival analysis was performed: the cost per month of OS for the sequence N $>$ C was 534,18 € while for the sequence C $>$ N was 874,46 €, heavily higher. **Conclusions:** In our real-world setting cohort, most of the pts received N as 2L treatment and a minority received C. Outcome of single drug are superimposable to published literature. With the limits of the retrospective nature of the study, with a cost per month of OS lower a much longer OS, the sequence N $>$ C appear to be a better treatment strategy. Research Sponsor: None.

Evaluation of cabozantinib (cabo) in combination with direct oral anticoagulants (DOAC) or low molecular weight heparin (LMWH) in renal cell carcinoma (RCC).

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Background: Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. Despite cabo improving RCC outcomes, VTE management in these patients remains a challenge, partly due to poor understanding of cabo safety profile and drug interactions with anticoagulants. Recent anti-Xa DOAC studies demonstrated comparable efficacy and safety with LMWH for VTE treatment in patients with cancer. Thus far, cabo clinical trials have largely allowed concurrent LMWH use but not DOACs. Herein, we investigated the hemostasis safety profile of cabo with different anticoagulants in patients with RCC. **Methods:** We performed a retrospective multicenter study (7 sites) of patients with advanced RCC receiving treatment with cabo. Patients were allocated into three groups: cabo with concomitant use (at least 1 week) of 1) DOACs (anti-Xa inhibitors), 2) LMWH, or 3) no anticoagulant. Primary endpoint was to evaluate the rate of major bleeding events (defined per the International Society of Hemostasis and Thrombosis criteria) in the above groups. Secondary endpoint was rate of new/recurrent VTE while on anticoagulation. Overall comparison between groups was analyzed by Fisher exact test. If a difference was found, then pairwise comparison was done. **Results:** Between 2016-2020, 172 patients with RCC received cabo (DOAC 50, LMWH 18, and no anticoagulant 104). At initiation, cabo median dose was 60 mg but 45% had dose reduction. Median age was 63 [IQR 57-69]. Most were males (77%), had clear cell histology (81.5%), underwent nephrectomy (76.7%), and had intermediate IMDC risk disease (59%). Cabo was first, second, and subsequent line of therapy in 19.8%, 34.9%, and 45.3% of patients, respectively. The table below shows major bleeding and VTE events between groups. An overall difference of major bleeding was found between the three groups comparison (p=0.009). There was no difference in major bleeding events between patients who received DOAC vs LMWH (p=0.28) and DOAC vs no anticoagulant (p=0.1) but there was a difference between LMWH vs no anticoagulant (p=0.02). Two patients died from bleeding (one in LMWH and one in DOAC group). **Conclusions:** This study highlights the first reported real world experience of cabo with different anticoagulants in patients with advanced RCC. Cabo use with a DOAC had a similar bleeding risk in comparison to patients not receiving any anticoagulation. In carefully selected patients, DOACs can be considered as concurrent medications in those receiving cabo. Given the low number of patients receiving LMWH, it is difficult to draw conclusions from this group. Data are currently being updated to expand subjects receiving DOAC and LMWH in our cohort. Research Sponsor: None.

		Major Bleeding N (%)		New/Recurrent VTE N (%)	
Groups	**N**	**Yes**	**No**	**Yes**	**No**
No anticoagulant	104	0 (0%)	104 (100%)	NA	NA
LMWH	18	2 (11.1%)	16 (88.9%)	0 (0%)	18 (100%)
DOAC	50	2 (4%)	48 (96%)	2 (4%)	48 (96%)

Association of cabozantinib residual concentration (Ctrough) and blood clearance (Cl/F) with toxicity (tox) and progressive disease (PD) in metastatic renal cell carcinoma (mRCC) patients (pts): Results from a monocentric pharmacokinetics (PK) study.

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Background: Cabozantinib is a TKI with a substantial efficacy in mRCC. It is associated with a relevant tox leading frequent dose modifications (DM) or drug discontinuations (DD). While an exposure/safety relation has been demonstrated for this drug, an exposure/efficacy relation is still unknown. Cl/F is a measure of elimination of a drug from blood or plasma and lower Cl/F of cabozantinib has been previously associated with increased DM rate in mRCC. **Methods:** We performed a monocentric PK (INDS MR 5612140520) study in patients with mRCC. Blood draw for assessment of cabozantinib PK was performed at least 8 hours from the last drug dose. Ctrough was estimated with the following equation: Ctrough=Cmeas*0,5DI-24/t1/2. Ctrough and Cl/F were compared in patients with or without a relevant tox and in PD pts vs SD/PR pts. Relevant tox was defined either as G3-4 tox or G2 tox leading to DM or DD. Differences in Ctrough and CL were assessed between the groups with Mann Withney U test. **Results:** From 01.10.19 to 31.08.20 66 pts were included in this analysis. Twenty one relevant tox and 29 PD were observed. Ctrough was higher in pts experiencing relevant tox than in those who did not: 624,6 ng/ml (IQR 494-1030,2 ng/ml) vs 505,2 ng/ml (IQR 329,2-910,2), p0.012. Conversely Cl/F was lower in relevant tox vs not tox1,85 l/h (IQR 1,4-2,2 l/h) vs 2.27 l/h (IQR 1,7-3,2), p 0.024. In PD pts, Ctrough was lower than in SD/PR pts: 419ng/ml (IQR 317,2 -549,1 ng/ml) vs 554 ng/ml (IQR 416,9-795,6), p 0.0105, while Cl/F was higher in PD patients: 2,6 l/h (IQR 2,14-3,44 l/h) vs SD/PR patients 1.9 l/h (1,930 l/h;IQR 1,35-2,53 l/h); p= 0.011. Time from day cycle 1 to PK blood draw was significatively longer in non-tox pts and numerically longer in PD pts, which have the lowest Ctrough and the highest Cl/F. **Conclusions:** Cabozantinib toxicity is associated to a higher Ctrough and a lower Cl/F. Cabozantinib PD is associated to a lower Ctrough and a higher Cl/F. Cl/F should be assessed alongside with Ctrough in Cabozantinib PK blood test; Ctrough may decrease and conversely Cl/F may increase with time on treatment. Research Sponsor: None.

Variable	Tox (21)	Non Tox(45)	p	PD(29)	SD/ PR(37)	p
Age median (IQR)	58 (52.5-66)	61 (55-69)	.37	58 (52-65)	61.5 (54.3-69)	.53
Histology (ccRCC)	16/21	36/45	.72	22/29	29/37	.26
Does intensity median (IQR)	40 (40-60)	42.8 (40-60)	.5	40 (40-60)	40 (28.8-55.7)	.15
Time from C1D1 to blood draw, weeks, median (IQR)	13 (4.3-45.7)	44 (12.2-95.3)	*.03*	39.4 (24.9-66.3)	17.8 (7.6-91)	.1

IQR: Interquartile range *Italics: p significative.*

Cabozantinib versus other TKIs after CPI treatment in the real-world management of patients with metastatic renal cell carcinoma (mRCC).

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Background: Checkpoint inhibitors (CPIs) are a treatment option for patients with metastatic renal cell carcinoma (mRCC), but there is limited clinical data on the efficacy of targeted therapies following CPI treatment. Cabozantinib is a tyrosine kinase inhibitor (TKI) that targets multiple receptor kinases implicated in tumorigenesis. In the US, cabozantinib is approved for use in patients with advanced RCC including after CPI treatment. **Methods:** This retrospective observational cohort study (NCT04353765) evaluated outcomes associated with cabozantinib or other TKIs (axitinib, lenvatinib, pazopanib, sorafenib, sunitinib) in patients with mRCC following CPI treatment. Eligible patients initiated TKI therapy between May 1, 2016 and Sep 31, 2019 and had received a CPI as their last systemic treatment prior to TKI therapy. Patients were identified from the US Oncology Network iKnowMed electronic health record database through structured queries and a targeted chart review. The following real-world outcomes were assessed: 6-month response rate ($RR_{6months}$; primary); overall response rate (ORR); overall survival (OS); time to treatment discontinuation (TTD); rates of dose reductions, and discontinuation due to adverse events (AEs). The *p* value for $RR_{6months}$ was used to test for non-inferiority. **Results:** Eligible patients (*n* = 247) had a mean (SD) age of 65.9 (10.5) years and 74.1% were male; 75.7% (*n* = 187) received cabozantinib and 24.3% (*n* = 60) received other TKIs. All patients had intermediate or poor MSKCC score; more poor-risk patients received cabozantinib than other TKIs (28.9% vs 20%). Outcomes data are shown in the Table. Compared with other TKIs, cabozantinib was associated with a significantly higher $RR_{6months}$ and ORR, and TTD was twice as long with cabozantinib. Discontinuation due to AEs was more frequent with other TKIs than with cabozantinib, although this was not statistically significant; 21.7% of discontinuations occurred during the first 3 months of treatment. AEs leading to discontinuation were consistent with the known safety profile of the products. **Conclusions:** In this mRCC population receiving routine care in the US, cabozantinib was used more frequently than other TKIs after CPI treatment. Cabozantinib was an effective and well tolerated option post-CPI, with a high response rate in the real-world setting.abozantinib was associated with a significantly higher response rate and a lower discontinuation rate due to AEs; TTD was double that of other TKIs. Research Sponsor: Ipsen.

	Cabozantinib (*n* = 187)	Other TKI (*n* = 60)	*p* value
$RR_{6months}$, %	50.8	33.3	< 0.001
ORR, %	53.5	38.3	0.041
Overall survival rate, % (95% CI)			
6 months	81.9 (75.5, 86.8)	75.1 (61.5, 84)	0.765
12 months	61.5 (53.5, 68.4)	59.6 (44.7, 71.8)	
18 months	51.7 (43.1, 59.6)	45.9 (29.6, 60.7)	
TTD, median months	6.2	3.1	0.015
Dose reductions, %	47.1	41.7	0.466
Discontinuation due to AEs, %	31.3	40.4	

Axitinib and avelumab (AA) as first-line treatment of metastatic renal cell carcinoma (mRCC): A real-world outcome review in the Northwest of England, United Kingdom.

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Background: The combination of the immune checkpoint inhibitor avelumab and VEGF-targeted, antiangiogenic tyrosine kinase inhibitor axitinib (AA) has demonstrated superior PFS and ORR compared to sunitinib in patients with mRCC and is an option for first line treatment across all IMDC risk scores. In this retrospective review we report our real world experience of this combination in three cancer centres in the Northwest of England. **Methods:** Treatment naïve mRCC patients receiving AA through the Early Access to Medicine Scheme at 3 cancer sites in the UK between May 2019 and July 2020 were identified. Primary outcomes of interest include overall response rate (ORR), adverse events (AEs) and preliminary survival observations. **Results:** A total of 44 patients were identified with a median follow up of 6.9 months (0.8-13.5 mo). Median age was 68 (48-81); 68% were male. The patients' adult comorbidity evaluation score (ACE-27) was calculated: 0 = 43%, 1 = 30%, 2 = 7% and 3 = 20% . 45%, 48% and 7% of patients had favourable (F), intermediate (I) and poor (P) IMDC risk scores respectively. All had clear cell histology with 16% demonstrating sarcomatoid change. Most patients had undergone a nephrectomy (70%) and 36% had a single organ site of metastatic disease. ORR in the whole cohort was 60% (CR 5%, PR 55%, SD 25%, PD 2%, NE 13 %). Median time to first response was 2.6 months (0.6- 8.2mo). At time of data cut-off, 64% of patients remain on treatment (80% F, 48% I and 67% P). 14% of patients discontinued treatment due to disease progression while 22% stopped due to toxicity. The majority of patients (68%) continued axitinib at the starting dose of 5mg BD. Dose escalation of axitinib was possible in 9% patients while 23% needed a dose reduction due to toxicities. AEs were observed in 36 (82%) patients (G3 36%); the commonest being mucositis 30%; hypertension 23% (G3 11%); fatigue 25%; thyroid dysfunction 18%; diarrhoea 20% (G3 5%); hepatitis 20% (G3 11%). 9% of patients experienced an infusion reaction to avelumab. Overall, 9 (20%) patients received steroids for suspected immune related adverse events (irAEs); 6 (14%) were managed as G3≤ irAEs. 9 (20%) patients required inpatient admission due to AEs; 5 (11%) were associated with irAEs. Of the patients who discontinued AA treatment, 50% received subsequent therapy (12.5%, 75% and 12.5% receiving combination checkpoint inhibitor therapy, other VEFG TKi and TKi/MTOR combination respectively). 4 patients remain on active surveillance with no evidence of progression. **Conclusions:** Our early experience of AA in this real world setting reports comparable clinical responses to the published data. Treatment is well tolerated, with lower than expected levels of G3 or above AEs which is reassuring in a non-trial selected population. Follow-up is ongoing and updated efficacy and safety outcomes will be presented. Research Sponsor: None.

Ipilimumab and nivolumab (I+N) as first-line treatment of metastatic renal cell carcinoma (mRCC): A real-world review in North West of England, United Kingdom.

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Background: Ipilimumab and Nivolumab (I+N) is now an established first line option for patients with advanced RCC of intermediate (I) or poor (P) IMDC risk score. In this retrospective review, we review our experience of this combination in two cancer centres in North West England with a focus on immune related adverse events (irAEs) and their impact on the patient pathway. **Methods:** Treatment naïve mRCC patients starting I+N between May 2019 and July 2020 were identified. Primary outcomes of interest include overall response rate (ORR), the management of irAEs and early survival observations. **Results:** A total of 69 patients were identified. Median age was 60yr (19-82yr), 77% had clear cell histology. The IMDC risk was 72% I and 28% P. Median follow-up was 11.0 mo (1-22mo). ORR was 45% (CR 9%, PR 36%, SD 28%, PD 23%, NE 4%) Median time to first response was 2.9mo. (1.8- 15.5mo). 10% of patients experienced pseudoprogression. Median PFS and OS are not yet reached with 86% of patients still alive at the time of data cut-off. The majority (75%) of patients completed all 4 doses of I+N. Of the 10% receiving less than 4 doses due to toxicity, 14% continued on single agent N. Overall, 15% discontinued therapy due to toxicity and 28% experienced at least one treatment delay. Any grade irAEs were seen in 74% of patients (G3 35%) with no treatment related deaths. The commonest irAEs were: rash/pruritis 39%; endocrinopathies 30%(G3 7%); diarrhoea 29% (G3 14%); hepatitis 22% (G3 6%); and nephritis 3% (G3 3%). Of the patients developing irAEs, 71% received steroids with 16% requiring additional immunosuppression including infliximab (6%) and mycophenolate mofetil (8%). A third of all patients required admission for irAE management with a total of 37 inpatient episodes across the cohort with a median length of 7 days (1-24). 7% of patients proceeded to surgery for either primary or metastatic disease, which contributed to ongoing disease response in these patients. At the time of data cut-off, 45% of patients were no longer on treatment due to PD (29%), toxicity (15%) or unrelated death (1%). Of those who stopped due to toxicity, 50% subsequently progressed with a median time to progression of 4mo (3-6 mo) and 50% remain on active surveillance with a median follow-up of 7.5mo (1-10). 62% of patients with PD received second line treatment; most frequently, cabozantinib (83%). **Conclusions:** Our experience of I+N shows comparable efficacy and toxicity profiles to available reports. irAEs requiring intervention are frequent and may be associated with prolonged hospital admission, and patients should be counselled appropriately. Data within mirrors published reports of ongoing responses in a subset of patients who stop treatment due to toxicity and also suggests a possible role for resection of residual or metastatic disease in disease control. Updated survival data will be presented. Research Sponsor: None.

Evaluation of germline genetic testing criteria in early-onset kidney cancer.

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Background: An estimated 5% of kidney cancers are associated with hereditary RCC syndromes. Current germline genetic testing guidelines for patients with kidney cancer were developed to identify carriers of known RCC-associated genes and have evolved in the panel-testing era. We evaluated the utility of the recent National Comprehensive Cancer Network (NCCN) recommendation of testing all patients with early-onset RCC (defined as age of diagnosis $\leq$ 46 years) for germline variants in genes implicated in hereditary RCC syndromes. **Methods:** We retrospectively identified patients with RCC diagnosed at age $\leq$ 46 years who underwent targeted germline testing at our institution through referral to clinical genetics service (n = 68, 29%) or through broad germline testing of $\geq$77 cancer susceptibility genes using next generation sequencing as part of a prospective matched tumor-normal genomic profiling initiative (n = 165, 71%). Diagnostic performance of referral criteria was assessed by the presence of pathogenic/likely pathogenic (P/LP) germline variants in RCC-associated genes and incidental cancer susceptibility genes. **Results:** Of 233 patients, 61% were male, 74% were Caucasian, 15% had family history of RCC, 15% had RCC-syndromic features, including 9% with multifocal renal tumors. Most patients (54%) had clear cell RCC (ccRCC). P/LP germline variants were identified in 42 (18%) patients but only 21 (9%) had mutations in RCC genes (12 *FH*, 4 *VHL*, 2 *SDHB*, 1 each in *BAP1*, *TSC1*, and *FLCN*). All 21 early-onset patients with germline variants in an RCC-associated gene also had one of the following risk factors: non-ccRCC histology, family history, or syndromic features. In 91 patients (39%) with a non-RCC germline variants or no alteration, none of these three risk factors were found. Of 21 patients with non-RCC P/LP germline variants, 9 had mutations in moderate/high penetrance genes (*BRCA1* [2], *ATM* [2], *CHEK2* [1], *TP53* [2], *PALB2* [1], and *RET* [1]); 8/9 (89%) met standard criteria for testing for those genes independent of early-onset RCC diagnosis. **Conclusions:** Patients with early-onset clear cell RCC and no suspicious personal or family history are unlikely to have an RCC-associated germline mutation. RCC-gene panel testing has highest utility in early-onset patients with either non-ccRCC histology, family history of RCC, or RCC-associated syndromic features. Given the high frequency of non-RCC P/LP variants, early-onset RCC patients should be counseled regarding broader testing beyond RCC-associated genes. Research Sponsor: U.S. National Institutes of Health.

297 **Poster Session**

Factors associated with palliative care (PC) utilization in advanced and metastatic renal cell carcinoma (RCC).

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Background: Palliative care (PC) offers various benefits for patient with cancer that include, but are not limited to, decrease in disease-specific symptoms and improvement in functional status. Several oncological guidelines have adopted early integration of PC into oncologic care to improve quality of life among patients with advanced malignancies. However, PC utilization patterns and factors associated with its use in advanced renal cell carcinoma (RCC) remain poorly understood. **Methods:** Using the National Cancer Database (NCDB), we abstracted patients with stage III and IV RCC from 2004-2014 and evaluated PC utilization amongst this cohort. Socioeconomic and clinical factors were compared for patient receiving and not receiving PC for advanced RCC. Multivariable logistic regression identified factors that were associated with receipt of PC. **Results:** We identified 20,122 and 42,014 patients with stage III and IV RCC, respectively. Among this cohort, 329 and 9,317 patients received PC for stage III and IV RCC, respectively. From 2004 to 2014, PC utilization has been stable at ~1% for stage III RCC and has significantly increased from 17% to 20% for stage IV RCC. Multivariable analysis demonstrated that Blacks, income >$48,000, regions outside of Northeast, stage III RCC, and patients that received surgery were less likely to receive PC. Patients that were female, with more comorbidities, uninsured or with government insurance, lower educational status, treated at academic or integrated cancer program, with sarcomatoid histology, receiving systemic therapy were more likely to receive PC. **Conclusions:** While PC utilization has significantly increased for stage IV RCC, there are several demographic, socioeconomic, and clinical factors that predict PC usage among patients with advanced RCC. Taken together, this suggests the need for more equitable and systematic use of PC among patients with advanced RCC. Research Sponsor: U.S. National Institutes of Health.

Q-TWiST analysis of tivozanib (T) versus sorafenib (S) in patients with advanced renal cell carcinoma (RCC) in the TIVO-3 study.

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Background: In the randomized phase III study TIVO-3, the VEGFR-TKI tivozanib (TIVO) increased progression-free survival with better tolerability but no difference in overall survival (OS) relative to sorafenib (SORA) as third- or fourth-line therapy in patients with metastatic RCC. These results provide motivation to apply quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) methods to quantify the net health benefits of TIVO, in the presence of similar survival, when compared to SORA. **Methods:** In application of Q-TWiST, patient-level OS was subdivided into three mutually exclusive states: time with toxicity (TOX), time without symptoms and toxicity (TWiST), and time after progression/relapse (REL). Mean Q-TWiST was calculated by applying utility coefficients of 0.5, 1.0, and 0.5 to the restricted mean (max 36 months follow-up) health states of TOX, TWiST, and REL, respectively; 95% CIs for the means and mean differences were estimated by bootstrap distributions. Relative Q-TWiST gain was defined as the mean absolute Q-TWiST difference divided by the SORA mean OS. **Results:** Mean TWiST was significantly longer for TIVO than for SORA (10.30 months v.5.35 months; Table). Mean REL time was significantly shorter for TIVO, with no difference in mean TOX time. Mean Q-TWiST was 15.04 and 12.78 months for TIVO and SORA, respectively, a statistically significant difference (p=0.0493). The relative gain for TIVO was 11.2%. Clinical trial information: NCT02627963. Values in table are mean (95% CI) in months or p-value for difference in treatment group means. **Conclusions:** The difference in Q-TWiST in TIVO-3 was primarily driven by benefits of TIVO in TWiST, partially offset by superiority of SORA in REL time. As a third- or fourth-line treatment for RCC, TIVO significantly increased Q-TWiST relative to SORA, primarily through an increase in TWiST, which is generally considered to be the state with highest utility to patients. Consequently, Q-TWiST may be considered an alternative patient-centered measure of benefit of TIVO in these settings. Research Sponsor: AVEO Oncology.

Restricted mean durations of health states with 36 month maximum follow-up.

Health State	Tivozanib (n=175)	Sorafenib (n=175)	Difference	p-value
TOX	1.29 (0.86, 1.81)	1.15 (0.86, 1.51)	0.14 (-0.45, 0.70)	0.65
TWiST	10.30 (8.32, 12.33)	5.35 (4.42, 6.48)	4.95 (2.56, 7.38)	<0.0001
REL	8.18 (6.35, 10.18)	13.71 (11.81, 15.59)	-5.53 (-7.84, -2.88)	<0.0001
Q-TWiST	15.04 (13.36, 16.74)	12.78 (11.56, 14.05)	2.25 (0.01, 4.51)	0.0493

299 **Poster Session**

Osteonecrosis of the jaw in metastatic renal cell carcinoma (mRCC) patients treated with zolendronic acid and denosumab: An observational retrospective multicenter trial.

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Background: Bone is one of the most common site of metastasis occurring in 30% of metastatic renal cell carcinoma (mRCC) patients (pts)3,4. Skeletal metastases from mRCC are usually osteolytic and associated to high rate of morbidity and complication through skeletal related events (SRE). Bone-targeted therapies (BTT) such as zolendronic acid (ZOL AC) and denosumab (Dmab), shown to decrease the time-to-first and subsequent SREs12. Osteonecrosis of the jaw (ONJ) is a rare but potentially serious adverse event associated with BTT. It occurs in 1-2% of pts treated with BTT and in 10-17% of mRCC pts treated with ZOL AC or Dmab. Vascular endothelial growth factor-Tyrosine kinase inhibitors (VEGF-TKI) represent the backbone treatment for mRCC. Nevertheless, it is unclear whether the association of DMAB and ZOL AC to VEGF-TKITTagents could be associated to higher incidence of ONJ. **Methods:** We retrospectively collected data, from 2 Italian referring centers for mRCC, about 74 pts with bone metastases from mRCC who received, concurrently or sequentially to VEGF-TKI or immune-oncology (IO), AC ZOL and DMAB from January 2013 to January 2020. All pts provided informed consent for inclusion in the study. **Results:** All pts received VEGF-TKI as first line treatment. 17 pts received AC ZOL whereas 57 received DMAB. All pts received odontological consultation and orthopantomography before start BTT. The median time of Dmab and AC ZOL exposure was 11.6 months. ONJ occurred in 10/74 pts (7.4%): 6/10 pts were on first line treatment and 4/10 on second line. Treatments administered at the time of ONJ diagnosis were nivolumab (1/10), cabozantinib (2/10), sorafenib (1/10), sorafenib (1/10), sunitinib (4/10) and one pts was off therapy. **Conclusions:** In this real-life Italian population, treatment with BTT in mRCC pts treated with VEGF-TKI inhibitors and IO is associated to higher incidence of ONJ compared to previous report of pts treated with BTT for bone metastasis and lower compared to previous reports in mRCC. Despite the retrospective collection, we provided one of the largest sample of pts treated concurrently with VEGF-TKI or IO and BTT. Physicians should be careful in the use of BTT combined with other treatments in mRCC pts. Research Sponsor: None.

ASSET: Alternative schedule sunitinib in metastatic renal cell carcinoma (RCC)—Cardiopulmonary exercise testing (CPET).

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Background: Sunitinib (SUN) is a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) approved for treatment of advanced RCC and high risk RCC after nephrectomy. Evidence suggests that a 2 week (wk) on, 1 wk off schedule (2/1) of SUN administration may be more tolerable than the standard 4 wk on, 2 wk off schedule (4/2). We investigated changes in cardiopulmonary function and related parameters over time in RCC patients treated with both schedules of SUN. **Methods:** Patients starting SUN for RCC, with KPS $\geq$80 and normal organ and marrow function, were enrolled and randomized 1:1 to schedule 4/2 or 2/1. Subjects were required to be able to walk and jog on a treadmill and to complete an acceptable CPET at baseline (BL). Primary endpoint was change in peak oxygen uptake (VO_2peak) on both schedules at 12 wk from BL. Key secondary endpoints were change from BL to 12 wk in: left ventricular ejection fraction (LVEF), upper and lower body strength (1-RM), functional measures (chair stand, timed up-and-go [TUG], 6-minute walk test [6MWT], quality of life (QOL; FACT-Fatigue, FKSI-19), anxiety and depression (HADS) and exercise behavior (Godin Leisure Score). ANCOVA models controlling for baseline values were used to analyze the primary and secondary endpoints. **Results:** Between 11/20/2017 and 6/24/2019, 9 out of a planned 30 patients consented to participate at Duke. Two patients declined to participate and 7 patients were enrolled on study: 4 on Arm A and 3 on Arm B. All 7 patients completed the 12 wk study. Median age, BMI, and VO_2peak were 65 yrs, 30.5 kg/m^2, and 19.2 ml kg^{-1} min^{-1}. We observed no difference in the primary endpoint of VO_2peak between arms (p=0.84). We report BL to 12 wk change scores for all patients starting SUN (Table). In addition, mean change scores (SE) for QOL by FACIT-Fatigue and FKSI-19 were -2.88 (1.5) and 1.2 [9.8]; anxiety and depression by HADS 1.14 (1.3); and physical activity 1.14 (1.7). **Conclusions:** We observed non-significant declines in most measures of physical fitness and function during the first 12 wk of treatment with SUN. To our knowledge, this is the first reported study of these parameters in patients with RCC. Given that a VEGF TKI, alone and with an immune checkpoint inhibitor, remains a standard of care for metastatic ccRCC, studies should be undertaken to examine whether exercise training can prevent declines in physical fitness and function. Clinical trial information: NCT03109015. Research Sponsor: Pfizer/Astellas (Medivation).

Variable (units)	Δ from BL to wk 12, Mean (SE)	95% CI	Effect Size
Relative VO_2peak (ml kg^{-1} min^{-1})	-1.19 (0.7)	(-2.82, 0.45)	0.67
Absolute VO_2peak (ml min^{-1})	0.00 (0.5)	(-0.45, 0.45)	0.006
LVEF (%)	-3.00 (3.3)	(-11.13, 5.13)	0.34
Leg Press 1-RM (lb)	36.29 (32.8)	(-43.92, 116.49)	0.42
Chest Press 1-RM (lb)	-6.29 (5.3)	(-19.21, 6.64)	0.45
Seated Row 1-RM (lb)	6.86 (9.4)	(-16.05, 29.76)	0.28
Chair Stand (sec)	-0.97 (0.45)	(-2.13, 0.19)	0.87
TUG (sec)	-0.29 (0.5)	(-1.56, 0.99)	0.20
6MWT (meters)	-28.84 (23.3)	(-85.97, 28.29)	0.47

301 Poster Session and Poster Highlights Session; Displayed in Poster Session

Efficacy and safety of avelumab plus axitinib (A + Ax) versus sunitinib (S) in elderly patients with advanced renal cell carcinoma (aRCC): Extended follow-up results from JAVELIN Renal 101.

