LBA358 **Oral Abstract Session**

Adjuvant nivolumab monotherapy vs placebo for localized renal cell carcinoma at high risk of relapse after nephrectomy: Results from Part B of the randomized, phase 3 CheckMate 914 trial.

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LBA359 **Oral Abstract Session**

Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal cell carcinoma (ccRCC).

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LBA360 **Oral Abstract Session**

Subcutaneous nivolumab (NIVO SC) vs intravenous nivolumab (NIVO IV) in patients with previously treated advanced or metastatic clear cell renal cell carcinoma (ccRCC): Pharmacokinetics (PK), efficacy, and safety results from CheckMate 67T.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the February 1, 2024, issue of the *Journal of Clinical Oncology*.

Belzutifan versus everolimus in participants (pts) with previously treated advanced renal cell carcinoma (RCC): Patient-reported outcomes (PROs) in the phase 3 LITESPARK-005 study.

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Background: In the randomized, open-label, phase 3 LITESPARK-005 (NCT04195750) study, belzutifan treatment showed superior PFS (primary endpoint; HR 0.75 [95% CI 0.63–0.90]; P<.001) and ORR (key secondary endpoint; estimated percentage-point difference 18.4 [95% CI 14.0–23.2]; P<.00001) vs everolimus in pts with advanced/metastatic clear cell RCC that progressed after prior immune checkpoint and anti-angiogenic therapies. We present PRO findings for belzutifan vs everolimus in LITESPARK-005. **Methods:** PROs were evaluated by FKSI-DRS and EORTC QLQ-C30 questionnaires in all randomized pts with ≥1 dose study treatment and ≥1 completed PROs assessment, administered electronically on d 1 of wk 1, 3, 5, and 9, Q4W thereafter, at treatment discontinuation, and d 30 after last dose. Time to deterioration (TTD) and least square (LS) mean change from baseline as measured by FKSI-DRS and QLQ-C30 global health status/quality of life (GHS/QoL) and physical functioning (PF) scales were prespecified as secondary endpoints. PROs were not formally statistically tested and 95% CI and P-values were nominal and descriptive. **Results:** As of June 13, 2023 (data cutoff date at second prespecified interim analysis), median (range) follow-up was 25.7 mo (16.8–39.1). Median (range) duration of treatment was 7.6 mo (0.1–35.8) with belzutifan vs 3.9 mo (0.0–33.2) with everolimus; 84 (22.6%) vs 18 (5.0%) pts remained on treatment. 366 of 374 pts randomized to belzutifan and 354 of 372 pts randomized to everolimus were included in the PRO analysis population. Completion rates for FKSI-DRS and QLQ-C30 were >90% at baseline and >55% at wk 17 (~4 mo) in each arm. Meaningfully longer TTD in FKSI-DRS and QLQ-C30 GHS/QoL scores were observed for belzutifan vs everolimus (Table). LS mean changes in FKSI-DRS and QLQ-C30 GHS/QoL scores suggested stability from baseline to wk 17 with belzutifan vs worsening with everolimus, and a potential greater worsening in PF scores with everolimus vs belzutifan. **Conclusions:** Belzutifan was associated with prolonged TTD in FKSI-DRS and EORTC QLQ-C30. Score changes from baseline to wk 17 also favored belzutifan over everolimus. Overall, PRO results indicate better disease-specific symptoms and quality of life among pts treated with belzutifan compared with everolimus. Clinical trial information: NCT04195750. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	FKSI-DRS	QLQ-C30 GHS/QoL	QLQ-C30 PF
Belzutifan median TTD, mo	Not reached	19.35	19.32
Everolimus median TTD, mo	11.99	10.19	13.83
TTD HR (95% CI)	0.53 (0.41-0.69)	0.75 (0.58-0.96)	0.93 (0.72-1.20)
Nominal P-value for TTD	<.0001	.019	.55
Belzutifan LS mean change (95% CI)	−0.17 (−0.70-0.36)	0.28 (−1.98-2.53)	−4.75 (−6.87-−2.63)
Everolimus LS mean change (95% CI)	−1.62 (−2.17-−1.06)	−6.11 (−8.51-−3.70)	−7.22 (−9.47-−4.98)
Difference in LS means (95% CI)	1.45 (0.70-2.19)	6.38 (3.21-9.55)	2.47 (−0.59-5.54)

Nivolumab plus cabozantinib (N+C) vs sunitinib (S) for previously untreated advanced renal cell carcinoma (aRCC): Results from 55-month follow-up of the CheckMate 9ER trial.

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Background: N+C demonstrated superior progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in patients (pts) with previously untreated aRCC in the primary analysis of the phase 3 CheckMate 9ER trial (18.1 mo median follow-up). N+C maintained efficacy benefits vs S with 44.0 mo median follow-up. Here, we report updated efficacy in intent-to-treat (ITT) pts and by International Metastatic RCC Database Consortium (IMDC) risk, and safety with extended follow-up. **Methods:** Pts with aRCC were randomized to N 240 mg every 2 weeks + C 40 mg QD vs S 50 mg QD (4 weeks of 6-week cycles) until disease progression or unacceptable toxicity, with up to 2 y of N. The primary endpoint was PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included OS, ORR per RECIST v1.1 by BICR, and safety. **Results:** Overall, 323 pts were randomized to N+C and 328 to S (ITT). With 55.6 mo median (48.1 mo min.) follow-up for OS, median PFS was 16.4 vs 8.4 mo (hazard ratio [HR] 0.58, 95% CI 0.49-0.70) and median OS was 46.5 vs 36.0 mo (HR 0.77, 95% CI 0.63-0.95) with N+C vs S. ORR (95% CI) was 55.7% (50.1-61.2) vs 27.7% (23.0-32.9); 13.6% vs 4.6% of pts achieved complete response (CR); 6.5% vs 13.7% had progressive disease (PD), respectively. Median (range) time to response (TTR) was 2.8 (1.0-22.2) vs 4.3 (1.7-30.4) mo for N+C vs S, and median (95% CI) duration of response (DOR) was 22.0 (18.0-25.2) vs 15.2 (10.9-19.3) mo. Efficacy by IMDC favorable (FAV) and intermediate/poor (I/P) risk groups is reported in the Table. Among all treated pts (320 pts each arm), any-grade (grade $\geq$ 3) treatment-related adverse events (TRAEs) occurred in 97.5% (67.5%) vs 93.1% (55.3%) with N+C vs S. Any-grade TRAEs led to discontinuation of N or C in 28.1% of pts (N only, 10.0%; C only, 10.3%; N+C simultaneously, 6.6%; N+C sequentially, 1.3%) and of S in 10.9% of pts. Additional analyses in subgroups of clinical interest will be presented. **Conclusions:** With 55.6 mo median follow-up, N+C continues to maintain meaningful long-term efficacy benefits over S. No new safety concerns were identified. These results continue to support N+C as a standard of care for previously untreated aRCC. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

	FAV N+C; n = 74	FAV S; n = 72	I/P N+C; n = 249	I/P S; n = 256
mPFS (95% CI), mo	21.4 (12.8–24.6)	12.8 (9.4–16.6)	15.4 (11.1–18.6)	7.1 (5.7–8.9)
PFS HR (95% CI)	0.69 (0.48–1.00)	–	0.56 (0.45–0.68)	–
mOS (95% CI), mo	52.9 (40.8–NE)	58.9 (46.1–NE)	43.9 (34.9–51.9)	29.3 (23.7–36.2)
OS HR (95% CI)	1.10 (0.69–1.75)	–	0.73 (0.58–0.91)	–
ORR (95% CI), %	66.2 (54.3–76.8)	44.4 (32.7–56.6)	52.6 (46.2–58.9)	23.0 (18.0–28.7)
CR, %	16.2	8.3	12.9	3.5
PD, %	2.7	2.8	7.6	16.8
mTTR (range), mo[a]	2.8 (1.5–19.8)	4.3 (1.7–30.4)	2.8 (1.0–22.2)	4.4 (1.7–18.1)
mDOR (95% CI), mo[a]	18.7 (13.9–22.2)	17.8 (11.1–19.4)	23.1 (17.3–30.5)	13.8 (7.1–23.5)

[a]Based on pts with an objective response. m, median; NE, not estimable.

Nivolumab plus ipilimumab (NIVO+IPI) vs sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC): Long-term follow-up data from the phase 3 CheckMate 214 trial.

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Background: First-line NIVO+IPI has provided substantial long-term survival benefits over SUN in patients (pts) with aRCC in CheckMate 214. We report survival, response per independent radiology review committee (IRRC) and safety after 6 y minimum (80 mo median) follow-up in all randomized pts, by IMDC risk and in pts with overall survival (OS) $\geq$ 6 y (long-term survivors; LTS). Longer follow-up data (minimum, 7.5 y) will be presented. **Methods:** Pts with clear cell aRCC were randomized 1:1 to NIVO 3 mg/kg + IPI 1 mg/kg Q3W$\times$4 then NIVO 3 mg/kg Q2W vs SUN 50 mg QD for 4 wk on, 2 wk off. Endpoints: OS, progression-free survival (PFS) and objective response rate (ORR; both per IRRC using RECIST v1.1) in IMDC intermediate/poor risk (IP; primary), intent-to-treat (ITT; secondary) and favorable risk (FAV; exploratory) pts. Exploratory outcomes in LTS pts were assessed post hoc. **Results:** OS with NIVO+IPI vs SUN remained superior in ITT (HR 0.72) and IP (HR 0.68) pts; OS benefits were similar between arms in FAV pts (HR 0.87; Table). Median PFS was consistent with previous reports. ORR per IRRC was higher with NIVO+IPI vs SUN, with more ongoing responses in ITT (60% vs 50%) and IP (60% vs 50%) pts. In FAV pts, ORR was lower with NIVO+IPI vs SUN, yet more responses were ongoing (59% vs 52%, respectively). Median duration of response (DOR) was longer and complete response (CR) rate was higher with NIVO+IPI vs SUN regardless of IMDC risk. Incidence of any and grade 3-4 treatment-related adverse events remained largely unchanged. One additional drug-related death occurred with NIVO+IPI and zero with SUN since the previous database lock. In the LTS subgroup (NIVO+IPI, n = 208; SUN, n = 151), ORR was higher (66% vs 53%), more pts had a CR (27% vs 9%) and fewer progressed (4% vs 11%) with NIVO+IPI vs SUN. Median DOR was longer with NIVO+IPI (n = 137) vs SUN (n = 80) among LTS with confirmed response (76 vs 40 mo). Updated survival, response and safety data with 7.5 y minimum follow-up, along with additional subgroup analyses, will be presented. **Conclusions:** NIVO+IPI demonstrated long-term survival and more durable response benefits vs SUN in ITT and IP pts. CR rates were higher and median DOR was longer with NIVO+IPI vs SUN regardless of IMDC risk group, and in LTS pts. No new safety signals emerged. Clinical trial information: NCT02231749. Research Sponsor: Bristol Myers Squibb.

	ITT		IP		FAV	
Arm; n	**NIVO+IPI; 550**	**SUN; 546**	**NIVO+IPI; 425**	**SUN; 422**	**NIVO+IPI; 125**	**SUN; 124**
OS HR (95% CI)	0.72 (0.62-0.83)		0.68 (0.58-0.81)		0.87 (0.62-1.24)	
mOS (95% CI), mo	53 (46-65)	37 (32-44)	47 (35-56)	26 (22-33)	79 (65-NE)	68 (56-79)
PFS per IRRC, HR (95% CI)	0.86 (0.73-1.01)		0.73 (0.61-0.87)		1.60 (1.13-2.26)	
mPFS (95% CI), mo	12 (10-16)	12 (10-15)	11 (8-16)	8 (7-10)	12 (10-18)	29 (22-38)
ORR per IRRC, % (95% CI)	39 (35–44)	32 (29-37)	42 (37-47)	27 (23-31)	30 (22-38)	52 (43-61)
CR per IRRC, %	12	3	11	2	13	6
mDOR (95% CI), mo	75 (59-76)	25 (20-30)	75 (51-76)	20 (15-25)	61 (28-NE)	33 (25-51)

m, median; NE, not estimable.

Subgroup analyses of efficacy outcomes by baseline tumor size in the phase 3, open-label CLEAR trial.

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Background: In the primary analysis of the phase 3 open-label CLEAR trial, lenvatinib + pembrolizumab (L+P) showed statistically significant and clinically meaningful improvements in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) compared with sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC) (Motzer NEJM 2021). Outcomes were further corroborated by results of the final prespecified analysis of CLEAR (Motzer ASCO 2023). We report efficacy outcomes per baseline tumor size in the L+P arm of CLEAR. **Methods:** 1069 treatment-naïve pts with aRCC and a clear-cell component were randomized (1:1:1) to: L 20 mg PO QD + P 200 mg IV Q3W; or L 18 mg + everolimus 5 mg PO QD; or S 50 mg PO QD (4 wks on/2 wks off). Stratification factors included geographic region and MSKCC prognostic risk group. IMDC risk groups (derived programmatically) are presented in this analysis. Efficacy outcomes were evaluated by quartiles of baseline sums of diameters of target lesions. Tumor assessments were performed by independent imaging review per RECIST v1.1. **Results:** Pts were grouped into 4 categories: ≤Q1 (34.72 mm), >Q1 - ≤Q2 (60.06 mm), >Q2 - ≤Q3 (108.56 mm) and >Q3 per baseline tumor sizes (Table). For pts with ≤Q1 baseline tumor sizes, 40.7% and 58.0% were in the favorable and intermediate + poor IMDC risk subgroups, respectively. For pts with >Q3 baseline tumor sizes, 6.3% and 93.8% were in the favorable and intermediate + poor IMDC risk groups, respectively. Median OS, PFS, ORR, complete response (CR), partial response (PR), and near-CR (PR with maximum tumor shrinkage ≥75%) by baseline tumor size categories are in the Table. **Conclusions:** In CLEAR, clinically meaningful efficacy with L+P was observed across pts with aRCC irrespective of their baseline tumor sizes. These results support the use of L+P for the 1L treatment of aRCC across pts with both low and high baseline tumor size. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

		Baseline Sums of Diameters of Target Lesions[a]			
	Overall	≤Q1	>Q1 - ≤Q2	>Q2 - ≤Q3	>Q3
N	355	81	80	81	80
Median OS, mos	53.7	NE	NE	51.8	39.5
(95% CI)[b]	(48.7, NE)	(49.9, NE)	(47.2, NE)	(36.6, NE)	(32.1, 48.7)
Median PFS, mos	23.9	27.6	25.3	27.7	22.1
(95% CI)[b]	(20.8, 27.7)	(13.1, 35.9)	(16.6, 37.0)	(16.7, 42.2)	(12.7, 25.9)
ORR, %	71.3	75.3	80.0	72.8	71.3
(95% CI)[c]	(66.6, 76.0)	(65.9, 84.7)	(71.2, 88.8)	(63.2, 82.5)	(61.3, 81.2)
CR Rate, %	18.3	29.6	22.5	11.1	2.5
(95% CI)[c]	(14.3, 22.3)	(19.7, 39.6)	(13.3, 31.7)	(4.3, 18.0)	(0.0, 5.9)
PR Rate, %	53.0	45.7	57.5	61.7	68.8
(95% CI)[c]	(47.8, 58.1)	(34.8, 56.5)	(46.7, 68.3)	(51.1, 72.3)	(58.6, 78.9)
Near-CR Rate,[d] %	16.6	19.8	20.0	24.7	8.8
(95% CI)[c]	(12.7, 20.5)	(11.1, 28.4)	(11.2, 28.8)	(15.3, 34.1)	(2.6, 14.9)

[a]Includes pts with baseline target lesion assessments.
[b]Median was estimated with Kaplan-Meier product-limit method and 95% CIs were constructed with a generalized Brookmeyer and Crowley method.
[c]95% CI was calculated using asymptotic normal distribution.
[d]PR with maximum tumor shrinkage ≥75%.

Development of a patient-centered health-related quality of life (HRQOL) measure for metastatic renal cell carcinoma (mRCC): A three-phase study.

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Background: Patients (pts) with mRCC require a tailored HRQOL assessment. Previous research (Bergerot et al. Oncologist 2023; Bergerot et al. J Clin Oncol 2023) explored FKSI-19, EORTC QLQ-C30, and EQ-5D item relevance. We aimed to develop a tailored HRQOL measure for pts with mRCC through a three-phase approach involving patient engagement, expert input, and advocacy. **Methods:** In Phase 1, 117 pts with mRCC (83:34 M:F, median age=64) from the US, Europe and Brazil participated in a survey study to assess the relevance of items from established measures (FKSI-19, EORTC QLQ-C30, EQ-5D). In this cohort, 88% of pts had clear cell histology and 35%, 30% and 19% received immunotherapy alone, targeted therapy alone or combination therapy, respectively. Questions identified as relevant (base on ≥66% consensus) were selected for inclusion in a preliminary survey. Phase 2 involved assembling a panel of 11 experts who rigorously reviewed and refined survey questions. In Phase 3, preliminary version were presented to 8 patient advocates (5:3 F:M; 6:2 pts:caregivers) to ensure alignment with pts' needs and experiences. **Results:** Phase 1 analysis identified 10 items. Pts requested the inclusion of a question about social/family issues and better coverage of emotional symptoms. An 12-item questionnaire was created, and the expert committee refined three items to incorporate patient suggestions and added one item related to functional status (Table). This questionnaire included 1 cancer-specific item, 3 cancer or treatment-specific items, 3 non-specific emotional items, and 4 non-specific physical items. Patient advocates provided feedback, agreeing with the items excluded from previous questionnaires and those included. They suggested minor edits to item wording. **Conclusions:** The novel approach holds the potential to replace traditional HRQOL measures that may lack relevance to specific clinical circumstances. Further validation is planned in a phase 3 trial, ensuring its applicability in clinical practice. Research Sponsor: Kidney Cancer Association.

Categories	Items	Relevance
Cancer or Treatment-specific	I have lack of energy	78.6%
Cancer or Treatment-specific	I have pain	67.5%
Cancer or Treatment-specific	I have good appetite	74.4%
Emotional non-specific	I am sleeping well	70.1%
Cancer-specific	I worry that my condition will get worse	74.4%
Emotional non-specific	I feel depressed	66.7%
Emotional non-specific	My family and friends have felt burdened by my condition or treatment	New
Treatment-specific	I am bothered by side effects of treatment	67.5%
Physical non-specific	I am able to work (include work at home)	75.2%
Physical non-specific	I can still engage in activities that bring me joy and happiness despite my condition or treatment	89.7%
Physical non-specific	I am capable of care for myself independently	New
Physical non-specific	I am satisfied with my overall health and current quality of life	92.3%

Real-world practice patterns, treatment-related toxicity, and survival outcomes in older patients with metastatic renal cell carcinoma: Results from the Canadian Kidney Cancer information system (CKCis).

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Background: There is a paucity of data with respect to optimal management of metastatic renal cell carcinoma (mRCC) in older adults. Real world data may help close this knowledge gap and improve care for older patients with mRCC. **Methods:** The Canadian Kidney Cancer information system (CKCis) was utilized to identify patients with mRCC, categorizing them as either older (defined as age ≥75 years) or younger (age <75 years). We compared first line (1L) mRCC management strategies and treatment-related toxicities. Secondary outcomes were overall survival (OS) and time to treatment discontinuation (TTD). Chi-Square and Fisher's Exact tests were used to compare groups, and survival outcomes were measured by Kaplan-Meier method. Cox's proportional hazard ratio (HR) were reported by age adjusting for IMDC risk groups, histology, and Charlson Comorbidity Index (CCI) for OS and TTD. **Results:** 2576 patients were included (n=2203 <75 years old; n=373 ≥75 years old). Baseline demographics were comparable between groups, though older patients had more comorbidities (5+, 95% vs. 67%, $p<0.0001$) and more frequently had Karnofsky Performance Status <70% (18% vs. 13%, $p=0.01$). Older patients underwent metastasectomy less frequently (15% vs. 25%, $p=0.0001$) and were less likely to be enrolled in clinical trials (10% vs. 24%, $p<0.0001$). Older patients received 1L tyrosine kinase inhibitor (TKI) monotherapy more frequently (79% vs. 69%, $p<0.0001$) than immune checkpoint inhibitor (ICI)-based treatment, even when adjusted by year to account for changes in practice patterns in the post-ICI era (65% vs. 44%, $p<0.0001$). Amongst all patients, the TKI monotherapy most frequently prescribed was sunitinib, though older patients were more likely to receive pazopanib than younger patients ($p<0.0001$). Amongst all patients who received 1L ICI-based treatment, there was no difference in the type of ICI regimen (i.e. doublet ICI versus ICI plus TKI) prescribed when compared by age ($p=0.61$). Older patients did not experience more frequent treatment-related toxicities with ICI-based treatment. They did however experience more grade 3+ toxicity with TKI monotherapy. Older patients had shorter OS even when controlling for IMDC score, CCI and histology (HR 1.21, 95% CI 1.03-1.43, $p=0.02$). There was no difference in TTD by groups. **Conclusions:** Patients ≥75 years of age received TKI monotherapy more frequently than those <75 years of age, though when they received ICI-based regimens, they did not experience more treatment-related toxicities nor more dose modifications. Clinicians should individualize treatments for older patients not solely based on age, but after discussion of all available options in a patient-centered manner, considering comorbidities, disease burden, and patient preferences. Research Sponsor: None.

Real-world efficacy and toxicity of ipilimumab and nivolumab as first line treatment of metastatic renal cell carcinoma (mRCC) in a subpopulation of elderly and poor performance status patients.

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Background: Ipilimumab and nivolumab (ipi/nivo) improved overall survival (OS) and response rates compared to sunitinib in the pivotal Checkmate 214 trial of intermediate/poor risk mRCC. A subgroup analysis showed no significant difference in OS for ipi/nivo in pts 65 to 75 years old (yo), as well as pts >75 yo. In another subgroup analysis, Karnofsky performance status (KPS) <70 was associated with worse median OS compared with pts with KPS ≥ 70. We evaluated efficacy and toxicity of ipi/nivo in an older and frailer population in a real-world cohort. **Methods:** Analysis was conducted on a real-world cohort with mRCC (N=378) treated with ipi/nivo as first line treatment from the Canadian Kidney Cancer Information System (CKCis) database from January 2011 to March 2022. Median follow-up was 14.3 m (range 0 to 87.6). A comparison was made between outcomes and toxicity in pts ≥ versus (vs) <70 yo, ≥ vs <75 yo, KPS < vs ≥70, and ≥70 yo with KPS <70 vs <70 yo with KPS >70. Toxicity was graded as per CTCAE v4.03 or any toxicity that resulted in a dose/schedule change. OS, progression free survival (PFS) and time to treatment failure (TTF) were calculated by Kaplan-Meier analysis. Log rank tests were used for comparison between groups. Multivariate analysis was done including IMDC for all outcomes. **Results:** Median OS was worse in older patients at 30.0 m in pts ≥ 70 yo vs 45.4 m in pts < 70 yo (p=0.060), and 19.0 m in the pts ≥ 75 yo vs 45.5 m in pts < 75 yo (p=0.003) despite similar disease control rates and toxicity. Median PFS was similar in younger and older pts: < vs ≥ 70 yo (p=0.560) and < vs ≥ 75 yo (p=0.296). Median TTF was comparable in < 70 yo and ≥ 70 yo (p=0.106) and < 75 and ≥ 75 yo groups (p-value=0.733). Median OS, PFS and TTF were comparable in pts KPS < 70 vs pts KPS ≥ 70 and in pts ≥70 yo with KPS < 70 vs pts < 70 yo with KPS >70. Adjusted and unadjusted analysis showed no difference in OS and PFS between groups. **Conclusions:** Use of ipi/nivo in mRCC in older patients was associated with inferior OS, while decreased performance status had equivalent OS. Both groups had equivalent TTF and PD without higher toxicity. We believe that ipi/nivo is a reasonable treatment option for older and low performance status patients. Research Sponsor: None.