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Background: In the phase III JAVELIN Renal 101 trial (NCT02684006), A + Ax demonstrated significantly longer progression-free survival (PFS) and a higher objective response rate (ORR) vs S in patients with previously untreated aRCC. The role of immune checkpoint + VEGFR inhibition in elderly patients remains unclear. Here we report the efficacy of A + Ax vs S by age group from the second interim analysis (IA) of overall survival (OS) and the safety of A + Ax by age group from the first IA. **Methods:** Patients were randomized 1:1 to receive A 10 mg/kg intravenously every 2 wk + Ax 5 mg orally twice daily or S 50 mg orally once daily for 4 wk (6-wk cycle). PFS and ORR per independent central review (RECIST 1.1), OS, and safety by age group ($<$65, $\geq$65 to $<$75, and $\geq$75 y) were assessed. **Results:** A total of 271/138/33 and 275/128/41 patients in each age group ($<$65, $\geq$65 to $<$75, and $\geq$75 y, respectively) were randomized to the A + Ax or S arm, respectively. The proportion of IMDC risk groups was generally well balanced between the A + Ax and S arm in each age group, although in the $\geq$75 y age group, the frequency of patients with intermediate risk was slightly higher in the A + Ax arm, and that of patients with favorable risk was slightly higher in the S arm. The percentages of patients with favorable/intermediate/poor risk in each age group were 19%/61%/19%, 28%/58%/13%, and 12%/76%/12% in the A + Ax arm vs 20%/63%/16%, 23%/60%/16%, and 24%/61%/15% in the S arm. At data cut-off (Jan 2019) for the second IA, median follow-up for OS and PFS was 19.3 vs 19.2 mo and 16.8 vs 15.2 mo for the A + Ax vs S arm, respectively. The table shows OS, PFS, and ORR by age group. In the A + Ax arm, the most common treatment-emergent adverse events (AEs) were diarrhea (62%/68%/42%), hypertension (49%/49%/55%), palmar-plantar erythrodysesthesia syndrome (37%/31%/15%), fatigue (37%/53%/30%), and nausea (34%/37%/21%) in each age group. Grade $\geq$3 treatment-emergent AEs and immune-related AEs were observed in 69%/74%/73% and 39%/40%/24% of patients in each age group, respectively. **Conclusions:** A + Ax demonstrated favorable efficacy across age groups, including patients aged $\geq$75 y. OS was still immature; follow-up for the final analysis is ongoing. The safety profile was generally consistent between age groups. Clinical trial information: NCT02684006. Research Sponsor: Pfizer, as part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

	<65 y A + Ax n=271	<65 y S n=275	≥65 to <75 y A + Ax n=138	≥65 to <75 y S n=128	≥75 y A + Ax n=33	≥75 y S n=41
mOS (95% CI), mo	NE (NE, NE)	28.6 (25.5, NE)	30.0 (30.0, NE)	NE (NE, NE)	25.3 (19.9, NE)	NE (19.4, NE)
Unstratified HR (95% CI)	0.74 (0.541, 1.022)		0.89 (0.546, 1.467)		0.87 (0.359, 2.106)	
mPFS (95% CI), mo	11.6 (8.4, 19.4)	6.9 (5.6, 8.4)	13.8 (11.1, 18.0)	11.0 (7.8, 16.6)	13.8 (7.0, NE)	9.8 (4.3, NE)
Unstratified HR (95% CI)	0.63 (0.501, 0.786)		0.88 (0.627, 1.231)		0.76 (0.378, 1.511)	
ORR (95% CI), %	49.4 (43.3, 55.6)	27.3 (22.1, 32.9)	60.9 (52.2, 69.1)	28.9 (21.2, 37.6)	42.4 (25.5, 60.8)	22.0 (10.6, 37.6)

m, median; **NE**, not estimable.

Efficacy of avelumab plus axitinib (A + Ax) versus sunitinib (S) by number of IMDC risk factors and tumor sites at baseline in advanced renal cell carcinoma (aRCC): Extended follow-up results from JAVELIN Renal 101.

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Background: In the phase III JAVELIN Renal 101 trial (NCT02684006), A + Ax demonstrated progression-free survival (PFS) and objective response rate (ORR) benefit across IMDC risk groups (favorable, intermediate, and poor) vs S in patients with previously untreated aRCC. Here we report efficacy of A + Ax vs S by number of IMDC risk factors (0, 1, 2, 3, and 4-6) and target tumor sites (1, 2, 3, and ≥4) at baseline from the second interim analysis of overall survival (OS). **Methods:** Patients were randomized 1:1 to receive A 10 mg/kg intravenously every 2 wk + Ax 5 mg orally twice daily or S 50 mg orally once daily for 4 wk (6-wk cycle). PFS and ORR per independent central review (RECIST 1.1) and OS were assessed. **Results:** At data cut-off (Jan 2019), median (m) follow-up for OS and PFS was 19.3 vs 19.2 mo and 16.8 vs 15.2 mo for the A + Ax vs S arm, respectively. The table shows OS, PFS, and ORR by number of IMDC risk factors and target tumor sites at baseline. A + Ax generally demonstrated efficacy benefit vs S across subgroups. **Conclusions:** With extended follow-up, A + Ax generally demonstrated efficacy benefit vs S across the number of IMDC risk factors and tumor sites at baseline in aRCC. OS was still immature; follow-up for the final analysis is ongoing. Clinical trial information: NCT02684006. Research Sponsor: Pfizer, as part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

	n A + Ax (N=442)	n S (N=444)	mOS (95% CI), mo A + Ax (N=442)	mOS (95% CI), mo S (N=444)	OS Unstratified HR (95% CI) (A + Ax vs S)	mPFS (95% CI), mo A + Ax (N=442)	mPFS (95% CI), mo S (N=444)	PFS Unstratified HR (95% CI) (A + Ax vs S)	ORR (95% CI), % A + Ax (N=442)	ORR (95% CI), % S (N=444)
No. of IMDC risk factors										
0	94	96	NE (NE, NE)	NE (NE, NE)	0.812 (0.336, 1.960)	24.0 (20.7, NE)	16.7 (12.6, NE)	0.626 (0.397, 0.986)	67.0 (56.6, 76.4)	39.6 (29.7, 50.1)
1	157	154	30.0 (30.0, NE)	28.6 (26.2, NE)	0.740 (0.468, 1.171)	11.1 (8.5, 15.2)	9.4 (6.9, 11.2)	0.822 (0.608, 1.111)	57.3 (49.2, 65.2)	27.9 (21.0, 35.7)
2	114	122	NE (24.6, NE)	NE (NE, NE)	1.044 (0.640, 1.705)	13.8 (7.0, 23.6)	8.2 (5.2, 9.8)	0.676 (0.478, 0.954)	47.4 (37.9, 56.9)	25.4 (18.0, 34.1)
3	43	43	25.3 (14.7, NE)	16.5 (9.9, 23.0)	0.693 (0.375, 1.279)	6.7 (2.8, 13.9)	5.5 (2.8, 6.5)	0.515 (0.298, 0.889)	30.2 (17.2, 46.1)	11.6 (3.9, 25.1)
4-6	29	28	19.9 (9.6, NE)	7.8 (4.2, 13.2)	0.349 (0.169, 0.720)	5.6 (1.8, 9.0)	2.7 (1.4, 3.1)	0.471 (0.251, 0.885)	34.5 (17.9, 54.3)	14.3 (4.0, 32.7)
No. of target tumor sites at baseline										
1	178	178	30.0 (30.0, NE)	NE (28.6, NE)	0.598 (0.354, 1.010)	16.1 (11.6, NE)	9.1 (6.9, 13.8)	0.670 (0.499, 0.902)	63.5 (56.0, 70.6)	30.3 (23.7, 37.7)
2	150	152	NE (24.4, NE)	27.4 (25.5, NE)	1.023 (0.672, 1.558)	12.5 (8.3, 18.0)	9.5 (6.9, 11.5)	0.769 (0.567, 1.043)	50.0 (41.7, 58.3)	29.6 (22.5, 37.5)
3	69	76	22.5 (17.7, NE)	18.9 (13.0, NE)	0.788 (0.485, 1.282)	9.7 (5.7, 15.2)	5.6 (2.8, 6.7)	0.646 (0.426, 0.980)	42.0 (30.2, 54.5)	23.7 (14.7, 34.8)
≥4	35	24	25.5 (21.2, NE)	7.8 (5.4, NE)	0.344 (0.139, 0.799)	6.8 (2.7, NE)	2.8 (1.6, 5.8)	0.516 (0.266, 1.000)	37.1 (21.5, 55.1)	12.5 (2.7, 32.4)

NE, not estimable.

303 **Poster Session**

The efficacy of bevacizumab plus erlotinib (B+E) in patients (pts) with renal medullary carcinoma (RMC).

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Background: RMC is a rare and highly aggressive malignancy with a median overall survival (OS) of only 13 months from diagnosis. RMC is thought to be completely refractory to the targeted therapies used against clear cell renal cell carcinoma and the recommended standard of care therapy is platinum-based cytotoxic chemotherapy, which only produces a best response rate of 29% in the first line setting (Shah et al. *BJU Int*., 2017). Comprehensive molecular profiling of RMC tissues revealed a decrease in genes related to the tricarboxylic acid (TCA) cycle and oxidative phosphorylation and an increase in genes involved in fatty acid synthesis, demonstrating a reliance on aerobic glycolysis to meet cellular bioenergetics needs (Msaouel et al. *Cancer Cell*, 2020). The combination of B+E is particularly effective in tumors such as fumarate hydratate – deficient renal cell carcinomas, which also rely on aerobic glycolysis. We therefore hypothesized that B+E would show clinical efficacy against RMC. **Methods:** We analyzed 10 pts with RMC treated with B+E at our institution. A blinded board-certified radiologist reviewed all restaging images to assess best radiographic response as defined by RECIST v1.1 and, when applicable, date of progression. Adverse events (AEs) were evaluated using the CTCAE version 5.0 grading estimated from chart documentation. Clinical-grade next generation genome sequencing for gene mutations, copy number alterations and fusions was performed in 6/10 pts using the Oncomine platform. **Results:** Between 05/2005 and 09/2020, we identified 10 pts with RMC that were treated with B+E (Table). B+E produced a partial response in 2/10 pts (20%) and stable disease as best response in 6/10 pts (60%), resulting in a median progression-free survival of 3.5 months (mo) with 95% CI 1.8 – 5.2 mo. Decrease in tumor burden was noted even in patients that had received 3+ prior therapies and irrespective of genomic alterations. The median overall survival (OS) from B+E initiation was 7.3 mo (95% CI 5.4 – 9.1) and the median OS from diagnosis was 20.8 mo (95% CI 15.4 – 26.1). B+E was well tolerated with no grade $\geq$ 4 AEs and only one grade 3 AE (skin rash). Dose reduction was only needed in 1/10 pts. **Conclusions:** B+E is clinically active and well tolerated in heavily pre-treated pts with RMC and is therefore a viable therapeutic option for this lethal disease. However, pts ultimately relapse and further investigation is needed to elucidate mechanisms of resistance and determine how to optimally target metabolic vulnerabilities in RMC. Research Sponsor: None.

Baseline Patient Characteristics	
Median Age - yr. (range)	31 (20-38)
Male Gender - no. (%)	9 (90%)
African American - no. (%)	9 (90%)
ECOG Performance Status ≤ 1 - no. (%)	9 (90%)
Right-sided Primary Tumor - no. (%)	7 (70%)
Cytoreductive Nephrectomy - no. (%)	8 (80%)
Prior Platinum-based Chemotherapy - no. (%)	9 (90%)
0-2 Prior Lines of Therapy - no. (%)	5 (50%)
3-5 Prior Lines of Therapy - no. (%)	5 (50%)

304 **Poster Session**

The comparison of cytoreductive nephrectomy (CN) with tyrosine kinase inhibitor therapy alone in patients with primary metastatic renal cell carcinoma (mRCC).

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Background: We aimed to compare overall survival (OS) between patients with metastatic renal cell carcinoma (mRCC) treated by cytoreductive nephrectomy (CN) and those not treated by CN. **Methods:** We retrospectively evaluated 278 patients with mRCC treated with first-line tyrosine kinase inhibitors (TKIs) between January 2008 and November 2019. Patients were divided into two groups, CN group (immediate or deferred CN) and systemic TKI therapies alone without CN (Ctrl group). The OS was compared in all patients between the Ctrl and CN groups, between the Ctrl and immediate CN groups, between the Ctrl and deferred CN groups, and between the deferred CN and immediate CN groups. Analyses were weighted using the propensity score–based inverse probability of treatment weighting (IPTW) method to adjust for group imbalances. **Results:** The median age of the patients was 65 (range 59–73) years. Of the 278 patients, 132 and 146 were in the Ctrl and CN (immediate: 107 and deferred: 39) groups, respectively. A significant difference was noted between the Ctrl and CN groups in age, clinical stage, IMDC risk factors, and the number of metastatic sites. An IPTW-adjusted Cox regression analysis revealed a significant difference in OS between the Ctrl and CN groups and between the Ctrl and immediate or deferred CN groups. However, there was no significant difference in OS between immediate and deferred CN groups. **Conclusions:** The OS in CN group was significantly longer than that in Ctrl group even after the adjustment of potential selection biases. Research Sponsor: JSPS.

305 **Poster Session**

Salvage nivolumab plus ipilimumab after prior PD-1/PD-L1 inhibitor treatment in metastatic renal cell carcinoma: A meta-analysis.

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Background: Although not officially approved, salvage nivolumab plus ipilimumab (nivo/ipi) treatment after prior PD-1/PD-L1 immune checkpoint inhibition is frequently used in metastatic renal cell carcinoma (mRCC). However, very limited data are available to guide such therapy. **Methods:** A search in Medline database and conference abstracts published in English before September 1, 2020 yielded 4 studies reporting salvage nivo/ipi outcomes of mRCC patients. We added additional information from 27 mRCC patients who received salvage nivo/ipi at The Ohio State University after prior PD-1 pathway inhibition. Hence, we performed a meta-analysis of five studies to further characterize the safety and efficacy of salvage nivo/ipi treatment. **Results:** Among 155 patients with measurable treatment response, we found that salvage nivo/ipi had an objective response rate of 19% (95% CI, 0.13-0.25), which was significantly lower than response to prior PD-1/PD-L1 inhibition (odds ratio, 0.35, 95% CI, 0.18-0.67; $p < 0.01$). Response to prior PD-1/PD-L1 inhibition did not correlate with salvage nivo/ipi response (odds ratio, 1.41, 95% CI, 0.51-3.87; $p = 0.51$). Additionally, salvage nivo/ipi was associated with 26% (95% CI, 0.19-0.33) grade ≥ 3 adverse events, which was lower than the toxicity in the upfront setting reported in Checkmate-214 trial. **Conclusions:** It is feasible to have salvage nivo/ipi treatment in mRCC. Salvage nivo/ipi treatment has a lower efficacy and lower toxicity compared with its use in the first-line setting. Research Sponsor: OSU startup fund.

Biomarker-based phase II study of sapanisertib (TAK-228), an mTORC1/2 inhibitor in patients with refractory metastatic renal cell carcinoma (mRCC).

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Background: Approved rapalogs inhibit mTORC1 and have limited activity in mRCC, possibly due to compensatory feedback loops. Sapanisertib addresses the incomplete inhibition of the mTOR pathway through targeting of both mTORC1 and mTORC2 with antitumour activity demonstrated in patients with mRCC. In this multicenter, single arm phase II trial, we evaluated the efficacy of sapanisertib in patients with mRCC progressing on standard therapies (NCT03097328). **Methods:** Eligible mRCC patients had an ECOG performance status of 0-2 and had progressed on standard therapies. Prior therapy with rapalogs (everolimus, temsirolimus) and variant RCC histologies were permitted. Patients had a baseline biopsy and received treatment with sapanisertib 30 mg by mouth weekly until unacceptable toxicity or disease progression. The primary endpoint was overall response rate (ORR) by RECIST 1.1. Tissue biomarkers of mTOR pathway activation were explored. **Results:** We enrolled 38 mRCC patients (clear cell = 28; variant histology = 10) between August 2017 and November 2019. The majority had intermediate (76%) or poor risk (11%) by IMDC criteria. Twenty (53%) had received $\geq$ 3 lines of therapy; 13 (34%) patients received prior rapalogs. Median follow-up was 10.4 months (range 1-27.4) and median duration of therapy was 1.6 (range 0.3-13.8) months. ORR by central review was 2 of 38 (5.3% 90%CI: 1%-15.6%). 31.6% of all patients and 30.7% of those with prior rapalog exposure had some tumor shrinkage during course of treatment. Median progression free survival (PFS) was 2.5 months (95% CI 1.8,3.7). Twelve patients (32%) developed treatment-related grade 3 adverse events (AEs) with no grade 4 or 5 toxicity reported; 6 patients (16%) required dose reduction and 4 (11%) discontinued therapy for AEs. Oncopanel tumor sequencing identified alterations in the mTOR pathway in 6 of 29 patients (*MTOR* n = 2, *PTEN* n = 3, *TSC1* n = 1.) Reduced PTEN expression by immunohistochemistry was seen in 7 of 19 patients. There was no association between mTOR pathway mutations or PTEN loss and response to sapanisertib. **Conclusions:** In this study we demonstrate minimal activity of sapanisertib in patients with treatment refractory mRCC with no clear benefit among patients with mTOR/PTEN pathway alterations. Additional treatment strategies are needed for patients with refractory mRCC. Research Sponsor: Takeda/Millendium.

307 **Poster Session**

Phase II trial of lenvatinib (LEN) at two starting doses + everolimus (EVE) in patients (pts) with renal cell carcinoma (RCC): Results by independent imaging review (IIR) and prior immune checkpoint inhibition (ICI).

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Background: LEN 18 mg + EVE 5 mg is approved for advanced RCC following anti-angiogenic therapy. Study 218 was a phase II study evaluating LEN 14 mg vs LEN 18 mg, both in combination with EVE 5 mg, for the treatment of clear cell RCC following treatment with a VEGF-targeted therapy. We have previously reported that the LEN 14 mg arm did not demonstrate noninferiority vs the LEN 18 mg arm for objective response rate (ORR) as of wk 24 by investigator assessment, the primary endpoint of the study. In this exploratory analysis of Study 218 data, we evaluated the efficacy of LEN 14 mg vs LEN 18 mg, both in combination with EVE 5 mg, per IIR assessment and by prior ICI status per investigator assessment. **Methods:** Pts with measurable clear cell RCC (1 prior VEGF-targeted therapy; prior PD-1/PD-L1 therapy permitted) were randomly assigned 1:1 to LEN 14 mg or 18 mg (starting dose) + EVE 5 mg daily. 115 pts in the LEN 14 mg arm were titrated to LEN 18 mg at cycle 2 as they did not experience intolerable grade 2 or any grade $\geq$3 TEAEs requiring dose reduction within cycle 1. We analyzed ORR and PFS by IIR per RECIST v1.1; additionally, efficacy endpoints (ORR, PFS, and OS) were analyzed by investigator assessment per RECIST v1.1 by prior ICI status. **Results:** 311 pts (LEN 14 mg arm, n=156; LEN 18 mg arm, n=155) were included in the efficacy analysis and 341 pts (LEN 14 mg arm, n=173; LEN 18 mg arm, n=168) were included in the summary safety analysis. ORR by IIR (LEN 14 mg arm: 39.7%, 95% CI 32.1–47.4; LEN 18 mg arm: 38.7%, 95% CI 31.0–46.4) was similar between treatment arms. PFS by IIR was numerically longer in the LEN 18 mg arm (median 12.9 mos, 95% CI 9.2–17.1) vs the LEN 14 mg arm (median 11.0 mos, 95% CI 9.3–12.9). OS was numerically longer in the LEN 18 mg arm (median not evaluable [NE], 95% CI 23.8–NE) vs the LEN 14 mg arm (median 27.0 mos, 95% CI 18.3-NE) (previously reported). In 82 pts with prior ICI, for the LEN 14 mg (n=43) vs 18 mg (n=39) arms (95% CI): ORR was 30.2% (17.2–46.1) vs 51.3% (34.8–67.6) by investigator assessment, respectively; median PFS was 12.0 mos (8.9–16.7) vs 12.9 mos (8.4–NE) by investigator assessment, respectively; and median OS was 17.1 mos (10.6–NE) vs 18.0 mos (13.1–NE), respectively. Endpoints were generally numerically improved in the LEN 18 mg arm in pts without prior ICI (data will be presented). As previously reported, the safety profile was similar in both treatment arms: 71.7% of pts in the LEN 14 mg arm and 76.8% of pts in the LEN 18 mg arm had grade 3/4 TEAEs. **Conclusions:** ORR was similar between treatment arms and PFS was numerically longer in the LEN 18 mg arm per IIR. Efficacy outcomes were generally numerically improved for the LEN 18 mg arm compared with the LEN 14 mg arm, regardless of prior ICI. As previously reported, safety was similar in both treatment arms. These results further support starting pts with RCC at the higher 18 mg dose of LEN + EVE 5 mg. Clinical trial information: NCT03173560. Research Sponsor: This study was sponsored by Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA.

308 Poster Session and Poster Highlights Session; Displayed in Poster Session

Nivolumab + cabozantinib (NIVO+CABO) versus sunitinib (SUN) for advanced renal cell carcinoma (aRCC): Outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER.

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Background: First-line NIVO+CABO met primary and secondary efficacy endpoints by improving progression-free survival (PFS; HR 0.51, $P < 0.0001$), overall survival (OS; HR 0.60, $P = 0.0010$), and objective response rate (ORR; 55.7% vs 27.1%; $P < 0.0001$) vs SUN in patients (pts) with aRCC in CheckMate 9ER (Choueiri et al. ESMO 2020). Efficacy benefits with NIVO+CABO vs SUN were consistent across prespecified subgroups including by IMDC risk group, and regardless of tumor PD-L1 expression (database lock for primary analysis, March 30, 2020). Updated analyses are needed to establish durability of benefit with first-line NIVO+CABO and assess outcomes in aRCC pts with sarcomatoid features (sRCC)—an aggressive histologic subtype associated with poor prognoses. **Methods:** In this phase III open-label trial, adults with confirmed aRCC (with a clear cell component including those with sRCC) were randomized 1:1 (stratified by IMDC risk score, tumor PD-L1 expression, geographic region) to NIVO 240 mg IV Q2W + CABO 40 mg PO QD vs SUN 50 mg PO (4 weeks of 6-week cycles). The primary endpoint was RECIST v1.1-defined PFS by blinded independent central review (BICR) in all randomized (intent-to-treat [ITT]) pts; secondary endpoints included OS, ORR by BICR, and safety. Pts with and without sRCC were identified by local pathology report, and outcomes in these pts were evaluated via prespecified supportive subset analyses. **Results:** The presence of sRCC was assessed in ITT pts (N = 651) at enrollment. Overall, 75 (11.5%) pts had sRCC and 557 (85.6%) did not; sRCC status was not reported in 19 pts (2.9%). Overall, 34 vs 41 pts with sRCC were randomized to NIVO+CABO vs SUN, respectively. At a median follow-up of 18.1 months, NIVO+CABO improved PFS, OS, and ORR in sRCC pts vs SUN (Table). Notable PFS, OS, and ORR benefits were observed with NIVO+CABO vs SUN in the subgroup of pts without sRCC. Median PFS was doubled, the risk of death was lower, and ORR was consistently higher with NIVO+CABO vs SUN regardless of sarcomatoid status. Key updated PFS, OS, response, and safety outcomes in the ITT population and in pts with and without sRCC will be reported with additional follow-up based on a September 10, 2020 database lock. **Conclusions:** NIVO+CABO demonstrated improved efficacy and prolonged survival vs SUN in previously untreated aRCC pts regardless of sarcomatoid status. Updated results with extended follow-up will assess the durability of outcomes in this trial. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

	With sRCC		Without sRCC[a]	
	NIVO+CABO n = 34	SUN n = 41	NIVO+CABO n = 279	SUN n = 278
PFS HR (95% CI)	0.39 (0.22-0.70)		0.54 (0.43-0.69)	
Median PFS, months	10.9	4.2	17.7	9.4
OS HR (95% CI)	0.36 (0.16-0.82)		0.68 (0.48-0.95)	
Median OS, months	NR	19.7	NR	NR
ORR, % (95% CI)	55.9 (37.9-72.8)	22.0 (10.6-37.6)	56.6 (50.6-62.5)	28.4 (23.2-34.1)

[a]Pts assessed for sRCC and were negative.

NR, not reached.

309 **Poster Session**

Nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma (nccRCC): Safety and efficacy from CheckMate 920.

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Background: The long-term efficacy and tolerability of nivolumab (NIVO) 3 mg/kg + ipilimumab (IPI) 1 mg/kg Q3W × 4 doses followed by NIVO 3 mg/kg Q2W for previously untreated advanced RCC (aRCC) demonstrated in the registrational CheckMate 214 clinical trial was based on patients (pts) with a predominantly clear cell component. CheckMate 920 (NCT02982954) is a US community-based, multi-arm, phase IIIb/IV clinical trial of NIVO+IPI treatment in pts with previously untreated aRCC and clinical features mostly excluded from phase III trials. Here, we present the safety and efficacy results for the cohort of pts with nccRCC from CheckMate 920, a patient population with a poor prognosis and without a definitive effective treatment. **Methods:** Pts with previously untreated advanced/metastatic nccRCC, Karnofsky performance status ≥ 70%, and any International Metastatic Renal Cell Database Consortium risk received NIVO 3 mg/kg + IPI 1 mg/kg (NIVO3+IPI1) Q3W × 4 doses followed by NIVO 480 mg Q4W for ≤ 2 years or until disease progression/unacceptable toxicity. The primary endpoint was incidence of any-causality grade ≥ 3 immune-mediated adverse events (imAEs) within 100 days of last dose of study drug. Key secondary endpoints: progression-free survival (PFS) and objective response rate (ORR) by RECIST v1.1 (both per investigator), duration of response (DOR), and time to response (TTR). Exploratory endpoints included overall survival (OS). **Results:** Of 52 treated pts with nccRCC, 69.2% were men; median age was 64 years (range, 23–86), and 28.8% had sarcomatoid features. Histological subtypes were papillary (34.6%), chromophobe (13.5%), translocation associated (3.8%), collecting duct (3.8%), renal medullary (1.9%), or unclassified (42.3%). With 24.1 months minimum follow-up, median duration of therapy (range) was 3.5 months (0.0–25.8) for NIVO and 2.1 months (0.0–3.9) for IPI. Median (range) number of doses received was 4.5 (1–28) for NIVO and 4.0 (1–4) for IPI. No grade 5 imAEs occurred. Grade 3–4 imAEs (n = 52) by category were diarrhea/colitis (7.7%), rash (5.8%), nephritis and renal dysfunction (3.8%), hepatitis (1.9%), adrenal insufficiency (1.9%), and hypophysitis (1.9%). ORR (n = 46) was 19.6% (95% CI, 9.4–33.9). Two pts achieved complete response (papillary, n = 1; unclassified pathology, n = 1), 7 achieved partial response (papillary, n = 4; unclassified pathology, n = 3), and 17 pts had stable disease. Median TTR was 2.8 months (range, 2.1–4.8). Median DOR was not reached (range, 0.03+–27.8+); 8 of 9 responders remain without reported progression. Median PFS (n = 52) was 3.7 months (95% CI, 2.7–4.6). Median OS (n = 52) was 21.2 months (95% CI, 16.6–not reached). **Conclusions:** In pts with previously untreated nccRCC, a population with high unmet medical need, treatment with NIVO3+IPI1 Q3W followed by NIVO 480 mg Q4W showed no new safety signals, and encouraging antitumor activity. Clinical trial information: NCT02982954. Research Sponsor: Bristol Myers Squibb.

Activity and safety of cabozantinib (cabo) in brain metastases (BM) from metastatic renal cell carcinoma (mRCC): An international multicenter study.

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Background: Cabo shows robust clinical activity in mRCC. Patients (pts) with BM have been underrepresented in clinical trials and effective systemic therapy is lacking. We retrospectively characterized the clinical activity and toxicity of cabo in pts with BM from RCC. **Methods:** Consecutive medical records from mRCC pts with BM treated with cabo monotherapy across 15 institutions were reviewed. Pts were grouped by radiologic presence (cohort 1) or absence (cohort 2) of progressing intracranial metastases. Brain-directed local therapy was allowed but radiological confirmation of intracranial progression at cabo start was required in cohort 1. Radiological response rate was investigator-assessed by modified RECIST 1.1 for intracranial and RECIST 1.1 for extracranial responses. Time to treatment failure (TTF) and overall survival (OS) were estimated by Kaplan-Meier. **Results:** We identified 69 pts with BM from RCC, 25 (36%) in cohort 1 and 44 (64%) in cohort 2. Majority were IMDC intermediate/poor (87%) and received cabo as ≥2nd line (75%). Median time from mRCC diagnosis to BM was 19.1 months (mos) (IQR 4.4-39.5). Overall, median number of BM was 3 (range 1-27) and median size of largest lesion was 1.2 cm (range 0.2-6.6) with frontal (62%) and parietal (48%) as the most frequent localizations. Prior brain directed therapy was used in 65% and 93% of pts in cohort 1 and 2 respectively. Median follow-up after cabo initiation was 11 mos (range 4-72). Twenty three percent of pts remained on therapy while 52% discontinued for progression and 9% for toxicity. Intracranial response rate was 61% (95%CI 39%-80%), with 3 complete responses, for cohort 1 and 57% (95%CI 41%-72%) for cohort 2. Only 10% (n = 7) had intracranial progression as best response. For cohort 1, extracranial response was 52% (95%CI 31%-72%), median TTF was 9.9 mos (95%CI 5.9-14.0) and OS was 14.7 mos (95%CI 7.7-23.0). For cohort 2, extracranial response was 41% (95%CI 26%-57%), TTF was 9.0 mos (95%CI 4.6-11.4) and OS was 14.1 mos (95%CI 11.0-22.0). Most common adverse events were fatigue (77%) and diarrhea (46%). Eight pts received concomitant brain-directed treatment during cabo therapy without neurological toxicities. **Conclusions:** Cabo shows significant intracranial activity and acceptable safety profile in pts with BM from RCC. Research Sponsor: None.

	Cohort 1 (n = 25)	Cohort 2 (n = 44)
Best intracranial response*, n (%)		
Complete response	3 (13)	0 (0)
Partial response	11 (48)	24 (57)
Stable disease	7 (30)	13 (31)
Progressive disease	2 (9)	5 (12)
Intracranial response rate*, % (95%CI)	61% (39%-80%)	57% (41%-72%)

* 4 pts excluded as BM < 5 mm

311 **Poster Session**

Phase II trial of stereotactic ablative radiation (SAbR) for oligometastatic kidney cancer.

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Background: Stereotactic ablative radiotherapy (SAbR) is a promising treatment option for selected oligometastatic renal cell carcinoma (RCC) patients that can provide longitudinal disease control while preserving quality of life. Retrospective data have shown a local control (LC) rate greater than 90% and longitudinal disease control of over a year without systemic therapy. However, prospective validation of SAbR for oligometastatic RCC is lacking. In this prospective phase II single arm trial, we evaluated the impact of SAbR on freedom from systemic therapy (FFST). **Methods:** Treatment naïve patients with RCC confirmed by pathology and radiographic evidence of three or fewer extracranial metastases received SAbR with curative intent to all measurable sites of disease. Follow-up included radiographic imaging at three-month intervals to assess disease control. The primary endpoint was FFST defined as time from SAbR to the initiation of systemic therapy. Secondary endpoints included LC, modified progression-free survival (mPFS) (time from first SAbR to progression not amenable to further SAbR), PFS on subsequent systemic therapy, cancer-specific survival (CSS), overall survival (OS), toxicity and health-related quality of life (QOL) indices as measured with EQ-5D-5L and FACT-G. A Wilcoxon signed-rank test was used to evaluate the QOL indices. **Results:** The trial completed accrual with the enrollment of 23 patients who received SAbR to a total of 38 sites. At a median follow-up of 12 months (interquartile range 1.8-16), 1-year FFST was 87% (95% CI: 56%-96%). The 1-year mPFS was 79% (95% CI:49%-93%), while the median mPFS has not yet been reached. Three patients had disease progression at individual time points of 3.5, 4.0, and 12 months. One of these patients developed brain metastases that were controlled with gamma knife radiosurgery without initiating systemic therapy. The LC, CSS, and OS were 100% (38/38), 100% (23/23), and 95% (22/23), respectively. When compared to baseline, no significant decline in QOL was detected. Three patients experienced treatment-related grade 1 toxicity; no $\geq$grade 2 toxicities were reported. One patient died of an unrelated cause. **Conclusions:** SAbR is a safe and effective treatment for oligometastatic RCC that can provide longitudinal disease control and preserve quality of life. These data support further evaluation of SAbR for oligometastatic RCC in a randomized study. Clinical trial information: NCT02956798. Research Sponsor: UT Southwestern.

A phase II study of sitravatinib (Sitra) in combination with nivolumab (Nivo) in patients (Pts) undergoing nephrectomy for locally-advanced clear cell renal cell carcinoma (accRCC).

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Background: Sitra is a spectrum-selective receptor tyrosine kinase inhibitor (TKI) that targets TAM receptors (TYRO3, AXL, MERTK), VEGFR2, c-Kit, and MET. These receptors regulate several immune suppressive cell types in the tumor microenvironment, including M2-polarized macrophages, MDSCs, and T regulatory cells, which are implicated in resistance to checkpoint inhibitors. ccRCC is characterized by upregulation of VEGF and overexpression of MET and AXL. Sitra may combine effectively with immune checkpoint inhibition to augment antitumor activity in ccRCC. About 39% of patients with accRCC who receive surgery with curative intent relapse representing an unmet need in this setting. Together these data support the evaluation of neoadjuvant sitra with nivo in accRCC. **Methods:** This phase II study (NCT03680521) evaluated sitra and nivo in pts with locally- advanced ccRCC who were candidates for curative nephrectomy. Single-agent sitra (120 mg) was administered daily (QD) for 2 weeks, with nivo (240 mg intravenously Q2W) added to sitra for 4-6 weeks. A plan for potential dose de-escalation was implemented using a modified toxicity probability interval method with a maximum toxicity of 20% at the tolerated dose. Pts underwent pathology/tissue evaluation at 3 timepoints: biopsy prior to treatment, biopsy prior to the addition of nivo, and nephrectomy specimen evaluation at time of nephrectomy. The primary endpoint was objective response (RECIST 1.1); secondary endpoints included safety, PK, and correlative immune effects (selected protein and gene expression and immune cell populations). **Results:** A total of 20 pts were evaluated for safety (95% had T3 or higher stage tumors, 65% with baseline hypertension). Dose-limiting toxicities (DLTs) led to a dose de-escalation, resulting in 7 pts treated at 120 mg QD sitra and 13 pts treated at 80 mg QD. DLTs included grade 3 (Gr3) hypertension (n=6); deep vein thrombosis and pulmonary embolism (Gr3) were observed in 1 additional pt. Median duration of sitra treatment was 6.3 weeks at the 80 mg dose and 7.1 weeks at the 120 mg dose. With a median follow-up of 9.4 months after initiation of systemic therapy, no pts have relapsed. In 17 pts evaluable for efficacy, the investigator-assessed confirmed ORR was 11.8%, including 2 PRs (33.3% ORR in pts who received 120 mg sitra). No pts experienced progressive disease while on therapy. Median DFS was not reached. There was 1 delayed surgery due to nivo-related thyroiditis that resolved. Reported TRAEs: Gr1/Gr2 in 55% of pts (dysphonia 50%, fatigue 45%, diarrhea 40%, hypertension 30%, increased ALT 30%), Gr3 in 45% of pts (hypertension 30%). There were no Gr4/Gr5 TRAEs. Correlative blood and tissue analyses will be presented. **Conclusions:** The combination of sitra and nivo is clinically active with a manageable safety profile as a neoadjuvant therapy for accRCC. Clinical trial information: NCT03680521. Research Sponsor: Mirati Therapeutics, Inc.

313 Poster Session and Poster Highlights Session; Displayed in Poster Session

Patterns of progression in patients treated with nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214.

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Background: First-line NIVO+IPI demonstrates superior survival and response benefits in intent-to-treat (ITT) patients (pts) with aRCC after long-term follow-up in the phase 3 CheckMate 214 trial. Data are scarce on tumor relapse and patterns of disease progression with immuno-oncology agents in this setting. This exploratory analysis of CheckMate 214 characterizes patterns of progression with NIVO+IPI vs SUN with 4 years minimum follow-up. **Methods:** Pts with clear cell aRCC were randomized to NIVO+IPI Q3W×4 followed by NIVO monotherapy Q2W, or SUN QD×4 weeks (6-week cycle). Patterns of progression were characterized in ITT pts and analyzed post hoc using descriptive statistics. Progression patterns were defined by ≥ 20% target lesion growth (T), unequivocal progression of nontarget lesions (NT), and new lesion(s) (NL). Response and progression were assessed per independent radiology review committee via RECIST v1.1. **Results:** Radiographic progression (RP) was documented in 299/550 (54.4%) ITT pts with NIVO+IPI vs 289/546 (52.9%) with SUN. Among ITT pts with a confirmed response (objective response = 215/550 [39.1%, NIVO+IPI] vs 177/546 [32.4%, SUN]), 71/215 (33.0%) vs 84/177 (47.5%) pts experienced post-response RP with NIVO+IPI vs SUN; 8/59 (13.6%) vs 3/14 (21.4%) progressed after complete response, and 63/156 (40.4%) vs 81/163 (49.7%) progressed after partial response, respectively. The pattern of RP differed between arms (Table). With NIVO+IPI, 106/299 (35.5%) RPs resulted from NL only vs 74/289 (25.6%) with SUN, and this differential was more pronounced in pts with an initial confirmed response (36/71 [50.7%] vs 23/84 [27.4%]). Most NL-only RPs in initial responders occurred in a single organ (34/36 [94.4%] for NIVO+IPI; 20/23 [87.0%] for SUN) with the most common being lymph nodes (11/34 [32.4%]), brain (8/34 [23.5%]), and lung (5/34 [14.7%]) with NIVO+IPI, and lymph nodes (7/20 [35.0%]), brain (4/20 [20.0%]) and adrenal gland (3/20 [15.0%]) with SUN. Additional progression details, baseline characteristics, and key efficacy outcomes in progressors will be reported. **Conclusions:** Differential patterns of tumor relapse and disease progression were observed after long-term follow up of patients treated with NIVO+IPI vs SUN in CheckMate 214. NL-only progression occurred more often with NIVO+IPI vs SUN, in particular in the subset of pts who progressed post-response. These patterns may have therapeutic implications. Clinical trial information: NCT02231749. Research Sponsor: Bristol Myers Squibb.

Pts w/ RP, n (%)	T only	NT only	NL only	Mixed	Unassigned
NIVO+IPI; all N = 299	71 (23.7)	27 (9.0)	106 (35.5)	71 (23.7)	24 (8.0)
SUN; all N = 289	75 (26.0)	33 (11.4)	74 (25.6)	86 (29.8)	21 (7.3)
NIVO+IPI; post-response N = 71	14 (19.7)	12 (16.9)	36 (50.7)	5 (7.0)	4 (5.6)
SUN; post-response N = 84	31 (36.9)	3 (3.6)	23 (27.4)	22 (26.2)	5 (6.0)

Mixed column includes T+NT, T+NL, NT+NL, and T+NT+NL.

Health-related quality-of-life outcomes from a phase II open-label trial of two different starting doses of lenvatinib in combination with everolimus for treatment of renal cell carcinoma following one prior VEGF-targeted treatment.

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Background: Renal cell carcinoma (RCC) is the most common type of kidney cancer, constituting 80% to 85% of primary renal neoplasms. Preserving health-related quality of life (HRQOL) is an important goal during RCC treatment, but HRQOL analyses in prospective clinical trials in RCC are limited. We report changes in HRQOL, a secondary endpoint of this phase II trial. **Methods:** HRQOL data were collected during a multicenter, randomized, open-label phase II study comparing the safety and efficacy of two different starting doses of lenvatinib (18 mg vs. 14 mg daily [QD]) in combination with everolimus (5 mg QD), following one prior vascular endothelial growth factor–targeted treatment (NCT03173560). HRQOL was measured using three different instruments, including the FKSI-DRS, EORTC QLQ-C30, and EQ-5D-3L. Change from baseline HRQOL was assessed using linear mixed-effects models. Deterioration events for time to deterioration (TTD) analyses were defined using established thresholds for minimally important differences in the change from baseline for each scale (i.e., 10 points for EORTC, 3 points for FKSI-DRS, 0.08 points for EQ-5D index, and 10 points for EQ-VAS). The distribution of TTD and median TTD for each treatment arm were estimated using the Kaplan-Meier method. **Results:** Baseline characteristics, including baseline scores of the 343 participants randomly assigned to 14 mg QD lenvatinib (n = 172) and 18 mg QD lenvatinib (n = 171), were well balanced. The average scores for the 18 mg QD group were generally higher, with lower symptom severity than the 14 mg QD group. The least squares mean estimates for change from baseline were favorable for the 18 mg QD group over the 14 mg QD group for the FKSI-DRS and most EORTC QLQ-C30 scales; however, the differences between treatments did not exceed the minimally important difference for clinical significance. Both study arms showed an increase diarrhea severity. Median TTD was longer among participants in the 18 mg QD group than those in the 14 mg QD group for most scales. **Conclusions:** In most scales, participants who received an 18 mg QD lenvatinib starting dose had better HRQOL and longer time to deterioration than those who received a 14 mg QD starting dose. These findings suggest that the approved treatment regimen of an 18 mg starting dose of lenvatinib in combination with everolimus remains favorable for RCC treatment, following one prior vascular endothelial growth factor–targeted treatment. Clinical trial information: NCT03173560. Research Sponsor: Eisai Inc. and Merck & Co Inc.

315 **Poster Session**

Safety and efficacy outcomes with nivolumab plus ipilimumab in patients with advanced renal cell carcinoma and low Karnofsky performance status: Results from the CheckMate 920 trial.

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Background: Combination therapy with nivolumab + ipilimumab (NIVO+IPI) has demonstrated long-term efficacy and tolerability for patients (pts) with previously untreated advanced renal cell carcinoma (aRCC). Most pivotal clinical trials in pts with aRCC have excluded pts with low Karnofsky performance status (KPS; $<$ 70%). CheckMate 920 is a multi-arm, phase IIIb/IV, open-label clinical trial of NIVO+IPI treatment in pts enrolled in a community practice setting with aRCC and a high unmet medical need. We present safety and efficacy results for the cohort of pts with aRCC of any histology and KPS 50%–60% from CheckMate 920 (NCT02982954). **Methods:** Pts with previously untreated advanced/metastatic RCC and KPS 50%–60% received NIVO 3 mg/kg + IPI 1 mg/kg Q3W $\times$ 4 doses followed by 480 mg NIVO Q4W for $\leq$ 2 years or until disease progression/unacceptable toxicity. The primary endpoint was incidence of grade $\geq$ 3 immune-mediated adverse events (imAEs) within 100 days of last dose of study drug. Key secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) by RECIST v1.1 (both per investigator). Exploratory endpoints included overall survival (OS). **Results:** Of 25 treated pts with KPS 50%–60%, 76% were men; median age was 67 years (range, 34–81). IMDC risk was favorable in 0%, intermediate in 32%, and poor in 68% of pts; 84% had clear cell and 16% had non-clear cell RCC histology. With a minimum follow-up of 25 months, median duration of therapy (95% CI) was 2.3 months (2.1–7.7) for NIVO and 2.1 months (2.1–2.1) for IPI. The median number of doses (range) received was 4 (1–27) for NIVO and 4 (1–4) for IPI; 76% of pts received $\geq$ 4 NIVO doses and 68% received all 4 IPI doses. The only grade 3–4 imAEs by category were hepatitis (4.0%) and adrenal insufficiency (4.0%). No grade 5 imAEs occurred. Overall, 4 (16%) pts discontinued due to any-grade adverse events (n = 1 each for elevated AST, malignant neoplasm progression, back pain, and acetabulum fracture). Of 18 evaluable pts, ORR was 33.3% (95% CI, 13.3–59.0); no pts had a complete response and 6 had partial response. Median time to objective response was 4.5 months (range, 2.5–24.7). Median duration of objective response was 20.6 months (range, 0.03+–24.2+). Median PFS was 4.6 months (95% CI, 2.5–14.8). Median OS was 15.6 months (95% CI, 5.3–25.1). **Conclusions:** NIVO+IPI demonstrated an acceptable safety profile and promising antitumor activity in pts with previously untreated aRCC and KPS 50%–60%. The combination was tolerated at a dose intensity similar to that observed in clinical trials conducted in pts with higher KPS ($\geq$ 70%). These data support the value of NIVO+IPI in pts who may not be considered ideal candidates for this therapy and consequently may have limited treatment options. Clinical trial information: NCT02982954. Research Sponsor: Bristol Myers Squibb.

Effectiveness of first-line immune checkpoint inhibitors (ICI) in advanced non-clear cell renal cell carcinoma (ccRCC).

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Background: Immune checkpoint inhibitors (ICI) have demonstrated impressive activity in metastatic clear-cell renal cell carcinoma (ccRCC) and have become standard treatment options in this setting. Data supporting the effectiveness of ICI based therapy in non-clear cell RCC (nccRCC) is more limited. **Methods:** We performed a retrospective analysis using the International Metastatic RCC Database Consortium (IMDC). Patients with nccRCC were classified into 3 groups based on first-line therapy: ICI based therapy (in monotherapy or in combination), vascular endothelial growth factor targeted therapy (VEGF-TT) monotherapy, or mammalian target of rapamycin (mTOR) inhibitor monotherapy. Primary outcome was overall survival (OS). Secondary outcomes were time to treatment failure (TTF) and objective response rate (ORR). We used Kaplan-Meier method to compare OS and TTF between treatment groups and Cox proportional hazards models to adjust for prognostic covariates. **Results:** We identified 1181 patients with nccRCC. In first-line, 78.2% received VEGF-TT, 15.8% mTOR inhibitors, and 5.5% ICI based therapy, of which 41.5% in monotherapy, 30.8% doublet-ICIs and 27.7% an ICI combined with VEGF-TT. Median OS in the ICI group was 28.6 months, compared to 19.2 and 12.6 in the VEGF-TT and mTOR groups, respectively. Median TTF was 6.9 months vs. 5.1 and 3.9 and ORR was 25% vs. 17.8% and 5.8% in the ICI, VEGF-TT and mTOR groups, respectively. After adjusting for IMDC risk group, histological subtype, and age, the hazard ratio (HR) for OS was 0.58 (95% CI 0.35-0.94, p=0.03) for ICI vs. VEGF-TT and 0.48 (95% CI 0.29-0.80, p=0.005) for ICI vs. mTOR. **Conclusions:** In advanced nccRCC, first-line ICI based treatment appears to be associated with improved OS compared to VEGF and mTOR targeted therapy. These results need to be confirmed in prospective randomized trials. Research Sponsor: None.

		VEGF targeted therapy (N=924)	mTOR targeted therapy (N=186)	ICI based therapy (N=65)
Histologic subtype	Papillary	452 (50.0%)	112 (60.2%)	26 (40.0%)
	Chromophobe	115 (12.4%)	27 (14.5%)	12 (18.5%)
	Unclassified	168 (18.2%)	25 (13.4%)	16 (24.6%)
	Collecting Duct	19 (2.1%)	5 (2.7%)	6 (9.2%)
	Translocation	39 (4.2%)	5 (2.7%)	4 (6.2%)
	Missing	121 (13.1%)	12 (6.5%)	1 (1.5%)
IMDC group	Favourable	181 (19.6%)	20 (10.8%)	14 (21.5%)
	Intermediate	503 (54.4%)	109 (58.6%)	34 (52.3%)
	Poor	240 (26.0%)	57 (30.6%)	17 (26.2%)
First-line therapy		Sunitinib (n=632, 68.4%) Pazopanib (n=171, 18.5%) Sorafenib (n=72, 7.8%) Savolitinib (n=16, 1.7%) Cabozantinib (n=12, 1.3%) Other (n=21, 2.3%)	Temsirolimus (n=141, 75.8%) Everolimus (n=45, 24.2%)	Nivo + Ipi (n=20, 30.8%) Atezo + Bev (n=14, 21.5%) Nivo (n=13, 20.0%) Pembro (n=13, 20.0%) Other (n=5, 7.7%)

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Long-term survival outcomes of cytoreductive nephrectomy combined with targeted therapy for metastatic renal cell carcinoma: A systematic review and individual patient data meta-analysis.

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Background: The role of cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma (mRCC) treated with targeted therapy agents remains controversial. We used reconstructed individual patient data (IPD) to compare the long-term survival outcomes of CN combined with targeted therapy vs. targeted therapy alone for mRCC. **Methods:** We performed a systematic review of the literature using the MEDLINE, Scopus, and Cochrane Library databases (end-of-search date: July 21, 2020). We reconstructed the Kaplan-Meier curves and subsequently recuperated IPD for overall (OS), progression-free (PFS) and cancer-specific survival (CSS) from individual studies. We performed one-stage random-effects frequentist and Bayesian meta-analyses of OS, PFS, and CSS using parametric and non-parametric estimates. We also performed a subgroup analysis focusing on upfront CN and excluding patients with deferred CN. The risk of bias was assessed using the ROBINS-I and RoB2 tools. **Results:** Fifteen studies fulfilling our inclusion criteria were identified, including fourteen retrospective cohort studies and one randomized controlled trial. No studies were found to be at critical risk of bias. A total of 3,990 patients were included, with 2,234 in the CN group and 1,756 in the non-CN group. Our frequentist meta-analysis showed superior OS (HR = 0.58, 95% CI: 0.54-0.62, $p<0.0001$) and CSS (HR = 0.63, 95% CI: 0.53-0.75, $p < 0.0001$) in favor of CN. No clinically meaningful differences were observed in the PFS between the two groups (HR = 0.90, 95% CI: 0.80-1.02, p=0.09). The OS benefit was also observed in the upfront CN subgroup (HR = 0.70, 95% CI 0.63-0.78, $p<0.001$). Similar results were obtained with non-parametric frequentist and Bayesian approaches (Table). **Conclusions:** The combination of CN and targeted therapy for mRCC is associated with superior long-term survival outcomes compared with targeted therapy alone. Careful patient selection based on prognostic factors is required to achieve optimal outcomes. Research Sponsor: None.

	OS		PFS		CSS	
	Relative Effect (95% CI/ CrI)	~P-value	Relative Effect (95% CI/ CrI)	~P-value	Relative Effect (95% CI/ CrI)	~P-value
Cox Proportional Hazards Model	0.58 (0.54-0.62)	< **0.0001**	0.90 (0.80-1.02)	0.093	0.63 (0.53-0.75)	< **0.0001**
Life Expectancy Difference (3 years)	6.0 months (5.2-6.8)	< **0.0001**	1.1 months (-0.2-2.3)	0.100	6.2 months (4.2-8.3)	< **0.0001**
Life Expectancy Ratio (3 years)	1.36 (1.30-1.42)	< **0.0001**	1.09 (0.98-1.20)	0.100	1.32 (1.20-1.46)	< **0.0001**
Life Expectancy Difference (5 years)	9.4 months (8.1-10.7)	< **0.0001**	1.4 months (-0.5-3.3)	0.150	9.4 months (6.1-12.8)	< **0.0001**
Life Expectancy Ratio (5 years)	1.48 (1.40-1.56)	< **0.0001**	1.10 (0.97-1.25)	0.150	1.39 (1.23-1.57)	< **0.0001**
One-stage Bayesian Meta-analysis (uninformative prior)	0.59 (0.55-0.63)	N/A	0.91 (0.80-1.02)	N/A	0.63 (0.53-0.75)	N/A

Efficacy of VEGFR-TKI plus immune checkpoint inhibitor (ICI) in metastatic renal cell carcinoma (mRCC) patients with favorable IMDC prognosis.

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Background: Combinations of a PD-1/PD-L1 immune checkpoint inhibitor (ICI) with a VEGFR-TKI as front-line/treatment-naïve therapy significantly improve the outcome of metastatic renal cell carcinoma (mRCC) patients. The benefit of these combinations is well evident in IMDC intermediate- and poor-risk population, while it is unclear in the subgroup of mRCC patients with favorable prognosis. We performed a meta-analysis with the aim to evaluate whether the addition of ICIs to VEGFR-TKIs is able to improve the outcome compared to VEGFR-TKIs alone in mRCC patients with favorable IMDC prognosis. **Methods:** This meta-analysis searched MEDLINE/PubMed, the Cochrane Library and ASCO Meeting abstracts for phase II or III randomized clinical trials (RCTs) testing the combination of VEGFR-TKI+ICI in mRCC. Data extraction was conducted according to the PRISMA statement. The hazard ratios (HRs) for PFS and OS with the relative 95% CIs were extracted from each study. Summary HRs was calculated using random- or fixed-effects models, depending on the heterogeneity of the included studies. **Results:** Three RCTs were selected for the final analysis, with a total of 605 patients (306 treated with VEGFR-TKI+ICI combinations and 299 who received sunitinib in the control arms). The combination of VEGFR-TKI+ICI improved PFS compared to sunitinib, with a 30% reduction of the risk of progression (fixed-effect, HR=0.70; p = 0.003). However, VEGFR-TKI+ICI combinations did not significantly prolong OS (fixed-effect; HR = 0.94; 95% CI 0.62–1.43; p = 0.77). **Conclusions:** Our analysis demonstrates a PFS benefit without an OS advantage for VEGFR-TKI+ICI combinations as first-line therapy for mRCC patients with favourable prognosis according to IMDC. Longer follow-up is required to definitely confirm the best therapy for treatment-naïve mRCC patients with favorable prognosis. Research Sponsor: None.

OS analysis of ICI+TKI combinations versus sunitinib in mRCC patients with favorable IMDC prognosis.

	Trial Design						
	Experimental		Control				
Trial	Drug	Pts* (N)	Drug	Pts* (N)	Jadad score	PFS HR, 95%CI	OS HR, 95%CI
KEYNOTE-426	Pembrolizumab + Axitinib	138	Sunitinib	131	3	0.79 (0.57 - 1.09)	1.06 (0.60 - 1.86)
JAVELIN Renal 101	Avelumab + Axitinib	94	Sunitinib	96	3	0.62 (0.39 - 0.98)	0.81 (0.33 - 1.96)
CheckMate 9ER	Nivolumab + Cabozantinib	74	Sunitinib	72	NA	0.62 (0.38 - 1.01)	0.84 (0.35 - 1.97)
Total	***~ICI+TKI combinations***	**306**	**Sunitinib**	**229**	**/**	**0.70 (0.56 - 0.89), p = 0.003 Heterogeneity: Chi^2 = 0.99, df = 2 (P = 0.61); I^2 = 0%**	**0.94 (0.62 - 1.43), p = 0.77 Heterogeneity: Chi^2 = 0.36, df = 2 (P = 0.83); I^2 = 0%**

* patients with favorable IMDC prognosis NA = not applicable

Active therapy or best supportive care after disease progression to both nivolumab and cabozantinib in metastatic renal cell carcinoma: The BEYOND study (Meet-Uro 19).