	Age< 70 yo vs ≥70 yo			Age< 75 yo vs ≥75 yo			KPS< 70 vs KPS ≥ 70			Age < 70 yo with KPS ≥70 vs Age ≥70 yo with KPS < 70		
	< 70 yo	≥70 yo	p	< 75 yo	≥75 yo	p	KPS < 70	KPS ≥70	p	< 70 yo with KPS ≥70	≥70 yo with KPS ≤70	p
N	284	94		335	43		207	171		335	43	
Median OS (m)	45.4	30.0	0.060	45.5	19.0	0.003	34.6	45.4	0.160	40.8	30.0	0.188
Median PFS (m)	9.6	5.8	0.560	9.2	5.9	0.296	7.4	10.2	0.448	9.3	7.7	0.910
Median TTF (m)	11.7	9.7	0.106	10.6	12.6	0.733	10.2	12.2	0.804	11.0	7.4	0.204
Progressive disease N (%)	95 (50.0)	24 (47.1)	0.709	108 (49.3)	11 (50.0)	0.951	65 (46.1)	54 (54.0)	0.227	107 (49.3)	12 (50.0)	0.949
Toxicity rates N (%)	66 (23.2)	20 (21.3)	0.694	76 (22.7)	10 (23.3)	0.933	45 (21.7)	41 (24.0)	0.606	76 (22.7)	10 (23.3)	0.933

Assessing tobacco-related mortality trends in genitourinary cancers: A 1990-2019 analysis.

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Background: Tobacco consumption is a well-established risk factor for genitourinary cancers like urothelial and renal cell. This study aims to examine mortality trends associated with tobacco use in these cancer types, both globally and within the U.S., over the period of 1990 to 2019. **Methods:** Data from the Global Burden of Disease database, based on the International Classification of Diseases versions 10 and 9, were utilized to extract mortality statistics for bladder cancer (BC) and kidney cancer (KC). Age-standardized death rates (ASDRs) for the overall population, as well as Tobacco Attributable Mortality (TAM) were collected by sex and year. TAM was calculated by applying population attributable fraction to cause-specific deaths and disability-adjusted life years by year, location, age group and sex. The database also provided Annual Percentage Change (APC) data. Trends were analyzed using Joinpoint regression. **Results:** Smoking rates as well as mortality due to tobacco consumption have steadily decreased for both cancers in both sexes globally as well as in the U.S. during the study period. Globally, ASDRs exhibited a decreasing trend for BC and KC, and for both sexes, excluding an increase in ASDR for KC in males (+0.2). In the U.S. ASDR decreased for KC but not for BC in males (Table 1). BC demonstrated the highest proportion of tobacco-induced mortality among the three cancer types, with a nearly 50% contribution globally among males in 1990 that reduced to 39% in 2019. Overall, the tobacco-induced ASDR for kidney cancer in males remained relatively constant globally. Despite reductions over three decades, BC still exhibited a high proportion of mortality attributed to tobacco, particularly among males (39% globally; 31% in the U.S.). In 2019, the U.S. continued to experience higher tobacco-induced mortality rates among females for both KC (17.1 vs. 8.8%) and BC (26.9 vs. 14.3%) compared to the global average. **Conclusions:** Despite the multiple advances in cancer treatment in the last decades, TAM remains minimally unchanged. While there has been a general reduction in smoking rates overall, a substantial burden persists for tobacco-related malignancies—particularly for BC and KC. These findings underscore the need for heightened awareness and more robust tobacco control policies both globally and within the U.S. Research Sponsor: None.

		ASDR (1990-2019) (APC)		ASDR (1990-2019) (APC) [Tobacco]		Percentage of mortality (1990-2019) [Tobacco]	
Cancer	Region	Male	Female	Male	Female	Male	Female
BC	Global	6.1 → 5.1 (-0.17)	1.7 → 1.4 (-0.2)	2.9 → 2.0 (-0.3)	0.3 → 0.2 (-0.4)	46.8 → 39.0 (-16.7)	19.3 → 14.3 (-25.9)
	U.S.	6.3 → 6.4 (+0.02)	1.9 → 1.8 (-0.04)	2.5 → 2.0 (-0.21)	0.6 → 0.5 (-0.18)	40.2 → 31.3 (-22.1)	31.7 → 26.9 (-15.1)
KC	Global	2.5 → 3.0 (+0.2)	1.4 → 1.3 (-0.02)	0.7 → 0.7 (-0.01)	0.2 → 0.1 (-0.26)	27.3 → 22.7 (-16.8)	11.7 →8.8 (-24.6)
	U.S.	5.3 → 5.2 (-0.02)	2.4 → 2.1 (-0.11)	1.5 → 1.1 (-0.24)	0.5 → 0.4 (-0.27)	28.5 → 22.0 (-22.5)	20.9 → 17.1 (-18.2)

Comparison of outcomes between patients of African and European descent with metastatic renal cell carcinoma receiving immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICIs) and ICI/ tyrosine kinase inhibitor (TKI) combinations are standard front-line tx options for pts with metastatic renal cell carcinoma (mRCC). However, <1% of pts enrolled into trials studying these agents were of African descent. The primary outcome of this study was to compare real world progression-free survival (rwPFS) in Black and White pts, respectively, with mRCC receiving front-line ICI-based therapies versus sunitinib. **Methods:** Pts with mRCC who received front-line ICI-based tx or sunitinib after 2011 were included from the Flatiron Health electronic health record-derived database.Pt demographics and clinical characteristics, including age, gender, ECOG score, documented insurance, stage at diagnosis, IMDC score, and year of diagnosis were described and compared using t-tests for continuous data, and Chi-squared tests for categorical data. We compared rwPFS in pts who received ICI versus sunitinib in strata defined by race. We first performed separate analyses in Black and White patients, and then formally tested the interaction between treatment type and race using the full cohort. Unadjusted rwPFS was summarized using Kaplan-Meier curves with log-rank tests. Multivariable Cox proportional hazards models adjusted for relevant factors were used to assess associations with outcomes. Since the benefit of ICI-based treatments increases after 10 months, these models were stratified at 10 months for estimating treatment effects at each interval. **Results:** Of 2,592 eligible pts, 2,379 (91.8%) were White, and 213 (8.2%) were Black. Of these, 1453 (56%) received ICI-based tx and 1139 (44%) received sunitinib, the proportion being the same in both groups. IMDC favorable, intermediate/poor and unknown risk was noted among 6%, 77.5% and 16.4% of White patients and 3.3%, 86.8% and 9.9% of Black patients (p=0.01). More Whites than Blacks had nephrectomies (65.2% vs 55.9%). Median age was 64 years. In adjusted analysis, the hazard ratio (HR) of rwPFS for Whites receiving ICI-based tx vs sunitinib was 0.872 (p=0.036) in the first 10 months and 0.664 (p<0.001) after 10 months. In Blacks, the HR of rwPFS was 0.641 (p=0.067) in the first 10 months and 0.514 (p=0.072) after 10 months in pts receiving ICI-based tx vs sunitinib. There was no differential tx effect by race in the first 10 months or after 10 months (p=0.113, p=0.751, respectively). Similarly, upon subgroup analysis by tx, no differential tx effect was noted between Black and White pts receiving ICI/ICI or ICI/TKI based tx compared to sunitinib. **Conclusions:** No significant differential treatment effect was seen between White and Black pts receiving ICI-based tx. Smaller numbers of Black pts and reliance on self-reported race may have affected our results. These results indicate that ICI-based first line tx should be considered for both Black and White pts. Research Sponsor: None.

Disparities in uptake of new FDA-approved therapies for metastatic clear cell renal cell carcinoma.

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Background: Multiple new therapies for metastatic clear cell renal cell carcinoma (mccRCC) have been approved in the past decade. Real-world (RW) data on access to novel therapies and the impact on health-related disparities are limited. This study assessed RW access to novel therapies along with racial and social disparities for mccRCC patients and their impact on clinical outcomes. **Methods:** The longitudinal Flatiron Health database was queried for adult patients with mccRCC who received systemic treatments from Jan 2011 to Dec 2022 with at least two documented clinical visits. Patients < 45 years old were excluded. Data was collected on age, gender, race, ethnicity, ECOG status, practice type, stage, smoking status, socioeconomic status (SES) defined by the Yost index, insurance status, overall survival (OS), and the first 14 treatments received. Patients were categorized as receiving a novel therapy if they received a first line mccRCC regimen during prespecified time windows starting on their first-line FDA approval date until 6 months later or when the next novel drug was approved, whichever date came later. Chi square test was used to assess variables across race. Univariable Cox proportional hazard models were used for OS analysis. R version 4.3.0 was used for programming. **Results:** 7,113 patients were included. 68.8% of the cohort was white, 7.1% Black, 1.4% Asian, 12.7% other, and 10.1% missing. Advanced age and receiving care in a community practice setting were associated with worse OS (CI 1.45-1.81 and CI 0.70-0.81, respectively), while SES was not (CI 0.81-1.01 for highest vs lowest group). Black race was associated with a 24% increased hazard of mortality compared to white race (CI 1.11-1.39, p=0.0003), and this was more pronounced in patients <65 years old (CI 1.17-1.63, p=0.0001). 31.4% of patients received at least one novel therapy during the study period, and there were no differences by race. Receipt of novel therapy was not statistically associated with improved OS (p=0.1660). **Conclusions:** This is the first study in the immunotherapy era to highlight the worse OS of Black patients with mccRCC. Access to care at an academic center was associated with improved OS. Access to novel therapies did not differ between racial groups in the US using RW data. Research Sponsor: Flatiron Health.

Receipt of novel therapy by race.

Therapy	FDA First-line Approval Date	White	Black	Other	Total
Pazopanib	10/19/09	846 (17.3%)	85 (16.9%)	246 (14.3%)	1177 (16.5%)
Cabozantinib	12/19/17	146 (3.0%)	14 (2.8%)	49 (2.8%)	209 (2.9%)
Ipilimumab, Nivolumab	5/16/18	276 (5.6%)	28 (5.6%)	110 (6.4%)	414 (5.8%)
Pembrolizumab, Axitinib	4/19/19	13 (0.3%)	0 (0%)	4 (0.2%)	17 (0.2%)
Avelumab, Axitinib	5/14/19	11 (0.2%)	0 (0%)	5 (0.3%)	16 (0.2%)
Nivolumab, Cabozantinib	1/22/21	252 (5.2%)	28 (5.6%)	104 (6.0%)	384 (5.4%)
Any novel therapy		1556 (31.8%)	158 (31.5%)	524 (30.5%)	2238 (31.4%)
No novel therapy		3335 (68.2%)	344 (68.5%)	1196 (69.5%)	4875 (68.5%)
Total		4891	502	1720	7,113

Association between thymectomy and incidence of renal cell carcinoma (RCC).

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Background: Recently, thymectomy in adults has been linked to a higher incidence of several malignancies (Kooshesh *et al* NEJM 2023). Accompanying translational studies suggest that depleted T-cell production (both CD4+ and C8+) and decreased clonality may selectively drive the pathogenesis of immunogenic cancers such as RCC. We sought to confirm this finding in a large population-based cohort. **Methods:** We interrogated the California Office of Statewide Health Planning and Development (OSHPD) database, which collects information from all inpatient admissions, emergency room visits, and inpatient/outpatient procedures in the state. Patients who underwent thymectomy and nephrectomy (specifically for RCC) were identified from Jan 1, 2012, to Dec 31, 2019, using CPT and ICD-9/10 codes. The frequency of nephrectomy following thymectomy was computed. The frequency of both surgical interventions in the general population was derived by comparing their respective incidence in the OSHPD database against age-matched California census data. Chi square test was used to determine differences among groups. Fisher's exact test was used to determine if the incidence of nephrectomy following thymectomy was different from the incidence of nephrectomy overall. **Results:** During the study period, 1,969 pts (mean age 56) underwent thymectomy and 31,093 pts (mean age 57) underwent nephrectomy. Relative to patients who underwent thymectomy, a larger proportion of patients undergoing nephrectomy were male (57% vs 45%) and Hispanic (28% vs 18%) ($p<0.01$)., while a smaller proportion was Asian (7% vs 18%) ($p<0.01$). Expressed as a percentage of the underlying age-matched population (18,343,792 pts), 0.01% of pts received thymectomy, and 0.17% of pts underwent nephrectomy. A total of 11 pts underwent nephrectomy following thymectomy, suggesting an incidence of 0.56% in this cohort. This was significantly higher than the incidence of nephrectomy in the population at large ($P=0.002$). The median age of patients who had a nephrectomy for RCC with a prior thymectomy was considerably younger than the general population who underwent a nephrectomy (mean age 52 vs. 57 years). **Conclusions:** In a large population-based study, we observed a significantly higher rate of nephrectomy for RCC in patients who had received prior thymectomy. These results bolster previous studies done in smaller datasets. Further work is needed to define causality and clarify the mechanism of this association. Research Sponsor: None.

Comparing molecular variations and outcomes in Hispanic and non-Hispanic patients with metastatic clear cell renal cell carcinoma (ccRCC).

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Background: Hispanic patients with renal cell carcinoma (RCC) have worse clinical outcomes than non-Hispanic White (NHW) patients. It is unclear if this disparity is related to biological differences or social determinants of health (SDOH). There is limited knowledge about potential genetic variations in RCC between these ethnic populations. **Methods:** Patients with metastatic ccRCC evaluated at UCSD were retrospectively identified from chart review or a single institutional database. Patients with genomic sequencing on tissue samples from primary kidney and/or metastatic sites were included for analysis. Patients were categorized as non-Black Hispanic or NHW based on self-identification. Logistic regression was applied for the presence of divergent frequencies of somatic mutations. Cox regression models evaluated the effect of additional factors on overall mortality, with correction for multiple tests using Benjamini-Hochberg method. **Results:** The analysis included 103 patients with metastatic ccRCC, of whom 46% were Hispanic. We did not observe statistically significant differences in median age at diagnosis (61 vs 62 years), BMI (28 in both), proportion of males (74% vs 73%), never smokers (47% vs 56%), sarcomatoid component (24% vs 17%), receipt of systemic therapy (92% vs 96%) or treatment initiated after 2017 (57% vs 56%) between Hispanic and NHWs. There were also no differences in the number or locations of metastases between ethnic groups. Hispanics were more likely to have public health insurance (34% vs 9%, $p<0.01$) and IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) intermediate/poor risk disease (81% vs 55%, $p<0.01$). Hispanics had a higher frequency of *BAP1* mutations (28% vs 7%, p=0.01) compared to NHWs, whereas NHWs had more frequent *TP53* (24% vs 4%, p=0.01) and *SETD2* alterations (29% vs 4%, $p<0.01$). *VHL* (80% vs 74%, p=0.51) and *PBRM1* (26% vs 36%, p=0.34) mutations were comparable between Hispanic and NHWs. First-line treatment regimens were similar between the two groups: tyrosine kinase inhibitor (TKI) monotherapy (45% vs 42%), immunotherapy (IO/IO) doublet (23% vs 27%) and combined IO/TKI (15% vs 11%). On multivariable analysis, there was a significant difference in OS between Hispanic and NHWs (HR 3.60, 95%CI 1.49-8.67, adjusted p= 0.04) after correcting for age, sex, smoking, insurance, IMDC risk group, number of metastatic sites, sarcomatoid feature, therapy regimen and *VHL*, *PBRM1*, *SETD2*, *TP53* and *BAP1* mutations. **Conclusions:** We demonstrated a marked association in survival outcomes and differences in the mutational landscape of ccRCC between Hispanic and NHW patients. These findings underscore the interplay between genetic variations and social determinants, especially given the observed insurance disparities. Our study emphasizes the need for further research in ccRCC across diverse ethnicities. Research Sponsor: None.

First-in-human safety, imaging and dosimetry of [^{68}Ga]Ga-DPI-4452, a novel CA IX-targeting peptide, in patients with clear cell renal cell carcinoma.

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Background: Carbonic anhydrase IX (CA IX) is overexpressed in clear cell renal cell carcinoma (ccRCC) and is associated with aggressive tumor behavior, treatment resistance and overall poor outcomes. DPI-4452 is a first-in-class, cyclic peptide that binds with high affinity to CA IX. Radiolabeling DPI-4452 with gallium-68 ([^{68}Ga]Ga-DPI-4452) or lutetium-177 ([^{177}Lu]Lu-DPI-4452) is an innovative, theranostic approach for identifying and treating patients with CA IX-expressing tumors. Compared with existing antibody approaches, a radiolabeled peptide may confer better characteristics for both PET-CT imaging and therapy. This first-in-human study (NCT05706129) is evaluating the theranostic potential of [^{68}Ga]Ga-DPI-4452 and [^{177}Lu]Lu-DPI-4452 in patients with unresectable metastatic ccRCC, colorectal cancer or pancreatic ductal adenocarcinoma tumors. Here we report safety, tolerability, pharmacokinetics, dosimetry and imaging characteristics of [^{68}Ga]Ga-DPI-4452 from the completed ccRCC imaging cohort. **Methods:** The DPI-4452 peptide contains a DOTA cage and is radiolabelled with [^{68}Ga]Ga. Following intravenous injection of [^{68}Ga]Ga-DPI-4452, patients underwent serial PET-CT imaging, urine and blood sampling to assess imaging characteristics, biodistribution, and dosimetry of [^{68}Ga]Ga-DPI-4452. Patients were followed for 7 days post-injection for safety observations. **Results:** A mean activity of 185 MBq [^{68}Ga]Ga-DPI-4452 was administered to 3 patients with ccRCC. No clinically significant toxicities were observed. PET-CT images showed rapid and sustained tumor uptake over 4 h, as well as rapid renal elimination. At 1 h, the maximum tumor standardized uptake value (SUV_{max}) across 36 lesions ranged from 6.8 to 211.6, with a mean of 64.6. Seventeen of these lesions (found in lymph nodes, lung, pancreas, parotid gland and other sites) were not detectable on prior contrast-enhanced CT. OLINDA dosimetry estimates revealed that the organs receiving the highest absorbed doses (mean [SD] mGy/MBq) were stomach wall (0.33 [0.10]), small intestine wall (0.33 [0.08]) and gallbladder wall (0.21 [0.12]), with a mean whole body effective dose of 0.06 [0.02] mSv/MBq. Absorbed doses in the kidney, liver and bone marrow were low. Over 80% of total administered radioactivity cleared from the bloodstream within 1 h. **Conclusions:** [^{68}Ga]Ga-DPI-4452 provides exceptional images in patients with ccRCC without clinically significant toxicity. Very high SUVs and tumor-to-background ratios suggest potential for use in both diagnostics and patient selection for therapy. The tumor retention and rapid elimination support potential of [^{177}Lu]Lu-DPI-4452 radioligand therapy. Clinical trial information: NCT05706129. Research Sponsor: Debiopharm International SA.

Patterns of early 18F-FDG PET response to nivolumab (NIVO) and ipilimumab nivolumab (IPINIVO) in patients with metastatic renal cancer (MRC).

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Background: Immunotherapy with IPINIVO and NIVO is a standard treatment in MRC. This leads to recruitment and activation of immune cells. The 'immune burst' is seen at 1-4 weeks. Glycolysis leads to cellular 18F-FDG uptake. This can reflect malignancy. Sensitivity for renal tumours is poor, though high SUV suggests aggressive behaviour. Sensitivity for metastases can be 90% This study investigated 18F-FDG uptake in patients with MRC prior to treatment with immunotherapy. A scan was also performed at 2 weeks to assess a possible 'flare', due to glycolysis of the immune infiltrate, before significant standard radiological change was expected. **Methods:** Twenty six patients with MRC were enrolled. 8 patients had IPINIVO first line, and 18 had NIVO second line. Patients had a PET scan before and 2 weeks after treatment. Maximal standardised uptake values (SUV) were measured and corrected (COR) to the hepatic SUV. **Results:** All patients had some 18F-FDG avid metastases. SUVs varied within the same patient. For IPINIVO patients SUVmax was 17, mean 5.8 (3.7 and 2.5 COR respectively) and for NIVO patients SUV max was 25.1, mean 5.1. (7.6 and 2.3 COR respectively). There was no difference in mean SUV in the 2 groups (p=0.5). For NIVO patients there was a trend for patients who had a longer response to first line tyrosine kinase inhibitor, hence better prognosis, to have a lower SUV. (p=0.18) For NIVO there was a 12.4 % mean increase in SUV (p=0.06) In 8/16 patients there was a >20% increase in SUV in the measured metastases (mean 50.4 % increase, range 22.2 – 142.9). Flare occurred at a range of tumour sites. Only metastases which were 18F-FDG avid had a flare. In 4 patients there was a >20% decrease in SUV. (Mean 41.2 Range -21.2% to -55.3%) For IPINIVO in 4/8 patients there was a >20% increase in SUV, mean 57.2 (Range 21-134%) Flare only occurred in lymph nodes and an adrenal gland. In 2 patients there was a >20% decrease in SUV. (Mean - 50.7 Range -21.2% to -64%) Two patients had normal tissue flare: in thyroid, and mediastinal nodes. **Conclusions:** This is the first study to demonstrate tumour 18F-FDG flare in patients with MRC following immunotherapy, which may be due to influx and activation of glycolytic immune cells. There is a suggestion that tumour biology, and response to first line tyrosine kinase inhibitor is reflected in the SUV of metastases in patients having treatment with second line nivolumab. Research Sponsor: Bristol Myers Squibb.

Baseline CD8 lymph node avidity with 89-Zr-crefmirlimab in patients with metastatic renal cell carcinoma and response to IO therapy.

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Background: Prior studies with crefmirlimab, a 89-Zr labeled antibody with specificity for CD8+ cells, have shown a strong correlation with SUV uptake and IHC of the same lesions validating its use (Pal 2023). We predicted that responders to IO therapy would have higher CD8 lymph node avidity than non-responders. **Methods:** Pts enrolled had a diagnosis of mRCC and must have received IO therapy (CPI/TKI, CPI/CPI, or CPI monotherapy). Pts obtained a crefmirlimab PET/CT within 1 week before CPI infusion as baseline. PET intensity was determined using SUV_{Max}, SUV_{Mean}, SUV_{Peak}. Highly avid lymph nodes ($SUV_{Max} > 10$) were quantified. Best overall response was determined using RECIST 1.1 criteria with SUV values and number of CD8 PET-avid lymph nodes compared using a Wilcoxon Signed Rank test in R. **Results:** A total of 17 pts (9 M: 8 F) were enrolled across 3 sites with 9 pts locally available for analysis. The median age of pts was 64 years old (54-71). Histology types included 12 clear cell (71%), 2 papillary (12%), and 3 indeterminate (17%). There were 3 responders (18%), 12 non-responders (71%), and 2 non-evaluable (12%). The most common treatment regimens patients received in descending order were cabozantinib + nivolumab (44.44%), nivolumab (33.33%), and ipilimumab + nivolumab (22.22%). Strong correlation was observed between CD8 cell density and SUV_{Mean} ($p < 0.0003$ by Spearman's correlation). The average number of CD8 PET-avid lymph nodes (defined as $SUV_{Max} > 10$) in responders was 6 versus 1.17 in non-responders ($p = 0.025$, 95% CI [1.99,7]). SUV_{Max}, SUV_{Mean}, SUV_{Peak} across all CD8 PET-avid lymph nodes for responders were 15.58, 12.63, 11.44 and for non-responders were 9.86, 8.53, 7.79 respectively. The difference between SUV_{Max}, SUV_{Mean}, SUV_{Peak} values reached statistical significance for all three values ($p = 0.023$ 95% CI [3.42,7.84], $p = 0.023$ 95% CI [2.64,5.84], $p = 0.029$ 95% CI [1.18, 5.41] respectively). **Conclusions:** Our results show that pts with higher number of CD8 PET-avid lymph nodes at baseline was associated with better response to IO therapy; responders also had overall higher SUV uptake in CD8 PET-avid lymph nodes than non-responders. Our findings suggest that those with a more enriched CD8 phenotype trended towards better outcomes and may be a reliable predictor for IO therapy response. Clinical trial information: NCT03802123. Research Sponsor: ImaginAb.

Germline pathogenic variants in universal screening of genitourinary malignancies: A multisite single institution prospective study.

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Background: Germline genetic testing (GGT) is becoming increasingly important in the management of genitourinary (GU) malignancies as novel targeted drug therapies emerge. Selection for genetic studies and testing has historically been highly selective and based on pathologic characteristics, family history, and age of diagnosis. The aim of our study was to investigate the prevalence of pathogenic variants (PGVs) in inherited cancer susceptibility genes utilizing a universal testing approach and to characterize the rate of PGVs that would have been missed based on current NCCN guidelines. **Methods:** A multisite single-institutional prospective study (INTERCEPT) offered GGT to all patients with new or active diagnoses of GU malignancies (bladder, prostate, and renal cancers) from April 1, 2018 to March 31, 2020 at Mayo Clinic Arizona, Mayo Clinic Florida and Mayo Clinic Rochester. Participants were offered GGT with a panel of >80 genes through Invitae Corp. Demographic, tumor characteristics and genetic results were evaluated. PGVs were classified as high-, intermediate-, or low- penetrance variants based on published literature. Respective NCCN GU GGT guidelines were used to determine if the PGVs discovered using our universal testing approach would have been missed with guideline-directed GGT. **Results:** A total of 3095 pan-cancer patients were enrolled in the study; 601 of which had a GU malignancy including: prostate cancer (358 patients), renal cancer (137), and bladder cancer (106). The mean age of enrollment was 66.8 years (SD 9.1), 89% were male, and 85.9% of patients were Non-Hispanic white. PGVs were identified in 82 of all GU patients (13.6%) and variants of undetermined significance (VUS) in 289 (48.1%) patients. PGV prevalence breakdown by cancer type was: 13.7% of prostate, 13.1% renal, and 14.2% bladder cancer patients. The proportion of high penetrance PGVs varied by malignancy type. Of all patients, 326 (54.2%) had advanced (stage III/IV) disease and 377 (64.4%) of these were metastatic upon initial evaluation. The majority of all PGVs identified were incremental, defined as PGVs that would not have been identified based on guideline-concordant GGT: 100% (15/15 patients) with bladder, 77.8% (14/18) with renal, and 57.1% (28/49) with prostate cancer. **Conclusions:** Universal GGT for prostate, renal and bladder cancer revealed that over 1 in 10 patients harbored potentially actionable PGVs, most of which would not have been identified with guidelines-based GGT. Utilization of GGT can impact our understanding of GU cancer pathogenesis, aid in familial cascade testing, and influence treatment decisions. Research Sponsor: None.

Prostate-specific membrane antigen expression in endothelial cells of renal tumor-associated neovasculature and risk of recurrence for renal cell carcinoma.

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Background: PSMA is highly expressed in prostate epithelial cancer cells and used not only for diagnostic but also for therapeutic purposes. Despite its name, PSMA is not specific in prostate cells and is also expressed endothelial cells within the neovasculature of other tumors including renal cell carcinoma. PSMA is particularly the correlation of increased PSMA expression with prostate cancer aggressiveness, but is unknown in renal cell carcinoma patients. Here we estimate whether PSMA expression in endothelial cells of renal tumor-associated neovasculature is associated with pathological venous invasion and prognosis for patients after renal tumor surgery. **Methods:** A total of 45 patients who underwent radical or partial nephrectomies performed at our institution were included in this study. We investigated pathological venous invasion and PSMA expression in tumor-associated vessels around renal cell carcinoma by immunostaining using removed tumor tissue. The PSMA immunostain was evaluated in tumor-associated vessels according to the staining intensity and divided into three groups: weak, moderate, and strong, respectively. **Results:** Higher PSMA expression group is increased the percentage of patients with histologically observed venous invasion. The level of PSMA immnostain were detected in 18 cases at weak, 11 at moderate, 16 at strong. Ten patients after surgery had recurrence during the observation period, and the prognosis was worse in the group with strong PSMA expression in tumor-associated vessels around renal cell carcinoma. **Conclusions:** PSMA expression in endothelial cells of renal tumor-associated neovasculature may be a novel prognostic factor for renal cell carcinoma. Research Sponsor: None.

Fluorescence in situ hybridization utility in the care management of renal cell carcinoma (prospective study, 30 cases).

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Background: In Morocco, Kidney cancer is the 18th most common tumour and the 19th lethal cancer in 2020. The average age of diagnosis is 65 years and men are more affected. Molecular studies of renal cell carcinoma (RCC) allowed the detection of several genetic abnormalities in each histological subtype. These aberrations got different diagnostic value depending on their specificity, prognostic implication and for some a therapeutic utility since the development of targeted therapies. The aim of our study is to evaluate the utility of fluorescence in-situ hybridization (FISH) in the diagnostic and the prognostic categorization of patients with renal cell carcinoma. **Methods:** We included prospectively cases of RCC diagnosed after histological examination and immunohistochemistry analysis for some cases. The methodology consisted in highlighting by FISH molecular abnormalities for each histological subtypes using Zytolight probes. Probes were chosen depending on the histological diagnosis and their corresponding molecular abnormalities. **Results:** A total of 30 cases of RCC were included. Clear cell carcinoma (ccRCC) represented 56,6%(17 cases) followed by papillary RCC (pRCC) with 20% (6 cases), chromophobe RCC (chRCC) with 10% (3 cases), 2 cases (6,6%) with uncertain diagnosis clear cell carcinoma or papillary carcinoma and one case of renal oncocytoma (RO) (3,3%), tubulo-cystic RCC tcRCC (3,3%). The FISH method supported the morphological diagnosis in all cases except in one biopsy diagnosed histologically as a ccRCC and this method allowed the diagnosis correction to a pRCC by the detection of a polysomy of chromosome 17 described in this histological subtype. The FISH method can also be used in prognostic categorisation of patients by the detection of some genetic aberrations with a prognostic implication like the loss of CDKN2a located in the long arm of chromosome 9 which predict a worse diagnosis. **Conclusions:** FISH method got an good performance in the diagnostic approach of RCC especially in cases with non-conclusive histology and immunohistochemistry. It can also be used in the prognosis of this tumour in addition to other histo-prognostic factors. This method will lead to more precision in diagnosis and better care management personalisation in RCC.
Research Sponsor: None.

Mayo Adhesive Probability score to predict renal function following partial nephrectomy.

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Background: Mayo Adhesive Probability (MAP) score, which measures adherent perinephric fat in renal cell carcinoma (RCC), is associated with surgical complexity and cancer progression in patients undergoing partial nephrectomy (PN). PN carries perioperative risk but preserves renal function versus radical nephrectomy (RN). We analyzed whether MAP score can predict long-term postoperative renal function in localized RCC patients who underwent PN. **Methods:** We reviewed our nephrectomy database to identify pT1-T3a RCC patients who underwent PN. Patients with metastatic disease, IVC thrombus, multiple masses, and prior nephrectomy were excluded. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2021 formula and patients with values <15mL/min/1.73m2 were excluded. We calculated MAP scores from preoperative cross-sectional imaging and dichotomized patients into low (1-3) versus high (4-5) cohorts. Continuous and categorical outcomes were compared using ANOVA and chi-square tests. A hierarchical generalized linear mixed effect model was used to evaluate predictors of long-term, postoperative eGFR following PN. **Results:** 314 patients were identified and 97 (30.9%) were classified with a high MAP score. These patients were older (64.5 vs. 58.3 years, p<0.001), more often male (85.6% vs. 52.5%, p<0.001), and white (79.4% vs. 67.7%, p=0.016). MAP score was associated with obesity (59.8% vs. 42.9%, p=0.006), diabetes (36.1% vs. 22.6%, p=0.013), hypertension (82.5% vs. 63.1%, p<0.001), and severe CCI (5+; 35.1% vs. 23.5%, p<0.001). No difference was observed in the rate of current or former smokers. Final tumor size was greater among patients with high MAP (4.1 vs. 3.4cm, p<0.001) but no difference was noted in pT stage. Rate of acute renal failure postoperatively (dialysis or eGFR <15 within 30 days) was similar between the two cohorts (1% vs. 1.4%, p=0.797). The tablepresents the model used to evaluate postoperative eGFR predictors. **Conclusions:** High MAP score predicts a greater eGFR decline following PN for localized RCC. Considering the risks of PN, MAP scoring may indicate surgical complexity and inform shared decision-making when considering nephron-sparing surgery for RCC. Research Sponsor: None.

Multivariable model used to predict long-term, post-operative GFR following PN.

Covariate	eGFR Estimate (SE)	p-value
Intercept	27.97	
MAP Score		
High (4-5)	-4.75 (-8.54, -0.96)	**0.014**
Low (0-3)	Ref	
Female	-2.81 (-6.29, 0.68)	0.115
Race		
Other	5.57 (-1.42, 12.56)	0.118
Black	-0.21 (-4.14, 3.73)	0.918
White	Ref	
Smoking Status		
Former	-0.02 (-3.63, 3.59)	0.990
Current	-0.18 (-5.44, 5.07)	0.946
Never	Ref	
ECOG PS		
≥1	-1.64 (-7.05, 3.76)	0.552
0	Reference	
Diabetes	1.94 (-1.91, 5.79)	0.324
Hypertension	-2.47 (-6.52, 1.59)	0.233
CCI		
Severe [5+]	-11.12 (-17.5, -4.75)	**<0.001**
Moderate [3-4]	-8.75 (-14.93, -2.58)	**0.006**
Mild [1-2]	-5.7 (-11.34, -0.06)	**0.048**
Normal [0]	Reference	.
Preoperative eGFR	0.78 (0.69, 0.86)	**<0.001**

Linear muscle segmentation for metastatic renal cell carcinoma.

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Background: Baseline sarcopenia and postoperative changes in muscle mass are independently associated with overall survival in patients with metastatic renal cell carcinoma (mRCC) undergoing cytoreductive nephrectomy (CN). Here we examine the relationship between preoperative (baseline) and postoperative changes in muscle quantity with survival outcomes following CN as determined by linear segmentation, a fast and clinic-friendly tool. **Methods:** Our nephrectomy database was reviewed for patients with clear cell, papillary, or chromophobe mRCC who underwent CN. Linear segmentation of bilateral psoas/paraspinal muscles was completed for baseline imaging within 60 days of surgery and imaging up to 1 year postoperatively. ANOVA for numerical and chi-square for categorical variables were used to test for differences according to change in linear muscle index (LMI, cm2/m2). Multivariable models estimated COX hazard ratios for cancer-specific survival (CSS) and overall survival (OS). Kaplan Meier curves estimated CSS and OS. **Results:** From 2004-2020, 190 patients were identified 48 stable LMI (25.3%; <5% change [0Δ]), 54 increase LMI (28.4%; +5% change [+Δ]), and 88 decrease LMI (46.3%; -5% change [-Δ]). Median time from baseline imaging to surgery was 18 days, while time from surgery to postoperative imaging was 119 days. Patients with +Δ had lower baseline LMI than -Δ or 0Δ (28.5 vs. 32.4 vs.32.5 cm2/m2; p=0.003). 0Δ LMI had lower rates of pN1 disease than other groups (27.1% [0Δ] vs. 42.6% [+Δ] vs. 45.5% [-Δ]; p=0.019). No other differences in pathology were noted. Median CSS and OS were highest among patients with 0Δ LMI (CSS: not reached [0Δ] vs. 61.9 [+Δ] vs. 37.4 [-Δ] months; p=0.0018 || OS: 67.2 [0Δ] vs. 48.5 [+Δ] vs. 26.4 [-Δ] months; p=0.0007). Median follow-up was 56 months for survivors. The table lists factors associated with increased risk of cancer-specific mortality. **Conclusions:** Change in muscle mass after CN, as measured by the linear muscle segmentation technique, is independently associated with OS and CSS in patients following CN. Of note, lack of change demonstrated greatest survival, potentially secondary to high baseline muscle mass. Research Sponsor: None.

Multivariable model estimating COX hazard CSS according to percent change LMI.

Covariate	N (%)	HR (95% CI)	p-value
Δ LMI (cm2/m2)			
0Δ LMI	48 (25.3)	0.42 (0.21-0.82)	**0.011**
-5% LMI	88 (46.3)	1.69 (1.01-2.83)	**0.046**
+5% LMI	54 (28.4)	Ref	
Age 60+	104 (54.7)	1.40 (0.91-2.16)	0.127
Obesity (BMI ≥30kg/m2)	67 (35.3)	0.86 (0.54-1.38)	0.538
Male	144 (75.8)	1.01 (0.59-1.71)	0.978
Black Race	30 (15.8)	2.23 (1.21-4.11)	**0.01**
ECOG ≥1	47 (24.7)	2.70 (1.66-4.41)	**<0.001**
Tumor Size (cm)		0.99 (0.93-1.05)	0.672
Clear Cell Histology	150 (78.9)	1.18 (0.61-2.31)	0.619
Nuclear High Grade	175 (95.1)	5.75 (1.26-26.38)	**0.024**
pT Stage			
T4	24 (12.6)	0.94 (0.45-1.96)	0.876
T1-3	166 (87.4)	Ref	
pN Stage			
N0	60 (31.6)	0.65 (0.35-1.20)	0.17
N1	76 (40)	1.33 (0.72-2.47)	0.361
NX	54 (28.4)	Ref	
pM1	154 (81.1)	2.72 (1.38-5.34)	**0.004**

Venous tumor thrombus destinations in patients with renal cell carcinoma.

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Background: Venous tumor thrombus (VTT) is associated with worse oncologic outcomes in clear cell renal cell carcinoma (ccRCC). It is unknown if VTT and pulmonary embolism (PE) predispose patients to pulmonary metastasis. **Methods:** We queried our institutional registry for ccRCC patients undergoing radical nephrectomy (1970-2019). Cox proportional hazards regression models, adjusting for factors associated with ccRCC progression, were used to determine if VTT and PE were associated with pulmonary metastasis. **Results:** Of 3,410 patients studied, 1,025 (30%) had VTT, and patients with VTT were more likely to present with pulmonary metastasis at nephrectomy (20% vs 7%, $p<0.001$). Within the VTT subset, level of VTT was not significantly associated with pulmonary metastasis at nephrectomy ($p=0.3$). For all patients who had metastatic disease at nephrectomy (n=643), pulmonary metastasis was more common in those with VTT versus those without VTT (68% vs 51%, $p<0.001$). Excluding patients with pulmonary metastasis at nephrectomy, on multivariable analysis, VTT remained associated with post-nephrectomy pulmonary metastasis (hazard ratio (HR) 1.31, $p<0.001$) without a notable difference in HRs between renal vein (1.27) and caval (1.38) VTT. Presence of PE in the setting of VTT was associated with increased pulmonary metastasis post-nephrectomy (HR 2.31, $p<0.001$). **Conclusions:** VTT is associated with disproportionately increased pulmonary metastasis at presentation and post-nephrectomy in ccRCC patients. Further, the presence of PE at nephrectomy for VTT was associated with increased pulmonary metastasis post-nephrectomy. These results support a metastatic predilection of ccRCC with VTT to the lungs. Research Sponsor: None.

Real-world treatment outcomes in patients with advanced renal cell carcinoma who receive axitinib plus pembrolizumab in the first-line setting in Canadian cancer centers.

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Background: The landscape of management of advanced renal cell carcinoma (aRCC) in the first line setting has changed dramatically over the past decade. Axitinib with Pembrolizumab (AP) is one of the combinations which demonstrated improved outcomes in the KEYNOTE 426 study. We report real-world outcomes and safety with this combination. **Methods:** The Canadian Kidney Cancer information system (CKCis) is a multi-institutional prospective RCC cohort. Patients ≥18 years with aRCC and clear cell histology who received AP as first-line therapy from January 1, 2017 to June 30, 2022 were included. Descriptive and actuarial statistics were reported for the following: progression free survival (PFS), overall survival (OS) and adverse events. **Results:** The cohort includes 222 patients.165 (74.3%) were male with a median age of 64.5 (37.0-87.7) years. Sixty-three (28.3%) patients were IMDC favourable-risk, 69 (31.0%) intermediate-risk, 45 (20.3%) poor-risk and 45 (20.2%) unknown. Median follow-up was 26.6 (range: 0.1 – 77.2) months. Of 222 patients, 119 discontinued treatment (53.6%) due to disease progression in 45.4% or toxicity in 29.4%. Median duration of treatment was 18.5 (range 0.1 to 72.4) months. PFS probability at 12 and 24 m was 63.8% and 49.9% respectively with a median PFS of 22.6 months (95% CI: 15.9-30.1). Survival probability at 12 and 24 m was 89.1% and 80.2% respectively with a median OS of 51.5 months (95% CI 38.0-NR). By IMDC criteria, intermediate risk median OS was 44.8 m (95% CI 41.5-61.6) and poor risk 33.6 m (18.5-NR). Most patients experienced toxicity requiring dose interruption/delay or discontinuation (n=180; 81.4%) The most common toxicities were diarrhea (73.3%), fatigue (54.4%), hepatotoxicity (50.0%), anorexia (26.1%), mucositis (22.2%), nausea (21.1%), palmar plantar erythrodysesthesia (15.6%), hypertension (13.3%), weight loss (13.3%) and proteinuria (11.7%). Others included pneumonitis (8.9%), thyroid dysfunction (6.7%) and colitis (4.4%). **Conclusions:** The real-world experience of patients with aRCC receiving AP in Canada is similar to the KEYNOTE-426 study in both outcomes and safety. These data continue to support its position as a standard of care in the first line setting for aRCC. Longer follow up and characterization of these patients is warranted. Research Sponsor: None.

Erectile function in patients with metastatic renal cell carcinoma treated with first-line therapy.

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Background: Sexual activity is an important part of social functioning and quality of life. Cancer diagnosis and concomitant treatment has a damaging effect on sexual function. The objective of this prospective study was to evaluate the incidence of erectile dysfunction (ED) in men with metastatic renal cell carcinoma (mRCC) receiving first-line therapy. **Methods:** All patients were evaluated for erectile function with the 5-item version of the International Index of Erectile Function (IIEF-5) and Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) before first and after four cycles/months of the first-line therapy with nivolumab plus ipilimumab (IO-IO), pembrolizumab plus axitinib/lenvatinib (IO-TKI) or sunitinib, pazopanib and cabozantinib (TKI). **Results:** Two hundred eighty-two male patients with mRCC were enrolled. Median age was 60.5 years (range 39–71 years) and 164 (58%) patients had at least one cardiovascular risk factor. Sixty-seven (24%) patients had favorable IMDC risk, 208 (74%) had ECOG $\leq$1, 214 (76%) had $\geq$2 organs with metastases, and 11 (4%) had non-clear cell mRCC. All patients were treated with IO-IO (32%), IO-TKI (26%), and TKI (42%). At baseline, IIEF-5 mean score was 17 (SD, 2.9) in ITT population. Patients with 2 and more IMDC risk factors had a lower IIEF-5 mean score (13; SD, 1.4). 182 (64.5%) patients reported a negative change in their sexual life since the start of the therapy. 90 (32%) patients had no sexual activity. After four treatment cycles/months IIEF-5 mean score reduced to 9 (SD, 3.5), which was statistically significant ($P<0.0001$). The IIEF-5 scores were associated with type of anticancer treatment, with the minimal change observed in IO-IO group ($P=0.2$) and highest change in TKI group ($P<0.0001$). A correlation was no found between FKSI-19 and IIEF-5 scoring systems. **Conclusions:** A prospective assessment in a large group of male mRCC patients revealed mild ED (17/25) in previously untreated patients and moderate ED (9/25) after four cycles/months of first-line therapy, especially in patients receiving TKIs. These changes did not correlate with kidney symptom index. Research Sponsor: Bureau for Cancer Research - BUCARE.

Health-related quality of life (HRQoL) profile and clinical outcomes in first-line (1L) advanced renal cell carcinoma (aRCC): A modelling analysis based on CheckMate 9ER (CM9ER) trial.

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Background: Cabozantinib plus nivolumab (CN) is a 1L therapy for aRCC. In the CM9ER trial CN had superior efficacy to sunitinib (SUN) and showed HRQoL benefit. We investigated the relationship between clinical outcomes, treatment and early deterioration in HRQoL dimensions in the CM9ER population. **Methods:** Using the CM9ER intention-to-treat (ITT) population (median follow-up 32.9 months) we: (a) explored time-to-event outcomes for CN vs SUN (b) identified determinants of HRQoL benefit by performing ordinal regression using the 19-item Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-19) item scores at week 13 (c) investigated relationships between early (week 13) deterioration in FKSI-19 items and clinical outcomes using a cox proportional modeling framework. First, univariate Cox proportional hazard modeling assessed the predictiveness of early FKSI-19 item deterioration (sig. threshold $p \leq 0.20$). Items with significant univariate associations with the outcome were included in multivariate regression modeling (sig. threshold $p \leq 0.10$). Treatment and baseline stratification factors (geographic region, baseline IMDC score, PD-L1 status) remained in all models. **Results:** All CM9ER ITT patients (N = 651; CN, 323; SUN, 328) were included. Compared with SUN, CN patients had a longer median duration of treatment (94.6 wks vs 36.5 wks), time to disease progression (83.1 wks vs 42.1 wks) and time to first grade 3/4 adverse event (16.3 wks vs 12.0 wks). FKSI-19 items with early deterioration favoring CN vs SUN ($p \leq 0.05$) were: lack of energy; pain; fatigue; bone pain; weak all over; nausea; bothered by treatment side effects; able to work. The table reports variables significantly associated with clinical outcomes ($p \leq 0.05$). **Conclusions:** Early deterioration in bone pain and sleep were associated with increased risk of mortality, and early deterioration in pain with reduced risk of toxicity-related discontinuation. We found no association between early FKSI-19 item deterioration and risk of progression or tumor shrinkage. Controlling for other variables, CN (vs SUN) treatment was positively and significantly associated with increased chance of tumor shrinkage, survival and progression-free survival, independent of early HRQoL deterioration. Clinical trial information: NCT03141177. Research Sponsor: Ipsen.