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Background: Nivolumab is approved in the second or further line of treatment for patients with metastatic renal cell carcinoma (mRCC); cabozantinib is approved in a similar setting of patients. Unfortunately, no evidence is currently available regarding the best treatment option after disease progression to both nivolumab and cabozantinib. The aim of this study is to compare the treatment choices after progression to nivolumab and cabozantinib including patients followed in best supportive care (BSC) or active therapy. **Methods:** In this retrospective observational study, we selected 42 patients from 8 Italian cancer centers. Enrolled patients had progressed to both nivolumab and cabozantinib and subsequently referred to active treatment or BSC. Primary endpoint of the study was the OS of patients on active treatment versus BSC. Secondary endpoints were ORR, PFS and OS of patients on active treatment who received sorafenib versus everolimus. **Results:** The median age was 65 years, 76.2% were male. The majority of patients had undergone nephrectomy (78.6%), had clear cell histology (83%) and were at intermediate-poor risk at the diagnosis (85.7%). The most frequent site of metastatic disease in the general population and in patients referred to BSC was the lung (73.8% and 88.9%, respectively). For patients referred to active treatment, the most frequent site of metastasis was bone (70.8%). Sunitinib (71.4%), nivolumab (64.3%), and cabozantinib (54.7%) were the most commonly used drugs in the I, II and III lines of treatment, respectively. After progression to both nivolumab and cabozantinib 42.9% of patients were referred to BSC, while 57.1% received active treatment (28.6% everolimus, 16.7% sorafenib, 4.8% sunitinib, 4.8% IL2-HD, 2.4% lenvatinib + everolimus). Median OS was 13 (95% CI: 4-NR) and 3 months (95% CI: 2-4) in patients on active treatment versus BSC (p=0.001). Patients treated with sorafenib had better disease control when compared with those treated with everolimus (SD 71.4% versus 16.7%, PD 14.3% versus 58.3%; p=0.03), but no significant advantage in terms of PFS (5 versus 3 months, 95% CI: 2-6 versus 2-5; p= 0.5) and OS (NR versus 13 months, 95% CI: 3-NR versus 2-NR; p=0.2) was observed. **Conclusions:** After treatment with both nivolumab and cabozantinib, when possible, the choice of an active treatment seems to produce an OS advantage when compared with BSC. However, although sorafenib seems to demonstrate better results, we cannot indicate which is the drug of choice, as no significant advantage was shown in terms of OS or PFS from the comparison between sorafenib and everolimus. The limitations of this study are given by the size of the sample examined and its retrospective nature. Further studies are needed to confirm whether active treatment choice is associated with improved OS. Research Sponsor: None.

Cabozantinib (Cabo) beyond progression improves survival in advanced renal cell carcinoma patients: The CABEYOND study (Meet-Uro 21).

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Background: The multikinase inhibitor cabozantinib (Cabo) is an effective treatment option for metastatic renal cell carcinoma (mRCC). However, data on the optimal sequencing of Cabo and other available therapies are lacking. In particular, the strategy of continuing Cabo administration after disease progression (PD) has never been investigated yet. In light of its ability of inhibiting MET and AXL, which are implied in VEGFR acquired resistance, the hypothesis of a prolonged efficacy in slowing tumor growth, despite first radiological PD, is worth to be investigated. **Methods:** We conducted a retrospective multicenter study of mRCC patients (pts) treated with oral Cabo as second or subsequent line between 2014 and 2020 in 11 Italian Oncology units. Our study population included pts treated beyond RECIST first PD due to the clinical benefit and tolerance to therapy demonstrated. As a control group we analyzed pts treated with other therapies (thyrosin-kinase inhibitors (TKIs), everolimus, nivolumab or other) after first radiological PD with Cabo. Our aim was to evaluate the post-progression outcome according the two treatment strategies: Cabo beyond PD or other subsequent therapy. **Results:** 89 pts were included in the analysis: 45 pts received Cabo beyond PD and 44 another therapy: 22 pts nivolumab, 7 everolimus, 6 sorafenib and the others lenvatinib plus everolimus, sunitinib, HD-IL2, pazopanib or axitinib. The median age of all pts was 61.6 years (22.7-83.2) and 77.5% were male. 40.4% and 31.5% of pts had received one or two prior treatment lines, respectively; the remaining 28.1% received Cabo $>$ 3 line. At Cabo start, 83.9% were intermediate-poor risk according IMDC score (77.8% in CABO beyond PD and 90.5% in the control group) and the most common metastatic sites were lung (76.4%), lymph nodes (69.7%), bone (56.2%), liver (30.3%) and brain (14.8%). The objective response rate to Cabo before PD was significantly higher in pts continuing Cabo beyond PD than in those who were treated with other after first radiological PD (46.7% vs 25%, p = 0.03) and a longer but not statistically significant PFS was observed (median 8.1 vs 5.9 months, p = 0.377). Moreover, the median number of prior therapy lines was significantly higher for pts who were treated with Cabo beyond PD than other (2 vs 1, p = 0.016). Median duration of treatment with Cabo beyond PD was 6.4 months. In addition, continuing Cabo beyond PD was associated with a significantly better post-progression overall survival (OS) than switching to other therapy at PD (median OS 16.9 vs 13.2 months, Hazard Ratio 0.66, 95%CI 0.48 – 0.92, p = 0.011). **Conclusions:** This study showed a longer post-progression OS in pts continuing Cabo beyond PD than in those who switched to another therapy. With the limitations of a retrospective analysis, this is the first evidence suggesting that maintaining Cabo beyond PD is an effective strategy in pts with mRCC. Research Sponsor: None.

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Nivolumab as second-line treatment and beyond for metastatic renal cell carcinoma: A real-life experience from Turkish Oncology Group Kidney Cancer Consortium (TKCC) Database.

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Background: Immune checkpoint inhibitors (ICIs) started a new era in the treatment of metastatic renal cell carcinoma (mRCC). CheckMate-025 and CheckMate-214 trials established the effect of ICIs in the second-line and upfront therapy of mRCC, respectively. This study aimed to share a real-life experience regarding nivolumab in the second-line treatment and beyond in mRCC **Methods:** We retrospectively searched the Turkish Oncology Group Kidney Cancer Consortium (TKCC) database, which is the multicenter registry system, and extracted patients treated with nivolumab in the second line and beyond. The patients treated with nivolumab plus targeted therapy or ipilimumab were excluded. The primary endpoint was overall survival (OS). The secondary endpoints were response rates and safety. **Results:** A total of 134 patients were included in this study. The median age at the starting of nivolumab treatment was 61 years (Inter Quartile Range (IQR):55-67). Three out of four patients were male. One hundred four patients (78%) had previous nephrectomy. The majority of patients had clear-cell pathology (83%). Thirteen patients (10%) had sarcomatoid features. According to International Metastatic RCC Database Consortium (IMDC) risk score, seventy patients (52%) were in the intermediate and poor prognostic group. The previous drugs administered in each line before nivolumab are shown in the table below. The number of patients treated with nivolumab was 63(47%), 45(33%), 17(13%), and 9(7%) in the second-, third-, fourth-, and fifth-line setting, respectively. The median OS was 34 months (95% Confidence Interval (CI): 24.1-43.8)) with the 15 months (IQR:5-26) median follow-up. Objective response rate (ORR) and disease control rate (DCR) was 33% and 57%, respectively. The most common grade 3 or higher AEs leading to treatment discontinuation were pneumonitis (%1.4) and colitis (<%1). **Conclusions:** In compliance with the CheckMate-025 trial results, nivolumab improved OS for mRCC patients treated in the second line and beyond. The median OS was slightly higher in our study than the CheckMate-025 (34 months versus 25.8 months). It may be associated with the patient population in our study. Patients up to the fifth-line setting of mRCC treatment were included in this study. Of note, there was no additional safety concern for nivolumab. Research Sponsor: None.

Nivolumab Line	Previous Systemic Therapy			
	First Line	Second Line	Third Line	Fourth Line
Second (n=63)	Sunitinib=36 Pazopanib=27			
Third (n=45)	Interferon=34 Sunitinib=6 Pazopanib=4 Sorafenib=1	Sunitinib=18 Pazopanib=16 Axitinib=8 Everolimus=3		
Fourth (n=17)	Interferon=14 Sunitinib=2 Pazopanib=1	Sunitinib=11 Everolimus=3 Pazopanib=2 Missing=1	Axitinib=14 Everolimus=2 Pazopanib=1	
Fifth (n=9)	Interferon=9	Sunitinib=6 Pazopanib=2 Axitinib=1	Everolimus=8 Axitinib=1	Axitinib=6 Sunitinib=2 Everolimus=1 Missing=1

Phase I with expansion clinical trial of seleno-l-methionine (SLM) in combination with axitinib in patients with relapsed clear cell renal cell carcinoma (ccRCC): Bench to bedside.

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Background: Hypoxia induced factor 1α/2α (HIFs) and vascular endothelial growth factor (VEGF) are overexpressed in ccRCC and associated with increased tumor angiogenesis, vascular instability and drug resistance. In xenografts, high dose SLM resulted in sustained down regulation of HIFs, normalization of tumor vasculature that resulted in increased drug delivery, and therapeutic synergy with anti-VEGF therapeutic. These effects were highly SLM dose, sequence, and schedule dependent. **Methods:** After completion of the escalating phase I (3+3) trial, the non-toxic SLM dose of 4000μg was administered orally twice daily (BID) for 14 days, followed by once daily in combination with axitinib 5 mg BID. The primary endpoint is safety and the secondary end point include overall response rate (ORR), progression free survival (PFS), and overall survival (OS). To assess the potential effects of SLM on tumor vascular function, dual energy computed tomography (DECT) was conducted at baseline, day 14 of SLM, and at 3 months of SLM + axitinib. **Results:** Thirty subjects are screened. Of whom 25 have efficacy data (3 subjects screen failure, 1 withdrew, 1 taken off study prior to first scan due to progression with brain lesions likely present prior to study entry). 13/25 (52%) have confirmed response (CR/PR). Two subjects had CR lasting for at least 35 and 44 months, 6 subjects achieved stable disease (SD) lasting at least 6 months accounting for disease control rate (DCR) of 76%, mPFS is 9.5 months. 5/30 patients have sarcomatoid features, all of which are evaluable for efficacy with 1 PR achieved (20%). In the 20 patients without sarcomatoid features, 12/20 achieved PR (60%). The most prevalent adverse events (AE) included fatigue, diarrhea, anorexia, nausea, hoarseness, weight loss, and hypertension. No deaths nor grade 4 toxicities observed. The blood selenium concentrations achieved in the 4000μg SLM dose cohorts are similar to those determined molecularly and therapeutically synergistic with axitinib in xenografts and are being achieved clinically without significant toxicity. DECT data demonstrated increased iodine uptake by tumor lesions, but not in normal tissues, on day 14 SLM treatment and decreased in these same lesions at 3 months of SLM/axitinib. **Conclusions:** Blood selenium concentrations and duration of treatment seem to be critical determinants of response. Pre and concurrent treatment with SLM enhance the ORR and PFS of axitinib, with no additional toxicity. Currently documented responses are similar across IMDC risk groups. Clinical trial information: NCT02535533. Research Sponsor: PfizerHCCC PACT Award.

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A pilot study of preoperative nivolumab in high-risk nonmetastatic renal cell carcinoma.

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Background: Immunotherapy improves survival in patients with advanced renal cell carcinoma (RCC), but has no established role for perioperative use in patients with localized RCC. Neoadjuvant immunotherapy is a promising strategy in several cancers, and may leverage the primary tumor as antigen source. **Methods:** We conducted a single institution pilot study of neoadjuvant nivolumab in patients with RCC undergoing nephrectomy with curative intent. Patients were eligible if their risk of metastatic recurrence within the first 12 years was >20% by an established nomogram. After confirmatory biopsy and renal MRI, patients were treated with standard dose nivolumab every 2 weeks for 4 treatments, with a follow-up renal MRI prior to nephrectomy. The primary end points of the study were safety and feasibility defined as being able to complete 3/4 treatments without surgical delay. We evaluated adverse events by CTCAE, surgical safety by Clavien-Dindo classification, and tumor radiographic response by RECIST 1.1. **Results:** Eighteen (11 men, 7 women; median age 60) were enrolled. All patients had clear cell RCC, median tumor size at baseline was 8.8cm (range 6.4-14.2cm). Median predicted 12-year probability of recurrence was 45% (range 25-71%). All received at least 1 dose of nivolumab; 16/18 patients completed all 4 doses. 17/18 (94%) patients completed at least 3 doses. No patient had notable delay in the timing of their nephrectomy. 4 patients had surgical complications per Clavien-Dindo classification, including 2 with grade 3a chylous ascites after lymphadenectomy. Two patients had nivolumab discontinued for immune-related adverse events, including grade 3 transaminitis and grade 2 arthralgias; a third patient developed grade 4 colitis 4 months after completing nivolumab. All patients had stable disease as the best response prior to surgery. Recurrence-free survival at 2 years was 0.74 (95%CI 0.45-0.90). We analyzed an additional 21 patients with metastatic RCC (20 ccRCC, 1 epithelioid AML) who subsequently had nephrectomy after standard immunotherapy. 15 patients had received ipilimumab+nivolumab, 6 received single-agent PD-1 or PD-L1 inhibitors. 3 (14%) patients achieved a near or complete pathologic response, including a patient with epithelioid AML. Analysis of radiologic and pathologic biomarkers of response are ongoing and will be presented at conference. **Conclusions:** In this pilot study, there were no new safety signals or delays in surgery with preoperative nivolumab. Neoadjuvant immunotherapy shows preliminary evidence of safety, feasibility and efficacy; biomarker studies may help identify individuals who may have a higher likelihood of response. Clinical trial information: NCT02595918. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

Efficacy of gemcitabine plus doxorubicin (Gem + Dox) in patients with renal medullary carcinoma (RMC).

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Background: Renal medullary carcinoma (RMC) is one of the most lethal renal cell malignancies with a median overall survival (OS) of only 13 months from diagnosis (Shah et al. *BJU Int.*, 2017). RMC predominantly affects young individuals of African descent and is characterized by loss of the tumor suppressor *SMARCB1* in all cases. Platinum-based chemotherapy produces a best response rate of 29% and is the recommended front line therapy for RMC (Msaouel et al. *Clin Genitourin Cancer*, 2019). However, there is little data on subsequent therapies. We recently showed that loss of *SMARCB1* induces replication stress that renders RMC cells vulnerable to nucleoside analogs such as gemcitabine (Gem) and topoisomerase inhibitors such as doxorubicin (Dox) (Msaouel et al. *Cancer Cell*, 2020). We therefore hypothesized that Gem + Dox would demonstrate clinical activity against RMC. **Methods:** We conducted a retrospective study of patients who were treated with Gem + Dox for metastatic RMC at our institution. A blinded board-certified radiologist reviewed all restaging images to assess best radiographic response as defined by RECIST v1.1 and, when applicable, date of progression. Adverse events (AEs) were evaluated using the CTCAE version 5.0 grading estimated from chart documentation. **Results:** Between 01/2005 and 09/2020, we identified 16 patients with RMC that were treated with Gem + Dox and were evaluable for survival outcomes (Table). All but 1 patient (94%) had received prior platinum-based chemotherapy. Gem + Dox produced a partial response in 3/14 evaluable patients (21.4%) and stable disease as best response in 10/14 (71.4%), resulting in a median progression-free survival of 3.0 months (mo) with 95% CI 1.5-4.5 mo. The median overall survival (OS) from the start of Gem + Dox was 9.8 mo (95% CI 3.3-16.2) and the median OS from diagnosis was 18.6 mo (95% CI 11.3-25.9). Gem + Dox was well tolerated with no grade $\geq$ 4 AEs and the most common grade 2 or 3 AE's were cytopenias (3/17), nausea (3/17), and fatigue (2/17). There were no grade $\geq$ 2 reported events of cardiotoxicity, but 3 patients discontinued treatment due to reaching recommended maximum dose of Dox. **Conclusions:** Gem + Dox demonstrated clinical benefit in patients with RMC and was well tolerated in most patients, supporting its use in patients with RMC whose disease progressed on prior platinum-based chemotherapy. Further investigation is warranted to determine and target mechanisms of resistance. Research Sponsor: None.

Baseline patient characteristics.

Median Age – yr. (range)	**29 (20-47)**
Male Gender – no. (%)	7 (44%)
African American – no. (%)	15 (94%)
Right Kidney Primary RMC – no. (%)	13 (81%)
ECOG Performance Status ≤ 1 – no. (%)	12 (75%)
Cytoreductive Nephrectomy – no. (%)	12 (75%)
Prior Platinum-based therapy – no. (%)	15 (94%)
0-1 Prior Lines of Therapy – no. (%)	11 (69%)
2-3 Prior Lines of Therapy – no. (%)	5 (31%)

325 **Poster Session**

UNISON - nivolumab then ipilimumab + nivolumab in advanced non-clear cell renal cell carcinoma (ANZUP 1602): Part 1—Nivolumab monotherapy.

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Background: Immune checkpoint inhibitors (ICI) are active in many cancers, but people with rare variant, non clear-cell renal cell carcinoma (nccRCC) have been excluded from most clinical trials in RCC. UNISON (NCT03177239) aimed to test 2 hypotheses; the activity of nivolumab in nccRCC (Part 1), and the benefit of adding ipilimumab to nivolumab, in people whose cancers progress on nivolumab (Part 2). **Methods:** 83 participants (pts) with advanced nccRCC with good (ECOG0/1) performance status, were enrolled including papillary type 1 (17%), papillary type 2 (28%), chromophobe (18%), Xp11 translocation (6%), hereditary leiomyomatosis renal cell carcinoma syndrome-associated renal cell carcinoma (6%), RCC unclassified (10%) and other (15%) histological subtypes. Participants took nivolumab (N) 240mg every two weeks in Part 1 in total. If they experienced progression and remained eligible they could take N (3mg/kg) plus ipilimumab (I; 1mg/kg) every 3 weeks for up to 4 doses (Part 2). Pts with disease control after N or N + I could continue N for up to 1 year. UNISON was powered to distinguish a clinically-relevant improvement in objective tumor response rate (OTRR) from 15% to 30% in people taking N+I in Part 2 in pts whose cancers were refractory to single-agent first-line N. Here we report results of Part 1. **Results:** Pts experience of N appeared similar to previous reports, with most experiencing mild adverse events. 12 treatment related SAE occurred in 11 patients (13%). 14 pts (17%) experienced treatment delays, or permanent treatment discontinuation (10%). The median time on treatment was 5.1 months. The OTRR was 17% with 3 complete responses and 11 partial responses. The median duration of response was 21 months. Stable disease occurred in 49% of pts and disease progression in 34%. The disease control rate at 6 months was 45% (95% CI: 34%, 56%). The median PFS was 4.0 months (95% CI: 3.6, 7.4). The 6 month progression-free survival (PFS) was 45% (95% CI: 34-55) and the 12 months PFS was 30% (95% CI: 21%, 40%). **Conclusions:** Pts with nccRCC treated with N experience similar adverse events compared to pts with other cancers. A substantial minority of people with nccRCC derive benefit, but many pts have cancers refractory to anti-PD1, similar to other reports. The activity of I and N in this PD1-refractory population is of considerable interest and will be reported at a later date. Clinical trial information: NCT03177239. Research Sponsor: BMSOther Government AgencyAustralian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

A phase II open-label study of cabozantinib after first-line treatment including an immune-checkpoint combination in patients with advanced or unresectable renal cell carcinoma: The BREAKPOINT trial (MeetUro trial 03 - EudraCT number 2018-000582-36).

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Background: Antiangiogenic therapy has been a milestone in the treatment of metastatic renal cell carcinoma (mRCC) for years. The positive results with immune-checkpoint inhibitors (ICI) are changing the frontline standard of care of mRCC patients (pts). To date, prospective data are lacking to determine the efficacy of antiangiogenic therapy in pts progressed to ICI. The multi-kinase inhibitor Cabozantinib (cabo) has shown prolonged survival in pre-treated mRCC pts. Moreover, by targeting multiple pathways and crucial kinases involved in microenvironment-driven immune-escape, it may represent an ideal agent to be used sequentially after ICI. **Methods:** This is the first prospective open label, single arm, multicenter, phase II study to evaluate efficacy and safety of Cabo in pts with mRCC pre-treated with adjuvant or first line PD-1/PD-L1-based therapy (as monotherapy or in combination with an TKI or anti CTLA-4). Cabo 60 mg once daily was administered until progressive disease (PD) or unacceptable toxicity. The primary endpoint was progression free survival (PFS), secondary endpoints were overall survival (OS), objective response rate (ORR) and safety. **Results:** Among 23 patients enrolled, 22 were included in the analysis (one was excluded for screening failure). Median age was 59.5 years (range: 29-74), 69.5% were male. At baseline, Karnofsky performance status was 100 in 59% of pts, 80-90 in 31.8% and 70-80 in 9%. 22.7% of pts had a good Heng score, 50% intermediate and 27.2% poor. Median duration of the previous therapy with anti PD-1 or anti-PD-L1 compounds was 4.3 months. Pts received an average of 4.7 months of Cabo. Among evaluable cases, 6 pts (27.2%) achieved a partial response and 5 pts (22.7%) stable disease. The median follow-up was 7.2 months and the median PFS was 7.2 months. 2 pts discontinued treatment for toxicity, 8 pts for PD, 1 patient discontinued treatment for different reason than PD, 11 pts are still on treatment. Grade (G) 3 adverse events (AEs) occurred in 22.7% of pts; the most common AEs were hand and foot syndrome (HFS) (G1 in 36.3% of pts, G2 18.1%, G3 4.5%), diarrhea (G1 31.8%, G2 18.1%), hypothyroidism (G1 9.09 %, G2 22.7 %), mucositis (G1 36.3%, G2 4,5%), and fatigue (G1 18.1%, G2 18.1%). Transitory withholding of cabo was observed in 63.6% of pts (14/22) and it was due to AEs in the 90% of the cases. For 5/22 pts (22.7 %), dose reduction was needed to manage AEs. The most common AEs leading to temporary drug interruption were HFS G1-3 (13.9%), liver disfunction G1-G2 (13.9%), diarrhea G1-G2 (11.6%), nausea and vomiting G2 (11.6 %) and fatigue G2 (9.3%). **Conclusions:** So far, the treatment with cabo after a I line anti-PD-1 based immunotherapy resulted active and well tolerated. Clinical trial information: NCT03463681. Research Sponsor: Società Ipsen S.P.A.

327 Poster Session and Poster Highlights Session; Displayed in Poster Session

Outcomes for patients in the pembrolizumab+axitinib arm with advanced renal cell carcinoma (RCC) who completed two years of treatment in the phase III KEYNOTE-426 study.

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Background: In the randomized, open-label, phase III KEYNOTE-426 study (NCT02853331), pembrolizumab + axitinib significantly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) versus sunitinib as first-line therapy for advanced RCC. Per protocol, patients could discontinue pembrolizumab or axitinib and continue the other agent. Pembrolizumab was stopped for all patients at 2 years. Axitinib could be continued until progression or toxicity. This exploratory subgroup analysis of KEYNOTE-426 describes outcomes of patients who completed 2 years of pembrolizumab. **Methods:** Patients included in KEYNOTE-426 were treatment naive, with clear cell RCC, KPS ≥70%, and measurable disease (RECIST v1.1). Patients were randomly assigned 1:1 to receive pembrolizumab 200 mg intravenously every 3 weeks for up to 35 doses + axitinib 5 mg orally twice daily or sunitinib 50 mg once daily (4 weeks on/2 weeks off) until progression, toxicity, or withdrawal. Primary end points of the original analysis were OS and PFS. Key secondary end points were ORR and safety. **Results:** Of 432 patients treated with pembrolizumab + axitinib, 129 (29.9%) completed 2 years of study therapy. Median (range) age of these patients was 61 (36-82) years, and 72.1% were male; 42 (32.6%) and 87 (67.4%) patients had International mRCC Database Consortium favorable and intermediate/poor risk, respectively, consistent with the intention-to-treat population (31.9% vs 68.1%). Median (range) follow-up (time from randomization to data cutoff) was 31.1 (24.0-37.7) months. For patients who completed 2 years of study therapy, the OS rates at 36 months was 93.8% (95% CI, 85.5%-97.4%). The PFS rates at 24 and 36 months were 72.7% (95% CI, 64.0%-79.7%) and 57.7% (95% CI, 46.3%-67.5%), respectively. The ORR was 85.3%, and the CR rate was 14.0%. 59.7% of patients experienced grade 3-5 treatment-related adverse events and 8.5% experienced grade 3-5 immune-mediated adverse events. **Conclusions:** In this exploratory analysis, a significant proportion of patients in the pembrolizumab + axitinib arm completed 2 years of pembrolizumab with ongoing clinical benefit. Clinical trial information: NCT02853331. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Phase Ib/II study of durvalumab and guadecitabine in advanced kidney cancer Big Ten Cancer Research Consortium BTCRC GU16-043.

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Background: Anti-PD1/PDL1 immune checkpoint inhibition (CPI) is active in advanced clear cell RCC, but not all patients benefit. Preclinical studies with the combination of hypomethylating agents and CPI resulted in reversal of immune evasion and tumor regression. We examined the combination of the hypomethylating agent guadecitabine (subcutaneously on Days 1-5), with the anti-PDL1 antibody durvalumab (intravenously at flat dose of 1500 mg on Day 8) in 28 day cycles in advanced RCC in a single arm trial. **Methods:** In the phase Ib portion (n=6; presented previously), guadecitabine dosing of 45 mg/m^2/day was selected as maximum tolerated dose. For the phase II portion of Cohort 1 (36 pts with no prior CPIs), eligible patients had metastatic RCC with clear cell component, ECOG PS of 0-1, and measurable disease by RECIST 1.1. We present pooled efficacy and toxicity data for the 42 CPI-naive pts from the phase Ib and phase II portions. An exploratory Cohort 2 (N=16) consisting of CPI-refractory pts is enrolling. **Results:** Of the 42 pts, 71% were men, median age was 67 years, ECOG PS was 0 in 57%, IMDC risk group was intermediate in 83% and poor in 17%, and histology was mixed in 21%. At a median follow-up of 20.1 m, best RECIST 1.1 response was PR in 9 pts (22%); SD in 25 pts (61%); PD in 7 pts (17%); and non-evaluable in 1 pt. Response categories were identical by irRECIST. Clinical benefit defined as either PR or SD $\geq$6 months was seen in 66%. Median OS had not been reached and median PFS was 17 m. Treatment was generally well tolerated with asymptomatic neutropenia the most frequent AE attributed to guadecitabine (38.1%), and asymptomatic lipase elevation the most common AE from durvalumab (11.9%). Grade 4 AEs were noted in 50.0% pts, grade 3 59.5%. Immune-mediated AEs were generally mild (all $\leq$ grade 3), included pruritus (14.3%), rash (14.3%), asymptomatic amylase or lipase elevations (16.7%), hypothyroidism (11.9%), diarrhea (16.7%), dyspnea (16.7%), pneumonitis (4.8%), myalgia (4.8%), and transaminitis (9.6%). Laboratory peripheral blood profiling (done at baseline, C1D8, C2D8) was associated on univariate unadjusted analysis at baseline with response in two major PBMC subsets - MDSCs (negative) and ILCs (positive). Further functional analysis revealed that increased expression of IL-22 in both CD4 and CD8 positive T cells positively correlated with response. Associations were noted for toxicity with IL-22 expressed by CD8-CD4- T cells, and CTLs T-bet level. Baseline archival tumor tissue next generation sequencing results will be presented. **Conclusions:** Guadecitabine in combination with durvalumab was well tolerated and had reasonable activity in first-line advanced ccRCC. MDSCs and regulatory T lymphocytes decreased in responders, increased Th17 subpopulations of T cells were associated with immune-mediated toxicities. Further study of this combination in CPI-refractory RCC pts is ongoing. Clinical trial information: NCT03308396. Research Sponsor: AstraZeneca Pharmaceuticals, LP, Astex Pharmaceuticals, Inc.

Treatment response in the intact primary renal mass (P-Rmass) and its relationship to the overall response to treatment in patients with metastatic renal cell carcinoma (mRCC).

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Background: With the approval of more effective systemic treatments (syst Rx) such as tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI), the impact of cytoreductive nephrectomy (CN) on response to Rx and survival remains unknown. The majority of patients (pts) previously enrolled in clinical trials have had radical nephrectomy (RN) or CN prior to syst Rx. Therefore, the response of the P-Rmass to ICIs and the effect of intact P-Rmass on response to syst Rx is not well described. **Methods:** A retrospective review of 209 pts with mRCC who were treated with ICI in the first or second-line was conducted. Following the appropriate regulatory process, collaborators from 5 US sites collected clinical, pathological, and outcome data via chart review. The response was investigator-assessed for all pts with at least one post-treatment scan or evidence of clinical progression after treatment initiation. Overall radiographic response (ORR) includes complete response (CR) and radiographic response (Rad-resp) to treatment. Disease control rate (DCR) includes CR, Rad-resp, and stable disease. **Results:** Median age at diagnosis was 63 yrs and 69% were male. 102 pts (49%) had localized disease at diagnosis and underwent radical or partial nephrectomy, 3 (1%) had ablation/radiation of P-Rmass, 26 (12%) had CN, 9 (4%) had CN after an excellent response to syst Rx, 12 (6%) had a previous nephrectomy but developed a new Rmass (measurable target lesion), and 57 (27%) did not have CN and had an intact P-Rmass. 176 (84%) pts had clear cell histology. 27 (14%) and 23 (12%) had known sarcomatoid and rhabdoid features, respectively. Overall, 77 (37%) pts had a measurable Rmass while receiving syst Rx. 84 (40%), 93 (45%), and 10 (5%) pts received ICI (Ipilimumab/Nivolumab or Nivo), TKI, or Pembrolizumab/Axitinib in the first-line. 143 (68%) and 70 (33%) pts received second- and third-line treatment. 103 (72%) and 28 (19%) pts received ICI and TKI in the second-line, respectively. The best ORR and the Rad-resp in the intact P-Rmass in evaluable pts are summarized in the table below. ORR to ICI in the first or second-line were numerically higher in pts with an intact P-Rmass compared to pts who had nephrectomy, but this difference was not statistically significant (p= .38 and .35 respectively). **Conclusions:** The intact P-Rmass had a good response (62-70%) to the first-line syst Rx. Although the overall Rad-resp rates to ICI are numerically higher in pts with intact P-Rmass, this difference was not statistically significant. Research Sponsor: None.

	ICI first-line	TKI first-line	ICI second-line	TKI second-line
ORR	26/58 (45%)	27/78 (35%)	15/73 (20%)	8/17 (47%)
DCR	38/58 (65%)	40/78 (51%)	27/73 (37%)	11/17 (65%)
Rad-resp in P-Rmass	16/23 (70%)	13/21 (62%)	7/20 (35%)	6/9 (66%)
ORR in pts with intact P-Rmass	11/21 (52%)	8/24 (33%)	6/22 (27%)	2/6 (33%)
ORR in pts without intact P-Rmass	15/37 (40%)	19/54 (35%)	9/51 (18%)	6/11 (54%)

Rechallenge of nivolumab in metastatic renal cell carcinoma, an ambispective multicenter study (RENIVO).

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Background: Immune checkpoint inhibitors (ICIs) in combination with another ICI or an antiangiogenic targeted therapy have been approved for frontline therapy in metastatic renal cell carcinoma (mRCC). However, progression disease (PD) often occurs and subsequent therapies are needed. Rechallenge of ICI may then be an option, but there is a lack of data regarding this strategy. **Methods:** This ambispective multicenter study included patients who received a rechallenge of Nivolumab (ICI-2) between January 2014 and September 2020, after a first-ICI therapy (ICI-1), regardless of the reason of the discontinuation. Patients could have either a non-ICI therapy or have a prolonged free-interval ($\geq$ 12 weeks) between ICI regimens. Those with ongoing rechallenge at inclusion were followed prospectively. Primary endpoint was investigator-assessed best ORR. **Results:** 45 rechallenges were included from 16 centers. Median age was 60 years (range, 42-90), 64% were male. Most of them had clear cell histology (91%) and a Fuhrman or ISUP grade $\geq$ 3 (80%). Single-agent Nivolumab and Nivolumab-Ipilimumab association were used in 78% and 11% during ICI-1 and in 93% and 7% during ICI-2, respectively. Discontinuation for PD, toxicity or clinical decision occurred in 49%, 27% and 24% for ICI-1 and in 94%, 3% and 3% for ICI-2, respectively. The ORR were 51% (n = 23) at ICI-1 and 16% (n = 7) at ICI-2. One patient had a complete response during both ICI-1 and ICI-2 and two had a partial response at ICI-2 although they had PD as best ICI-1 response. After a median follow-up of 14.9 months (mo), median duration of response for ICI-2 was 5.1 mo (95% CI, 2.7-not reached [NR]). For ICI-1 and ICI-2: median progression-free survival (PFS) was 11.4 mo (95% CI, 9.8-23.5) and 3.5 mo (95% CI, 2.8-9.7); median overall survival was NR (95% CI, 37.8-NR) and 24 mo (95% CI, 9.9-NR). Poor prognostic factors for PFS at ICI-2 were Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\geq$ 2, presence of liver metastases, inflammatory syndrome and PFS under ICI-1 $>$ 6 months. Grade $\geq$ 3 immune-related adverse events occurred in 24% (n = 11) during ICI-1 but only in 4% (n = 2) during ICI-2. There was no treatment-related death. **Conclusions:** Our study suggests that resumption of ICI with Nivolumab has a moderate efficacy in mRCC and acceptable tolerance. Predictive factors of response are needed to propose this strategy to selected mRCC patients. Larger prospective cohorts are needed to confirm these results. Research Sponsor: Foncer contre le cancer.

Prognostic factors for PFS ICI-2.

Prognostic factors	Hazard Ratio (95% CI)	*p*-value (univariate)
ECOG PS (n = 45)		
2-3 vs 0-1	4.80 (2.05 - 11.26)	$<$ 0.01
Liver Metastases (n = 42)		
Yes vs no	2.55 (1.17 - 5.58)	0.02
Inflammatory syndrome		
Leukocytes (n = 38)	1.19 (1.01 - 1 .40)	0.04
Platelets (n = 38)	1.005 (1.001 - 1.009)	0.01
PFS ICI-1 *(vs < 6 months)* (n = 45)		
6 - 12 months	0.40 (0.15 - 1.01)	$<$ 0.01
> 12 months	0.16 (0.07 - 0.40)	

Safety and efficacy of nivolumab in older patients (pts) with renal cell carcinoma: Results of a sub-group analysis of the GETUG-AFU 26 NIVOREN multicenter phase II study.

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Background: NIVOREN GETUG AFU 26 study, is a french multicenter prospective study to evaluate safety and efficacy of Nivolumab (N) in a broad "real world setting" in mRCC after failure of 1 or 2 tyrosine kinase inhibitors. **Methods:** Between February 2016 and July 2017, 729 pts were enrolled across 27 institutions. Primary objective of the trial was safety assessed by grade ≥ 3 treatment related adverse event (TRAE). We report here results of older patients above 70 years old ([70;75[; [75;80[; ≥ 80) compared with their younger counterparts. **Results:** Overall, 720 patients were treated (median age 64 (22;90)). Among them 205 pts were ≥ 70 (28.5%) divided as follow: [70-75[:107 (14.9%) / [75-80[: 68 (9,4%) / ≥ 80: 30 (4,2%). Patients' characteristics (Table) were similar in younger and older patients except for IMDC risk groups (IMDC) classification with less poor prognostic in pts ≥ 75 and fewer brain metastasis in pts ≥ 70. Treatment duration was similar across age groups despite a rate of discontinuation for TRAE increasing with age. Regarding efficacy, there was a non-significant trend toward improved response rate and progression free survival and lower specific survival with increasing age. **Conclusions:** In this large "real world" setting study a significant number of old pts were included. Prognostic profile appears better in older pts included. There is no signal for an excess of toxicity in this population and efficacy is comparable to younger patients. Age alone should not prevent prescribing N in mRCC. Clinical trial information: NCT03013335. Research Sponsor: BMS.

	< 70 (n=515)	[70-75[(n=107)	[75-80[(n=68)	≥ 80 (n=30)	ALL PTS (n=720)
IMDC risk groups (fav/int/poor) n(%)	87 (17%) / 286 (56%) / 140 (27%)	18 (17%) / 61 (57%) / 28 (26%)	19 (28%) / 36 (53%) /13 (19%)	7 (23%) / 21 (70%) / 2 (7%)	131 (18%) / 404 (56%) / 183 (26%)
>2 prior lines	109 (21.2%)	28 (26.2%)	18 (26.5%)	7 (23.3%)	162 (22.5%)
Brain metastasis	72 (14.7%)	7 (7.3%)	4 (6.2%)	0	83 (12.3%)
Median (min; max) treatment duration (m)	5.1 (0.5; 32.7)	5.6 (0.5; 32.2)	5.2 (0.5; 28.1)	5.5 (0.5; 25.3)	5.2 (0.5; 32.7)
≥ 1 Gr III AE related to Nivolumab	83 (16.1%)	19 (17.8%)	17 (25.0%)	10 (33.3%)	129 (17.9%)
At least one AE Gr I to V related to Nivolumab leading to treatment discontinuation	41 (8%)	8 (7.5%)	10 (14.7%)	5 (16.7%)	64 (8.9%)
Objectif Response Rate	107 (21.5%)	16 (15.7%)	13 (21.3%)	8 (29.6%)	107 (21.5%)
Median (CI95%) progression free survival (m)	3.1 (2.8-4.4)	2.8 (2.6-4.9)	5.2 (2.8-7.4)	8.2 (2.8-12.2)	3.7 (2.9-4.6)
12 months specific overall survival rate (CI95%)	74.3% (70.2-77.9)	66.8% (56.9-74.9)	70.7% (57.9-80.2)	64.5% (43.9-79.1)	72.4% (68.9-75.6)

332 **Poster Session**

Long-term survival of favorable-risk patients with metastatic renal cell carcinoma treated with second-line axitinib in a multicenter phase II study.

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Background: Tyrosine kinase inhibitors remain possible treatment options in favorable risk patients newly diagnosed with metastatic renal cell carcinoma (mRCC). In phase II study (FavorAx), axitinib showed the activity in mRCC patients with a favorable risk and history of prior VEGFR-directed therapy. Here we present the outcomes from expansion study cohort with 4 years follow-up. **Methods:** Patients were required to have clear-cell mRCC, favorable risk according to IMDC criteria, and to have received first-line treatment with sunitinib or pazopanib. Prior treatment with other agents was not permitted. Axitinib was given orally at a starting dose of 5 mg twice daily with possible dose titration. Treatment was continued until disease progression according to RECIST version 1.1, unacceptable toxicity, death, or withdrawal of consent. All patients were assessed for efficacy. Endpoints included progression-free survival (PFS, primary); overall survival (OS), objective response rate (ORR), and safety (secondary). **Results:** A total of 55 patients were assessed, 58% of whom were male. Median age was 64 years. 29 (53%) patients had 2 and more metastatic sites. 73% and 27% of patients received first-line sunitinib or pazopanib. The median PFS was 19 months (95% CI, 15–23) and the median OS was 29.4 months (95% CI, 21.5–37). The 4-year OS rate was 36%. The objective response rate was 31% and 2 (3.6%) patients achieved a complete response. Disease progression was the single reason for discontinuation of axitinib. After disease progression, 62% of patients received third-line therapy. The toxicity was consistent with previously reported data. The most common adverse events associated with axitinib were hypertension, fatigue, and diarrhea, each occurring in more than 20% of patients. **Conclusions:** Second-line axitinib continues to show efficacy in favorable risk patients with mRCC. Long-term OS and PFS were observed with axitinib. Clinical trial information: NCT02700568. Research Sponsor: Kidney Cancer Research Bureau.

333 **Poster Session**

Phase II study of the oral hypoxia-inducible factor 2α (HIF-2α) inhibitor MK-6482 for Von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC).

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Background: Patients (pts) with VHL disease are at risk of developing benign and malignant tumors, including ccRCC, pancreatic lesions tumors, CNS hemangioblastomas, and retinal lesions. Inactivation of *VHL* leads to stabilization of HIF-2α, which drives tumor growth. In a phase 1/2 study, MK-6482, a potent, selective, oral small molecule HIF-2α inhibitor, demonstrated favorable safety and antitumor activity in advanced ccRCC. We present results of the open-label phase 2 study of MK-6482 for VHL disease–associated ccRCC (NCT03401788). **Methods:** Adults with germline *VHL* alterations, measurable, localized/non-metastatic ccRCC, no prior systemic anticancer therapy, and ECOG PS 0/1 received MK-6482 120 mg once daily until progression, intolerable toxicity, or decision to withdraw. Primary end point: ORR of VHL-associated ccRCC tumors per RECIST v1.1 by independent review committee (IRC). Secondary end points: DOR, time to response (TTR), PFS, and safety. **Results:** As of June 1, 2020, 61 pts enrolled. The majority (82%) of pts had ECOG PS 0, and median number of prior surgeries per pt was 5 (range, 1-15). Lesions outside the kidney (non-RCC tumors) evaluable by IRC included pancreatic lesions (100%) and CNS hemangioblastomas (70%). Median duration of treatment was 68 wk (range, 8-105), and 92% of pts remain on therapy. There were 22 confirmed responses (ORR, 36% [95% CI, 24%-49%]) and 7 (11%) unconfirmed (documented at 1 time point, to be confirmed at subsequent time point) responses; all PRs. In pts with confirmed PR, median DOR was not reached (range, 12-62 wk) and median TTR was 31 wk (range, 12-61); 14 (64%) pts had response duration of ≥26 wk. 56 pts (92%) had any decrease in size of target lesions. PFS rate at 52 wk was 98% (95% CI, 89%-100%). Overall, pretreatment median linear growth rate of ccRCC tumors was +3.6 mm/y (range, −3.4 to +33.1), compared with −4.5 mm/y (range, −12.8 to +5.1) while on treatment. For non-RCC tumors, ORR in pancreatic lesions was 64% (39/61, including 4 CRs) and in CNS hemangioblastomas was 30% (13/43, including 5 CRs). Median (range) TTR was 35 wk (11-60) and 12 wk (10-60) for pancreatic lesions and CNS hemangioblastomas, respectively. 11/16 (69%) pts with evaluable retinal lesions at baseline showed improvement. Of those 16 pts, 29 eyes were followed for retinal lesions; 16 eyes (55%) showed improvement, 12 (41%) remained stable, and no follow-up evaluation was available for 1 (3%) eye. Treatment-related AEs (TRAEs) occurred in 98% of pts, none grade 4/5. Most common TRAE was anemia (87%), considered to be an on-target toxicity. One pt discontinued treatment due to a TRAE (grade 1 dizziness). As of data cutoff, 1 pt (2%) required surgery for ccRCC tumors after treatment. **Conclusions:** MK-6482 is an active and well-tolerated therapy for VHL disease-associated ccRCC, pancreatic lesions, as well as CNS and retinal hemangioblastomas. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

334 **Poster Session**

Combination therapy with avelumab (Ave) and cabozantinib (Cabo) in patients (pts) with newly diagnosed metastatic clear cell renal cell carcinoma (mccRCC).

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Background: Immune therapy combinations are now standard first-line therapy for pts with mccRCC. Cabo modulates key components of the immune system such as decreasing regulatory T-cells and increasing T-effector cell populations and is approved for treatment of mRCC. We hypothesize that Ave + Cabo will be safe and show clinical activity in mccRCC. **Methods:** Prospective phase I clinical trial using a 3+3 design with three planned dose cohorts: Cabo 20mg/day, 40mg/day and 60mg/day + Ave (10mg/kg q2weeks) in each arm. The primary endpoint was safety and identification of the recommended phase II dose (RP2D). Key secondary endpoints included objective response rate (ORR) and radiographic progression free survival (PFS). No dose modifications were allowed for Ave but dose delays were permitted. Dose reductions were allowed for Cabo. There were an additional 3 patients included in the final dose cohort as a confirmation of the RP2D. RECIST 1.1 was used to determine ORR. Treatment beyond progression was allowed. **Results:** Twelve patients with newly diagnosed mccRCC were enrolled from 08/2018 through 03/2020. Three patients were enrolled into the 20 and 40mg cohorts each, six patients enrolled in the 60mg cohort. IMDC risk: favorable 4 patients, intermediate 6 patients, poor 2 patients. No dose limiting toxicities were observed in any cohort. Only one SAE related to study treatment was observed, thromboembolism, after the DLT period. Immune related adverse events (irAE) occurred in six patients (50%) and included hypothyroidism, colitis, nephritis, allergic rhinitis and rash. Six patients required dose reductions of cabozantinib after the DLT period: one in the 40mg cohort and five in 60mg cohort, most frequently due to oral mucositis and hand foot syndrome. One patient discontinued Ave due to irAE (nephritis). No patients discontinued Cabo due to toxicity. The ORR was 33% (all PR). The clinical benefit rate (CR+PR+SD) was ~ 92%. One patient experienced PD on the first scan and then continued on the protocol treatment without further progression at the time of this report (follow up to date ~ 7 months). Seven of 12 pts are still on protocol treatment. **Conclusions:** Ave + Cabo in mccRCC is safe and preliminarily efficacious. Even though the DLT was not met in any of the cohorts, based on dose reduction required in 5 of 6 pts in the Cabo 60 mg cohort after the DLT period, the recommended RP2D dose for the combination is Cabo 40mg/day and Ave 10mg/kg q2 weeks. Safety and efficacy data will be elaborated in the meeting. * NA & BLM: equal contribution Clinical trial information: NCT03200587. Research Sponsor: EMD Serono.

335 **Poster Session**

A framework for living evidence synthesis in cancer: Living, interactive network meta-analysis for first-line treatment of metastatic renal cell carcinoma (mRCC).

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Background: Systematic reviews are outdated quickly when the evidence is rapidly evolving as the process is laborious and there is little incentive for primary author team of an index SRMA to update the evidence. Consequently, there is an epidemic of redundant SRMAs performed by different teams—sometimes with conflicted results—for treatment of first line mRCC. **Methods:** We have created a living, interactive systematic review (LISR)and network meta-analysis(LINMA) for the treatment of first line mRCC using an Artificial intelligence (AI) assisted framework for evidence synthesis (Living, Interactive evidence synthesis framework) (LIvE). The framework is implemented in five-layered architecture (application layer, shared module layer, core service layer, middleware layer, and storage layer) which work together to automate the identification of new studies and analysis and semi-automate the screening and data extraction. Dynamic features such as interactive tables, figures and evidence maps are enabled using Python and JavaScript programming languages. **Results:** We have maintained a living, interactive evidence profile for the first line treatment mRCC since September 2019 (LIVING WEBSITE) . Living search strategy identifies new studies as they become available. As of October 13, 2020 LISR, includes data 14 clinical trials (PRISMA). Baseline characteristics are summarized in an interactive table (TABLE). Cabozantinib& Nivolumab (Cabo-Nivo) is the highest ranked drug for improving Overall Response (OR), Progression Free Survival (PFS) and Overall Survival (OS) whereas Ipilimumab in combination with Nivolumab (Ipi-Nivo) is highest ranked drug for achieving complete response (CR). Ipi-Nivo and Atezolizumab & Bevacizumab (Ate-Bev) ranked highest and Cabo-Nivo ranked lowest for treatment related Adverse events (TRAEs). Results of network meta-analysis are summarized as interactive tables and plots (NMA), summary of findings tables (MULTIPLE COMAPRISONS) and evidence maps (MAP). **Conclusions:** LISRs can potentially reduce redundancy, increase transparency, reproducibility, enable shared-decision making (at a guideline level, or in a patient-clinician dyad) and support living guidelines. Research Sponsor: None.

336 **Poster Session**

Exploring the synergistic effects of cabozantinib (cabo) and a programmed cell death protein 1 (PD1) inhibitor in metastatic renal cell carcinoma (mRCC) with artificial intelligence (AI).

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Background: Nonclinical and clinical data suggest that cabo with a PD1 inhibitor provides synergistic antitumor activity in patients with mRCC, possibly by a cabo-induced switch to an immunopermissive tumor microenvironment. We used a complementary, unbiased, AI approach to gain a holistic view of the complex interplay between multiple pathways, cells and molecules and identify the mechanisms that may underpin this synergism. **Methods:** Biological targets associated with mRCC pathophysiology or drug actions were identified from proteomic, genomic and transcriptomic databases and literature. Using systems- and AI-based technology, the data were integrated using machine learning into mathematical models of the human mRCC protein network topology. The combined effects of cabo and a PD1 inhibitor on biological targets were simulated assuming target receptors were fully activated or fully inhibited. Relevant effects on known cancer processes (e.g. angiogenesis, metastasis, cell proliferation, immune evasion) were identified using artificial neural networks. Biologically plausible synergistic mechanisms were described with sampling methods. **Results:** Inhibition of VEGF/VEGFR and GAS6/TAMR axes by cabo enhanced the known effects of PD1 inhibitors on immune evasion mechanisms by modulating multiple humoral and cellular components of the innate and adaptive immune responses (Table). PD1 inhibitors further enhanced the anti-angiogenic and tumor pro-apoptotic effects of cabo by modulating pro- and anti-angiogenic factors and T cell cytotoxicity. **Conclusions:** These data provide a mechanistic rationale and further support for the beneficial combination of cabo and a PD1 inhibitor and may guide future nonclinical and clinical research. Research Sponsor: Ipsen.

Cell type	Effectors	Effects
Tumour	↓ HIF1A, GAS6	↓ immune evasion
T	↑ IL-2, IFNG; ↓ IL-10, IL-6, SMAD3, EZH2, VEGF	Immunosurveillance, cytotoxicity
Myeloid-derived suppressor	↓ IL-10, IL-6, ARG1	↓ immune suppression
Dendritic	↑ IL-2 ↓ IL-10, IL-6, GAS6, ARG1	Maturation
Macrophages	↓ IL-10, IL-6, HIF1A, GAS6, EZH2, ARG1	M1 polarization
Natural killer	↑ IFNG; ↓ EZH2, IL-10	Cytotoxicity

337 **Poster Session**

First assessment of the stool mycobiome in patients (pts) with metastatic renal cell carcinoma (mRCC) receiving targeted therapy (TT) or immunotherapy (IO).

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Background: Previous studies have associated specific stool bacterial species with response to both targeted therapy and immunotherapy (Routy *et al* Science 2018; Dizman *et al* Cancer Med 2020). Abundant fungal elements also constitute the human microbiome (the so-called "mycobiome"); we explore whether these could be related to clinical benefit (CB) from TT. **Methods:** Pts from 2 simultaneously conducted studies were included in the analysis. Both studies enrolled patients with histologically confirmed RCC with metastatic disease; in one study, pts received standard of care (SOC) TT, while in the other pts received SOC IO. In both studies, stool was collected at baseline and at multiple timepoints thereafter. Whole metagenome sequencing was performed for fungal microbiome composition (TGen North, AZ). Linear discriminant analysis (LDA) effect size (LEfSe) was used for comparison of the gut mycobiome in patients who obtained clinical benefit (CB; complete response, partial response or stable disease $>$ 6mos) versus no clinical benefit (NCB; progressive disease or stable disease $\leq$6mos) from TT or IO. **Results:** A total of 50 samples from 24 pts (19:5 M:F) were included in the analysis. The majority of pts (19; 79%) had clear cell histology. 15 pts received TT while 9 pts received IO. The fungal genera demonstrating the highest abundance was *Saccharomyces* with a median relative abundance of 86.9% (range, 11%-99%). LEfSe performed in different taxonomic levels revealed *Malassezia globosa* (LDA = 4.93; P = 0.038) and *Alternaria infectoria* (LDA 4.94; P = 0.018) as gut mycobiome components associated with NCB, and order Russulales associated with CB from TT (LDA = 4.93; P = 0.018). In contrast, no association was identified between mycobiome profile and CB in the IO-treated group. The presence of several pathogenic fungi such as *Candida albicans* and *Aspergillus fumigatus* was noted in a minority of pts and did not have any bearing on clinical outcome. In pts with serial samples, a trend towards decreasing *Saccharomyces* spp. (the most abundant species) and increasing fungal diversity was noted. **Conclusions:** Our study is the first to highlight potential associations between the mycobiome and CB with TT. Our finding of *Malassezia* spp resulting in lack of CB with TT bolsters findings from Aykut *et al* (Nature 2019), implicating the same genera in progression of pancreatic cancer. Confirmation of these findings in larger series is underway. Research Sponsor: Institutional funds.

Plasma exosome microRNAs in patients with advanced renal cell carcinoma treated with nivolumab and ipilimumab: Potential biomarkers of response to therapy.

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Background: There is a critical unmet need for predictive biomarkers in the management of metastatic renal cell carcinoma (mRCC). We sought to quantify plasma exosome microRNAs (miRNAs) and correlate with response to first line nivolumab and ipilimumab (N/I) to potentially serve as such a biomarker. **Methods:** We evaluated the expression of 11 miRNAs in 19 patients with mRCC (prior to initiation of N/I) and in 32 healthy volunteers. Exosomes were extracted from 500 uL of plasma (qEV original, Izon Science) and once confirmed, were used for miRNAs extraction. MiRNAs expression was evaluated by real time polymerase chain reaction using a TaqMan miRNA assay (Applied Biosystems). The relative quantity of each miRNA in patients was compared to healthy volunteers. The expression of each miRNA was correlated to the best response to N/I, categorizing patients as either responders or non-responders. **Results:** Clinical characteristics are summarized in the table below. Median age at the start of systemic therapy was 64.3 years. MiR200b demonstrated a significantly higher expression in mRCC patients than in healthy volunteers (unpaired t-test; p=0.04). We observed a variable pattern of miRNA expression based on response to N/I. Although not statistically significant, 4 miRNA (miR138, 155, 200b, 221) were upregulated in non-responders, while two (miR200a and 497) were upregulated in responders. Of note, the only patient to achieve a complete response had the lowest expression of miR138 and the highest expression of miR497. **Conclusions:** Although preliminary and limited by a small number of patients, these initial observational results are promising and suggest a potential role for miRNAs as predictive biomarkers in mRCC. MiR138 and 497 are known to regulate CTLA-4 and PD-L1, respectively. We speculate that these miRNA are potentially involved in response to immune checkpoint therapy. Ongoing work in evaluating expression of these and other miRNAs in blood and in tissue along with clinical correlation continues. Research Sponsor: Genitourinary Medical Oncologists of Canada (GUMOC) fellows research grant, Kidney Cancer Research Network of Canada-Kidney Cancer Canada-Canadian Urologic Association Scholarship Foundation (KCRNC-KCC-CUASF) Research Grant.

Baseline characteristics of the mRCC cohort.

Characteristic (N=19)	Number of patients (%)
IMDC risk stratification	
Favourable	2 (10.5)
Intermediate	9 (47.4)
Poor	8 (42.1)
Underwent nephrectomy	13 (68.4)
Pathologic subtype	
Clear cell	15 (78.9)
Papillary	1(5.3)
Other	3 (15.8)
Sites of metastases	
Pulmonary	16 (84.2)
Lymph nodes 13 (68.4)	
Bone	11 (57.9)
Liver	4 (21.1)
Muscle	3 (15.8)
Best response to therapy	
Complete response	1 (5.3)
Partial response	12 (63.2)
Stable disease	1 (5.3)
Progressive disease	5 (26.3)

339 **Poster Session**

The very favorable metastatic renal cell carcinoma (mRCC) risk group: Data from the International Metastatic RCC Database Consortium (IMDC).