Outcome	Variable	Hazard Ratio (95% Confidence Interval)
Disease Progression	IMDC Score: 0 vs 3–6; 1–2 vs 3–6	0.59 (0.42,0.83); 0.69 (0.52,0.93)
	Treatment: CN vs SUN	0.57 (0.46, 0.70)
Tumor Shrinkage	IMDC Score: 0 vs 3–6; 1–2 vs 3–6	2.19 (1.41, 3.40); 1.75 (1.16, 2.63)
	Treatment: CN vs SUN	2.13 (1.64, 2.75)
Death	Bone Pain (deterioration): N vs Y	1.45 (1.09, 1.93)
	Sleeping well (deterioration): N vs Y	1.45 (1.10, 1.90)
	IMDC Score: 0 vs 3–6	0.42 (0.27, 0.65)
	Treatment: CN vs SUN	0.71 (0.53, 0.94)
Discontinuation due to toxicity	Pain (deterioration): N vs Y	0.42 (0.22, 0.79)

Preliminary analysis of baseline characteristics, patient reported outcomes (PROs), and treatment selection in ODYSSEY.

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Background: Tyrosine kinase inhibitors (TKI) and immuno-oncology (IO) agents alone or in combination have revolutionized the landscape of management for untreated metastatic renal cell carcinoma (mRCC). Baseline quality of life (QOL) outside of interventional clinical trials and rationale for management decisions in mRCC are poorly understood. **Methods:** In this prospective observational study of 800 mRCC pts in the US, pts must: have a diagnosis of mRCC (any histology) with no prior systemic therapy (ST) for mRCC; be age ≥19 at informed consent; be able to comply with completion of PROs. Exclusion criteria include being treated for active malignancy other than mRCC or not intending to follow up at a study site within PCORnet. Pts undergo consent and baseline assessments by the study site team, with subsequent follow up by the central coordinating center. The primary objective is to determine distinct patterns of change in QOL and symptom burden of mRCC pts. A key secondary objective is to identify patterns of clinical management in the real world setting of mRCC across treatment regimens. Minimally important differences are defined as 3- and 7-points for FKSI-19 and FACT-G respectively. ClinicalTrials.gov ID: NCT04919122. **Results:** As of 9/1/2023, 173 pts have been enrolled (126 ST, 47 no ST [NST]): 75% male, 87% white, 73% clear cell, 52% intermediate risk and 47% poor risk. 47% had radical nephrectomy and 22% another solid tumor. ST pts as compared to NST pts were more likely to be poor risk (52% vs 16%); but differences in baseline pain were not significant. Of ST pts, 44 were treated with IO-IO (ipilimumab + nivolumab), 50 with IO-TKI (cabozantinib + nivolumab 38%, axitinib + pembrolizumab 38%, lenvatinib + pembrolizumab 24%) and 32 other (IO alone 34%, TKI alone 31%, investigational drug 25%). Reasons for NST included active surveillance (AS, 50%), other (21%), local therapy (13%). Mean differences between ST and NST for baseline FKSI-19 and FACT-G were 5.7 (95% CI: 1.2 – 10.2) and 3.3 (-2.6 – 9.3). There were no differences in pain or PROs between IO-IO and IO-TKI pts. Mean differences in FKSI-19 and FACT-G between AS vs IO-IO were 10.6 (4.8 – 16.4) and 8.6 (1.1 – 16.0); and vs IO-TKI were 11.0 (4.9 – 17.0) and 10.3 (3.5 – 17.1). On physician surveys, primary reasons for treatment selection were (in order of % selected): complete response (CR), prolonged survival (OS), prognostic factors (Px), treatment-free interval for IO-IO; versus delaying progression (PFS), OS, CR, Px for IO-TKI. **Conclusions:** Our data suggest differences in baseline QoL in pts treated with ST vs NST, as well as AS vs IO-IO or IO-TKI, in the real world. Reasons for selection of ST regimen differed among combination regimen classes. Completion of ODYSSEY will clarify baseline and longitudinal differences in pain and PROs among management strategies and give novel insights into the rationale for real world management of untreated pts with mRCC. Clinical trial information: NCT04919122. Research Sponsor: Bristol Myers Squibb; Exelixis; Merck; Pfizer.

A UK real-world observational study of avelumab + axitinib (A + Ax) in advanced renal cell carcinoma (aRCC): Outcomes at 36 months post treatment initiation.

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Background: In patients with previously untreated aRCC, A + Ax combination therapy has shown superior progression-free survival (PFS) and objective response rate (ORR) vs sunitinib across all International Metastatic RCC Database Consortium (IMDC) risk groups. This study reports real-world outcomes at up to 36 months post treatment initiation in patients with aRCC receiving A + Ax in the UK. **Methods:** Retrospective data were collected from medical records of patients aged ≥18 years diagnosed with aRCC, who initiated A + Ax on or after August 1, 2019, via the Early Access to Medicines Scheme at 10 UK sites. Patients were followed until July 31, 2023. Primary endpoints were overall survival (OS), PFS, ORR, and best response at 36 months post A + Ax initiation. Data were analyzed descriptively. **Results:** 130 patients were included. Median age at baseline was 67.1 years (range, 38.5-87.0 years); 74% (n=96) were male; 69% (n=90) were White, 4% (n=5) were Asian/Asian British, and ethnicity was not recorded in 27% (n=35); 94% (n=122) had an Eastern Cooperative Oncology Group score of 0 or 1. IMDC risk status was favorable in 39% (n=51), intermediate in 40% (n=51), and poor in 19% (n=25). Median time from aRCC diagnosis to A + Ax initiation was 2.5 months (range, 0.03-115.4 months). Clear cell histology was the most prevalent (88%; n=115); 68% (n=88) had undergone nephrectomy, and 78% (n=102) had 1 or 2 metastatic sites at index. The OS rate (95% CI) at 12, 24, and 36 months was 81.5% (75.1%-88.5%), 65.3% (57.6%-74.0%), and 53% (45.2%-62.9%), respectively. The PFS rate (95% CI) at 12, 24, and 36 months was 53.1% (45.1%-62.5%), 36.4% (29.0%-45.8%), and 27% (20.3%-36.0%), respectively. Median PFS was 13.5 months (95% CI, 10.2-17.7 months). ORR (n=127) at 36 months was 62% (95% CI, 53.8%-70.6%), including a best response of complete response (CR) in 5% (n=6) and partial response (PR) in 57% (n=73); best response was stable disease in 31% (n=39) and progressive disease in 7% (n=9; best response was not recorded in 3 patients). Median duration of response was 14.9 months (95% CI, 12.0-23.5). Median time to discontinuation (TTD) of A or Ax was 11.7 months (95% CI, 9.0-17.6), and for A + Ax combined was 14.7 months (95% CI, 11.0-24.4). Adverse events (AEs) were reported in 68% (88/129) of patients, who had a total of 519 nonserious AEs due to A + Ax treatment; 13% (17/129) of patients had a total of 27 serious AEs. The most common AEs (number of patients) were diarrhea (n=49), fatigue (n=33), and oral mucositis (n=24); 9 patients discontinued A and/or Ax due to AEs, including diarrhea in 3 patients. **Conclusions:** In this UK-based real-world study of first-line A + Ax treatment in patients with aRCC, OS, PFS, ORR, and best response observed at 36 months were in line with findings from clinical trials, with no newly emerging AEs. Research Sponsor: This study was sponsored by Pfizer and was previously conducted under an alliance between Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Treatment options and outcome of patients with metastatic renal cell carcinoma with brain or bone metastases: Real world evidence from a German retrospective multi-center analysis.

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Background: Brain (BM) and bone metastases (BOM) in renal cell carcinoma (RCC) are associated with poor outcome. We evaluated real-world treatment paradigms of RCC patients with BM and BOM. **Methods:** We retrospectively analyzed RCC patients with BM and/or BOM treated at 18 German tertiary cancer centres from 2003 to 2023. Adverse events (AE) were reported according to CTCAE 5.0, objective response rate (ORR) according to local standard. Overall survival (OS) was calculated from start of treatment to progression or death, respectively and determined by KM plots. **Results:** We included 453 patients with a median age of 64 years (IQR 56-71). 93% of all patients had BOM, 15% BM and 8% both. Most patients (79%) had clear cell RCC, 7% of all patients had sarcomatoid differentiation. 82% of patients had an ECOG PS of 0/1. IMDC risk was favorable/intermediate/poor in 20/56/24%. 64% received prior nephrectomy. Patients with BOM received first-line IO-combinations in 61% (IO-IO: 38%, TKI-IO: 62%), TKI-monotherapy in 39%, while patients with BM received IO-combinations in 68% (IO-IO: 37%, TKI-IO: 63%) and TKI in 32%. IO-based first-line therapy increased from 2003 to 2023. AE of all grades occurred in 87% and 69% during IO-based therapy or TKI monotherapy, and CTCAE grade $\geq$ 3 in 42% or 25%. Best ORR and survival outcomes with median follow-up of 23 months (IQR 9-42) are described in table 1. 56% and 58% of all patients with BOM and BM received second-line treatment, with Cabozantinib (34%; 34%) and Nivolumab (17%, 23%) being the most common treatment options. In the subgroup of RCC with sarcomatoid features (n=36), 34 patients had BOM and 7 had BM, of which were treated with IO-combinations in 88% (BOM; IO-IO: 41%, TKI-IO: 59%) or 66% (BM; IO-IO: 50%, TKI-IO: 50%) and TKI-monotherapy in 12% (BOM) or 34% (BM) of all patients. Response rates (ORR/SD/PD) were 48%/28%/24% for IO-based therapy and 0%/50%/50% for TKI-monotherapy in RCC with sarcomatoid features, mOS was 41 months (95% CI 16.7-65.3). **Conclusions:** RCC patients with BOM and BM are increasingly treated with IO-combinations but lead to higher rates of AE grade $\geq$ 3. In patients with BOM, IO-TKI revealed higher ORR compared to IO-IO combination, but not in patients with BM. However, the small sample size and retrospective design are major limitations of our analysis. Prospective studies evaluating treatment options for BOM and BM in patients with RCC is critical. Research Sponsor: None.

Parameter	Total (n=327)			BOM (n=306)			BM (n=51)		
	TKI n=119	IO-IO n=78	IO-TKI n=130	TKI n=112	IO-IO n=71	IO-TKI n=123	TKI n=15	IO-IO n=14	IO-TKI n=22
% sRCC	2%	12%	11%	2%	13%	11%	9%	12%	7%
ORR	41%	40%	55%	38%	39%	55%	67%	50%	46%
SD	36%	27%	31%	38%	28%	32%	27%	29%	18%
PD	23%	33%	14%	24%	32%	13%	6%	21%	36%
ORR vs. SD vs. PD	p=0.009			p=0.007			p=0.325		
mOS; months, 95% CI	48 (39.7-56.3)			48 (39.5-56.5)			45 (29.9-60.1)		

Criteria and indicators to evaluate quality of care in genitourinary tumor boards.

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Background: Multidisciplinary Tumor Boards are an essential component of patient management, as they integrate input from various healthcare professionals to make comprehensive decisions about patient care. Management of patients with genitourinary (GU) tumors particularly relies on these multidisciplinary Tumor Boards. However, there are no guidelines on how these groups should operate. **Methods:** A systematic literature review was conducted to identify criteria useful to evaluate quality in GU Tumor Boards (GUTB); publication dates were January 2016 to December 2021. A scientific committee—comprising 12 GU specialists from several disciplines—reviewed the literature findings, proposed a list of criteria, and developed and selected indicators using the Delphi method in a first round. Thirty-nine experts from various disciplines (urology, radiation oncology, radiology, medical oncology, nuclear medicine, hospital pharmacy, and pathology) participated in the second round of the Delphi method to evaluate the indicators. In both rounds the appropriateness and utility of the criteria and/or indicators were scored using a 9-point Likert scale (1, extremely inappropriate or not useful; 9, extremely appropriate or useful). Consensus was defined as at least two-thirds of Delphi respondents selecting a score sub-category (1–3, 4–6, or 7–9) that encompassed the median score of the group. **Results:** Forty-eight articles were selected from the literature review and were used to develop a list of 67 initial criteria. The scientific committee narrowed these criteria down to 45 to evaluate the quality of GUTB, covering five dimensions: organization (11 criteria), personnel (5 criteria), protocol and registry (21 criteria), resources (6 criteria), and interaction with patients (2 criteria). Then, 33 indicators were developed and evaluated in the first round of Delphi, which led to a selection of 26 indicators. In the second round the group of experts reached consensus on the appropriateness of all 26 indicators and on the utility of 24 of them. Finally, indicators were compiled into a list, including how they should be measured, so that they can be easily used in clinical practice. **Conclusions:** Criteria and indicators were developed by this working group to evaluate the quality of GUTB, aiming to serve as a guide to improve quality of care and achieve better outcomes in patients with GU. Research Sponsor: None.

Management, outcomes and predictors of recurrence in chromophobe renal cell carcinoma: Results from the Canadian Kidney Cancer information system (CKCis).

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Background: Chromophobe RCC (chRCC) make up 5% of all RCC however data regarding baseline demographics, management, outcomes, and predictors of recurrence and survival is lacking. **Methods:** The Canadian Kidney Cancer Information System (CKCis) is a multi-institutional prospective cohort. Patients (pts) with clinically localized chRCC between Jan 2011-Aug 2023 were included. Descriptive statistics were used, time to recurrence and death were estimated using Kaplan-Meier estimates and associations were determined using Cox proportional hazards models. **Results:** chRCC made up 5.3% of all RCC pts in CKCis and only 2.4% presented with metastatic disease. This study cohort includes 797 pts who presented with localized disease. Median follow up 4.1 yrs, mean age 58.4 yrs and male in 58.5%. Management included: surgery 90.2%, surveillance 5.5%, or other local modalities 3.3%. Recurrence occurred in 59 pts (7.4%): 50 (85%) with metastases, 7 (12%) with local recurrence, and 2 (3.4%) with contralateral tumors. Median time to recurrence was 2 yrs. Management of recurrences included: systemic therapy in 46%, radiation in 29%, metastasectomy in 25%, surveillance in 8%. 5 and 10 year overall survival was 95% and 83% in all pts, 97% and 90% if no recurrence and 75% and 44% if recurrence. In the 90.2% (718 pts) treated with curative surgery, predictors of recurrence on multivariate analysis include: higher T stage, necrosis, and sarcomatoid features. Predictors of worse survival include: sarcomatoid features, larger tumor size, higher T stage, and higher number of comorbidities. **Conclusions:** In this large Canadian cohort, patients with chRCC usually present with localized disease and have relatively favorable oncologic outcomes, even when they recur. Larger tumors with sarcomatoid features have a worse survival and more intensive follow up may be beneficial. The favorable 5 and 10 year outcomes in chRCC are a reminder that studies must be conducted and reported for individual histologies and not as a large cohort of non clear cell RCC. Research Sponsor: None.

	OS			RFS		
Variable	**Hazard Ratio**	**95% CI**	**P value**	**Hazard Ratio**	**95% CI**	**P value**
pT3T4 vs. T1	2.94	1.68-5.14	0.0002	4.94	2.44-9.99	<.0001
Yes vs. No sarcomatoid	6.81	1.26-36.87	0.026	12.13	3.83-38.46	<.0001
Increase in T size	1.09	1.00-1.18	0.045			0.97
Increase in Charleson Comorbidity Index by 1	1.59	1.43-1.78	<.0001			
Yes vs. No LVI			0.58	2.29	0.99-5.31	0.053
Yes vs. No Necrosis			0.41	2.30	1.08-4.92	0.031

LVI: lymphovascular invasion, OS: overall survival, RFS: recurrence free survival.

Treatment-free survival after first-line therapies for metastatic renal cell carcinoma: An International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) analysis.

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Background: Patients treated with immune checkpoint blockade (ICB) may experience disease control without need for ongoing systemic therapy, a period not well described by conventional time-to-event endpoints. Treatment-free survival (TFS) represents a novel endpoint to quantify this period. **Methods:** We identified patients with mRCC from the IMDC dataset initiating first-line systemic therapy with VEGFR monotherapy (sunitinib, pazopanib), combination ICB-VEGFR therapy ([axitinib or envatinib]-pembrolizumab, cabozantinib-nivolumab, axitinib-avelumab), or ICB doublet therapy (ipilimumab-nivolumab) between February 1, 2014, and February 1, 2023. Overall survival from treatment initiation was partitioned into periods including TFS, time on first-line therapy, and survival after subsequent therapy initiation utilizing differences in restricted mean survival time (RMST) over 36-months. TFS was defined as the difference between the 36-month RMST between: (1) time from treatment initiation to discontinuation of first-line therapy, death, or censor at last follow-up and (2) time from treatment initiation to subsequent therapy initiation, death, or censor at last follow-up. **Results:** 3,758 patients with mRCC initiated first-line VEGFR monotherapy (n=2,635; median age 62 years; 19.1% IMDC favourable risk), ICB-VEGFR regimens (n=354; median age 60 years; 33.3% IMDC favourable risk), or doublet ICB (n=769; median age 62 years; 0% IMDC favourable risk). Patients with favourable IMDC risk initiating VEGFR monotherapy and ICB-VEGFR regimens experienced a TFS duration of 8.5% (3.1 mos 95% CI 1.5 - 4.6) and 10.1% (3.7 mos 95% CI 0.2-7.2) of the 36-month period respectively. Among intermediate/poor risk patients, those treated with VEGFR monotherapy, ICB-VEGFR regimens, and ICB doublet therapy experienced 5.9% (2.1 mos 95% CI 1.4 - 2.8), 10.3% (4.7 mos 95% CI 1.0-6.4), and 14.6% (5.3 mos 95% CI 3.8-6.8) of the 36-month period alive and treatment free respectively. **Conclusions:** Patients receiving VEGFR monotherapy or ICB-VEGFR combination therapies spent at most 10% of the 36-month period surviving treatment free, while IMDC intermediate/poor risk patients treated with ICB doublet therapy experienced a TFS period of 15% of the 36-month period. Research Sponsor: None.

Survival states over the 36-month period since therapy initiation for patients with mRCC.

	Favourable Risk		Intermediate/Poor Risk		
	ICB-VEGFR n=118	VEGFR n=504	ICB Doublet n=769	ICB-VEGFR n=236	VEGFR n=2131
OS	32.1 (89.1)	31.3 (86.9)	25.7 (71.3)	27.9 (77.4)	21.2 (58.9)
Months (% of 36-mo)					
Time on First-Line Therapy	22.2 (61.7)	16.2 (44.9)	11.6 (32.3)	17.2 (47.8)	10.6 (29.5)
Months (% of 36-mo)					
TFS	3.7 (10.1)	3.1 (8.5)	5.3 (14.6)	3.7 (10.3)	2.1 (5.9)
Months (% of 36-mo)					
Time after Subsequent Therapy Initiation	6.2 (17.3)	12.1 (33.6)	8.8 (24.4)	7.0 (19.3)	8.5 (23.5)
Months (% of 36-mo)					

Gastrointestinal metastases in renal cell carcinoma: A retrospective multicenter GETUG (Groupe d'Etude des Tumeurs Uro-Genitales) study.

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Background: Among patients with renal cell carcinoma (RCC), bone and visceral metastases have a poor prognosis, while endocrine gland metastases have a more favorable prognosis. Gastrointestinal metastases (GIMs) are rare, and their prognosis is still poorly understood. Objectives: To report clinical presentations, patients' characteristics, therapeutic strategies, and prognosis of GIMs from RCC. **Methods:** We retrospectively collected data from RCC patients presenting GIMs, in 10 French GETUG centers, between 2000 and 2021. **Results:** We identified 74 patients with 87 GIMs, mostly gastric or duodenal. The median age at GIM diagnosis was 69 years and 76% of the patients already had other metastases. GIMs occurred after a median of 5.4 years (IC95%=[4.2-7.1]) and 1.9 years (IC95%=[1.2-3.8]) from RCC diagnosis and first metastasis, respectively. GIMs were symptomatic in 52 patients (70%), with anemia in 41 patients (55%) and/or gastrointestinal bleeding in 31 patients (42%). Only 22 asymptomatic patients (30%) were fortuitously diagnosed. The management of GIMs consisted of systemic treatment only in 29 GIMs (33%), local treatment only in 23 GIMs (26%), and both local and systemic treatment in 18 GIMs (21%). For 17 GIMs (20%), there was no therapeutic modification. After diagnosis of GIM, median overall survival was 19 months. **Conclusions:** We report the largest retrospective cohort of GIMs in RCC patients. They should be suspected in case of anemia or gastrointestinal bleeding in any patient with a history of RCC. Their management varies widely depending on their location in the digestive tract and whether they are symptomatic. Research Sponsor: None.

Real world evidence from a retrospective multi-center analysis on first-line therapy for metastatic renal cell carcinoma with non-clear cell and/or sarcomatoid histologies.

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Background: Papillary (pRCC), chromophob (chRCC) and predominantly sarcomatoid renal cell carcinoma (sRCC) as well as RCC with sarcomatoid features are rare cancers. We evaluated real-world treatment outcomes of 1st line treatment in these cohorts in Germany. **Methods:** We retrospectively analyzed patients with non-clear cell RCC treated at 17 German tertiary cancer centres. Adverse events (AE) were reported according to CTCAE 5.0, objective response rate (ORR) according to RECIST 1.1. Progression free survival (PFS) and overall survival (OS) were calculated from start of treatment to progression or death, respectively and determined by KM plots. **Results:** We included 189 patients with a median age of 63 years (IQR 54-72). Of these, 49% were pRCC, 12% chRCC, 12% sRCC. 17% of all RCC had a sarcomatoid features. 87% had an ECOG PS of 0/1. IMDC risk was favorable/intermediate/poor in 15/54/31%. 74% received prior nephrectomy. Lymphatic (63%) and pulmonary (51%) metastases were the most common metastatic sites. 72% patients received first-line IO-combinations (IO-IO: 36%, TKI-IO: 64%) and 28% patients TKI-monotherapy, predominantly sunitinib. AE of all grades occurred in 86% and 72% during IO-based therapy or TKI monotherapy, and CTCAE grade ≥ 3 in 46% or 36%, of which led to discontinuation of treatment in 42% or 29% of patients, respectively. ORR and survival outcomes with median follow-up of 17 months (IQR 9-30) are described in the table. **Conclusions:** IO-combinations are frequently applied in pRCC, chRCC and sRCC. Our data suggests that first-line IO-combinations yields higher ORR compared to single agent TKI in sRCC, but not in chRCC. However, the retrospective nature and small sample size are major limitations of our analysis. Additional analyses to tailor treatment strategies in patients with metastatic nccRCC or sRCC is warranted. Research Sponsor: None.

Parameter	pRCC (n=70)		chRCC (n=17)		sRCC + sarcomatoid features (n=38)	
	TKI	IO	TKI	IO	TKI	IO
	n=29	n=41	n=4	n=13	n=4	n=34
ORR (CR+PR)	38%	46%	50%	31%	0%	59%
SD	34%	32%	25%	23%	25%	15%
PD	28%	22%	25%	46%	75%	26%
ORR vs. SD vs. PD	p=0.867		p=0.007		p=0.072	
Parameter	pRCC (n=92)		chRCC (n=19)		sRCC + sarcomatoid features (n=38)	
	TKI	IO	TKI	IO	TKI	IO
	n=37	n=55	n=6	n=13	n=4	n=34
mPFS, months,	7 (5.2-8.8)		3 (0.2-5.8)		4 (2.5-5.5)	
95% CI	8 (4.9-11.1)	6 (4.2-7.7)	10 (4.9-15.1)	1 (NA)	2 (NA)	4 (2.8-5.2)
mOS;	34 (23.2-44.8)		28 (21.7-34.3)		34 (11.3-56.7)	
months, 95% CI	38 (19.7-56.8)	32 (16.6-47.4)	24 (7.0-41.0)	28 (17.5-38.5)	22 (0-52.4)	not reached

Ipilimumab/nivolumab (I/N) compared to axitinib/pembrolizumab (A/P) in metastatic renal cell carcinoma (mRCC): Insights from a Canadian population.

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Background: First-line treatment for mRCC includes I/N and A/P. These two regimens have not been compared in a randomized clinical trial as both CM-214 and KN-426 used single-agent tyrosine kinase inhibitors (TKIs) as the comparator. Meta-analyses suggest improved efficacy outcomes with A/P, but increased likelihood of complete response with I/N. We compared these treatments in the real-world. **Methods:** Data of consented mRCC patients with clear cell histology from the Canadian Kidney Cancer information system (CKCis) was obtained from January 2013 to December 2021. Treatment outcomes adjusting for age including overall survival (OS), progression free survival (PFS), and response rate (RR) for all patients and intermediate-poor risk patients were completed. Chi-square tests compared the frequency of side effects. **Results:** Among 547 patients, 360 received I/N and 187 received A/P. Median follow-up was 30.0 (0.1-112.1) months. Median duration of treatment was 6.9 (0.0-68.4) months for I/N and 20.2 (0.1-72.4) months for A/P. Intermediate-poor risk patients were higher in the I/N compared to A/P cohort (91.9% vs. 66.2%; $p<0.0001$). Cox regression for OS showed no difference between I/N compared to A/P (aHR 1.1, 95% CI [0.77-1.58], p=0.61). PFS showed no statistical difference but a trend for worse with I/N at 12.1 months compared to 22.3 months for A/P (aHR=1.2, 95% CI [0.95-1.62], p=0.11). RR was 40.9% with I/N compared to 56.0% in A/P (aOR 0.52, 95%CI [0.33-0.83], p=0.005). Subgroup analyses for the intermediate-poor risk mRCC patients showed no differences in OS (aHR 0.95, 95%CI [0.65-1.38], p=0.79) and PFS (aHR 1.21, 95%CI [0.90-1.62], p=0.21) between treatment groups but improved RR (aOR 0.58, 95%CI [0.35-0.96], p=0.06) with A/P. 61.7% of I/N patients compared to 79.1% of A/P suffered adverse events that led to a dose or schedule change ($p<0.001$). Most common toxicities for both groups include diarrhea, fatigue, transaminitis, rash, and anorexia. **Conclusions:** There was no difference in OS between mRCC patients treated with I/N compared to A/P. A/P demonstrates improved RR and a trend towards longer PFS at the expense of increased frequency of side effects. Despite a median follow-up of 30 months, the data is limited by a high amount of censoring. Research Sponsor: None.

Summary of safety in patients who developed AEs leading to dose or schedule change.

Patients, n (%)	I/N (N=222)		A/P (N=148)	
AE > 10% in either arm	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhea	88 (39.6)	27 (12.2)	110 (74.3)	9 (4.1)
Fatigue	71 (32.0)	8 (3.6)	82 (55)	11 (5.0)
Transaminitis	67 (30.2)	35 (15.8)	83 (56.1)	33 (14.9)
Rash	32 (14.4)	10 (4.5)	33 (22.3)	1 (0.5)
Anorexia	21 (9.5)	1 (0.5)	42 (28.4)	2 (0.9)
Nausea	27 (12.2)	5 (2.3)	28 (18.9)	1 (0.5)
Mucositis	21 (9.5)	7 (3.2)	30 (20.3)	2 (0.9)
Colitis	44 (19.8)	34 (15.3)	5 (3.4)	4 (1.8)

Real-world outcomes of patients with operable renal cell carcinoma from the German translational cancer research consortium (DKTK) network.

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Background: Nephrectomy and risk-adapted adjuvant pembrolizumab are standard treatments in localized renal cell carcinoma (RCC). Risk of recurrence from clinical trials is utilized to council patients. However, recurrence and survival in real-world practice may differ. We report real-world outcome data of patients with RCC from the German Cancer Consortium's Clinical Communication Platform, a federated data warehouse infrastructure for oncological real-world evidence. **Methods:** Adult patients from routine care and nephron sparing surgery (NSS) or nephrectomy (Nx) for non-metastatic RCC between 2013-2022 at tertiary German cancer centers were retrospectively analyzed. Clear cell (cc), papillary (p) or NOS histologies were eligible. Kaplan-Meier-analyses were conducted stratified by pathological stage for DFS (Disease-Free-Survival) and OS (overall Survival). **Results:** 1,291 patients received NSS/Nx. 1,271 (98.5%) were R0/1. Median follow-up: 37.8 mo. (IQR 13.08; 65,74). 754 patients had ccRCC with a mean age of 63.5 y (SD: 12.1), 40% were female. 221 had pRCC, mean age was 62.1 (SD 12.6) and 36.8% were female. 165 had NOS, mean age was 63.3 (SD 12.4) and 36.8% were female. 151 patients had other histologies. Survival outcomes are reported in table 1. **Conclusions:** Morphologic RCC types and T-stages inform on recurrence and prognosis. Our study advises on real-world recurrence and survival rates in patients with different RCC types, which may be used to counsel patients with regards to adjuvant therapy in the clinic. A major limitation is the retrospective nature of the analysis. Research Sponsor: DKTK.

	ccRCC n=754				pRCC n=221				NOS n=165			
T-stage, fraction by RCC type	Total	T1 40.9%	T2 20.8%	T3 30.8%	Total	T1 51.4%	T2 23.5%	T3 22.0%	Total	T1 47.1%	T2 11.4%	T3 28.6%
5-year DFS (%, 95%CI)	83.2 (80.6-86.9)	84.6 (81.6-87.7)	83.3 (74.4-93.3)	80.3 (73.7-87.5)	85.9 (81.2-90.8)	88.3 (83.6-93.4)	85.7 (72.0-100)	70.0 (52.5-93.3)	87.0 (82.0-92.5)	87.5 (81.4-94.1)	91.7 (77.3-100)	87.1 (76.1-99.7)
5-year OS (%, 95%CI)	82.7 (79.2-86.3)	85-6 (82.6-88.6)	86.7 (78.5-95.7)	83.5 (77.2-90.2)	82.0 (75.9-88.7)	88.3 (83.6-93.4)	85.7 (72.0-100)	75.0 (58.2-96.6)	77.2 (68.8-86.6)	88.5 (82.5-94.8)	91.7 (77.3-100)	87.1 (76.1-99.7)

Real world outcomes of first line (1L) nivolumab and ipilimumab (NIVO IPI) in metastatic renal cell carcinoma (mRCC): An update from the International mRCC Database Consortium (IMDC).

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Background: NIVO IPI is one of several 1L treatment options for mRCC and is limited to intermediate and poor risk disease in many jurisdictions. We report the outcomes of 1L NIVO IPI from the IMDC. **Methods:** All IMDC patients who received 1L NIVO IPI were retrospectively analyzed. Key outcomes were compared between IMDC risk groups and included overall survival (OS), time to treatment discontinuation (TTD), time to next treatment (TTNT; defined as time from 1L initiation to next treatment) and response rates. Conditional OS by 6- and 12-month survival are described. **Results:** 1145 patients received 1L NIVO IPI, including 94 favourable, 559 intermediate, and 313 poor risk patients. 818/980 (86%) of patients had clear cell histology and 14% had sarcomatoid features. The median follow up was 20.0 months. 837/1145 (73%) patients had stopped 1L NIVO IPI and 363/1145 (32%) were deceased. Key outcomes of interest are summarized in Table 1. Subsequent 2L therapy was received by 438/727 (60%) patients and was most frequently sunitinib (37%) and cabozantinib (28%). 3L therapy was received by 160/477 (34%) patients, most often cabozantinib (29%). Immune related adverse events were documented in 48% (274/572) of patients. Conditional survival analysis showed that if a patient was alive at 6 months after starting 1L NIVO IPI, they had an 81% likelihood of being alive for an additional year and a 68% likelihood of surviving two years. If alive at 12 months, there was an 81% chance of surviving one additional year and 68% chance of surviving two additional years. If a patient remained on 1L NIVO IPI for 6 months, there was a 91% likelihood of being alive for one additional year and 76% likelihood of being alive for two years. If they remained on NIVO IPI for 12 months, there was a 94% chance of being alive for one additional year and an 84% chance of surviving two additional years. **Conclusions:** This large cohort of real-world patients provides benchmark data for clinical trial design and patient counselling, with a median OS surpassing 50 months for intermediate risk patients. Research Sponsor: None.

Outcomes of interest by IMDC risk group.

	IMDC Favourable Risk (n=94)*	IMDC Intermediate Risk (n=559)	IMDC Poor Risk (n=313)	P-value
OS (months; 95%CI)	47.8 (40.8-93.0)	51.1 (44.4-NR)	18.3 (13.9-26.3)	<0.001
TTD (months; 95%CI)	6.5 (4.3-13.6)	5.7 (4.6-7.1)	3.6 (2.8-5.5)	0.002
TTNT (months; 95%CI)	24.3 (14.3-38.1)	11.8 (10.1-15.2)	8.2 (6.4-10.1)	<0.001
Response Rate	CR: 4/84 (5%)	CR: 30/488 (6%)	CR 9/258 (3%)	0.166
	PR: 18/84 (21%)	PR: 132/488 (27%)	PR: 87/258 (34%)	
	SD: 27/84 (32%)	SD: 169/488 (35%)	SD: 82/258 (32%)	
	PD: 35/84 (42%)	PD: 157/488 (32%)	PD: 80/258 (31%)	

*Interpret with caution as this is a highly selected population in the real-world.

From guidelines to accountability: Examining adherence to ASCO Language of Respect in renal cell carcinoma (RCC) abstracts.

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Background: ASCO Language of Respect Guidelines were developed in advance of the 2020 ASCO Annual Meeting to promote use of patient-respectful language in abstracts and presentations and to ensure that speakers received equitable treatment at the podium. Herein, we aimed to assess adherence to these guidelines among RCC abstracts presented at the 2023 ASCO Annual Meeting. **Methods:** In this observational study, six researchers reviewed all RCC abstracts accepted for the 2023 ASCO Annual Meeting and collected adherence data pertinent to the Language of Respect Guidelines. Collected statements were reviewed by two independent researchers and standardized into three major categories in accordance with the guidelines: (1) Do not blame patient, (2) Respects the role of the patient, and (3) Do not dehumanize patients. Descriptive statistics were used to summarize characteristics of the abstracts and authors, and univariate and multivariate analyses were performed to identify factors associated with odds of including at least one statement against the language of respect guidelines. **Results:** A total of 184 abstracts were evaluated. The majority were accepted as poster presentation (64.1%) followed by online publication only (23.4%). 75.5% of the abstracts had a first author institutional affiliation where English is the native language. Authors from institutions in a single county constituted 65.8% of the abstracts whereas 34.2% of the abstracts were products of multi-country collaborations. 55.1% of the abstracts contained at least one statement that deviated from the guidelines. Proportions of abstracts with at least one statement violating "Do not dehumanize the patient", "Do not blame", and "Respect the role of the patient" clauses were 42.4%, 18.5% and 2.2%, respectively. Univariate analysis showed higher odds of violating guidelines among abstracts originating from author groups in a single-country and those with a first author in a non-Native English-speaking country (OR 1.97 [95% CI 1.06-3.65], p=0.032 and OR 2.79 [95% CI 1.33-5.85], p=0.007). In multivariate analysis, the presence of a first author from an institution in a non-Native English-speaking country was associated with greater odds for including a statement violating guidelines (OR 2.80, 95% CI 1.29-6.10, p=.009). **Conclusions:** A significant proportion of RCC abstracts were found to contain language inconsistent with the ASCO Language of Respect guidelines. Our results underscore the importance of disseminating the guidelines in a culturally sensitive multi-lingual format. As we recognize people living with cancer as partners in research and clinical care, we implore the scientific community to cultivate greater awareness and adherence to patient-respectful language and for conference sponsors to promote accountability with these best practices. Research Sponsor: None.

Real-world metastatic renal cell carcinoma (mRCC) treatment trends in Mexico: A public vs private sector analysis.

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Background: Metastatic renal cell carcinoma (mRCC) treatment avenues have expanded, yet Mexico's fragmented healthcare system could impact real-world setting, scarce information is available, and little is known regarding this issue. This study aims to characterize the treatment patterns for mRCC in Mexico's public and private healthcare sectors. **Methods:** De-identified patient data collected from 180 oncologists (03/2022 to 02/2023) using Evidera LiveTracker were assessed. Data from adult mRCC patients outside clinical study protocols were included. Patients were categorized by healthcare sectors, and line of treatment (L). A descriptive analysis was conducted. **Results:** Of 651 patients, 182 (28.0%) were favorable risk-stratified, 332 (51.0%) intermediate, and 137 (20.0%) high-risk. Treatment in 1L involved 542 (83.3%), 96 (14.7%) in 2L and 13 (2.0%) ≥3L. Sectors were evenly split: 327 (50.2%) public and 324 (49.8%) private. Among patients in 1L, 60.7% underwent TKI monotherapy (72.8% public vs 48.1% private) mainly with sunitinib (49.8%) and pazopanib (20.9%). Immunotherapy (IO) combination IO+IO was indicated in 26.2% (17.0% public vs 35.7% private), and IO+TKI in 7.9% (5.4% public vs 10.5% private). similar disparities trends were observed in 2L, where TKI monotherapy increased to 70.8% (84.5% public vs 58.8% private), whereas 21.9% (13.3% public vs 29.4% private) and 4.2% (2.2% public vs 5.9% private) received IO monotherapy and IO+TKI, respectively (Table). **Conclusions:** Despite clinical practice guidelines favoring the use of IO for mRCC 1L treatment, many Mexican patients receive currently TKI monotherapy, particularly in public healthcare, and this is consistent in subsequent lines of treatment. Potential access barriers warrant further exploration. Research Sponsor: Pfizer.

Percentage per sector by line of treatment.

Line of Treatment	Therapy	Public n=327 (%)	Private n=324 (%)	Total n= 651 (%)
1L	IO+TKI	15 (5.4)	28 (10.5)	43 (7.9)
	IO+IO	47 (17.0)	95 (35.7)	142 (26.2)
	TKI's	201 (72.8)	128 (48.1)	329 (60.7)
2L	IO	6 (13.3)	15 (29.4)	21 (21.9)
	IO+TKI	1 (2.2)	3 (5.9)	4 (4.2)
	TKI's	38 (84.5)	30 (58.8)	68 (70.8)
3L	IO	0 (0)	2 (28.6)	2 (15.4)
	IO+TKI	1 (16.7)	2 (28.6)	3 (23.1)
	TKI's	3 (50.0)	2 (28.6)	5 (38.4)

Residual percetages correspond to other treatments including VEGF, MTOR and non-pharmacological treatments.

Treatment patterns and costs among patients with metastatic renal cell carcinoma (mRCC) in the United States: A real-world study using integrated claims and clinical data.

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Background: The treatment landscape for mRCC has evolved in recent years with the use of tyrosine kinase inhibitors (TKI) and immuno-oncology (IO) therapies. This study examined patient characteristics, treatment patterns, costs, and survival for individuals with mRCC who received either IO-IO or IO+TKI as first-line (1L) regimens. **Methods:** This retrospective cohort study used an administrative claims dataset from a commercial health plan integrated with clinical data from a cancer care quality program (CCQP) and socioeconomic data from national surveys. Eligible patients began treatment for mRCC between 04/01/2018 and 1/31/2023, were aged ≥ 18 years old, and had ≥ 6 months of health plan enrollment prior to and ≥ 1 month after their 1L treatment. Patient characteristics and 1L and second-line (2L) regimens were described. Costs were summarized per patient per month (PPPM) within time intervals. The Kaplan-Meier method was used to estimate treatment-free interval (TFI) and survival times. **Results:** The study identified 824 eligible mRCC patients; mean age was 60, 77% were male, and 85% White/6% Black race. Patients receiving 1L IO-IO (n = 471; nivolumab plus ipilimumab) or IO+TKI regimens (n = 353; pembrolizumab plus axitinib [63.7%], nivolumab plus cabozantinib [21.8%], pembrolizumab plus lenvantinib [14.4%]) had similar baseline characteristics with the exception of health plan type, body mass index, and risk score (Table 1). As 2L therapy, patients most often received TKI monotherapy (56%) or IO+TKI (26%). Treatment costs were higher for IO-IO in the first 3 months but lower in subsequent time intervals compared with IO+TKI. Medication costs represented 80% of total costs on average. Between IO-IO and IO+TKI arms, median TFI (1.1 and 1.2 months, respectively) and cumulative survival time (75.1% and 78.3% at 12 months, respectively) were similar. **Conclusions:** The study described treatment patterns for mRCC and found patients receiving 1L IO-IO and IO+TKI regimens were similar demographically, though IO-IO patients started with poorer risk scores. Although IO-IO was associated with higher treatment costs in the first 3 months, the subsequent monthly costs were lower vs IO+TKI. Results also indicated that retreatment with IO in the 2L setting is occurring in real-world practice. Research Sponsor: Bristol Myers Squibb.

Key metrics by 1L therapy.

	IO-IO n = 471	IO+TKI n = 353
Median follow-up, months (range)	12.8 (0.3, 58.3)	9.9 (0.5, 46.2)
Patients with RCC risk score[a], %	55.4	43.9
Intermediate or poor risk	89.7	76.1
2L therapy, n (%)	213 (45)	98 (28)
TKI mono, %	58.2	51.0
IO+TKI, %	29.1	19.4
IO or IO-IO, %	5.6	13.3
Cost PPPM[b]		
months 1-3/4-6/25-36	$62,799/$28,096/$20,050	$52,689/$36,814/$22,438

[a]Hierarchically selected IMDC (calculated with lab data) before MSKCC (calculated) and CCQP (as reported by providers) risk scores. [b]Among patients followed in interval, excerpt.

Pembrolizumab plus lenvatinib vs nivolumab plus cabozantinib in patients with metastatic renal cell carcinoma: A matching adjusted indirect comparison (MAIC).

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Background: Nivolumab plus Cabozantinib (nivo/cabo) and Pembrolizumab plus Lenvatinib (pem/len) have been approved and available for patients in first-line metastatic renal cell carcinoma (RCC). There is no direct evidence of the relative efficacy between pem/len and nivo/cabo from head-to-head clinical trials. Therefore, we conducted MAIC to better inform clinical decision-making on treatment choices. **Methods:** Individual patient data in the intention to treat (ITT) population from KEYNOTE-581 (pem/len vs. sunitinib; 50.1 months median follow-up) were compared to published aggregated data in the same population from CheckMate-9ER (nivo/cabo vs. sunitinib; 44 months median follow-up). Efficacy outcomes compared were overall survival (OS), progression free survival (PFS), objective response rate (ORR) and complete response (CR). Effect modifiers identified included liver/bone metastasis, sarcomatoid features and IMDC risk category. Using a MAIC, KEYNOTE-581 data were reweighted to match the effect modifiers distribution of CheckMate-9ER participants. Then, matching-adjusted hazard ratios (HR) for OS and PFS, and risk difference (RD) for ORR and CR of pem/len vs. sunitinib were calculated using the reweighted KEYNOTE-581 data. Bucher method was subsequently applied to indirectly compare pem/len to nivo/cabo on these outcomes. Two-sided *p*-values were calculated. **Results:** MAIC analyses show that, while OS were comparable between treatments (HR: 1.06 [95% CI:0.77,1.48]; *p*=0.7072), PFS (HR: 0.75 [95% CI:0.56,0.99]; *p*=0.0457) and ORR (RD: 11.29 [95% CI:1.10,21.49]; *p*=0.030) showed a statistically significant result in favor of pem/len when compared to nivo/cabo. The CR rate among pem/len users was higher compared to nivo/cabo but was not statistically significant (RD: 5.75 [95% CI:-0.64,12.15]; *p*=0.078). **Conclusions:** In first-line metastatic RCC patients, the MAIC shows a statistically significant result in favor of Pembrolizumab plus Lenvatinib in PFS and ORR, and comparable CR and OS benefit. Research Sponsor: None.

Evaluating intermediate endpoints (IE) for overall survival (OS) in metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICI): An IMDC study.

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Background: In Ph3 trials, assessment for primary endpoint of OS necessitates extended follow-up (f/u) periods, larger pool of events, and higher associated costs. We sought to determine if shorter IEs like Time to Treatment Failure (TTF) and Time to Next Therapy (TTNT) are associated with OS in patients (pts) receiving ICI-based trt. **Methods:** We included all International mRCC Database Consortium (IMDC) pts who received contemporary approved first line(1L) ICI from 2013 to 2023. IEs were defined from ICI start until drug cessation or death for TTF, and initiation of next line or death for TTNT, or censored at date of last f/u. Associations of OS with TTF and TTNT status at 6-mo landmark were assessed using Cox regression adjusting for IMDC risk groups, metastatic sites, histology, age, and prior nephrectomy, stratified by treatment (trt) and yrs of ICI start. Endpoint associations across all f/u time were evaluated using Kendall's Tau (KT) correlation by Clayton copula. A KT >0.49 indicates a strong correlation (*Wicklin R., 2023).* **Results:** The cohort consisted of 1667 pts with a median f/u of 15.4 mo (IQR: 7.1-28.6). Median age at 1L start was 63 yrs (IQR: 56-70), with 73% being male and 65% undergoing nephrectomy before starting 1L. 1132 patients received dual ICI, while 535 received an ICI+TKI combination. Pts who discontinued their 1L regimen within the 6-mo landmark demonstrated poor OS, with a hazard ratio (HR) of 2.74 (95% CI: 2.15-3.49). Additionally, those who transitioned to a 2L therapy within the first 6 mo showed worse OS, reflected by an HR of 2.82 (2.22-3.59). KT correlation with OS across all follow up was 0.49 (0.45, 0.52) for TTF and 0.67 (0.64, 0.69) for TTNT. Consistent results were seen across all subgroups with the strongest association in the ICI+TKI group (Table). **Conclusions:** TTNT demonstrated the strongest association with OS, particularly in the ICI+TKI subgroup, making it a potentially clinically meaningful intermediate endpoint for evaluating efficacy in ICI-based regimens. Research Sponsor: None.

Association of intermediate endpoints with OS in whole cohort and by IMDC and trt group.

	At 6-mo Landmark		All f/u	
	TTF	TTNT	TTF	TTNT
Evaluable N	1255*	1276*	1628	1656
	Adjusted Hazard ratio (95%CI) (with vs. without IE event)		Kendall's tau correlation	
Overall N=1667	2.74(2.15-3.49)	2.82(2.22-3.59)	0.49(0.45-0.52)	0.67(0.64-0.69)
IMDC risk groups N=1397				
Favorable N=240	1.92(1.03-3.60)	3.33(1.66-6.71)	0.44(0.32-0.56)	0.66(0.55-0.76)
Intermediate N=748	2.81(1.99-3.96)	2.93(2.09-4.10)	0.46(0.40-0.52)	0.63(0.57-0.68)
Poor N=409	3.72(2.39-5.79)	3.00(1.90-4.74)	0.56(0.50-0.61)	0.68(0.63-0.73)
Trt				
ICI+ICI N=1132	2.47(1.86-3.26)	2.75(2.09-3.61)	0.43(0.39-0.48)	0.63(0.58-0.66)
ICI+TKI N=535	3.41(2.19-5.31)	3.10(1.88-5.11)	0.61(0.54-0.66)	0.73(0.66-0.78)

*Excluding pts who died within 6 mo or had not been followed more than 6 mo.