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Background: The IMDC criteria have been used as a prognostic tool for patients with mRCC receiving single agent VEGF-targeted drugs, and more recently combination immuno-oncology (IO) +/- VEGF-targeted agents, which improve outcomes over VEGF TKI monotherapy. We sought to identify a subset of patients with very favorable outcomes, for which less intensive therapy might be considered. **Methods:** Utilizing the IMDC dataset, 1638 patients with IMDC favorable risk disease received first-line systemic therapy. Patients were randomly selected in a 2:1 ratio to the training and testing sets, stratified by year of systemic therapy initiation. Multivariable Cox regression estimated prognostic factors for overall survival (OS). **Results:** Median age was 63 (range 21-95) years and 98% had received prior nephrectomy. First-line systemic therapy consisted of targeted therapy (91%), IO-combination regimens (8%), or other (1%). From the training data, three variables (primary diagnosis to systemic therapy <3 vs ≥ 3yr; Karnofsky Performance Status 80 vs >80; presence of brain, liver, or bone metastasis) significantly predicted for OS in the multivariable model (hazard ratio 1.4~1.5, p-values<0.05). The model had similar performance in the test dataset (C-index=0.64). Using the 3 included risk factors, patients were classified to very favorable risk (0 risk factors, 29% of patients) or favorable risk disease (≥ 1 risk factors, 71% of patients). Clinical outcomes for the two risk groups are presented in the table below. **Conclusions:** We identified a very favorable risk group in the IMDC criteria in RCC patients treated with first-line therapy. External validation including populations receiving IO containing therapies is ongoing. Research Sponsor: None.

	Very Favorable (n=454)	Favorable (n=1091)	Hazard Ratio (Favorable vs. Very Favorable) p-value
Median OS, months (95% CI)	64.8 (58.8 - 70.8)	45.6 (42.0 - 50.4)	1.84 (1.56 - 2.20) <0.001
Median time to treatment failure, months (95% CI)	16.3 (14.8 - 18.2)	12.0 (11.2 - 12.9)	1.31 (1.16 -1.48) <0.001

340 **Poster Session**

A dual drug therapy for sunitinib resistant RCC: An in vitro analysis.

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Background: Over the last decade, medical treatment for metastatic renal cell carcinoma has made significant advances through the development of tyrosine kinase inhibitors (TKI) like sunitinib. However, of patients initiated on TKI therapy, 70% respond well while 30% are believed to be primarily resistant to treatment. Additionally, 30% of patients who initially respond to treatment gain secondary drug resistance and present with increased tumor burden. In this study, we seek to develop a combination therapy of Tipifarnib + Sunitinib to target exosome conferred drug resistance. **Methods:** 786-0, 786-0 Sunitinib Resistant (SR), and 293-T cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, 2mM L-glutamine, and 1% penicillin/streptomycin (P/S). Exosomes were collected from conditioned media treated with Tipifarnib and isolated using differential ultracentrifugation. Exosomes were analyzed using the qNano IZON system. Colony forming units assay and Immunoblot analysis were used to further characterize or samples. **Results:** Exosomes collected from 786-0, 786-0 SR, and 293-T cells treated with 0.5 uM of Tipifarnib were compared using our qNANO IZON system. Exosome concentrations of all cell lines showed a decrease after Tipifarnib treatment. However, our 293-T cells showed a 16% decrease in exosome concentration while our 786-0 and 786-0 SR lines displayed a 66% and 75% decrease respectively. To assess the pathway Tipifarnib used to decrease exosome concentrations, immunoblot assay was used after treating cells with 0, 0.1, 0.25, 0.5, 1 uM of tipifarnib. 293-T cells showed a dose dependent increase in ESCRT-dependent marker Alix and no change in either ESCRT-independent marker nSMase or trafficking marker Rab27a. Conversely, our 786-0 and 786-0 SR cell lines showed a decrease in all 3 markers: Alix, nSMase, and Rab27a. Furthermore, a colony forming units assay was used to assess the drug combination of tipifarnib + sunitinib ability to alter cell growth. After 48hr, 293-T cell showed no decrease in colony forming units when compared to DMSO control. Our drug combination showed a synergistic ability to decrease colony forming units in the RCC 786-0 cell line. 786-0 SR cells were resistant to sunitinib treatment, showing comparable CFUs to DMSO control. When treated with the combination of sunitinib and tipifarnib, CTUs of 786-0 SR cells dropped significantly when compared to unaccompanied sunitinib and tipifarnib treatments. **Conclusions:** Tipifarnib has the ability to attenuate both the exosome ESCRT–dependent and –independent pathways. Our study also showed that when used injunction with sunitinib, tipifarnib is effective at decreasing cell proliferation. This drug combination is also pre-clinically useful in sunitinib resistance cancer cells. We believe this drug combination to be efficacious at decreasing tumor burden through blocking exosome biogenesis and secretion. Research Sponsor: None.

341 **Poster Session**

Association of the neutrophil to eosinophil ratio with response to immunotherapy-based combinations in metastatic renal cell carcinoma.

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Background: Neutrophilia is known to be associated with worse prognosis in metastatic renal cell carcinoma (mRCC); however, less is known about the role of eosinophils in the response to immunotherapy (IO). We investigated the association of the baseline neutrophil to eosinophil ratio (NER) with outcomes to IO-based combination treatment in mRCC. **Methods:** Patients with mRCC treated with ipilimumab plus nivolumab, pembrolizumab plus axitinib, or avelumab plus axitinib at the Vanderbilt-Ingram Cancer Center were retrospectively identified. Patients on >10mg prednisone and patients with prior IO were excluded. Baseline NER (at time of first IO) and association with progression free survival (PFS), overall survival (OS), and objective response rate (ORR) were investigated. Data cutoff was 9/1/2020. Analysis for PFS and OS was performed using the log-rank test and Mantel-Haenszel method, and analysis of the odds ratio for ORR was performed using Fischer's exact test. **Results:** Sixty-one patients were identified: 89% clear cell histology, 74% prior nephrectomy, 69% IMDC intermediate risk, and 72% treatment-naïve. Patients with baseline NER < median (N=31) had improved clinical outcomes compared to patients with baseline NER > median (N=30) (Table). Improvement in PFS by NER was maintained when stratified by anti-PD-1/CTLA-4 and anti-PD(L)-1/VEGF (p= 0.0062 and p= 0.049); however, differences in OS and ORR were no longer significant. The median baseline NER among patients with partial response (PR) was significantly lower at 22.7 (95% CI 18.9-31.1) vs. 51.6 (95% CI 39.5-93.1) among those with progressive disease (PD) (p= 0.0054). For comparison, the median neutrophil to lymphocyte ratio was not significantly different between PR (2.60) and PD (3.84, p= 0.056). **Conclusions:** Patients with a low baseline NER treated with IO-based combinations had improved clinical outcomes compared to patients with a high baseline NER. Additional investigation of this parameter in larger cohorts is warranted. Research Sponsor: None.

Clinical outcomes according to median neutrophil to eosinophil ratio (NER).

All Patients (N= 61)	**NER < median (N= 31)**	**NER > median (N= 30)**	
Median PFS	17.9 months	3.2 months	HR 0.32 (95% CI: 0.17- 0.62); p= 0.0007
Median OS	Not reached	27.3 months	HR 0.27 (95% CI: 0.11- 0.70); p= 0.0070
ORR	52%	20%	OR 4.27 (95% CI: 1.45-14.38); p=0.0159
Treatment			
Ipi+Nivo	58% (18)	67% (20)	
Pembro+Axi	29% (9)	23% (7)	
Avel+Axi	13% (4)	10% (3)	
IMDC Risk Category			
Favorable	29% (9)	10% (3)	
Intermediate	68% (21)	70% (21)	
Poor	3% (1)	20% (6)	
Ipi+Nivo Only (N= 38)	**NER < median (N= 18)**	**NER > median (N= 20)**	
Median PFS	8.5 months	2.6 months	HR 0.34 (95% CI: 0.16- 0.74); p= 0.0062
IO/VEGF Only (N= 23)	**NER < median (N= 13)**	**NER > median (N= 10)**	
Median PFS	26.7 months	12.8 months	HR 0.29 (95% CI: 0.08- 0.99); p= 0.0493

Analysis of plasma KIM-1 as a biomarker for recurrence risk after resection for localized renal cell carcinoma.

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Background: Recurrence is common after nephrectomy for renal cell carcinoma (RCC), but no circulating biomarkers are available to identify patients at highest risk of recurrence who may benefit from adjuvant therapy. Kidney injury molecule-1 (KIM-1) is overexpressed in RCC and its ectodomain circulates in plasma. We investigated whether plasma KIM-1 is a prognostic biomarker in patients with localized RCC after nephrectomy. **Methods:** Banked plasma samples were analyzed from the ECOG-ACRIN 2805 (ASSURE) trial evaluating adjuvant sunitinib, sorafenib, and placebo in resected high-risk RCC. KIM-1 levels were measured at trial enrollment 4-12 weeks post-nephrectomy (baseline) and on cycle 2 day 1 (C2D1) using a previously validated microbead assay. A lognormal accelerated failure time model was used to test for association between circulating KIM-1 and disease-free survival (DFS). **Results:** Plasma samples from 418 patients were analyzed. In univariable and multivariable analyses, higher post-nephrectomy KIM-1 was associated with worse DFS across all study arms. This association remained independently significant after adjustment for Fuhrman grade, T-stage, N-stage, and tumor histology (survival time ratio 0.56 for 75^{th} vs 25^{th} percentile of KIM-1, 95% CI 0.42-0.73, $p < 0.001$). The association between KIM-1 and DFS was stronger among patients with pathologic nodal involvement. The addition of baseline KIM-1 improved the concordance of both the SSIGN and UISS prognostic models (SSIGN concordance 0.57 vs 0.43, p = 0.05; UISS concordance 0.60 vs 0.40, p = 0.0005). C2D1 KIM-1 was not an independent predictor for DFS after adjusting for baseline KIM-1. **Conclusions:** Elevated plasma KIM-1 level at post-nephrectomy baseline is associated with worse DFS in RCC. This is consistent with the hypothesis that post-nephrectomy plasma KIM-1 may be a biomarker for microscopic residual disease. The model was additionally adjusted for papillary and chromophobe histology, sex, and ECOG performance status. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

Multivariable lognormal accelerated failure time model of KIM-1 and DFS.

		Survival Time Ratio	95% CI
KIM-1	25^{th} percentile vs 75^{th} percentile	0.56	(0.42, 0.73)
N-stage	N1/N2 vs. N0/NX	0.41	(0.21, 0.80)
Fuhrman grade	4 vs < 4	0.34	(0.21, 0.54)
T-stage	1 vs. 3	2.01	(1.14, 3.55)
	2 vs. 3	1.51	(1.01, 2.26)
	4 vs. 3	1.79	(0.46, 6.98)
Sarcomatoid features	Present vs. absent	0.76	(0.43, 1.34)

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Angiogenic and T-effector subgroups identified by gene expression profiling (GEP) and propensity for PBRM1 and BAP1 alterations in clear cell renal cell carcinoma (ccRCC).

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Background: With the emergence of multiple active treatment options in RCC, predictive biomarkers for optimal treatment selection are lacking. Gene expression data from IMmotion151 and Javelin Renal 101 clinical trials generated anti-angiogenic and immune signatures that warrant further validation. We aimed to describe the genomic and gene expression profiles in a multi-institutional database of patients with ccRCC, and its association with other biomarkers of interest. **Methods:** Whole transcriptome sequencing was performed for ccRCC patient samples submitted to a commercial CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ) from February 2019 to September 2020. Tumor GEP and hierarchical clustering based on the validated 66-gene signature (D'Costa et al, 2020) were used to identify patient subgroups. Samples from both primary tumors and metastatic sites were included. **Results:** A total of 316 patients with ccRCC, median age 62 (range 32-90), 71.8% men, were included. Tissue samples were obtained from primary tumor (46.5%), lung (12.3%), bone (9.5%), liver (4.7%) and other metastatic sites (27%). Gene expression analysis identified angiogenic, mixed and T-effector subgroups in 24.1%, 51.3% and 24.7%, respectively. Patients with angiogenic subgroup tumors compared to those with T-effector subgroup tumors were more likely to be older (63 versus 60 years, p=0.035), female (40.8% versus 16.7%, p=0.0009) and more frequently found in pancreatic/small bowel metastases (75% versus 12.5%, p=0.0103). Biomarkers of potential response to immunotherapy such as PD-L1 (p=0.0021), TMB (not significant), and dMMR/MSI-H status (not significant) were more frequent in the T-effector subgroup. PBRM1 mutations were more common in the angiogenic subgroup (62.0% vs 37.5%, p=0.0034) while BAP1 mutations were more common in the T-effector subgroup (18.6% versus 3.0%, p= 0.0035). Immune cell population abundance (e.g. NK cells, monocytes) and immune checkpoint gene expression (TIM-3, PD-L1, PD-L2, CTLA4) were also increased in the T-effector subgroup. **Conclusions:** Our hierarchical clustering results based on the 66-gene expression signature were concordant with results from prior studies. Patient subgroups identified by evaluation of angiogenic and T-effector signature scores exhibit significantly different mutations and immune profiles. These findings require prospective validation in future biomarker-selected clinical trials. Research Sponsor: None.

Change in neutrophil to lymphocyte ratio (NLR) as a predictor of treatment failure in renal cell carcinoma patients: Analysis of the IROC (Investigating RCC Outcomes) cohort.

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Background: IROC is an expanding multi-institution collaborative database which includes socio-economic, genomic, pathologic, clinical and laboratory data in metastatic RCC patients (pts), primarily in the modern setting. Elevated baseline NLR is now an established poor prognostic factor in renal cell carcinoma (RCC) but currently has limited practical use. We hypothesized that an increase in NLR of 3 or more (NLR Failure) at 2 months on therapy could be a predictor of eventual treatment failure and shorter overall survival and thus augment the utility of this marker. **Methods:** Patients with complete data on NLR at time = 0 and +2 months of therapy were analyzed. Information on comorbidities, previous therapy, demographics were collected for adjusted analysis. NLR failure was defined as an increase of 3 or more compared to baseline NLR. Cox proportional hazard models were used to analyze the risk of progression and death with NLR failure at 2 months (+/- 2 weeks). Kaplan Meier graphs were constructed to trace survival functions for PFS and OS by NLR. **Results:** Among 165 pts; 121 were eligible (Table). NLR failure at 2 months was associated with a highly statistically significant increase in the risk of death in $<$ 1 year (HR 6.82, 95% CI [3.16-14.70], p$<$0.001). In a model adjusted for NLR change, the value of baseline NLR to predict OS $<$1 year was non-significant (HR 1.02, p = 0.65). Similarly, NLR failure increased the risk of treatment failure in less than 6 months (HR 4.83 95% CI [2.29-10.19], p$<$0.001), while baseline NLR did not predict it (HR 1.03, p = 0.34). These findings were unaffected by immunotherapy vs TKI therapy. NLR failure at 2 months had a 78% (11/14) positive predictive value for survival $<$1 year and 86% (12/14) [p=.0001] for treatment failure in 6 months. **Conclusions:** In this multi-institutional cohort of RCC pts; an increase in NLR of 3 or more at 2 months following therapy start predicts for an increasing risk of death and impending treatment failure with a high PPV. The prognostic value of baseline NLR is non-significant when adjusting for NLR change. NLR failure should be validated in prospective studies and could have clinical utility in management of RCC pts. Research Sponsor: None.

Baseline characteristics.

Sex		N	%
	Male	98	81
	Female	23	19
Race			
	Caucasian	89	73
	African American	15	12
	Others	17	15
Pathology			
	Clear Cell	92	81
	Papillary	8	7
	Chromophobe	1	1
	Medullary	2	2
	Xp11 translocation	2	2
	Unclassified and others	8	7
Treatment			
	I/O combination therapy	32	27
	I/O monotherapy	44	36
	TKI monotherapy	30	25
	Other	15	12

345 **Poster Session**

Absolute eosinophil count as predictive biomarker of irAEs in patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICIs).

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Background: Nivolumab and ipilimumab are associated with immune-related adverse events (irAEs) and, to date, few biomarkers predictive of ICIs toxicity are reported in mRCC. **Methods:** We conducted a single-center, observational, retrospective study at Clinical Oncology Unit, Careggi University Hospital, Florence, Italy. We evaluated 43 patients (pts) with mRCC treated with ICIs from April 2013 to May 2020. Absolute Eosinophil Counts (AEC, N°/μL) were registered at baseline and at time of occurrence of irAEs. This study aims to evaluate whether the AEC could be a predictive biomarker of irAEs in patients with mRCC treated with ICIs. **Results:** Median age was 65 years and males were 81.4%. 10 pts received Nivolumab+Ipilimumab, while 33 pts received Nivolumab single agent. 74.4% pts (32/43) developed at least 1 irAE, 11.6% with G3-G4 irAEs. The most frequent first irAE was endocrine event (40.6% pts; 37.5% with hypo-/hyper-thyroidism). The baseline mean AEC was 163.1/μL in our cohort, in particular 132.2/μL in pts who did not develop irAEs and 176.7/μL in pts who developed irAEs (p=0.134). Among the pts who developed irAEs, the mean AEC was lower in pts with G1-G2 (153.1/μL) than in those with G3-G4 (330/μL; p=0.0013) irAEs. At the time of onset of the first irAE, the mean AEC increased to 247/μL (Δ 140.1%). Analyzing the trend of AEC from baseline to time of occurrence of irAE for the 32 pts who had developed at least one irAE, 53.1% (17 pts) showed an increasing trend; among these pts, the most frequent irAEs were endocrine occurring in 4/17 pts (23.6%). An increasing trend was also observed in the majority of pts who developed G1-2 (14/27, 51.9%) and G3-4 (3/5, 60.0%) irAEs. Additional analyzes are ongoing to identify appropriate cut-offs of AEC to better stratify patients. **Conclusions:** There is little evidence in the literature about the potential role of absolute eosinophil counts as a predictive biomarker of irAEs in patients with solid tumors treated with ICIs, and most refer to patients with melanoma. In this study we observed that the baseline AEC values in patients that will develop irAEs are higher than in those without irAEs and, among the former, the values are lower for patients with toxicity G1-G2 vs G3-G4. We also found an increase of the mean AEC from baseline to the onset of the first irAE. Of the patients who experience toxicity, most have an upward trend in AEC at the onset of the first irAE. Compatibly with all the limitations of a retrospective analysis, our is the first experience exploring the role of the eosinophil count in the development of irAEs in mRCC patients treated with ICIs, and a prospective study is ongoing in our Unit to confirm the role of the eosinophil count in patients treated with ICIs. Research Sponsor: None.

346 **Poster Session**

DNA damage repair (DDR) pathway alteration in advanced renal cell carcinoma (RCC) is association with good progression-free survival with tyrosine kinase inhibitor (TKI) therapy.

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Background: Alterations in DNA damage repair (DDR) genes are associated with human tumorigenesis and may be as potential biomarkers for vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) therapy in renal cell carcinoma. However, biologic significance and relevance to TKI targeted therapy in metastatic RCC are unknown. **Methods:** Genomic data and treatment outcomes were retrospectively collected for patients with metastatic RCC. Tumor and germline DNA were subject to targeted next generation sequencing across 642 genes of interest, including 60 DDR genes. Patients were dichotomized according to underlying DDR gene alteration into (1) DDR gene alterations present (Mut DDR); (2) wildtype (WT) DDR gene alterations present (WT DDR). Association between DDR status and therapeutic benefit was investigated separately for and vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) therapy. **Results:** Mut DDR were detected in 17/40 patients (42.5%). The most frequently DDR altered genes were TP53. For patients with TKI treatment, Mut DDR status was associated with superior progression free survival (log-rank p = 0.048), but not with superior overall survival (log-rank p = 0.39); after adjusting for International Metastatic Renal Cell Carcinoma Database Consortium risks and extent of prior therapy, the HR for Mut DDR was 2.68 (95% CI: 0.96–7.46; p = 0.059). **Conclusions:** DDR alterations are recurrent genomic events in patients with advanced RCC and were mostly clonal in this cohort. Dysfunction events in these genes may affect outcome with TKI therapy in adanced RCC, and these hypothesis-generating results deserve further study. Research Sponsor: None.

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Illustration of temporal evolution in patients with metastatic renal cell carcinoma (mRCC) using both circulating tumor DNA (ctDNA) and tissue-based genomic data.

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Background: We have previously demonstrated the feasibility of ctDNA assessment in mRCC and preliminarily showed agreement between ctDNA and tissue-based genomic findings (Zengin *et al* ESMO 2020). Our data suggested that the degree of agreement is dependent upon the temporal separation of blood and tissue samples. We sought to further explore this temporal impact in a separate validation cohort. **Methods:** Patients (pts) with mRCC who underwent ctDNA genomic profiling were identified. ctDNA analysis was performed using a CLIA-certified 73-74 gene panel (Guardant360). From this cohort we identified a subset of pts who also underwent tissue-based genomic profiling using either a whole exome sequencing platform (GemExtra [TGen, Phoenix, AZ]) or a targeted next generation sequencing platform (Foundation Medicine [Cambridge, MA] or Tempus [Chicago, IL]). Only alterations covered by both assays were included for the current analysis. The difference in the proportion of alterations detected on tissue and ctDNA was compared between these cohorts and at a 6-mo landmark using the χ^2 test. **Results:** In total, ctDNA and tissue based genomic profiling was assessed in 112 pts (M:F, 81:31); with most common histology was clear cell (85.7%). Median time between ctDNA and tissue assessments was 9.8 months (IQR 1.15-23.7). When examining paired samples in which $>$1 ctDNA alteration was detected, 32% (43/133) of alterations detected on tissue were also detected in ctDNA. This proportion increased to 43% (29/67) when samples collected within 6 months of each other, and was 51% (28/55) in samples collected within 3 months of each other. There was no significant difference in the frequency of shared mutations between the cohorts (P=0.09; Table). **Conclusions:** Our study confirms that ctDNA and tissue-based genomic profiling continue to provide consistently high levels of agreement. Notably, the percentage of samples with $\geq$1 ctDNA alteration detected was significantly lower in both cohorts compared to previous studies in RCC. More shared alterations were found on ctDNA when both ctDNA and tissue-based assessment were obtained at closer intervals. Research Sponsor: None.

Percentage of alterations detected on tissue also detected on ctDNA.

	Time between ctDNA and tissue assessment		
	≤ 6 mos	>6 mos	Overall
Discovery cohort (n=27)	79% P = 0.003	31%	46%
Validation cohort (n=44)	34% P=0.02	12%	25%
Combined (n=71)	43% P=0.007	21%	32%

Prognostic biomarkers of systemic inflammation in patients on active surveillance for metastatic renal cell carcinoma (mRCC): A biobank analysis.

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Background: A subset of patients with metastatic renal cell carcinoma (mRCC) follow an indolent disease course. Given the toxicity and non-curative nature associated with systemic anti-cancer therapy (SACT), some patients may benefit from initial active surveillance (AS). However, selecting patients suitable for this approach is challenging. Biomarkers of systemic inflammation predict survival in mRCC, both independently and as part of the International Metastatic Database Consortium (IMDC) risk score. We sought to use these biomarkers to characterise the time to initiation of SACT (tSACT) in mRCC patients on AS. **Methods:** 126 mRCC patients clinically assessed and commenced on AS prior to any systemic therapy were retrospectively identified from a regional mRCC clinical database. Patients who underwent metastasectomy for oligometastatic disease at any time were excluded. The primary endpoint, tSACT, was defined as the time from radiological diagnosis of mRCC until SACT initiation, or death, or censorship if continuing AS at follow-up date. Inflammatory biomarkers from routine blood tests (haemoglobin, white cell count, neutrophil count, platelets, C-reactive protein (CRP), albumin) and the IMDC score, measured at the time of diagnosis of mRCC, were recorded. The relationship between these and tSACT was examined using Kaplan-Meier and Cox-regression methods. **Results:** 66 (52%) patients had commenced SACT. 17 (13.5%) had died without commencing SACT (median survival of the 17 was 40.4 months, range 9.1-130.2 months, and comorbidities may have affected fitness for starting therapy or led to all-cause mortality). 43 patients remained on AS, with minimum and median follow-up of 12.6 months and 39.6 months respectively. The median tSACT was 17.2 months (IQR 8.8-34.8 months). On univariate analysis, CRP and albumin were predictive of time on AS (p= 0.01 and p= 0.049 respectively). On multivariate analysis, only CRP was independently associated with tSACT (p= 0.035), stratifying tSACT from 9.1 months (CRP $>$ 10) to 20.9 months (CRP$\leq$10) (p= 0.009). 111 (88.1%) patients were IMDC 0-1, while 12 (9.5%) and 3 (2.4%) were IMDC 2 or 3 and may have had comorbidities that influenced the initial AS decision. In our cohort the IMDC risk score did not predict time on AS. **Conclusions:** These results highlight that some patients with mRCC may undergo active surveillance for a marked time period before SACT initiation. We identify routine biomarkers of the systemic inflammatory response that predict time to systemic therapy. In particular CRP, a simple measure of inflammation, stratifies the time to initiation of SACT across a clinically significant time period. This simple, widely available test may help to objectively inform clinical decisions about AS in patients in mRCC. Additional experience is necessary to further define the risks and benefits of this approach. Research Sponsor: None.

349 Poster Session and Poster Highlights Session; Displayed in Poster Session

Sarcomatoid (srcRCC) versus clear cell (ccRCC) renal cell carcinoma: A comparative comprehensive genomic profiling (CGP) study.

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Background: srcRCC is a well-described histologic entity often featuring rapid progression and aggressive clinical course when compared with classic ccRCC. We queried whether CGP would uncover opportunities for targeted and immunotherapy (IO) for srcRCC patients that could individualize their treatment and entry into clinical trials. **Methods:** Using a hybrid capture-based CGP assay to evaluate all classes of genomic alterations (GA), 160 cases of srcRCC and 1,664 cases of ccRCC were sequenced from FFPE tissue samples. Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on up to 114 loci. PD-L1 expression was determined by IHC (Dako 22C3) with low tumor cell positive staining set at 1-49% and high staining >50% expression. **Results:** Gender and age distributions for both tumor types were similar. srcRCC featured significantly higher GA/tumor than ccRCC ($P < .0001$). CGP revealed major differences with ccRCC associated more frequently with tumor suppressor gene (TSG) losses in *VHL*, *PBRM1*, *TSC2* and *SETD2* (all $P < .0001$). In contrast, srcRCC is associated with cell proliferation with increased inactivation of cell cycle regulatory genes including *TP53*, *CDKN2A/B*, *MDM2* and *TERT* (all $P < .0001$). *RB1* GA in srcRCC may reflect neuroendocrine differentiation occasionally found in these tumors. *NF2* GA were more frequent in srcRCC ($P < .0001$). **Conclusions:** CGP reveals striking differences between srcRCC and ccRCC which may in part explain the differing histologic appearances and typical clinical course of these 2 aggressive malignancies. ccRCC is driven more by TSG loss and srcRCC is driven more by cell cycle dysregulation. Targeted therapy opportunities were uncommon for both tumor types although each featured biomarkers potentially predictive of mTOR inhibitor responses (*TSC2* in ccRCC and *NF2* in srcRCC). Although the higher *PBRM1* GA frequency in ccRCC may explain the IO benefit well-known for this tumor type, the srcRCC group features significantly increased TMB, *CD274* amplification and PD-L1 staining which may also create IO opportunities for srcRCC patients. Research Sponsor: Foundation Medicine Inc.

	ccRCC	srcRCC	Significance
Number of Cases	1,664	160	
Females	30%	33%	NS
Males	70%	67%	
Median age (range)	60 (15-90+)	60 (16-90+)	NS
GA/tumor	3.5	4.6	< .0001
TP53	13%	38%	< .0001
VHL	76%	41%	< .0001
BAP1	15%	14%	NS
PBRM1	44%	10%	< .0001
SETD2	26%	11%	< .0001
CDKN2A	13%	41%	< .0001
CDKN2B	11%	32%	< .0001
ARID1A	4%	3%	NS
PTEN	12%	12%	NS
NF2	3%	18%	< .0001
TSC1	7%	2%	< .0001
PIK3CA	5%	2%	NS
SMARCB1	1%	4%	P = .01
TERT	8%	20%	< .0001
RB1	1%	8%	< .0001
MDM2	1%	5%	P = .001
CD274	1%	6%	< .0001
MSI-High	0%	1%	NS
Median TMB	2.5	3.5	
Mean TMB	2.9	3.8	P = .009
TMB > 10 mut/Mb	1%	3%	P = .04
TMB > 20 mut/Mb	0%	1%	NS
PD-L1 IHC Low (1-49%)	24% (411 cases)	17% (24 cases)	NS
PD-L1 High (> 50%)	4%	38%	P < .0001

350 **Poster Session**

Prognostic value of simple blood biomarkers of systemic inflammation for metastatic renal cell carcinoma (mRCC) patients who undergo cytoreductive nephrectomy (CNx).