Kidney cancer metastases to breast and other genitourinary (GU) organs: A pooled analysis.

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Background: As the number of kidney cancer survivors increases, the appearance of second malignancies and unusual metastatic patterns is increasing. We performed a pooled analysis to assess the clinicopathologic findings, treatment, and outcomes of cases involving breast and GU organs. **Methods:** Pooled analysis of published case reports and case series of renal cell carcinoma (RCC) metastasis to breast and genitourinary (GU) organs, including four cases from our institution. Parameters were compared between GU organ cohorts using a one-way ANOVA test and subgroup analysis. **Results:** 127 patients with GU metastasis of RCC were analyzed. The overall mean age was 61.2 years (Range: 14-92). GU organs with reported metastasis included 24 to testis (18.9%), 18 to penis (14.2%), 18 to breast (14.2%), 17 to vagina (13.4%), 17 to bladder (13.4%), 14 to ovary (11%), 7 to prostate (5.5%), and 6 to urethra (4.7%). Median Fuhrman grade was 2.5 overall, with penis metastases (n=4) having a median grade of 4. 95 of 111 (86%) cases reported patients with GU metastasis that had a prior nephrectomy for RCC. Patients with breast metastasis (n=16) had a significantly longer time between nephrectomy and metastatic diagnosis (90.1±63.1 months) than penile (12.7±16.1 months, n=6, $p<0.01$), bladder (28.7±26.6 months, n=15, $p<0.01$), or vaginal cohorts (6.7±5.2 months, n=3, $p<0.05$). Co-metastasis to extra-GU sites were most prevalent in penile metastasis (47.4%, n=9). The primary treatments for metastases were excisional surgery (79%), immunotherapy (18%), radiotherapy (14%), and tyrosine kinase inhibitors (13%). The breast cohort (n=10) reported a 90% survival rate at final follow-up, while the vaginal (n=8) and penile (n=12) cohorts reported survival rates of 50%. The urethra cohort (n=2) had a median survival time of 53 months, while the breast cohort (n=10) had a median survival time of 6 months. **Conclusions:** While kidney cancer's metastasis to other GU organs is relatively uncommon, it presents unique diagnostic and therapeutic challenges. Recognizing these patterns and understanding the biology behind such spread can offer insights into RCC's behavior and drive more effective treatments. Research Sponsor: None.

Metastatic Site	Vagina	Testis	Penis	Bladder	Prostate	Breast	Ovary	Urethra
N	17	24	18	17	7	18	14	6
Median Age	58	65.5	64	61	57	70	69	54
Sex (M/F)	0/17	24/0	18/0	12/5	7/0	1/17	0/14	5/1
Clear cell RCC	17	19	11	8	6	16	11	5
Median Time To Mets Post-Nephrectomy (months)	7.5	33.5	6	18	108	72	39	47
Survival (months)	8	15	10	11	15	6	24	53

Real world evidence comparison of first-line (1L) immune-oncology(IO)/tyrosine kinase inhibitor (TKI) vs. IO/IO combination therapy in renal cell carcinoma (RCC).

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Background: IO/IO and IO/TKI are the preferred first-line combinations for treatment of RCC. While these combinations have been superior to sunitinib, no head-to-head clinical trials have been completed, which leaves uncertainty about the preferred combination. Here, we have leveraged ASCO Cancerlinq data to compare overall survival for RCC patients (pts) receiving first line IO/IO vs. IO/TKI combinations. We hypothesized that IO/IO and IO/TKI would have similar survival. **Methods:** We performed a retrospective cohort study comparing IO/IO vs IO/TKI therapy for pts with metastatic RCC. We used the Atropos health platform, which is a commercial platform and queried ASCO CancerLinq data for this study. We identified pts with kidney cancer who received IO/IO or IO/TKI combinations between 2019 and 2023. For our primary analysis, we included only pts with ICD10 code consistent with clear cell [cc]RCC, but also did a secondary analysis including all pts with kidney cancer. The IO/TKI pts received either avelumab/axitinib, pembrolizumab/axitinib, nivolumab/cabozantinib, pembrolizumab/lenvatinib, or atezolizumab/cabozantinib within two weeks of each other. The IO/IO pts were identified as pts receiving ipilimumab and nivolumab within 2 weeks of each other without interceding TKI. We conducted a survival analysis of time to death using Cox proportional hazards regression to compare the two groups. The analysis was performed under three different confounder adjustment scenarios: without adjustment, with basic matching on sex and age, and with high dimensional propensity score (hdPS) using inverse probability of treatment weighting. **Results:** A total of 584 pts (286 IO/IO and 296 IO/TKI) with kidney cancer and 146 with ccRCC (75 IO/IO and 71 IO/TKI) were included. Mean age was 63-65 years and 30-35% female sex across groups. Table shows the restricted mean survival time (RMST) and HR for the Cox models. In the ccRCC cohort, 20 pts with IO/IO and 7 with IO/TKI died with RMST of 947 and 1071 days, respectively (hdPS HR 0.35, p=0.03). In the RCC cohort, 76 pts with IO/IO vs 49 with IO/TKI died with RMST 1126 vs 1017 (hdPS HR 0.61, p=0.04). **Conclusions:** In this exploratory, hypothesis-generating analysis of CancerLinq data, pts treated with IO/TKI had longer OS vs those treated with IO/IO. Limitations include the retrospective nature of the study, low power, lack of randomization, and potential unmeasured confounding factors (e.g., confounding by indication). Further investigation and prospective validation are needed to confirm these findings. Research Sponsor: None.

	RMST (days)	OS HR (95%CI), unmatched	OS HR (95% CI), basic match	OS HR (95% CI), hdPS
ccRCC IO/IO (N=75)	947	Ref	Ref	Ref
ccRCC IO/TKI (N=70)	1071	0.47 (0.20-1.12)	0.56 (0.23-1.39)	0.35 (0.14-0.89)
RCC IO/IO (N=283)	1017	Ref	Ref	Ref
RCC IO/TKI (N=294)	1126	0.65 (0.45-0.93)*	0.55 (0.37-0.83)*	0.61 (0.39-0.97)*

* $p<0.05$.

Optimal timing of delayed cytoreductive nephrectomy in metastatic renal cell carcinoma during the immunotherapy era.

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Background: The CARMENA study found no survival benefit from cytoreductive nephrectomy (CN) in poor-risk metastatic renal cell cancer (mRCC) patients treated with first line Sunitinib. Although retrospective studies have reported survival benefits with CN following immunotherapy (IO)-based therapy, the timing remains unclear. We aimed to investigate the ideal timing of CN following IO using the National Cancer Database. **Methods:** 783 patients with de novo mRCC were diagnosed between 2016 and 2020 who received upfront systemic therapy and underwent CN, 343 patients met our criteria. Patients were categorized into four groups based on the timing of nephrectomy: CN ≤3 months (Group A), 4 to 6 months (Group B), 7 to 9 months (Group C) and ≥ 10 months (Group D) following the initiation of IO-based therapy. Descriptive analysis was performed to examine the demographic and clinical characteristics. Follow up time was measured from the date of surgery to reduce bias. Kaplan-Meier plots were used to analyze survival curves, and a multivariable cox regression analysis was performed to explore associations between timing and survival. **Results:** 343 patients who received upfront IO -based therapy were divided into four groups: 104 (30%) in A, 114 (33%) in B, 74 (22%) in C and 51 (15%) in D. 71%were male, white (90%), age 40 – 64 (62%), comorbidity index 0 (70%), clear cell histology (69%), sarcomatoid (14%). 54% were treated in academia, 57% had bone metastasis, 50% had lung, 11% had liver, and 7% had brain metastases. 66% received only IO, and 34% received IO + TKI. No significant association between CN timing and survival observed in multivariate cox regression model. (HR 0.87, 95% CI: 0.5- 1.7, p = 0.84). Compared to group A, the HR were 0.96 (95% CI, 0.73 to 1.27; p=0.78), 0.77 (95% CI, 0.53 to 1.13; p=0.19), and 0.66 (95% CI, 0.37 to 1.20; p=0.17) respectively for groups B, C and D. **Conclusions:** Our study did not find significant survival improvement with an optimal timing of CN following IO-based therapy, while HRs were reduced after 6 months of delay, though insignificant. This could be due to the small sample size or other confounders. Research Sponsor: None.

Impact of corticosteroid (CS) exposure on acquired resistance to immune checkpoint inhibitor (ICI) therapy in patients (pts) with metastatic renal cell carcinoma (mRCC): A single centre experience.

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Background: ICI therapy with Ipilimumab and Nivolumab (I/N) is a first line standard of care option in pts with intermediate – poor risk mRCC, with the longest durable response in this setting. Nonetheless, a high percentage of pts eventually progress on ICI treatment. Currently contributing factors for acquired ICI resistance remain unclear. The impact of CS use on acquired ICI resistance remains controversial and data in mRCC pts is particularly lacking. **Methods:** We conducted a retrospective analysis of consecutive mRCC pts with primary non-progression to first line I/N. We analysed the use of concurrent CS for all indications including immune related adverse events (IRAE) and compared baseline characteristics of pts who received CS (Cohort A) vs those who did not (Cohort B). Association between CS use, progression and mortality was analysed using multivariable Cox regression model. Adjustment for casemix included IMDC risk score, best response, presence of sarcomatoid/rhabdoid features and brain/liver metastases. Progression free (PFS) and overall survival (OS) were estimated using Kaplan-Meier analysis. **Results:** 64 pts treated with 1L I/N at the Royal Marsden Hospital with primary non-progression between 2016 - 2022 were included. The commonest histological subtype was clear cell (87.5%) with 30% having sarcomatoid/rhabdoid features. All pts had intermediate - poor IMDC risk, with 34% having poor IMDC risk. 47 pts received CS for any indication (Cohort A) and of these 44 pts for IRAE. 17 pts received no CS (Cohort B). Baseline characteristics including IMDC risk, grade and presence of liver/brain metastases were not statistically different between cohorts. 57 pts were eligible for survival analysis with 33 progression events. Median follow up was 22.5 months overall. At multivariable analysis no factors were significantly associated with PFS or OS. Median PFS was 16 months (95% CI 10, 33) in cohort A vs 25 months (95% CI 8, not reached [NR]) in cohort B. PFS was 39% (95% CI 23%, 55%) in Cohort A vs 50% (95% CI 19%, 75%) in Cohort B at 2 years, and 30% (95% CI 15%, 47%) vs 38% (95% CI 10%, 66%), at 3 years respectively. Median OS was 55 months (95% CI 21, NR) in cohort A and NR in cohort B. OS was 60% (95% CI 41%, 74%) in cohort A vs 65% (95% CI 23%, 88%) in cohort B at 2 years and 55% (95% CI 36%, 71%) vs 65% (95% CI 23%, 88%) at 3 years. Cumulative doses and time of CS initiation will be included in the final analysis to determine their impact on above outcomes. **Conclusions:** Although no statistically significant association was seen between CS use and PFS or OS, our results suggest a trend towards shorter time to progression and survival with CS use in pts on 1L I/N for mRCC. While further analyses regarding the dosage and timing of CS are underway, given this is a single centre retrospective analysis, these results would need to be confirmed in larger studies. Research Sponsor: None.

CRP kinetics to predict long-term efficacy of first-line immune-checkpoint inhibition combination therapies in metastatic renal cell carcinoma: An updated multicenter real-world experience applying different CRP kinetics definitions.

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Background: Although biomarkers predicting therapy response in 1st line metastatic renal carcinoma (mRCC) therapy remain to be defined, C-reactive protein (CRP) kinetics have recently been associated with immunotherapy (IO) response. To assess the predictive and prognostic power of two contemporary CRP kinetics definitions in a large, real-world 1st line mRCC cohort. **Methods:** mRCC patients treated with IO-based 1st line therapy within 5 years were retrospectively included in this multi-center study. According to Fukuda et al., patients were defined as 'CRP flare-responder', 'CRP responder' and 'non-CRP responder'; according to Ishihara et al., as 'normal', 'normalized' and 'non-normalized' based on their early CRP kinetics. Patient and tumor characteristics were compared, and treatment outcome was measured by overall (OS) and progression-free survival (PFS), including multivariable Cox regression analyses. **Results:** Out of 316 mRCC patients, 227 (72%) were assigned to CRP groups according to Fukuda. Both CRP flare- (HR [Hazard ratio]: 0.59) and CRP responders (HR: 0.52) had a longer PFS, but not OS, than non-CRP responders. According to Ishihara, 276 (87%) patients were assigned to the respective groups, and both normal and normalized patients had a significantly longer PFS and OS, compared to non-normalized group. **Conclusions:** Different early CRP kinetics may predict therapy response in 1st line mRCC therapy in a large real-world cohort. However, further research regarding the optimal timing and frequency of measurement is needed. Research Sponsor: None.

Evolving metastatic renal cell carcinoma (mRCC) treatment landscape in the post vascular endothelial growth factor (VEGF) and immune checkpoint inhibitor (IO) setting.

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Background: IO and VEGF based therapies have transformed the front-line treatment paradigm for patients with mRCC. This study's objective is to describe treatment patterns and clinical outcomes among mRCC patients in the post IO and VEGF setting. **Methods:** Adult patients diagnosed with mRCC between Jan 2015 - Dec 2022 and received IO and VEGF (in combination or sequence) in the first three lines of therapy after mRCC diagnosis were identified from Optum's de-identified Clinformatics® Data Mart Database, a large retrospective claims database. Index date was defined as the date of the first (index) treatment in the post IO and VEGF setting. Patients were required to have continuous enrollment of 6 months prior to index date. Patients were categorized into 3 cohorts based on lines of index treatment (2L, 3L, 4L). Treatment patterns were described and real world (rw) time on treatment (ToT), time to next treatment (TTNT), and overall survival (OS) were estimated by Kaplan Meier analysis. **Results:** A total of 664 patients were included (2L:186, 3L:429, 4L:49). 37% received IO and VEGF in combination prior to index line of therapy. Median age at mRCC diagnosis was 67.0 years, with 72.7% male and 68.1% White; 11.6% died and 7.4% disenrolled during index treatment. Post IO and VEGF, cabozantinib was the most used therapy across 3 cohorts (2L: 43.5%, 3L: 35.2%, 4L: 30.6%) (Table). Median rwToT and rwTTNT for 2L, 3L, and 4L cohorts were 4.4, 5.0, and 5.6 months and 10.7, 11.7, and 9.5 months, respectively. Median OS from mRCC diagnosis was similar across the 3 cohorts (2L: 41.6, 3L: 38.7, 4L: 40.6 months); median OS from index date decreased with advancement in LOT (2L: 20.6, 3L: 14.1, 4L: 10.3 months). **Conclusions:** Our study is one of the largest and comprehensive study giving a unique perspective into evolving treatment patterns and outcomes for mRCC patients in the post IO and VEGF setting. Post IO+VEGF, the most common treatments were tyrosine kinase inhibitor-based treatments, and the median ToT was less than 6 months. Hence, novel treatments are needed to improve clinical outcomes for mRCC patients in the post IO and VEGF setting. Research Sponsor: his abstract was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Clinical outcomes and top 4 most used treatments in post IO and VEGF setting.

Outcomes, Median in Months (95% Confidence Interval)	2L Cohort (n=186)	3L Cohort (n=429)	4L Cohort (n=49)
Time on Tx	4.4 (3.4-5.3)	5.0 (4.4-6.0)	5.6 (2.1-8.3)
Time to next Tx	10.7 (8.6-20.6)	11.7 (10.4-14.8)	9.5 (6.4-14.2)
OS from mRCC diagnosis	41.6 (30.6-64.0)	38.7 (35.5-42.6)	40.6 (36.0-48.8)
OS from index date	20.6 (14.6-NE)	14.1 (11.5-16.0)	10.3 (8.8-16.7)
Most used Tx for index Tx, n (%)			
Cabozantinib	81 (43.5%)	151 (35.2%)	15 (30.6%)
Everolimus + lenvatinib	20 (10.8%)	71 (16.6%)	7 (14.2%)
Ipilimumab + nivolumab	21 (11.3%)	9 (2.1%)	0 (0%)
Axitinib	5 (2.7%)	34 (7.9%)	6 (12.2%)

NE, not estimable; OS, overall survival; Tx, treatment.

Impact of renal function eligibility criteria in clinical trials and real-world survival outcomes among patients with metastatic renal cell carcinoma.

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Background: Registration trials in metastatic renal cell carcinoma (mRCC) establishing the efficacy of first-line (1L) combination regimens employed strict renal function eligibility criteria (NCT02853331, NCT02811861, NCT03141177, NCT02231749); however, pharmacokinetics and safety of immune checkpoint inhibitors and anti-vascular endothelial growth factor therapies have been shown to be similar regardless of baseline renal function. Therefore, we aim to evaluate the impact of renal function eligibility criteria used in previous trials on real world outcomes. **Methods:** Data from the US nationwide Flatiron Health electronic health record-derived de-identified database included adult patients (pts) with mRCC who received any 1L systemic treatment on or after 4/16/2018 (first FDA combination regimen approval), had hemoglobin level ≥9 g/dL and ECOG performance status (ECOG) 0-1 at 1L. Renal function eligibility criteria at 1L (-60 days to +7 days) include serum creatinine (≤1.5 vs >1.5 x ULN), eGFR (≥30 vs <30 ml/min/1.73m^2) and calculated CrCl (≥40 vs <40 ml/min) based on registration trial protocols. Outcomes include real world progression free survival (rwPFS), time to next treatment (rwTTNT), and overall survival (rwOS) from 1L. Inverse probability of treatment weighted (IPTW) Kaplan Meier methods and Cox proportional hazard models with multiple imputation were applied. **Results:** Of 2038 pts in this cohort, 1390 (68.2%) met all criteria for renal function (included), 140 (6.9%) met at least one criteria (relaxed), 46 (2.3%) met none (excluded), and 462 (22.7%) had unknown renal function. Compared to included pts, excluded pts were more likely to be older (median age: 74 vs 66), female (35% vs 27%), have recurrent disease (61% vs 53%), less likely to have ECOG 0 (24% vs 40%) and favorable IMDC risk (9% vs 14%). Excluded pts are also more likely to be Non-Latinx Black (13% vs 6%) and have lowest SES quintile (22% vs 15%) compared to included pts. Although, after weighting included pts had higher median rwPFS of 9.3 (95% CI 8.4 - 10.1) vs 6.9 (95% CI 3.7 - 9.9), rwTTNT 12.0 (95% CI 11.0 - 13.1) vs 9.1 (95% CI 5.5 - 16.4) and rwOS 38.5 mo (95% CI 35.9 - 44.5) vs 19.3 mo (95% CI 16.6 - 41.8) compared to relaxed/excluded pts, none of the hazard ratios (HRs) were statistically significant after multiple imputation (Table). **Conclusions:** In this real world study, we found that although only 68.2% of patients met all renal function eligibility criteria, survival outcomes were not different across pts groups. This suggests that mRCC patients with reduced renal function may benefit similarly to 1L treatment and should not be excluded from clinical trials. Research Sponsor: This study was sponsored by Flatiron Health, Inc., which is an independent member of the Roche Group.

Weighted HRs and 95% CIs with MI.

	Excluded/Relaxed vs Included	Excluded vs Relaxed/Included
rwPFS	1.04 (0.87 - 1.24)	0.96 (0.74 - 1.23)
rwTTNT	0.94 (0.79 - 1.13)	0.94 (0.73 - 1.21)
rwOS	1.06 (0.84 - 1.33)	0.90 (0.65 - 1.26)

Comparison of financial toxicity among patients with non-metastatic versus metastatic renal cell carcinoma.

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Background: Little is known about the financial impact of renal cell carcinoma (RCC). We sought to ascertain real world data on financial implications and how financial toxicity (FT) impacts quality of life in patients with localized RCC versus patients with metastatic RCC. **Methods:** An online survey was conducted by the Kidney Cancer Research Alliance (KCCure), a non-profit patient advocacy organization, from 7/22 to 9/22. The survey included questions about costs and financial concerns and the COST questionnaire. Pearson's correlation (r) and Kendal's tau test were used to analyze the COST questionnaire, financial burden and hardship. **Results:** Out of 1062 responders 623 had localized RCC. Out of these patients 395 did not recur and 204 were willing to answer questions related to cost and financial hardship. 289 responders had metastatic disease and were on systemic therapy and 177 pts answered the COST questionnaire. In localized disease 28% reported that their diagnosis has not reduced their income, in 26% the diagnosis had reduced their income very much.31% experienced insurance denials for imaging, 30% faced delays in care due to pre-approval requirements, 45% faced high out-of-pocket costs for medical care. 24% of patients reported taking a hardship withdrawal from a retirement account, 28% stopped funding or lowered contributions to an existing retirement account, 20% borrowed from friends or family. In metastatic patients 14% reported difficulties to pay their premiums. 28% reported that their medical situation has not reduced their income and 26% claimed that their disease reduced their income very much. 36% reported high out of pocket costs are a barrier to care. 44% have received financial support through a manufacturer or a foundation. Median COST score in non-metastatic RCC was 32 (range 19-44)) and was significantly correlated to age, NCCN distress score, risk of recurrence and supplement intake ($p < 0.05$). Metastatic patients had a significantly higher median COST score of 22 (range 4-36)) that was also correlated to age, NCCN distress score, time since diagnosis and supplement intake ($p < 0.05$). **Conclusions:** RCC imposes financial hardship on patients. Younger patients with a higher NCCN distress score and a shorter time since diagnosis are more likely to suffer financial hardships. Patients are willing to pay for supplements. Financial counseling should be considered in these patient subgroups regardless of stage. Research Sponsor: None.

Median age, years (range)	Localized RCC 54 (range 19-84)	Metastatic RCC 61 (range 19-89)
Race white	89 %	91 %
Living in the US	84 %	87 %
Bachelors degree and above	53 %	53 %
Household income	13 %	17 %
> 50.000US$ > 100,000US$ > 250,000US$	32 %	41 %
	17 %	15 %
Insurance	65 %	61 %
Private Insurance Medicare/Medicaid Uninsured	16 %	27 %
	0.5 %	0.6%
Supplement Spending	25 %	23 %
> 100 US$/month > 250 US$/month	6 %	8 %

Real world data on treatment of chromophobe renal cell carcinoma.