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Background: The role of cytoreductive nephrectomy (CNx) in patients with metastatic renal cell carcinoma (mRCC) is currently in question. Assessing the benefits and risks of CNx is challenging, with a lack of validated prognostic tools. Biomarkers of the systemic inflammatory response have prognostic utility in mRCC and are included in the IMDC score used to predict survival in patients with mRCC treated with systemic therapy. We sought to investigate their role in patients with mRCC who had undergone CNx. **Methods:** A cohort of 68 patients, suitable for first-line VEGFR inhibitor (VEGFRi) systemic therapy, who had undergone CNx for mRCC, were identified from a clinical database of patients referred to a regional mRCC service. Inflammatory biomarkers from routine blood tests (haemoglobin, white cell count, neutrophil count, platelets, C-reactive protein (CRP), albumin) and the IMDC score, measured at the time of diagnosis of mRCC, were recorded. The relationship between these and overall survival and time to VEGFRi (tVEGFRi) was examined using Kaplan-Meier and Cox-regression methods. **Results:** Data were available for 68 patients. Median survival was 33.7 months. On multivariate analysis, albumin ($<$ 35g g/dL v $\geq$35 g/dL) and CRP ($\leq$ 10 mg/L v $>$ 10 mg/L) were independently associated with overall survival (p = 0.027 and p = 0.034 respectively). Albumin stratified survival from 24.7 to 87.2 months ($p < 0.0001$) and CRP from 29.4 to 82.3 months (p = 0.004). 40 (59%) patients subsequently commenced VEGFRi therapy. Median tVEGFRi was 18.1 months, with only 5 (7%) patients commencing treatment within 3 months. 16 (24%) patients yet to receive systemic therapy remain alive after a median 54.0 months follow-up. On multivariate analysis, albumin was also predictive of tVEGFRi (p = 0.037), stratifying tVEGFRi from 6.07 to 45.7 months (p = 0.002). **Conclusions:** These results highlight that biomarkers of the systemic inflammatory response are strong prognostic factors in mRCC patients who have undergone CNx. Albumin and CRP, but not IMDC, predict survival in this patient group. Significantly, the population investigated here differ from those included in the CARMENA and SURTIME studies, with a majority undergoing surveillance prior to VEGFRi therapy. Our results support a role for CNx in patients where deferred systemic therapy strategies may be employed. Albumin may assist in clinical decision making when considering when to start systemic therapy. We advocate further studies to investigate the prognostic role of these simple, routine clinical tests in patients with mRCC undergoing CNx. Research Sponsor: None.

351 **Poster Session**

Associations between plasma cytokine levels and gut microbiota composition in metastatic renal cell carcinoma (mRCC).

Alex Chehrazi-Raffle, Nazli Dizman, Paulo Gustavo Bergerot, Misagh Karimi, Joann Hsu, John D Gillece, Megan Folkerts, Lauren J Reining, Sarah K Highlander, Sumanta K. Pal; City of Hope National Medical Center, Duarte, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; City Of Hope Medical Grp, La Verne, CA; Translational Genomics Research Institute, Flagstaff, AZ; Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Plasma cytokines and the gut microbiome have been shown separately to influence the response to systemic therapy in mRCC. We sought associations between serum cytokines and gut microbial composition in patients (pts) with mRCC. **Methods:** Eligibility requirements included histologically proven mRCC and an intent to receive either vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) or immune checkpoint inhibitor (ICI). Blood samples were collected prior to treatment initiation and immunologic profiles were evaluated using a Human Cytokine 30-plex protein assay (Invitrogen). Stool was collected at baseline and shotgun metagenomic sequencing was performed to quantify gut microbial populations using previously published methods (Salgia *et al* Eur Urol 2020). **Results:** A total of 50 pts were studied (36:14 M:F) with a median age of 67 (range, 32-85). Twenty pts and 30 pts had subsequent initiation of VEGF-TKI and ICI therapy, respectively. Levels of *Akkermansia* spp were significantly higher in pts who were IL-6 low (P = 0.023). In contrast, pts who were IL-6 high had higher levels of enteric pathogens, including *Salmonella* spp and *Enterococcus* spp. Both *Akkermansia* spp and *Bacteroides* spp levels were higher in pts who were IL-8 low. Associations between cytokine levels, microbiome composition, and treatment response will be presented. **Conclusions:** Given studies suggesting the role of *Akkermansia* spp in enhancing ICI response (Routy *et al* Science 2018), our data provide a critical link between the gut microbiome and systemic immunomodulation. Research Sponsor: None.

Distinct cytokines predict response to immunotherapy and targeted therapy in metastatic renal cell carcinoma (mRCC).

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Background: Previous studies have suggested a link between plasma cytokines and mRCC outcomes with systemic therapy. In a prospective study, we assessed whether plasma cytokines could separately predict outcome with immunotherapy or targeted therapy. **Methods:** Eligible patients (pts) had histologically proven mRCC with intent to receive a vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) or an immune checkpoint inhibitor (ICI). Immunologic profiles were evaluated at several time points using a Human Cytokine 30-plex protein assay (Invitrogen). Clinical benefit (CB) was defined as complete response, partial response, or stable disease $\geq$ 6 months. **Results:** A total of 56 pts (40:16 M:F) were enrolled; 23 pts and 33 pts received VEGF-TKI and ICI, respectively. The most common VEGF-TKI was cabozantinib; the most common ICI was nivolumab. CB was similar between VEGF-TKI and ICI arms (65% vs 54%). Pts with CB from VEGF-TKIs had lower pretreatment levels of IL-6 ($p = 0.02$), IL-1RA ($p = 0.03$), and G-CSF ($p = 0.02$). Major shifts in plasma cytokines were seen as early as one month; these data will be presented. **Conclusions:** Distinct plasma cytokines predict benefit with VEGF-TKIs and ICIs. Ongoing work will incorporate analysis of pts receiving VEGF-TKI and ICI combination therapy. Research Sponsor: None.

353 Poster Session and Poster Highlights Session; Displayed in Poster Session

Therapy-relevant gene signatures in the high risk localized renal cell carcinoma setting: Transcriptomic data from patients receiving placebo on a randomized phase III trial (PROTECT).

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Background: Transcriptomic profiling of the renal cell carcinoma (RCC) tumor microenvironment (TME) has revealed gene signatures predictive of response to therapies in the metastatic setting. High expression of angiogenesis genes correlate with responses to tyrosine kinase inhibitors. Adenosine in the TME exerts immunosuppressive effects that can facilitate tumor growth. Adenosinergic agonism has revealed gene signatures, comprised of inflammatory myeloid mediators, that correlated with response to adenosine pathway inhibition on a previously reported cohort of patients. Given these promising data from the metastatic space, we sought to interrogate prognostic gene expression in the TME from patients with localized disease. **Methods:** Clinicopathologic and whole-gene microarray data were acquired from 202 patients in the placebo arm of the PROTECT trial (NCT01235962). Transcriptomic scores assessing angiogenesis and adenosine signaling with individual annotations above/below median categorized patients into four groups (angiogenesis high vs. low; adenosine high vs. low). Categorical association with disease free (DFS) and overall survival (OS) was tested with logrank testing and assessed interdependence with the UCLA Integrated Staging System (UISS) in a cox regression model. **Results:** Overall, 37% of the cohort developed recurrence and 81% were alive at last follow up. Kaplan-Meier analysis showed $Adeno^{hi}$ and $Angio^{lo}$ signatures were individually associated with decreased DFS and OS, compared to $Adeno^{lo}$ and $Angio^{hi}$, respectively. Upon integrating these signatures, we found the $Adeno^{hi}Angio^{lo}$ group exhibited the worst and the $Adeno^{lo}Angio^{hi}$ group had the best DFS and OS. These associations were validated in the TCGA cohort. Multivariate Cox regression models showed $Adeno^{hi}Angio^{hi}$ (HR 3.75; 95% CI, 1.72-8.21; p = 0.0009) and $Adeno^{hi}Angio^{lo}$ (HR 6.44; 95% CI, 3.06-13.54; $p < 0.0001$) groups ($Adeno^{lo}Angio^{hi}$ as reference group) and pathologic T4 (HR 8.69; 95% CI, 2.66-28.36; p = 0.0003) were significantly associated with worse DFS, but not UISS score (HR 0.56; 95% CI, 0.24-1.31; p = 0.18) and T3 tumors (HR 1.54; 95% CI, 0.8-2.94; p = 0.2; T2 as reference group). **Conclusions:** RCC TME subgroups stratified into adenosinergic and angiogenic expression profiles carry independent prognostic significance in patients with localized RCC. On multivariate analysis, these gene signatures enhanced conventional clinicopathologic risk stratification variables in predicting DFS after nephrectomy. Given the early data fueling interest in developing the prognostic capacity of these gene signatures in the metastatic space, and their ability to predict outcomes in the post-nephrectomy setting, these biologically relevant subgroups should be explored as a guide for future biomarker-driven adjuvant therapy trials. Research Sponsor: Novartis.

354 **Poster Session**

Impact of concurrent ACE inhibitors and ARBs on outcomes with immune-checkpoint inhibitors (ICIs) for patients (pts) with metastatic renal cell carcinoma (mRCC).

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Background: The renin-angiotensin system (RAS) is involved in regulation of angiogenesis and cell proliferation and may improve drug delivery by enhancing tumor perfusion partly by down-regulating transforming growth factor (TGF)-β. Since (TGF)-β appears to be associated with resistance in patients receiving immune checkpoint inhibitors (ICIs), we investigated whether angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) may enhance the outcomes of mRCC pts receiving ICI. **Methods:** Data from mRCC pts who received ICIs at the Dana-Farber Cancer Institute (DFCI) was obtained. Data for ACEI and ARB administration was collected with concurrent administration defined as ongoing therapy from the time of starting ICI . The Kaplan-Meier method and Cox were used to evaluate the impact of concurrent ACEI/ARB on overall survival (OS). **Results:** Data was available for 134 pts. The mean age was 63 years (Range 37-85)). 94 (70%) pts were male. The therapies included Nivolumab+/-Other (104), Atezolizumab+/-Other (21), Pembrolizumab+/-Other (8) and Durvalumab +Tremelimumab (1). 35 (25%) pts received ICI as first line treatment, 52 (39%) received as second line treatment, and 48 (36%) received as third line or higher. Out of the 134 pts, 39 (29%) had been treated with an ACEI or ARB during ICI treatment. Out of the 39 pts who had ACEI or ARB, 2 (5%) had complete response (CR) as best response, 11 (28%) had partial response (PR), 17 (46%) had stable disease (SD) and 9 (23%) had progressive disease (PD). Out of the 95 pts who did not receive ACEI or ARB, 3 pts (3%) had CR as their best response to ICI, 19 (21%) had PR, 39 (43%) had SD, and 29 (32%) had PD, (5 patients' best response were unevaluable). The median OS for those who had ACEI/ARBs and did not have ACEI/ARBs was 32 months and 20 months respectively. Univariable analysis revealed that patients who received ACEI/ARBs had improved OS (Logrank p-value = 0.002; HR = 2.5 [95%CI: 1.4 - 4.5]). **Conclusions:** In this hypothesis-generating study, concurrent ACEI/ARBs are associated with better outcomes for mRCC pts receiving ICIs. Given the availability of ACEI/ARBs, it is important to validate this result in a larger dataset and after controlling for known prognostic factors. Research Sponsor: None.

355 Poster Session and Poster Highlights Session; Displayed in Poster Session

Gene expression profiling (GEP) to identify metabolic gene signature predictive of recurrence after surgery in stage III clear-cell renal cell carcinoma (ccRCC).

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Background: Management of patients with localized or locally advanced renal cell cancer (RCC) involves surgical resection. However, 20-40% of all localized kidney cancer patients experience a recurrence. Adjuvant treatment in high-risk kidney cancer has not proven to successfully improve overall survival (OS) and the only drug approved so far in this setting is vascular endothelial growth factor (VEGF) inhibitor, sunitinib. As multiple trials are evaluating drugs including immune checkpoint inhibitors in patients with high risk localized clear cell RCC, there is an urgent need to identify biomarkers to help with therapeutic decisions as well as for risk stratification. Here we present analysis pertaining to genes involved in metabolic reprogramming in kidney cancer. **Methods:** A deep transcriptomic analysis of patients with stage III ccRCC in the TCGA KIRC Firehose Legacy cohort was undertaken. Caucasian males with stage III ccRCC in the TCGA cohort for whom recurrence data was available with a minimum follow-up of 2 years were identified for the analysis. Expression profiles of differentially expressed genes were clustered using the Bayesian infinite mixture model and samples clustered using average linkage hierarchical clustering based on pairwise Pearson's correlations as the measure of similarity. Enrichment analysis of up- and down-regulated genes was performed using logistic regression. R package was used to generate Kaplan-Meier curves and assess statistical significance of differences in overall and disease-free survival using log-rank test. **Results:** The cohort evaluated for this study included Caucasian male patients that remained disease free for at least 24 months after surgery (n = 22) and patients whose cancer recurred within 24 months (n = 20). We identified metabolic genes, encoding subunits of mitochondrial electron transport chain as well as malate aspartate shuttle (MAS), where loss of coordinated co-expression between these genes identified patients at risk of recurrence after surgery. The gene signature stratified the 42 patients into three subtypes: significantly enriched for a) recurrence (subtype 1), for b) disease free status (subtype 2) and b) intermediate (subtype 3). Work is underway to combine the use of individual gene expression and ratios of gene expression within the signature to optimize prognostic biomarkers for localized ccRCC. **Conclusions:** In this analysis, we have identified a novel metabolic gene signature which can help identify patients with localized ccRCC at high risk of recurrence after surgery to guide aggressive therapy. These findings require further validation in tumors collected from patients with stage III ccRCC. Research Sponsor: None.

356 **Poster Session**

Trends in the use of administrative databases in urologic oncology: 2000 – 2019.

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Background: Administrative databases (AD) provide investigators with nationally representative study populations to answer research questions using large sample sizes. We aimed to quantify the trends and incidence of AD use in published manuscripts in urologic oncology. We examined six commonly used databases: National Cancer Database (NCDB), Surveillance, Epidemiology and End Results Database (SEER), SEER-Medicare (SEER-M), Nationwide Inpatient Sample (NIS), National Surgical Quality Improvement Program (NSQIP), and Premier Healthcare Database (PHD). **Methods:** A literature review powered by PubMed and DistillerSR from 7/1/2000 to 6/30/2019 aggregated manuscripts that used the aforementioned databases to study a genitourinary malignancy. Included publications were categorized by database used, corresponding author department affiliation, organ, journal, year, and contribution – defined as temporal treatment trends, outcomes and survival, comparative effectiveness research, or cost-effectiveness. **Results:** There were 2,265 publications across 302 journals that met the inclusion criteria. Between 2000 and 2019 the compound annual growth rate of these publications was 18.7%. SEER contributed most heavily over the study period, with a 14.6% growth rate. NCDB use grew 75.6% annually starting in 2012. Prostate cancer comprised the majority of publications (51.3%), followed by kidney (23.1%) and bladder (22.5%) cancer. Journals publishing these manuscripts had a median impact factor of 3.28 (IQR = 1.84 – 5.74) in 2019. Urologists published 52.5% of AD manuscripts over the study period. **Conclusions:** Our results show substantial growth in the use of ADs for the study of urologic oncology. Given the broad use of ADs, investigators and specialty societies should advocate for continued improvement in the data captured by them. Research Sponsor: U.S. National Institutes of Health.

357 **Poster Session**

Quantifying publication rates and time to publication for urologic oncology podium presentations.

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Background: The American Urological Association (AUA) annual meetings serve as a large platform for unpublished research. Among the selected abstracts, podium presentations represent the most impactful submissions. Furthermore, between large meeting attendance and social media promotion, authors can disseminate their findings to a potentially large audience prior to final manuscript publication. While all AUA abstracts do undergo peer review, it is not with the same level of scrutiny that full-length manuscripts receive. Thus, we investigated the publication rates, impact factors, and time to publication of urologic oncology podium presentations at the AUA. **Methods:** Of 875 podium presentation abstracts from the 2017 AUA Annual meeting, 394 (45.0%) were classified as urologic oncology. We chose 2017 to allow for a three-year window for publication. Abstracts were assessed for subsequent publication between January 1, 2015 and May 31, 2020 with a pre-determined PubMed search protocol. Abstract authors were searched for individually, with key terms being added sequentially until <30 results were generated in PubMed. Each search result was then reviewed until a matching publication was found. Abstracts were deemed published if at least one author of the presented abstract was a manuscript author and/or at least one conclusion in the presented abstract was included in the conclusions of the publication. Publication rates, time to publication, and 2019 journal impact factors were collected. **Results:** Of 394 urologic oncology podium presentations at the 2017 AUA, 228 (57.9%) focused on prostate cancer, while 81 (20.6%) and 58 (14.7%) presentations focused on kidney and bladder cancer, respectively (table). Overall, 211 (53.6%) podium presentations were published. Median time from presentation to publication was 13.6 months (IQR: 7.5-21.5). There were 9 (2.3%) publications that were published prior to the submission deadline and 57 (14.5%) podium presentations that were published prior to the 2017 AUA meeting. The number of articles published at one, two and three years after the meeting was 90, 170 and 202, respectively. The median journal impact factor of all published works was 3.4 (IQR: 2.7-5.9). **Conclusions:** While AUA podium presentations disseminate valuable data, approximately half of these presentations were not published in peer-reviewed journals within three years. Therefore, care must be taken when promoting data or adopting new practices based on these presentations alone. Research Sponsor: None.

	Publication			Time to Publication (months)			Impact Factor		
	Yes	No	Rate	Median	IQR		Median	IQR	
Bladder	27	31	46.6%	14.6	10.5	23.5	2.9	1.9	2.9
Kidney	39	42	48.2%	19.5	9.5	23.5	3.0	2.3	5.9
Penile	7	1	87.5%	12.5	11.5	22.5	2.9	2.8	5.9
Prostate	131	97	57.5%	11.5	5.5	19.5	4.8	2.9	5.9
Testis	6	6	50.0%	8.5	3.5	19.5	3.2	2.7	4.8
Urethral	0	2	0.0%	-	-	-	-	-	-
Upper Tract Urothelial	1	4	20.0%	8.5	8.5	8.5	5.9	5.9	5.9
Total	211	183	53.6%	13.6	7.5	21.5	3.4	2.7	5.9

IQR = interquartile range

358 **Poster Session**

Insights on oncologist and urologist gaps in bladder (UC) and kidney (RCC) cancer education.

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Background: Treatment paradigms for bladder (UC) and kidney (RCC) cancers is evolving with the advent of novel treatment approaches, personalized medicine, and combinatorial strategies. As the medical literature in the space evolves, identifying oncologists' (oncs) and urologists' (uros) educational gaps is important to inform continuing medical education (CME) needs and, ultimately, to improve patient outcomes. **Methods:** Medscape Oncology conducted a 16 question, online, incentivized survey in June 2020 targeting genitourinary (GU) cancer physicians. Respondents' confidentiality was maintained and responses were de-identified and aggregated for analysis. **Results:** Results are reported for 100 respondents (50 oncs & 50 uros): In UC: Learners identified CME as mostly/very important for: Managing treatment related adverse events (trAEs) – 84% Clinical trial outcomes – 77% Timely/appropriate biomarker testing – 68% Understanding mechanism of action (MOA) and rationale of novel agents – 66% Treatment planning CME was considered mostly/very important for: All stages: non-muscle invasive (NMIBC), muscle-invasive (MIBC), and first line (1L) metastatic – 72%, 85%, 92% respectively Determining the optimal role for immunotherapy (IO) – 82% Sequencing therapies – 72% In subgroup analyses More oncs vs. uros identified biomarker testing and treatment selection as mostly/very important ($p < .01$) More general oncs vs. GU oncs identified education on clinical trial outcomes and sequencing of therapies as mostly/very important ($p < .05$) More uros vs. oncs identified NMIBC treatment education as mostly/very important ($p < .01$) More low vs. high volume treaters identified education on sequencing and MIBC as mostly/very important ($p < .01$) Rating % very experienced: Counseling on trAEs – 41% but mitigating AEs of FGFR therapies, ADCs, or IO was only: 16%, 19%, and 26% respectively In RCC: Learners identified CME as mostly/very important for: Selecting optimal 1L therapy – 80% Clinical trial outcomes – 77% Sequencing therapies – 69% Managing trAEs – 64% Understanding MOA and rationale of novel agents – 62% In subgroup analyses More general oncs vs. GU oncs identified importance of education on clinical trial outcomes and 1L treatment selection ($p < .05$) More low vs. high volume treaters identified importance of education on 1L treatment selection and clinical trial outcomes ($p < .05$) Rating % very experienced: Counseling on trAEs – 30% but mitigating AEs of targeted therapy or IO was only: 22% and 23% respectively Determining risk score – 22% Selecting 1L therapy – 28%. **Conclusions:** Medscape Oncology surveys provide valuable information to guide education for oncs and uros and individualize education unique to their treatment setting, patient volume, and practice coverage. Research Sponsor: None.

359 **Poster Session**

Association of statins and nivolumab activity in patients with metastatic renal cell carcinoma (mRCC): Results from the phase II nivoren–GETUG AFU 26 trial.

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Background: Statins are HMG-CoA inhibitors that regulate several mechanisms involved in tumor growth, including mitochondrial metabolism, activation of oncogenic signaling pathways, and immune modulation. Population-based studies showed that statin intake may be negatively associated with RCC onset. The impact of statins on response to immunotherapy in mRCC is unknown. Herein we study the association between statin administration and outcomes in patients with mRCC treated with nivolumab in the NIVOREN-GETUG AFU 26 phase II trial (NCT03013335). **Methods:** Patients with mRCC who failed previous VEGFR inhibitors were included. We assessed nivolumab activity, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) according to statin intake at baseline. Toxicity was assessed using CTCAE v4.0. **Results:** Overall,133 patients were treated with statins at baseline among 702 evaluable for concomitant therapies (19%). Among them, median age was 68 (49-90), 84% were male, 85% had a performance status $\geq$ 80%, 42% were overweight and 20% obese. Patients treated with statins had mostly good (23%) or intermediate (58%) IMDC risk, 64% had grade 3 or 4 tumors, and nivolumab was given in a third line setting or more in 55%. Median follow-up was 23.9 months (95%CI 23.0-24.5) in the overall cohort. The ORR was 26% in patients treated with statins, PFS 5.0 months (CI95% 3.0 – 5.5), OS 27.9 months (CI95% 19.4-30.3). Outcomes of patients with or without statins did not differ significantly. Similar rates of grade 3-5 TRAE were reported in patients with (20%) or without (18%) statin intake. **Conclusions:** This is the first study to evaluate statin intake and outcomes with nivolumab in patients with mRCC. Despite numerically higher ORR, statins were not significantly associated with improved outcomes. These data require other analyzes considering other factors such as BMI and other comorbidities. Further studies may help better understand the interplay between immunity and metabolic reprogramming in RCC. Research Sponsor: None.

360 **Poster Session**

Impact of comorbidity burden on renal cell carcinoma prognosis: A Danish nationwide cohort study.

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Background: The incidence of renal cell carcinoma is increasing worldwide and have a 5-year relative survival rates of around 75%. Comorbidity has been found to be associated with complications and mortality after renal cancer surgery. No studies have focused on comorbidity as a prognostic factor in a nationwide cohort of patients with renal cell carcinoma with long-term follow-up. **Purpose:** The primary aim was to evaluate the prognostic impact of comorbidity on survival in older (≥70 years) and younger (<70 years) patients diagnosed with renal cell carcinoma. **Methods:** We established a nationwide register-based cohort of 7,894 patients aged 18 or more diagnosed with renal cell carcinoma in Denmark between 2006 and 2017, and followed their vital status for up to 13 years. We computed 1- and 5-year overall survival and hazard ratios (HRs) of death according to comorbidity status using Charlson Comorbidity Index (CCI) among patients aged < 70 years and ≥ 70 years. **Results:** In all, 36% of the patients had registered comorbidity at the time of diagnosis. Survival decreased with increasing CCI score. It did though increase for all groups of CCI scores (0, 1-2 and 3+) over time. For patients without comorbidity diagnosed in 2006-2008 and 2015-2017, 5-year survival rate increased from 57% to 69%. For patients with a CCI score of 1-2 vs 3, the 5-year survival rate increased from 46% to 62% vs 39% to 44%. In age- and gender-stratified analyses, patients with a CCI score of 1-2 and 3+ had increased mortality compared to patients without registered comorbidity (HR 1.15, 95 % CI 1.06-1.24) and (HR 1.56, 95 % CI 1.40-1.73). Patterns were similar for older (≥70 years) and younger (<70 years) patients. Particularly, diagnoses of congestive heart failure, peripheral vascular and cerebrovascular disease, dementia, chronic pulmonary disease, preexisting renal and liver disease, diabetes and lymphoma led to increased mortality. **Conclusions:** Comorbidity leads to inferior survival outcomes in patients with renal cell carcinoma, irrespective of age, despite an overall increasing survival. These data may guide patient counseling and prompt initiatives for controlling comorbidity. Research Sponsor: None.

361 **Poster Session**

A retrospective study of primitive neuroectodermal tumor (PNET) of the kidney in a tertiary cancer center in India.

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Background: Primitive neuroectodermal tumours (PNET) of the kidney are rare tumours with aggressive behaviour. This study was conducted to review the diagnosis and management of patients with renal PNET at our centre. **Methods:** This was a retrospective study conducted at a tertiary cancer care centre in Mumbai, India. The demographic and clinical data of 17 patients treated by the uro-oncology services were retrieved from electronic medical records. Descriptive analysis was performed for baseline characteristics.Overall & progression-free survival was determined using the Kaplan Meier method. Cox regression was used for multivariate analysis. **Results:** There were 12 male and 5 female patients in this cohort with a median age of 27 years. At diagnosis 2 patients had metastatic disease and 15 patients had non-metastatic disease. Median follow up in this cohort was 22 months (range 2-30 months). Presenting complaints were hematuria, abdominal pain, flank pain, fever, bone pain, and incidentally detected renal mass. All patients were Mic -2 positive and 13 were FLI-1 positive on immunohistochemistry. Fourteen patients underwent radical nephrectomy. One (5.9%) patient received both neoadjuvant and adjuvant chemotherapy, 8 (47.1%) received adjuvant and 2 (11.8%) received palliative chemotherapy upfront. Eight patients received adjuvant radiation to the renal bed.There was disease progression in12 patients,10 of 15 patients with non metastatic disease at diagnosis eventually developed metastasis.The median progression free survival (PFS) was 10.55 months.The pathological feature that was associated with a shorter PFS was tumor size $\geqslant$10 cm(p = 0.044).The median overall survival was 20.04 months (95% CI 9.49 -not reached). The presence of metastasis and treatment received significantly impacted overall survival (OS). Median OS in patients with non-metastatic disease was not reached versus 14.1 months in those with metastatic disease (p = .019).The median OS in patients treated with multimodality approach was 20.11 months. Patients did not undergo surgery had a median OS of 5.45 months ($p < .001$) and those who did not receive any chemotherapy had a median OS of 4.57 months (p = .024).Thus, patients who received multimodality treatment had better outcomes. **Conclusions:** PNET kidney is an aggressive tumor which should be treated with a multimodality approach. Tumor size $\geqslant$10 cm was an adverse prognostic factor. Research Sponsor: None.

Renal sarcomas: Epidemiology, treatment and outcomes.