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Background: Chromophobe renal cell carcinoma (ChRCC) is the third most common subtype of renal cell carcinoma (RCC), accounting for 5%–7% of all RCCs. ChRCCs are generally viewed to have a favorable clinical outcome compared to clear cell RCC, yet up to 10% of patients with ChRCC will develop metastases. To date, there are no genomic biomarkers that predict post-surgical metastatic recurrence, and no standard of care exists for treating metastatic chRCC. We sought to better understand real world patient experiences in this underrepresented and understudied patient population. **Methods:** The survey was developed by the Kidney Cancer Research Alliance (KCCure) and was broadcast between 07/2022 and 09/2022 to patients via website, mailing lists and social media platforms. Those who agreed to participate were surveyed for demographics (age, gender, race, income, country) and clinical characteristics (date of the diagnosis, disease stage, treatment history). Out of 1,062 participants 121 patients self-identified with chRCC, 34 patients had metastatic disease, and 23 patients had received systemic therapy. **Results:** The majority of patients were from the United States (75%), median age was 49.7 years (range 19-74), 70 percent of patients identified as female, and 30 percent of patients identified as male. Stage distribution at initial diagnosis was stage 1 in 37.3%, 27.3% were stage 2 and stage 3 respectively, 8.3% were metastatic at diagnosis. 14% of patients reported having sarcomatoid dedifferentiation. 20 percent of patients (24) experienced re-current metastatic disease after a median duration of 3.3 years (range 1-6). Of the 23 patients who received treatment, first line therapy consisted of TKI monotherapy (9), combination IO and TKI (7), combination IO/IO (4), mTOR mono-therapy (1), other therapies (2). Second and later line therapies were combination IO/IO (3), IO and TKI (9), Lenvatinib and everolimus (7), TKI monotherapy (5), mTOR monotherapy (5) and other therapies (5). Median duration of therapy was 43 months (range 2-196). The most used TKIs were cabozantinib and lenvatinib. In the metastatic setting, 4 patients reported being treated as part of a clinical trial, 9 patients reported that no one had ever talked to them about participating in a clinical trial. 6 patients said that no trials were being held at their treating center. **Conclusions:** Patients reported higher rates of recurrence than what is usually reported in ChRCC, however this could reflect sample bias as patients with more aggressive disease may be more likely to engage with patient communities. No standardized treatment for metastatic disease could be identified. Overall treatment duration was comparable to clear cell carcinoma. Very few patients had access to clinical trials. ChRCC-specific clinical trials and tailored treatment regimens are urgently needed. Research Sponsor: None.

Retrospective study assessing the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers to reduce toxicity from tyrosine kinase inhibitors in metastatic renal cell carcinoma.

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Background: The main toxicities associated with tyrosine-kinase inhibitors (TKIs) in the treatment of renal cell carcinoma (RCC) are proteinuria and hypertension. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have established reno-protective and anti-hypertensive effects and can help with toxicity in mRCC. We hypothesize that use of ACEIs/ARBs is an effective method to decrease the degree of proteinuria and hypertension in patients treated with TKIs for metastatic/advanced renal cell carcinoma (mRCC). **Methods:** Single Institution retrospective study; mRCC patients (pts) who received TKI and ACEIs/ARBs and had urine protein measurements available at baseline and at 4-6 wk follow up post ACEs/ARBs were included in the analysis. Primary endpoints included improvement in grade of proteinuria and BP in mRCC pts on TKI treatment at baseline and with addition of ACEIs/ARBs. Secondary endpoints included number of dose interruptions (DI), BUN and creatinine changes. Paired statistical tests were used to compare the selected outcome variables between baseline and post ACE/ARB measures: for example, nonparametric Wilcoxon Signed-rank test for paired quantitative data and McNemar test for paired binary data. **Results:** Out of 71 screened patients between 2020-2023, N of 22 mRCC (N=22, 72.7% male, 77.3% white; 9% Hispanic; N=14 for TKI+ immunotherapy; N=8 TKI alone) pts were selected. ACEIs/ARBs treatment was associated with significantly reduced levels of proteinuria at 4–6wk follow-up. At baseline vs. follow-up, pts were found to have significantly lower proteinuria overall after ACEI/ARBs ($p=0.0147$), and 45.4% of pts had clinically insignificant proteinuria vs. 22.7% at baseline. Additionally, DI rates for TKI were significantly lower for pts placed on ACEIs/ARBs, with an 81% chance that pts with prior DI would not experience similar event in the follow-up period ($p=0.003$). Reductions in BP, creatinine, and TKI dosing were seen but not statistically significant ($p>0.05$ for all measures). **Conclusions:** In our small study, degree of proteinuria was notably reduced with administration of ACEIs/ARBs. Further findings show fewer DI of TKIs with ACEIs/ARBs use. Our findings suggest a potential role for ACEIs/ARBs in managing toxicity in patients undergoing TKI based therapy for mRCC. Future studies are needed to evaluate the use of ACE/ARB from the time of initiation of TKI based therapy to reduce the toxicities and improve the adherence to mRCC treatment which may result in better outcomes.
Research Sponsor: None.

Health-related quality of life (HrQoL) of first-line treatments in metastatic renal cell carcinoma (mRCC): A network meta-analysis.

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Background: Previously we have reported comparative effectiveness data regarding survival of first line (1L) treatment options in mRCC. However, it is not known how the life-prolonging frontline combinations compare to patient-reported outcomes. **Methods:** Electronic databases including MEDLINE and EMBASE were searched from each database's inception through July 1st 2023. Phase III randomized controlled trials (RCTs) assessing 1L immune-checkpoint inhibitor (ICI) combination therapies for mRCC and reporting HrQoL were included. Small sample size adjusted standardized mean differences (SMD; Hedges' *g*) with 95% confidence intervals (CI) were computed for global, physical, functional, and emotional QoL. Positive SMD indicated an improvement. A network meta-analysis was conducted to assess the comparative HrQoL across different treatment options. P-scores were computed to assess relative treatment rankings. **Results:** Of 5770 citations identified, five trials (nine references) were included in this analysis. Patient-reported outcomes have not been reported in the JAVELIN Renal 101 or COSMIC-313 trials yet. Global QoL was significantly improved with cabozantinib-nivolumab (CaboNivo) as compared to Nivo-ipilimumab (SMD 2.74, 95% CI 2.54; 2.93), lenvatinib-pembrolizumab (LenPem; 2.79, 2.53; 3.06), sunitinib (2.87, 2.72; 3.03), Pem-axitinib (PemAxi; 3.09, 2.89; 3.30) and atezolizumab-bevacizumab (AteBev; 3.24, 3.04; 3.45). Global QoL improvement was also observed with NivoIpi compared to sunitinib (0.14, 0.02; 0.25), PemAxi (0.36, 0.18; 0.54) and AteBev (0.51, 0.33; 0.68). Physical QoL improvement were consistent with CaboNivo. Likewise, LenPem significantly improved QoL compared to sunitinib (0.26, 0.04; 0.47), PemAxi (0.38, 0.13; 0.64) and NivoIpi (0.51, 0.27; 0.76). Significant functional QoL benefits were only observed with CaboNivo (0.32, 0.17; 0.48) and NivoIpi (0.19, 0.08; 0.31) compared to sunitinib. No significant mixed treatment comparisons were observed for emotional QoL, however, currently available data suggests that LenPem (rank 1) may potentially improve QoL (Table). **Conclusions:** CaboNivo and NivoIpi as 1L therapy may offer an improved overall HrQoL compared to other contemporary treatment options in mRCC. Research Sponsor: None.

	Global		Physical		Functional		Emotional	
Drug	**P-score**	**Rank**	**P-score**	**Rank**	**P-score**	**Rank**	**P-score**	**Rank**
CaboNivo	1	1	1	1	0.89	1	0.49	3
NivoIpi	0.73	2	0.02	5	0.54	2	NA	NA
LenPem	0.61	3	0.75	2	NA	NA	0.75	1

The feasibility of an educational and monitoring smartphone application for patients with advanced renal cell carcinoma undergoing combination immunotherapy.

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Background: Renal Cell Carcinoma (RCC) is a global public health burden with over 400,000 new cases and over 175,000 deaths annually. Immune checkpoint inhibitors (ICI) in combination with vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKI) has become an integral part of the management of patients with advanced RCC which requires adaptation of healthcare systems to provide information and optimize the management of drug-related adverse events. This study aims to improve the education on therapy-related symptoms and the quality of life of patients with RCC treated with these drugs. **Methods:** We created a smartphone application (mHealth) that combines educational data, patient-reported outcomes, and peer-to-peer interactions. We aim to assess the feasibility of expansion of this pilot study. We prospectively enrolled stage IV RCC patients (n=20) undergoing treatment with combination ICI and VEGF-TKI. Therapy-related symptom education, knowledge PRO questionnaires, and peer-to-peer support were provided at baseline and at different time points throughout this study duration (Table 1). Time-course data of PROs were visualized using line plots and then compared with paired t-tests. The study's primary endpoint was to assess acceptability and feasibility of mHealth, defined as acceptable if 50% of patients offered participation agree to be enrolled and feasible if 50% of enrolled patients complete the intervention with 70% of these completing at least 50% of survey instruments. **Results:** Eighty percent of patients were male, 80% were white, 75% had at least some college education, 70% were married, and the mean age of the cohort was 66 years.A total of 22 patients were approached for the study with an acceptance rate of 90%. Sixty percent of patients completed every questionnaire and knowledge assessment at every timepoint of the intervention and 75% of those completed at least 50% of instruments. PROs data showed no significant difference compared to baseline in global health status, functional scales, and symptom scales across the 24 weeks. We noticed an improvement in the patients' knowledge assessment on symptom management after completion of the mHealth knowledge component. **Conclusions:** Our pilot study was considered acceptable and feasible, showing preliminary evidence of improvement in patient knowledge with mHealth. Our future direction will be to assess, in a larger randomized study, the efficacy of mHealth in improving the quality of life of patients with advanced RCC treated with ICI and VEGF-TKI. Clinical trial information: NCT05579847. Research Sponsor: H. Lee Moffitt Cancer Center and Research Institute.

Study calendar.

Instrument	Baseline	3w	4w	6w	8w	12w	16w	20w	24w
Screening and eligibility form	X								
Patient enrollment survey	X								
Educational component	Over 6 weeks								
Knowledge assessment	X	X		X					X
PRO instruments	X		X		X	X	X	X	X
Peer-to-peer component	Over 24 weeks								

Abbreviations: w, weeks; PRO, patient-reported outcomes.

Comparative analysis of outcomes of neoadjuvant and adjuvant systemic therapy in non-metastatic renal cell carcinoma: A propensity score-matched analysis from the INMARC registry.

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Background: Receipt of adjuvant therapy has become a standard of care for management of high risk localized renal cell carcinoma (RCC), with emerging literature demonstrating longer disease-free survival. Neoadjuvant approaches have been utilized investigationally to facilitate complete surgical resections in high risk and complex renal masses. We sought to evaluate outcomes of patients treated with neoadjuvant or adjuvant therapy in non-metastatic RCC utilizing a propensity score model. **Methods:** We queried the INMARC database for patients with localized surgically treated RCC who underwent systemic neoadjuvant or adjuvant therapy. Neoadjuvant therapy was defined as presurgical therapy given in the setting of localized disease and adjuvant therapy as systemic therapy given postoperatively in the absence of documented metastases. Patients with metastases at time of diagnosis were excluded from the analysis. A propensity score match (PSM) model in a 1:3 ratio was conducted within a caliper width of 0.1 including: age, sex, hypertension, Charlson Comorbidity Index, tumor size, tumor necrosis, stage, surgical margin, tumor grade and type of surgery [radical vs. partial nephrectomy]. Primary outcome was all-cause mortality (ACM), and secondary outcome was cancer-specific mortality (CSM). Multivariable analysis (MVA) via Cox regression was fitted for the outcomes of interest. Kaplan-Meier analysis (KMA) for overall (OS), cancer specific survival (CSS) was conducted for 5-year survival assessment. **Results:** After PSM 293 patients were analyzed [adjuvant n=203, (69.2%), 109 targeted therapy (TT) vs. 94 immunotherapy; neoadjuvant n=90, (30.7%), 59 TT vs. 31 immunotherapy]; median follow up was 50 (IQR 20-76) months from surgery . MVA revealed adjuvant vs. neoadjuvant (HR 1.98, p=0.007) and positive margin (HR 2.01, p=0.046) to be associated with increased risk of ACM; immunotherapy vs. TT (HR 0.47, p=0.001) was associated with a decreased risk. MVA for CSM revealed that adjuvant vs. neoadjuvant (HR 2.18, p=0.016) and positive margin (HR 2.41, p=0.028) were associated with increased risk of CSM, while immunotherapy vs. TT (HR 0.35, $p<0.001$) was associated with decreased risk. KMA comparing neoadjuvant vs. adjuvant 5-year OS was 80.4% vs. 64.8% (p=0.04), while CSS was 88.1% vs. 76.2% (p=0.03). **Conclusions:** In a comparison of patients with localized RCC who underwent adjuvant or neoadjuvant systemic therapy, receipt of neoadjuvant therapy was associated with superior survival outcomes. These findings are hypothesis generating and call for consideration for a clinical trial to compare outcomes of adjuvant vs. neoadjuvant therapy in high-risk localized RCC. Research Sponsor: None.

Association of radiographic and pathologic outcomes in patients (pts) with advanced renal cell carcinoma (RCC) with and without thrombus receiving preoperative immune checkpoint inhibitor (ICI) regimens and circulating biomarkers.

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Background: Primary RCC tumors and associated IVC thrombus have similar histology, however response to ICI is not always concordant. RCC with IVC thrombus is often difficult to manage, and perioperative ICI treatment responses remain largely unstudied. **Methods:** We conducted a retrospective analysis of pts with advanced RCC receiving preoperative ICI-based regimens at UTSW stratified by the presence of tumor thrombus. The primary objectives were pathologic change in both groups and radiographical response by RECIST 1.1 criteria for tumor and thrombus level change. The secondary objective was to evaluate biomarkers associated with thrombus. Comparisons were performed using a two-sample t-test or aChi-square test. **Results:** 65 pts were included (median age 64 years), 31 (48%) with baseline thrombus (9 (29%) renal vein thrombus; 6 (19%) level 1 IVC thrombus; 10 (32%) level 2; 2 (7%) level 3; and 4 (13%) level 4). 28 pts (43%) received ICI+ICI, while 20 pts (31%) received ICI+TKI and the rest received ICI monotherapy. 18/31 pts (58%) with thrombus and 20/34 without thrombus (59%) had metastasis at baseline. Pathological Tumor (pT) downstaging occurred in 13 pts with and 11 pts without thrombus; of these, 12 pts had received ICI+TKI and 12 pts ICI+ICI. Radiographic tumor (cT) downstaging occurred in 8/31 pts with thrombus and 7/34 pts without. 12/31 pts experienced thrombus downstaging. 5 pts with thrombus vs 2 pts without had complete tumor necrosis/pCR in the primary and radiographic PR, of whom 4/7 received ICI+TKI. In pts with IVC thrombus, preoperative ICI based regimens reduced median tumor size from 9.1 to 7.7 cm. Among responders in pts with IVC thrombus, ICI+TKI had a trend toward higher tumor shrinkage median (-3.3 vs -1.9 cm, *p=0.3*) and thrombus downstaging median (-2 vs -1 levels, *p=0.27*) than ICI+ICI. Baseline anemia (Hemoglobin (Hgb), 11.1 vs 13.1 g/dL, *p=0.002)*, lower Absolute Lymphocyte Count (ALC) (1.35x10^3 vs 1.55 x10^3 cells/uL, *p=0.03*), and higher Neutrophil-to-Lymphocyte ratio (NLR) (3.6 vs 3.2, *p=0.03*) were observed in pts with IVC thrombus. **Conclusions:** ICI+TKI regimens tend to have tumor downstaging, complete tumor necrosis/pCR in primary tumors, and some IVC thrombus control compared to ICI+ICI regimens. IVC thrombus is associated with lower Hgb and ALC and higher NLR levels. Prospective trials are ongoing to investigate perioperative treatment in pts with IVC thrombus. Research Sponsor: None.

	IVC Thrombus (+)			IVC Thrombus (-)		
	Pre-treatment	*Post-treatment*	*p-value*	*Pre-treatment*	*Post-treatment*	*p-value*
Tumor (T)	T0 (n=0) T1 (n=1) T2 (n=2) T3 (n=17) T4 (n=11)	T0 (n=5) T1 (n=3) T2 (n=1) T3 (n=19) T4 (n=3)	0.0094*	T0 (n=0) T1 (n=1) T2 (n=10) T3 (n=20) T4 (n=3)	T0 (n=2) T1 (n=9) T2 (n=4) T3 (n=18) T4 (n=1)	0.0045*
Median Hgb	11.1			13.1		0.002**
Median ALC	1.35			1.55		0.03**
Median NLR	3.6			3.2		0.03**

Impact of timing of immunotherapy and cytoreductive nephrectomy on outcomes in metastatic renal cell carcinoma: Results from the CKCis database.

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Background: Immunotherapy-based systemic treatment (ST) is the standard of care for most patients diagnosed with metastatic renal cell carcinoma (mRCC). Cytoreductive nephrectomy (CN) has historically shown benefit for select patients with mRCC but its role and timing are not well-understood in the era of immunotherapy. The primary objective of this study is to assess patient outcomes in patients who received ST only, CN followed by ST (CN-ST) and ST followed by CN (ST-CN). **Methods:** The Canadian Kidney Cancer information system (CKCis) database was queried to identify patients with de novo mRCC who received immunotherapy-based ST for mRCC between January 2014 to June 2023. These patients were classified into three categories as described above. Cox proportional hazards models were used to assess the impact of the timing of ST and CN on overall survival (OS) and progression free survival (PFS), after adjusting for IMDC risk group. Complications of ST and CN for these cohorts were collected. **Results:** A total of 588 patients were included in this study. 331 patients received ST only, 215 patients received CN-ST and 42 patients received at least one dose of ST prior to CN. Patient and disease characteristics including age, gender, performance status, IMDC risk category, comorbidity, histology, type of ST and metastatic sites are reported and globally well-balanced. OS analysis favoured patients who received ST-CN (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.13-0.68) and CN-ST (HR 0.68, CI 0.47-0.97) over patients who received ST only. PFS analysis showed a similar trend for ST-CN (HR 0.45, CI 0.26-0.77) and CN-ST (HR 0.9, CI 0.68-1.17). The most common cause of ST delay or cessation was treatment toxicity, followed by progression of disease. The most common perioperative complication was bleeding, followed by infection. **Conclusions:** This study examined baseline features and outcomes associated with the use and timing of CN and ST using real world data through the CKCis database. Patients selected to receive CN after ST seem to have improved outcomes. There were no appreciable differences in ST toxicity or perioperative complications across groups. Limitations include the small number of patients in the CN-ST group and residual confounding and selection bias that may influence the outcomes in patients undergoing CN. Research Sponsor: None.

Systemic and surgical treatment in renal cell carcinoma: Does timing matter?

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Background: Today, targeted systemic therapy is standard 1st line treatment of advanced/metastatic renal cell carcinoma (aRCC). Upfront cytoreductive nephrectomy (CN) has been an important treatment option. Recently its role is under debate, especially in combination with the new 1st line treatments. Our study evaluated the current relevance of initial surgical intervention and the role of inductive systemic therapy in aRCC. **Methods:** We included 33 patients with aRCC from the University Hospitals in Essen and Münster initiating 1st line treatment from 03/18 to 01/23 pre or post surgery. We retrospectively formed two cohorts, either CN followed by systemic therapy (cohort 1; 13 patients) or vice versa (cohort 2; 20 patients). Patients received either Ipilimumab/Nivolumab (Ipi/Nivo) (42.4%) or a checkpoint inhibitor and tyrosine kinase inhibitor (CPI/TKI) combination (57.6%). Progression-free survival (PFS) was estimated with Kaplan-Meier-method from initiation of systemic therapy or CN to progression or death. In Cohort 2, we additionally analyzed the radiologic response of the primary measured by change of the longest diameter. The radiographic response was analysed according to RECIST1.1. **Results:** Patients' age ranged from 44 to 80 years with a median of 63 years. Intermediate and poor prognosis occurred in 61.3% and 38.7% of cases. The two cohorts did not differ significantly regarding baseline characteristics. Median PFS was 8 vs. 23 months (p=0.03) in cohort 1 (95% CI 0.9-15.1) compared to cohort 2 (95% CI 18.8-27.2). In cohort 2 the time between start of systemic therapy and surgery was in median 8.5 months (95% CI 3.3-21.1), the primary had a median diameter of 10.7 cm (95% CI 4.5-13.3). Median reduction of the primary was in total 32.2%, 28.9% in the Ipi/Nivo and 34.7% in the CPI/TKI group (p=0.74). In seven patients (35%) response led to modification of the surgical approach, enabling partial instead of radical nephrectomy. **Conclusions:** The sequence of systemic therapy followed by surgery was associated with a significant PFS benefit. In addition, prior systemic therapy led to a primary reduction and better operability, in some cases even to kidney sparing surgery. Major limitation is the retrospective nature of our analysis and a potential selection bias. However, the sequence of prior systemic therapy followed by surgery in aRCC was associated with notably better outcomes. Research Sponsor: None.

FDA pooled analysis of overall survival according to depth of response as a continuous variable in frontline advanced immuno-oncology renal cell carcinoma trials.

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Background: Retrospective analyses of individual studies of immune-oncology-containing combinations (IOC) for advanced renal cell carcinoma (aRCC) suggest that depth of response (DepOR; % reduction from baseline in sum of target lesion diameters) is associated with overall survival (OS). However, these analyses are limited by use of DepOR categories with a small number of patients and guarantee-time bias. We therefore sought to investigate the relationship of week 12 DepOR as a continuous variable with OS, hypothesizing not only complete but also deep partial responses might portend favorable longer-term survival. **Methods:** We pooled data from patients with treatment (tx)-naïve aRCC enrolled in randomized IO-based frontline aRCC trials submitted to FDA that included a Week 12 imaging assessment. We developed 36-month (mo) overall survival (OS) prediction models based on Week 12 DepOR per Independent Review Committee using Cox proportional hazards with natural spline in the IO-TKI combination (IOC) and sunitinib (SUN) groups. To avoid guarantee-time bias, OS was defined from date of an individual patient's 12-week imaging, among the subset of patients who were alive and in follow-up at the Week 12 scan. **Results:** Four trials met inclusion criteria (KEYNOTE-426, JAVELIN Renal 100, CheckMate 9ER, CheckMate 214); in total there were 1364 patients in the IOC group and 1267 patients in the SUN group. Eligibility criteria, baseline patient characteristics, and endpoints were similar both between the trials and between tx groups. Deepest response occurred at median 31 weeks (interquartile range [IQR], 18-55) in the IOC group and 29 weeks (IQR range, 17-48) in the SUN group. At Week 12, 34.7% of patients had DepOR of at least 30%; median DepOR was 27.6% (interquartile range [IQR] 8.7 to 43.4%) in the IOC and 13.7% (IQR 2.5 to 26.3%) in the SUN group. DepOR and 36-month OS were correlated throughout the entire range of DepOR in both tx groups; at each DepOR, the IOC group had slightly higher 36-mo OS over SUN. We saw similar results modeling 24-month OS compared to 36-month OS. **Conclusions:** This pooled exploratory analysis suggests that deeper response is associated with better 36-month OS in patients treated with IOC or SUN and slightly higher probability of 36-month OS for any given DepOR for IOC vs. SUN. We saw no plateau in OS as DepOR approached complete response. However, caution should be used when interpreting DepOR at the tails due to sparse data. Further work characterizing the relationship between DepOR and OS at the trial level may advance understanding of the utility of DepOR as an early endpoint in signal-seeking trials and to facilitate efficient drug development. Additionally, identifying patients with favorable long-term prognosis based on DepOR provides hypotheses for new trial designs. Research Sponsor: None.

Efficacy, safety, and tolerability of tivozanib (TIVO) in heavily pretreated patients (pts) with advanced clear-cell renal cell carcinoma (ccRCC).