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Background: Renal sarcomas are a rare malignancy in adults and have been inadequately evaluated on a US national level regarding epidemiology, treatment, and outcomes. **Methods:** The 2004-2016 NCDB and SEER databases were queried for adult patients diagnosed with sarcomas of renal origin. Age-adjusted incidence rates were derived from the SEER database. Overall survival (OS) was assessed using multivariable Cox proportional hazards models adjusting for demographics, tumor and treatment variables. **Results:** 1,279 renal sarcomas comprising 39 subtypes were reported from 2004-2016, contributing 0.3% of all NCDB renal malignancies. As shown in the table below, the most common subtypes were leiomyosarcoma (LMS), angiosarcoma (AS), malignant rhabdoid tumor (MRT), dedifferentiated liposarcoma (DL) and primitive neuroectodermal tumors (PNET). Over the study period, renal sarcoma incidence rates remained constant at 0.5 cases / 1 million citizens. Sex-specific incidence differences were evident with female predominance for LMS, and male predominance for AS. Age at diagnosis and tumor diameter varied according to sarcoma subtypes: for example, median age in LMS was 62y compared to 30y in Ewing sarcoma patients; median tumor diameter was 18cm for solitary fibrous tumors and 7.5cm for synovial sarcoma. Renal sarcoma was staged as T3 in 33.3% and T4 in 14.2%, while distant metastases were evident in 29.1% of cases at diagnosis. Most T1-T3 stage renal sarcomas underwent surgical resection (992/1098, 84%), compared to 71% for T4 renal sarcomas (128/181). Systemic therapy was administered in 32.1% of renal sarcoma cases (23.5% combined with surgical resection). Renal sarcoma 1-,2-, and 5-year OS rates were 48%, 24%, and 13%. OS was worse for T4 vs T1-3 sarcomas (HR=1.6, $p<0.001$), and cases with distant metastases vs none (HR=3.2, $p<0.001$). As summarized in the table, OS varied according to sarcoma subtypes with worse OS for AS compared to PNET (HR=1.5, p=0.04). **Conclusions:** Accounting for 0.3% of renal malignancies in adults, renal sarcomas include 39 different histological subtypes with distinct demographics, tumor parameters and outcomes. Renal sarcomas commonly present with advanced T stage at diagnosis and are treated with surgical resection with or without systemic therapy. Research Sponsor: None.

OS rates of the 5 most common renal sarcoma subtypes.

Subtype	n	1-year OS	3-year OS	5-year OS
Leiomyosarcoma	329	70%	48%	40%
Angiosarcoma	164	36%	12%	7%
Malignant rhabdoid tumor	156	57%	31%	23%
Dedifferentiated liposarcoma	87	73%	52%	43%
Primitive neuroectodermal tumor	66	74%	54%	46%

363 **Poster Session**

The use of 3D printed models on trainee and patient experience for partial nephrectomies.

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Background: 3D printing is a growing tool in surgical education due to the ability to visualize organs, tissue, and masses from multiple angles before operating on a patient. Previous studies using highly detailed and expensive 3D models costing between $1,000-250 per model have been shown to enhance patient and trainee comprehension of tumor characteristics, goals of surgery, and planned surgical procedure for partial nephrectomies. In our study we aim to use simpler and less expensive models in a greater range of patients receiving partial nephrectomies to determine the use of 3D models in patient, resident, and fellow education. **Methods:** 3D models of the effected kidney, mass, renal artery, and renal vein were created using preoperative imaging of undergoing partial nephrectomies at Thomas Jefferson University Hospital (TJUH) costing $35 per model. Residents and fellows filled out 3 surveys assessing their surgical plan and their confidence in the chosen plan at 3 time points: 1) Before seeing the model, 2) After seeing the model before surgery, and 3) After surgery. Ten patients filled out 2 surveys about their understanding of the kidney, their disease, the surgery they will undergo, and the risks involved with surgery before and after seeing the model. **Results:** Based on surveys to assess for surgical plan and confidence given to resident and fellow surgeons before and after seeing the 3D model, confidence significantly increased. Surveys given after surgery assessing anatomic and surgical comprehension found that resident and fellow surgeons rated the helpfulness of the models on their anatomical comprehension 7.6 out of 10 and the help of the models on their surgical confidence 7 out of 10. Patient understanding of their kidney, disease, and surgery significantly increased after seeing the 3D model, but the risks associated with surgery did not significantly increase. The extent that the model helped the patients learn about the kidney, their disease, the surgery, and the risks related to surgery were rated an average of 8.33, 9.67, 9.5, and 8.83 out of 10, respectively. **Conclusions:** Patient-specific 3D models for partial nephrectomies increase resident and fellow confidence in surgical approach and helped patients learn about their disease and feel comfortable going into surgery. Thus, it is important to continue to explore 3D models as an educational tool for both trainees and patients and potentially include 3D models as part of the standard of care. Further research could continue to explore the utility of 3D models as a pre-operative educational tool for both patients and trainees in other surgical fields. Research Sponsor: None.

TPS365 **Trials in Progress Poster Session**

Phase I/IB trial of sitravatinib (Sitra) + nivolumab (Nivo) + ipilimumab (Ipi) in patients (pts) with advanced clear cell renal cell carcinoma (accRCC) or other solid malignancies.

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Background: Sitra is a spectrum-selective receptor tyrosine kinase inhibitor (TKI) that targets TAM receptors (TYRO3, AXL, MERTK), VEGFR2, c-Kit, and c-MET. Sitra has shown antitumor activity in accRCC, and reduces type 2 tumor-associated macrophages, regulatory T-cells and myeloid-derived suppressor cells and enhances T cell–mediated antitumor immune responses. The combination of sitra with anti-PD1 immune checkpoint inhibitors (ICIs), such as nivo, has an acceptable safety profile and demonstrates efficacy across multiple tumor types, including accRCC (Msaouel et al. *J Clin Oncol*, 2020, abstr 612). Ipi enhances the efficacy of nivo through distinct but complementary pathways to those targeted by sitra. We hypothesize that the triple combination of sitra + nivo + ipi will lead to more potent antitumor responses. This study is designed to determine the optimal dose of sitra when combined with nivo + ipi, and assess the safety as well as the preliminary efficacy of this combination in accRCC, and potentially other cancers, that have shown favorable responses to nivo + ipi. **Methods:** This phase I/Ib study (NCT04518046) is evaluating sitra + nivo + ipi in frontline advanced or metastatic ccRCC or other solid malignancies. The primary endpoint of the trial is safety and tolerability of this regimen. Secondary endpoints include: objective response rate (RECIST 1.1), duration of response, progression-free survival, overall survival, and pharmacokinetic measurements. The phase I dose escalation portion of the trial will enroll approximately 30 pts with intermediate- or poor-risk accRCC by International Metastatic RCC Database Consortium (IMDC) criteria, who will receive escalating doses of sitra (starting dose 35 mg orally QD) following the Time-to-Event Bayesian Optimal Interval (TITE-BOIN) design (Yuan et al. *Clin Cancer Res*, 2018), combined with nivo 3 mg/kg and ipi 1 mg/kg (NIVO3/IPI1) every 3 weeks (wks) for up to 4 doses, followed by maintenance nivo (240 mg every 2 wks or 480 mg every 4 wks). The phase Ib dose expansion cohorts will be initiated following identification of the recommended dose of sitra in combination with NIVO3/IPI1 and will enroll up to 31 pts for each of 2 cohorts: pts with intermediate-/poor-risk accRCC (Cohort A) and pts with favorable-risk accRCC (Cohort B). Pts will receive study treatment until disease progression, unacceptable adverse events, or pt withdrawal of consent. Future dose expansion cohorts may be added to include other solid tumors in which favorable activity has been previously demonstrated with nivo + ipi, such as metastatic urothelial carcinoma, melanoma, non–small-cell lung cancer, hepatocellular carcinoma, and colorectal cancer. The study is currently enrolling at 1 US site and additional sites may be added at dose expansion. At the time of the abstract submission, 3 pts have been enrolled. Clinical trial information: NCT04518046. Research Sponsor: Mirati Therapeutics, Inc.

TPS366 **Trials in Progress Poster Session**

PDIGREE: An adaptive phase III trial of PD-inhibitor nivolumab and ipilimumab (IPI-NIVO) with VEGF TKI cabozantinib (CABO) in metastatic untreated renal cell cancer (Alliance A031704).

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Background: First-line treatment of mRCC has rapidly changed to include IPI-NIVO or CABO, with clinical benefit of each based on the Checkmate 214 and CABOSUN (A031203) trials. Combination immunotherapy with VEGF therapies has shown benefit over sunitinib in the JAVELIN 101 and KEYNOTE 426 trials. It is yet unclear which patients (pts) benefit most from combination immunotherapy-VEGF inhibitors, and the optimal sequence of drugs. **Methods:** In an adaptive, randomized, multicenter phase III trial (Alliance A031704, PDIGREE), pts start treatment with induction IPI 1 mg/kg and NIVO 3 mg/kg intravenously (IV) once every 3 weeks. Key inclusion criteria include clear cell mRCC, International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk, Karnofsky performance status >70, and no prior treatments for mRCC. Based on 3-month radiographic assessment (after completing IPI-NIVO combination), pts with complete responses (CR) undergo maintenance NIVO 480 mg IV every 4 weeks; pts with progression of disease (PD) switch to CABO 60 mg oral daily; pts with non-CR/non-PD are randomized to NIVO 480 mg IV every 4 weeks versus NIVO 480 mg IV every 4 weeks with CABO 40 mg oral daily. Randomization is stratified by IMDC risk criteria and presence of bone metastases. The primary endpoint of the study is overall survival (OS). We hypothesize that 3-year OS will improve to 70% for NIVO-CABO compared to 60% for NIVO alone; to achieve 85% power with a two-sided alpha of 0.05 and exponential distribution, 696 patients will be randomized. Accounting for 30% patients with either CR or PD, and 5% dropout from toxicity, up to 1046 pts will be enrolled. Key secondary endpoints include progression-free survival, 12-month CR rate, overall response rate based on RECIST 1.1 and iRECIST criteria, and toxicity profiles. Quality of life will be assessed based on the FKSI-19, PROMIS-fatigue, and EQ5D-5L questionnaires. Biomarkers associated with CR, tissue-based and plasma-based biomarkers will be assessed. Updated enrollment through January 2021 will be presented. Clinical trial information: NCT03793166. Research Sponsor: U.S. National Institutes of Health.

TPS367 **Trials in Progress Poster Session**

Denosumab and pembrolizumab in clear cell renal carcinoma (KEYPAD): A phase II trial (ANZUP1601).

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Background: Inhibitors of the programmed death-1 pathway (PD-1) are effective in clear cell renal cell cancer (ccRCC). Preclinical data and case reports suggest that denosumab, an inhibitor of Receptor Activator of Nuclear Factor κ-B Ligand (RANKL) signaling, could potentiate the anti-tumour effects of anti-PD1 inhibitors without overlapping toxicities. We aim to determine the activity and safety of combining denosumab and pembrolizumab in advanced ccRCC. **Methods:** This single arm, multi-center, phase II trial will recruit 70 participants with metastatic or unresectable ccRCC, progressing during or after treatment with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors, and with no prior treatment with immuno-therapy or denosumab. Participants will receive pembrolizumab 200mg IV every 3 weeks plus denosumab 120mg SC on days 1, 8 and 22 and then every 3 weeks until disease progression, prohibitive toxicity or maximum treatment of 24 months. Response will be assessed at weeks 12, 18, 24, then every 12 weeks until disease progression. Bloods for translational studies are collected at baseline, week 6 and on disease progression. The primary endpoint is objective tumour response rate (OTRR) per RECIST 1.1. Secondary endpoints include OTRR per iRECIST, progression free survival (PFS), time to OTRR, time to first skeletal related event, adverse events, and frequency of treatment delays/discontinuations. Correlative studies will include identification of prognostic and/or predictive biomarkers relating to immune and RANKL signaling. A sample size of 70 provides 90% power with a 1-sided type 1 error rate of 10% to distinguish the observed OTRR (and PFS at 6 months) from an OTRR of 40% (worthy of pursuit) versus 25% (not worthy of pursuit). 15 sites are open across Australia. As of September 23, 2020, 40 patients have been recruited. Clinical trial information: NCT03280667. Research Sponsor: Merke Sharp & Dohme; AmgenOther Government AgencyAustralian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP);.

TPS368 **Trials in Progress Poster Session**

MK-6482, a hypoxia-inducible factor 2α inhibitor (HIF-2α), versus everolimus in heavily pretreated, immune checkpoint–inhibitor–resistant, advanced clear cell renal cell carcinoma (ccRCC): Phase III study.

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Background: In ccRCC, HIF-2α is involved in the activation of genes such as *VEGFA*, *cyclin D1*, and *CXCR4,* which are associated with angiogenesis, tumor progression, and metastasis. HIF-2α can accumulate and be overactivated due to the inactivation of the Von Hippel-Lindau (*VHL*) tumor suppressor gene, which occurs in most RCC cases. MK-6482 is a potent and selective small molecule inhibitor of HIF-2α that has shown antitumor activity in a phase I/II study in patients with pretreated, advanced ccRCC (NCT02974738). In the study, the objective response rate was 24%, the disease control rate was 80%, and the safety profile was acceptable. **Methods:** A phase III, open-label, multicenter, randomized, active-controlled study (NCT04195750) will evaluate the efficacy and safety of MK-6482 versus everolimus as second- to third-line therapy in advanced ccRCC. Eligibility criteria include age ≥18 years; unresectable, locally advanced, or metastatic ccRCC; measurable disease per RECIST v1.1; and a history 1 to 3 systemic regimens for locally advanced or metastatic RCC—including at least 2 doses of a PD-L1 inhibitor and a VEGF-targeted therapy alone or in combination, which resulted in progression. Exclusion criteria include diagnosis of hypoxia defined by pulse oximetry <92% at rest or requiring supplemental oxygen, prior HIF or mTOR inhibitor therapy, kinase inhibitors within 2 weeks of randomization and any systemic anticancer antibody within 4 weeks, and known central nervous system metastases and/or carcinomatous meningitis. The study will enroll approximately 736 patients, who will be randomly assigned 1:1 to MK-6482 120 mg or everolimus 10 mg, both orally once daily until documented disease progression, withdrawal of consent, or other discontinuation event. Stratification factors for this study are International Metastatic RCC Database prognostic scores (0 versus 1-2 versus 3-6) and the number of prior anti-VEGF–targeted therapies received for advanced RCC (1 versus 2-3). The planned imaging (CT/MRI) for response evaluation per RECIST v1.1 by blinded independent central review is as follows: imaging at week 8 from the date of randomization, then every 8 weeks through week 49, and every 12 weeks thereafter. Adverse events will be monitored throughout the study and for 30 days after treatment (90 days for serious adverse events). Progression-free survival per RECIST v1.1 and overall survival will be the dual primary endpoints. Objective response rate, duration of response, patient-reported outcomes, and safety will be secondary endpoints. Event rates over time will be summarized using the Kaplan-Meier method, and hazard ratios will be estimated using a stratified Cox regression model. Stratified Miettinen and Nurminen method will be used for analysis of ORR. Recruitment began in December 2019. Clinical trial information: NCT04195750. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS369 **Trials in Progress Poster Session**

An open-label phase II study comparing two doses of MK-6482 for the treatment of advanced renal cell carcinoma (RCC) following progression on prior systemic therapy.

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Background: Treatment options for RCC in the late-line setting after immunotherapy and vascular endothelial growth factor (VEGF)-targeted therapy are limited. Hypoxia-inducible factor (HIF)-2α is a transcription factor that has been established as an oncogenic driver in clear cell RCC (ccRCC). The first-in-class small molecular HIF-2α inhibitor, MK-6482, recently showed promising antitumor activity in a cohort of heavily pretreated ccRCC patients (pts) and in pts with von Hippel-Lindau–disease-associated RCC for which the FDA granted Breakthrough Therapy Designation to MK-6482. **Methods:** This randomized, open-label, multicenter phase II trial will evaluate the efficacy and safety of 2 doses of MK-6482 in pts with advanced RCC who have experienced progression after prior systemic therapy (NCT04489771). Eligible pts are male or female aged $\geq$18 years with histologically confirmed locally advanced or metastatic ccRCC (measurable disease per RECIST v1.1) who have experienced progression after 1-3 prior systemic therapies comprising an anti-PD-1/L1 agent combined with a VEGF-targeted tyrosine kinase inhibitor (TKI) or an anti-cytotoxic T lymphocyte-associated antigen-4 agent and have undergone no more than 3 prior systemic regimens; and a Karnofsky Performance Scale $\geq$70. Treatment progression on anti-PD-1/L1 combination therapy was defined as pts who received at least 2 doses of anti-PD-1/L1 therapy and demonstrated radiographic disease progression as assessed by the investigator. Pts who have received prior treatment with MK-6482 or another HIF-2α inhibitor, and those requiring intermittent or chronic supplemental oxygen, or with a baseline hemoglobin less than 10 g/dL, a history of human immunodeficiency virus, hepatitis B or hepatitis C infection, or active central nervous system metastases will be excluded. Approximately 150 pts will be randomly assigned 1:1 to oral MK-6482 120 mg once daily (QD) or 200 mg QD; treatment will continue until progression, unacceptable toxicity, or withdrawal. Pts will be stratified by International Metastatic RCC Database Consortium prognostic scores (0, 1-2, 3-6) and the number of prior TKI-containing therapies (0, 1, or 2-3). Imaging with computed tomography or magnetic resonance imaging will be undertaken on Week 9 from the date of randomization, every 8 weeks through Week 49, and every 12 weeks thereafter. Adverse events will be monitored throughout the study and for 30 days after treatment (90 days for serious adverse events). The primary end point is objective response rate per RECIST v1.1 by blinded independent central review (BICR). Secondary end points are progression-free survival, duration of response and clinical benefit rate per RECIST v1.1 by BICR, overall survival, pharmacokinetics, and safety. Safety will be analyzed using a tiered approach. This study is recruiting. Clinical trial information: NCT04489771. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS370 **Trials in Progress Poster Session**

CONTACT-03: Randomized, open-label phase III study of atezolizumab plus cabozantinib versus cabozantinib monotherapy following progression on/after immune checkpoint inhibitor (ICI) treatment in patients with advanced/metastatic renal cell carcinoma.

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Background: Combining anti-angiogenic drugs with immune checkpoint inhibitors (ICI) after progression on ICIs presents a promising therapeutic approach in renal cell carcinoma (RCC). Atezolizumab (anti-PD-L1 mAb) has shown activity in combination with anti-angiogenic therapy after prior progression with ICI. Cabozantinib (VEGFR-TAM-TKI), a standard of care therapy in RCC, promotes an immune-permissive environment and may enhance atezolizumab activity. In phase Ib COSMIC-021, cabozantinib + atezolizumab safety and efficacy was favorable in clear-cell(cc) RCC and non(n)-ccRCC (Pal et al [702O] and McGregor et al [709P], ESMO 2020). The phase III CONTACT-03 study is further evaluating cabozantinib + atezolizumab vs cabozantinib in second-line/third-line RCC after prior ICC therapy. **Methods:** CONTACT-03 (NCT04338269) is a phase III, open-label, randomized, multicenter study that will enroll ≈500 patients across more than 150 sites globally. The trial opened in July 2020 and is actively recruiting adult patients with RCC. Key inclusion criteria include histologically confirmed locally advanced or metastatic ccRCC or nccRCC (papillary or unclassified); radiographic disease progression during or following first-line/second-line ICI treatment; measurable disease (RECIST 1.1); KPS score ≥70%; and availability of an archival tumor specimen and fresh biopsy (if clinically feasible). Patients must have adequate hematological and end organ function. Prior ICI therapy must be a PD-1/PD-L1 inhibitor (mono- or combination therapy) and must be in the immediate preceding line of therapy. Key exclusion criteria include prior treatment with cabozantinib or a mTOR inhibitor. Patients with symptomatic, untreated, or actively progressing CNS metastases or significant other intercurrent illness are not eligible. Stratification factors are IMDC risk group (0 vs 1-2 vs ≥3); line of most recent prior ICI therapy (first vs second); and histology (dominant cc without sarcomatoid vs dominant non-cc [papillary or unclassified] without sarcomatoid vs any sarcomatoid component [cc or ncc]). Patients will be randomized 1:1 to receive atezolizumab (1200 mg/IV/q3w) plus cabozantinib (60 mg/oral/qd) or cabozantinib alone (60 mg/oral/qd) until unacceptable toxicity or loss of clinical benefit. Patients will not be allowed to crossover from the control arm to the experimental arm. Multiple primary endpoints are independent review facility (IRF)-assessed PFS and OS. Additional endpoints include investigator-assessed PFS, IRF- and investigator-assessed ORR and DOR; HRQOL, biomarkers and safety. Radiographic efficacy will be assessed per RECIST 1.1. Clinical trial information: NCT04338269. Research Sponsor: F. Hoffmann-La-Roche Ltd.

TPS371 **Trials in Progress Poster Session**

Phase II trial of cytoreductive surgery in kidney cancer plus immunotherapy (nivolumab) and targeted kinase inhibition (cabozantinib) (Cyto-KIK).

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Background: Despite recent therapeutic advancements in metastatic renal cell carcinoma (mRCC), only 5-10% of patients will achieve a complete response (CR) to therapy. Cytoreductive nephrectomy removes a large portion of the tumor which may be a source of immunosuppression driven by tumor cell-intrinsic factors in the tumor microenvironment. A pre-clinical orthotopic mouse model of aggressive metastatic triple negative breast cancer showed that neoadjuvant anti-PD-1 checkpoint inhibition generated enhanced and sustained antitumor immune responses with improved survival compared to adjuvant therapy (Liu J et al. Cancer Discov. 2016:1382). Clinical validation of improved outcomes with neoadjuvant compared to adjuvant immune checkpoint inhibitors has been demonstrated in trials for patients with non-small cell lung cancer, advanced melanoma, and recurrent glioblastoma (Forde, P.M., et al. N Engl J Med. 2018:1976; Amaria, R.N., et al Nat Med. 2018:1649; Cloughesy T.F., et al. Nat Med 2019:477). Recent data from a phase III trial in subjects with untreated mRCC, demonstrated the superiority of combination cabozantinib and nivolumab over sunitinib and established a new standard of care for mRCC (Choueiri T.K., et al. Annals of Onc, 2020;31 (suppl; abstr 6960). We hypothesize that if tumor specific immune responses to immunotherapy are greatest prior to nephrectomy, then treatment with nivolumab (nivo) and cabozantinib (cabo) prior to cytoreductive nephrectomy will lead to maximal peripheral and intratumoral specific immune responses and higher rates of CR during the course of treatment. **Methods:** This is an open label phase II, multicenter clinical trial of combination nivo and cabo prior to cytoreductive nephrectomy in patients with mRCC (NCT04322955). 48 treatment- naïve subjects with radiological or histological diagnosis of mRCC will be enrolled with the primary endpoint of CR rate according to RECIST version 1.1. Subjects will receive cabo (40mg) daily and nivo (480mg) every 4 weeks for 12 weeks prior to nephrectomy and a 3+3 design will be used to evaluate the safety of the interval (21 or 14 days) between the discontinuation of cabo and nephrectomy. Post-operatively, subjects will resume treatment with cabo and nivo until evidence of disease progression. Secondary endpoints include median size reduction of the primary tumor, response rate, PFS, OS, and surgical outcomes using the Clavien-Dindo classification system. Tissue based assays will quantify treatment related changes in the renal tumor microenvironment through polychromatic immunofluorescence, single cell RNA sequencing of the biopsy and nephrectomy specimen, and multiplex assessment of circulating serum cytokines. Dynamic contrast-enhanced MRI will be performed in a subset of subjects to assess radiologic correlates of response. The study is currently open to enrollment. Clinical trial information: AAAS6927. Research Sponsor: Exelixis Inc., Bristol-Myers Squibb.

TPS372 **Trials in Progress Poster Session**

Phase III study evaluating efficacy and safety of MK-6482 + lenvatinib versus cabozantinib for second- or third-line therapy in patients with advanced renal cell carcinoma (RCC) who progressed after prior anti-PD-1/L1 therapy.

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Background: There is an unmet need for treatment options in the second-line or later setting following anti–PD-1/L1 or VEGF tyrosine kinase inhibitor (TKI) therapy in patients with advanced RCC. Hypoxia-inducible factor (HIF)-2α is a transcription factor that has been established as an oncogenic driver in clear cell RCC (ccRCC). Promising antitumor activity has been reported for the first-in-class small molecular HIF-2α inhibitor, MK-6482, in heavily pretreated patients with ccRCC and patients with VHL disease–associated RCC. HIF-2α also regulates *VEGF* gene expression and plays a role in resistance to anti-VEGF therapy. Therefore, combining MK-6842 with a VEGF receptor TKI, such as lenvatinib, is an attractive treatment option in the advanced RCC setting. **Methods:** This is a randomized, open-label, active-controlled, multicenter phase III trial evaluating the efficacy and safety of MK-6482 + lenvatinib compared with cabozantinib in patients with advanced ccRCC who have progressed on prior anti–PD-1/L1 therapy (NCT04586231). Eligibility criteria include age ≥18 years; histologically confirmed, unresectable, locally advanced or metastatic ccRCC; disease progression on or after first- or second-line systemic treatment with an anti–PD-1/L1 therapy (monotherapy or in combination with other agent[s]) for locally advanced or metastatic disease, the immediately preceding line of treatment must be an anti–PD-1/L1 therapy; no more than 2 prior systemic regimens, with only 1 prior anti–PD-1/L1 therapy; measurable disease per RECIST v1.1; and Karnofsky performance status ≥70%. Patients must provide tissue for biomarker analysis. Approximately 708 patients will be randomly assigned in a 1:1 ratio to receive MK-6482 120 mg orally once daily (QD) + lenvatinib 20 mg orally QD or cabozantinib 60 mg orally QD. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. The stratification factors are International mRCC Database Consortium prognostic scores (0, 1-2, or 3-6), number of prior lines of therapy (1 or 2), and geographic region (North America, Western Europe, or rest of the world). Imaging will be assessed by CT or MRI every 8 weeks through week 80, then every 12 weeks thereafter. The dual primary end points are progression-free survival per RECIST v1.1 as assessed by blinded independent central review (BICR) and overall survival. Secondary end points are objective response rate and duration of response per RECIST v1.1 as assessed by BICR, and safety. Safety and tolerability will be evaluated using a tiered approach. Clinical trial information: NCT04586231. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS373 **Trials in Progress Poster Session**

The SPARC-1 trial: A phase I study of neoadjuvant combination interleukin-1 beta and PD-1 blockade in localized clear cell renal cell carcinoma.

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Background: Immune checkpoint blockade has significantly improved outcomes for patients with renal cell carcinoma (RCC) in the metastatic setting. However, there is currently no neoadjuvant systemic therapy that improves outcomes for patients with localized RCC. Emerging data suggests that immunosuppressive myeloid cell populations within the tumor microenvironment (TME) represent a key mechanism of adaptive immune resistance. In pre-clinical models, targeting interleukin 1 beta (IL-1beta) can successfully re-establish anti-tumor immunity by shifting the myeloid cells towards M1-like tumor associated macrophages (TAM) and decreasing infiltration of immunosuppressive myeloid-derived suppressor cells (MDSCs). The SPARC-1 study is testing the hypothesis that neoadjuvant therapy with combined IL-1beta blockade (canakinumab) plus PD-1 blockade (spartalizumab) is safe and can successfully remodel the myeloid compartment towards a pro-inflammatory state in patients with localized RCC. **Methods:** This is a single-center, single-arm, phase I trial of patients with localized clear cell RCC (ccRCC) planned for nephrectomy (stage T1b-T4NanyM0). 14 patients will receive immunotherapy with combination canakinumab (300mg IV) plus spartalizumab (400mg IV) every 4 weeks x 2 doses given 6 weeks prior to nephrectomy. The primary endpoints are safety and feasibility. Secondary endpoints include tumor CD8 T cell infiltration, tumor MDSC infiltration and objective response rate. SPARC-1 offers a unique opportunity to utilize fresh tumor tissue to identify changes in the immune TME with single-cell discrimination following therapy. Therefore, correlative studies will include single-cell RNA-sequencing, multi-color flow cytometry and multiplexed immunofluorescence to quantify changes in the density and spatial proximity of distinct immune cell populations within the TME. The study is open with 4 patient currently enrolled at the time of submission. Clinical trial information: NCT04028245. Research Sponsor: Novartis.