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Background: TIVO, a potent tyrosine kinase inhibitor that predominantly targets vascular endothelial growth factor receptors, is approved as a third or later line therapy for advanced RCC based on improved progression-free survival (PFS) compared with sorafenib in the TIVO-3 trial. However, TIVO-3 was conducted before immune checkpoint-based therapies (ICT), cabozantinib (CABO), and lenvatinib/everolimus (LEN/EVE) became fully incorporated in the sequential treatment paradigm for advanced ccRCC. Hence, an appraisal of the role of TIVO in the current RCC treatment landscape is warranted. **Methods:** We performed a retrospective study of pts with advanced ccRCC treated with TIVO at MD Anderson Cancer Center during 6/2021-7/2023. Demographic and clinical data were abstracted from the electronic medical records. A blinded radiologist assessed tumor response by RECIST v1.1. We assessed objective response rate (ORR), clinical benefit rate [percentage of all treated pts who achieved a complete or partial response (PR) or had stable disease (SD) for ≥6 months (mo)], time on treatment (TOT), PFS, overall survival (OS), and safety. **Results:** 30 pts (23 males, 7 females; median age 66 years, range 43-80) were included in this analysis. Median follow-up was 10.8 mo. At initiation of TIVO, 77% of pts had ECOG PS 0/1, 23% had PS ≥2; 53% had intermediate-risk and 47% had poor-risk disease by IMDC; 83% had ≥3 metastatic sites; 80% had prior nephrectomy. Median number of prior therapies was 4 (range, 1-8). All pts received prior ICT (30% nivolumab/ipilimumab), 40% received prior axitinib, 87% CABO and 60% LEN +/- EVE. 23 pts (76.7%) started TIVO at full-dose (1.34 mg/day, 3 weeks on, 1 week off) and 7 pts (23.3%) at 0.89 mg/day, 3 weeks on, 1 week off. Of 26 pts with evaluable radiographic response, 2 pts had a confirmed PR (ORR 7.7%) and 5 pts had SD for ≥6 mo (clinical benefit rate 23.3%). Median TOT was 3.2 mo (range, 0.1-13.5), median PFS 3.7 mo (range, 0.7-13.5); median OS has not been reached (13 pts had died at time of analysis). 7 pts (23.3%; 5 pts who started at 1.34 mg/d and 2 pts who started at 0.89 mg/d) required dose-reduction due to treatment related adverse events (TRAEs). 15 pts (50%) had ≥1 any grade TRAE; 4 pts (13.3%) had any grade hypertension. There were 6 Grade ≥3 TRAEs [congestive heart failure (3), hypertension, mucositis, GI perforation]. 5 pts (16.6%) were continuing treatment with TIVO at time of analysis; 20 pts (66.7%) discontinued TIVO due to progressive disease, 3 pts (10%) for TRAEs, and 2 pts for other reasons (infection, worsening of prior ICT-mediated neuropathy). 1 pt died of TIVO-related GI perforation. **Conclusions:** In this cohort of heavily pretreated pts with advanced ccRCC, TIVO yielded a modest clinical benefit in a minority of pts who received prior ICT, CABO, and LEN +/- EVE. TRAEs observed with TIVO were consistent with previously published reports. Research Sponsor: None.

A phase II study of neoadjuvant tislelizumab and axitinib in patients with locally advanced non-metastatic clear cell renal cell carcinoma (accRCC).

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Background: PD-1/PD-L1 combined with vascular endothelial growth factor (VEGF) inhibitors improves survival in patients with advanced renal cell carcinoma (RCC), but the role of perioperative application in patients with localized RCC has not been established. In this phase II trial, we investigate the safety and role of tislelizumab and axitinib in downsizing tumors in patients with non-metastatic clear cell RCC prior to surgical resection. **Methods:** In this investigator-initiated study, 20 patients with high-risk non-metastatic ccRCC (clinical stage T2a-4 and/or N1, M0 lesions) were enrolled to receive 12 weeks of neoadjuvant ticelizumab and axitinib prior to nephrectomy. The primary endpoint was the objective response rate (complete and partial response) after neoadjuvant treatment according to RECIST v1.1. Secondary endpoints were disease-free survival (DFS), overall survival (OS), surgical outcome and safety. **Results:** By September 2023,13 eligible pts were enrolled. 11 pts have completed neoadjuvant therapy, with a median age of 60 (range 45-73) years, among whom 9 pts underwent surgery as planned without any delay. One patient progressed during treatment and received further systemic therapy. In 9 pts evaluable for efficacy, the investigator-assessed confirmed ORR was 55.5%. The median reduction of primary renal tumor size was 26.2% (range 12.5-45%). Pathologic results showed that one patient (11.1%) achieved a complete response (CR) by RECIST 1.1 and four patients achieved a partial response (PR). One patient who was considered unresectable became resectable at the end of treatment. Two patients were converted from radical to partial nephrectomy. The most common neoadjuvant therapy-related AEs were hematologic toxicity, hypothyroidism, nausea, vomiting, decreased appetite, fatigue, diarrhea, and elevated ALT/AST. There were no Gr4/Gr5 TRAEs. No direct intraoperative complications and no drug-related surgical complications postoperatively. **Conclusions:** As a neoadjuvant therapy for accRCC, the combination of tislelizumab and axitinib has clinical efficacy and a manageable safety profile. Clinical trial information: NCT05172440. Research Sponsor: None.

Pembrolizumab plus lenvatinib (P+L) versus alternative therapies in first-line (1L) advanced renal cell carcinoma (aRCC) by IMDC risk status: A network meta-analysis (NMA).

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Background: The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk criteria is a widely used prognostic model in advanced RCC. Pembrolizumab plus lenvatinib (P+L) demonstrated a significant improvement in ORR, PFS, and OS versus sunitinib in subjects with cc aRCC in the KEYNOTE-581/CLEAR trial. This NMA indirectly compared the efficacy of P+L to other therapies in 1L aRCC subjects within IMDC risk groups using data from randomized clinical trials (RCTs). **Methods:** A systematic literature review was conducted to identify systemic therapies in 1L aRCC. Trials reporting results for IMDC favorable risk and/or intermediate+poor risk groups were included. A Bayesian NMA with fixed-effect models was performed to indirectly compare P+L to alternate therapies using sunitinib as the common comparator. Hazard ratios (HRs) for OS and PFS were calculated with 95% credible intervals (CrIs). The NMAs assuming constant hazard ratios (HRs) for OS and PFS were performed for all IMDC risk group categories. For the proportion of patients experiencing response, a binomial likelihood and logit link were used, and relative effects were expressed as odds ratios (OR). **Results:** For the IMDC favorable risk subgroup, P+L demonstrated statistically significant increase in ORR compared to nivolumab + ipilimumab (N+I) (OR=5.35; 95% CrI: 2.59, 11.41) and nivolumab (OR=8.41; 95% CrI: 1.84, 43.77). For PFS, P+L resulted in a statistically significant improvement in PFS compared to N+I (HR=0.31, 95% CrI: 0.17-0.56). For OS, no significant differences were observed compared to other alternatives in the network. For the IMDC intermediate+poor risk subgroup, P+L demonstrated statistically significant increase in ORR compared to nivolumab + cabozantinib (N+C) (OR=1.77; 95% CrI: 1.02, 3.10), N+I (OR=3.15; 95% CrI: 1.94, 5.10), and nivolumab + ipilimumab + cabozantinib (N+I+C) (OR=2.34; 95% CrI: 1.34, 4.12), pembrolizumab + axitinib (P+A) (OR=2.65; 95% CrI: 1.57, 4.44) and nivolumab (OR=4.68; 95% CrI: 1.84, 12.02). For PFS, P+L resulted in a statistically significant improvement compared to N+I (HR=0.59; 95% CrI: 0.41, 0.84) (P+A) (HR=0.64; 95% CrI: 0.44, 0.93), and avelumab + axitinib (A+A) (HR=0.65; 95% CrI: 0.46, 0.93). For OS, no significant differences were observed compared to other alternatives in the network. **Conclusions:** PFS analysis favored P+L over all alternative therapies in the network in favorable or intermediate+poor IMDC risk groups. ORR analysis favored P+L over all alternative therapies in the network in intermediate+poor IMDC risk groups. No significant difference in OS was observed between P+L and other alternative therapies in the network. Research Sponsor: Merck & Co., Inc.

Pembrolizumab plus lenvatinib (P+L) versus alternate therapies in first-line (1L) for advanced renal cell carcinoma (aRCC): A network meta-analysis (NMA).

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Background: Patients with advanced renal cell carcinoma (aRCC) have poor prognosis resulting in significant burden. In the KEYNOTE-581/CLEAR trial, pembrolizumab plus lenvatinib (P+L) as 1L therapy showed statistically significant and clinically meaningful improvements in overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) versus sunitinib in patients with aRCC. This NMA synthesized evidence from randomized clinical trials (RCTs) to indirectly compare the relative treatment effects of P+L vs alternate therapies in treatment-naïve aRCC. **Methods:** A systematic literature review was conducted to identify systemic therapies in 1L aRCC. A Bayesian NMA with fixed-effect models was performed to indirectly compare P+L to alternate therapies using sunitinib as the common comparator in 1L aRCC. Hazard ratios (HRs) for OS and PFS were calculated with 95% credible intervals (CrIs). NMAs assuming constant hazard ratios (HRs) and time-varying HRs were performed for OS and PFS. For the proportion of patients experiencing response, a binomial likelihood and logit link were used, and relative effects were expressed as odds ratios (OR). **Results:** A total of 33 unique RCTs met the inclusion criteria and were included in the analyses. The constant HR analysis resulted in no significant differences in OS between P+L and alternatives in network. Results showed statistically significant higher ORR for P+L compared to nivolumab + ipilimumab (N+I) (OR=3.19; 95% CrI: 2.14, 4.82) and pembrolizumab + axitinib (P+A) (OR=1.84; 95% CrI: 1.21, 2.80). The analysis also favored P+L over nivolumab + cabozantinib (N+C) (OR=1.35; 95% Crl: 0.86, 2.12) and avelumab + axitinib (A+A) (OR=1.46; 95% Crl: 0.96, 2.23), but was not statistically significant. The constant HR analysis showed that P+L resulted in a statistically significant improvement in PFS compared to N+I (HR=0.55; 95% CrI: 0.40, 0.75), A+A (HR=0.68; 95% Crl: 0.49, 0.96) and P+A (HR=0.69; 95% CrI: 0.51, 0.94). The analysis also favored P+L over N+C (HR=0.81; 95% Crl: 0.58, 1.14), but was not statistically significant. **Conclusions:** NMA indicates P+L has higher ORR and improved PFS compared to other regimens in 1L aRCC. No significant differences in OS were observed between P+L and competing interventions. Research Sponsor: Merck & Co., Inc.

Key parameters that influence surgical strategy in localised kidney cancer.

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Background: The goal of this studywas to select the key factors affecting choice between radical nephrectomy (RN) and partial nephrectomy (PN) for patients with localized RCC based on clinical and nephrometry data. **Methods:** A special retrospective cohort study was conducted in National Cancer Institute of Ukraine, which results were further validated on patient dataset in urological department of University Clinic of Cologne. The Institutional Review Boards and the local ethics committees of both high-volume centres approved the study. The main nephrometry parameters of tumor location in the kidney were analysed according to the R.E.N.A.L nephrometry score. The remaining functional parenchymal volume (RFPV) was calculated using the special formula. To determine the relationship between the risk of RN or PN, the multivariate predictive modelling method containing 12 parameters was used (Artificial Neural Networks [ANN]). Data validation based on referential centre experience using ROC-curve analysis to detect clinical applicability of the null hypothesis was performed. **Results:** Based on the analysis, for polary and laterally located tumors, the risk of RN was conditioned only by RFPV. The average critical value of RFPV for polar lesions was $X6_{crit}$ = 58% (in $X6 < X6_{crit}$, RN was predicted); for lateral tumors - $X6_{crit}$ = 67% (in $X6 < X6_{crit}$, RN was predicted). For medial location, the risk of RN only depended on the tumor size. Average critical value of the tumor size in the medial location was $X7_{crit}$ = 38 mm (in $X7 > X7_{crit}$, RN was predicted). Based on the ROC curve comparison, there were no statistically significant differences between the AUC_{Lin_12} and AUC_{MLP_3} (p = 0.12); thus, the reduced amount of the factor indicators from 12 to 3 did not worsen the model predictive qualities. Designed during primary analysis hypothesis was successfully validated in a referent centre on the cohort of 300 patients. Out of the cohort - 14 (4.6%) patients experienced false positive/negative outcome, which resulted in a radical/partial nephrectomy out of the hypothesis margins. Predictive model is characterized by high sensitivity (95.2%) and specificity (95.4%) in selecting patients for partial nephrectomy. **Conclusions:** For the polar and lateral tumor locations, the functioning parenchymal volumes of over 58 and 67% respectively serve as PN indications. However, for the medial lesions, the primary PN indication is a tumor size less than 38 mm. Research Sponsor: None.

Impact of renin-angiotensin system inhibitors on response to PD1/L1 inhibitors in patients with metastatic renal cell carcinoma (mRCC).

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Background: The renin-angiotensin system (RAS), traditionally associated with blood pressure regulation and fluid balance, also plays a role in tumor development and growth among several cancer types. Renin-angiotensin system inhibitors (RASI), such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), have been shown in studies of various malignant neoplasms to be associated with improved outcomes. In metastatic urothelial cancer, the use of ACEI and ARBs has been associated with higher rates of tumor regression among patients (pts) receiving immunotherapy (IO) with PD1/L1 inhibitors. One potential mechanistic explanation is RASI-induced downregulation of TGF-beta, for which high expression is a known mechanism of PD1/L1 inhibitor resistance. While the development of novel IO therapies has changed the treatment landscape for mRCC, only one study to date has examined the impact of RAS inhibition in pts with mRCC receiving IO. We hypothesized that concurrent RASI in pts with mRCC receiving IO is associated with increased tumor regression. **Methods:** We conducted a retrospective analysis of pts with mRCC receiving immunotherapy as a first or second line of treatment from 2016-2023 at the University of Virginia. A logistic regression model was used to evaluate the impact of concurrent RASI on tumor regression. The primary endpoint in this study was any regression of tumor on imaging. **Results:** Data were available for 147 pts with mRCC who received IO as a first- (n=104, 70.7%) or second- (n=43, 29.3%) line treatment. 52 pts (35.4%) received ACEI/ARBs during IO; 42 pts (40.4%) who received IO as first-line treatment were on ACEI/ARBs and 10 patients (23.2%) who received IO as a second-line treatment were on ACEI/ARBs. Analysis showed that pts who received ACEI or ARBs during IO were more likely to have tumor regression compared to pts who were not on concurrent RASI (OR 7.43 [95% CI 2.70-23.53], p=0.0002). This held true regardless if pts received IO as a first-line (OR 6.02 [95% CI 1.84-23.38], p=0.005) or second-line (OR 9.71 [95% CI 1.51-122], p=0.032) treatment. **Conclusions:** Our hypothesis generating study suggests that in our RCC population the concurrent use of RASI in pts with mRCC receiving IO was associated with a significantly increased likelihood of tumor regression. These findings highlight the potential therapeutic advantage of RASI in combination with IO for mRCC pts. Further exploration of this association is warranted in prospective studies to improve treatment outcomes for this patient population. Research Sponsor: None.

Association of ACEI/ARB with tumor regression.

Dataset	Variable	Level	Odds Ratio (95% CI)	P
All Data	ACEI or ARB	Yes	7.43 (2.70-23.53)	<0.001
		No	N/A	N/A
IO First Line	ACEI or ARB	Yes	6.02 (1.84-23.38)	0.005
		No	N/A	N/A
IO Second Line	ACEI or ARB	Yes	9.71 (1.51-122)	0.032
		No	N/A	N/A

The role of cytoreductive nephrectomy (CN) in the immune checkpoint inhibitor (ICI) era of metastatic renal cell carcinoma (mRCC): A systematic review and individual patient data (IPD) meta-analysis of 2319 patients.

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Background: The combination of CN and systemic therapy has been established as one of the mainstay treatments for mRCC during the targeted therapy era. However, the role of CN in the ICI era remains unclear. **Methods:** We performed a systematic search of the MEDLINE, EMBASE, and Web of Science databases until August 26th, 2023, for studies comparing the combination of CN + ICI vs. ICI alone in mRCC. Using published Kaplan-Meier overall survival (OS) curves, we reconstructed IPD and then performed one-stage and two-stage meta-analyses with both parametric and non-parametric effect estimates. To account for immortal time bias, we performed 6-month and 12-month landmark analyses. We also performed a subgroup analysis according to ICI line of treatment. The risk of bias was assessed using the ROBINS-I tool. **Results:** We identified eight retrospective cohort studies fulfilling our inclusion criteria. Only two out of eight studies adjusted for immortal time bias and none of them adequately adjusted for all predetermined confounding factors. A total of 2319 (1264 CN + ICI and 1055 ICI only) patients were included in our analysis. Patients in CN + ICI group were younger (median age 58.2 vs. 62.8), had lower proportions of non-clear cell histology (8.8% vs. 15.2%), ≥2 metastatic sites (60.0% vs. 68.5%), liver metastases (9.0% vs. 21.9%), and poor IMDC risk score (21.7% vs. 43.9%), but had higher proportions of sarcomatoid histology (15.6% vs. 10.6%) and ≥2nd line treatment (38.1% vs. 17.1%). The combination of CN + ICI was associated with superior OS in the one stage (HR: 0.45, 95% CI 0.38–0.52), 6-month landmark (HR: 0.45, 95% CI 0.37–0.54), 12-month landmark (HR: 0.50, 95% CI 0.31–0.50) and two-stage (HR: 0.38, 95% CI 0.29–0.49) meta-analyses. Similarly, the combination of CN + ICI was associated with superior OS in the subgroup of patients receiving first-line ICI (HR 0.39, 95% CI: 0.30–0.48). **Conclusions:** The combination of CN + ICI for mRCC may be associated with superior OS compared to ICI alone, but currently available data are subject to selection bias. More studies, including well-designed randomized controlled trials, are needed to determine the role of CN in the ICI era. Research Sponsor: None.

Analysis	Outcome Measure	Value	95% CI	p-value
One-stage meta-analysis	HR	0.45	0.38–0.52	<0.001
One-stage meta-analysis (6-month landmark)	HR	0.45	0.37–0.54	<0.001
One-stage meta-analysis (12-month landmark)	HR	0.50	0.31–0.50	<0.001
Two-stage meta-analysis	HR	0.38	0.29–0.49	<0.001
1-year life expectancy difference	Months	1.05	0.74–1.35	<0.001
1-year life expectancy ratio	Ratio	1.11	1.07–1.14	<0.001
3-year life expectancy difference	Months	7.12	5.75–8.48	<0.001
3-year life expectancy ratio	Ratio	1.36	1.28–1.44	<0.001
First-line ICI only (6-month landmark)	HR	0.39	0.30–0.48	<0.001

Effect of dipeptidyl protease 4 (DPP4) inhibitors on progression-free survival in patients with metastatic renal cell carcinoma: A single-center retrospective analysis.

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Background: Dipeptidyl peptidase IV (DPP4) is a cell surface receptor with exopeptidase activity that is expressed on most cell types, and possesses numerous substrates including growth factors, chemokines, and vasoactive peptides. These effects have implicated DPP4 in tumor growth and metastasis. Prior SEER-Medicare and retrospective studies have suggested an association between DPP4 inhibition and increases in both progression-free survival (PFS) and overall survival (OS) in patients with colorectal and lung cancers. Similar studies have shown no associated OS benefit from DPP4 inhibition in breast or pancreatic cancers, and increased OS but not PFS in prostate cancer. However, no studies to date have explored the impact of DPP4 inhibitors (DPP4i) in renal cell carcinoma (RCC). Thus, in this study we present a first-time analysis examining the impact of DPP4i use on PFS in patients with metastatic RCC and type 2 diabetes mellitus. **Methods:** We performed a single-center retrospective analysis of patients with diabetes and metastatic RCC at University of Virginia. The control group included patients who were on metformin, a sulfonylurea or SGLT2 inhibitor during treatment for metastatic RCC, while the study group included those who were taking a DPP4i with or without metformin and other diabetes medications during treatment. The primary and secondary endpoints of this study were PFS and OS, respectively. **Results:** Fifty-nine patients were eligible for the study, 11 of whom were taking a DPP4i with or without other diabetic medications during RCC treatment, while 48 were taking metformin with or without other non-DPP4i medications. Cancer progression occurred in 81.8% of patients in the DPP4i group compared to 66.7% of patients in the control group with an odds ratio of 1.58 (95% CI: 0.672-3.71), p = 0.57. No statistically significant difference on PFS (HR: 1.60; 95% CI: 0.75-3.43; p = 0.24) or OS (HR of death: 0.73; 95% CI: 0.27-1.97; p = 0.52) was found in this study. **Conclusions:** This retrospective study explored the effect of DPP4i on outcomes in patients with metastatic RCC and diabetes. While DPP4i have been shown in previous SEER-Medicare and retrospective studies to have favorable effects on PFS and OS in certain cancers such as colorectal and lung, the results of this study suggest that DPP4i do not confer clinical benefit in patients with RCC, similar to pancreatic and breast cancers. Given the small sample size in this study, larger studies are warranted to better elucidate the effect of DPP4i in metastatic RCC as well as the mechanisms underlying differential tumor response to these agents. Research Sponsor: None.

Cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with immunotherapy: A systematic review and meta-analysis.

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Background: lmmunotherapy is changing the treatment of patients with metastatic renal cell carcinoma (mRCC). In recent years, many immune checkpoint inhibitors (ICls) have been introduced, and ICl-combination therapies have changed the treatment landscape for patients with mRCC. However, the role of cytoreductive nephrectomy (CN) in patients with mRCC receiving ICls is not clear. We aimed to assess the role of ICl-combination therapies in patients receiving /not receiving CN. **Methods:** PubMed, Embase, and Cochrane Library databases were searched for English-language clinical trials, cohort studies, and case-control studies evaluating OS in patients with mRCC who underwent /did not undergo CN (end-of-search date: 1 April 2023). The hazard ratio [HR] and 95% confidence interval [CI] for OS obtained by multivariate analysis were extracted and aggregated. Meta-analysis was performed using Review manager 5.4.1, and $p<0.05$ was defined as a statistical significance. **Results:** Eleven studies met the eligibility criteria. Receiving CN+ICI combination therapy was associated with significantly better OS than patients receiving ICI combination therapy alone (HR: 0.56 , 95% CI: 0.46-0.69, $P < 0.001$). In subgroup analyses, thinking about the number of lines for immunotherapy, CN provided OS benefit when immunotherapy was used as either first-line (HR: 0.54, 95% CI: 0.41-0.70, $P < 0.001$) or non-first-line treatment (HR: 0.59, 95% CI: 0.44-0.81, $P = 0.001$). In terms of tumor pathologic type, CN also provided OS benefit no matter the pathologic type was only clear cell renal cell carcinoma (ccRCC) (HR: 0.52, 95% CI: 0.28-0.95, $P = 0.03$) or not (HR: 0.54, 95% CI: 0.39-0.75, $P < 0.001$). For the choice of drugs, CN provided OS benefits with nivolumab/nivolumab + ipilimumab (HR: 0.50, 95% CI: 0.32-0.79, $P = 0.003$) or immunotherapy combined with tyrosine kinase inhibitors (HR: 0.59, 95% CI: 0.48-0.73, $P < 0.001$). About the timing of CN, CN also provided OS benefit when performing before immunotherapy (HR: 0.63, 95% CI: 0.54-0.73, $P < 0.001$) or no strictly restricted (HR: 0.49, 95% CI: 0.33-0.74, $P = 0.0007$). **Conclusions:** CN brings good effect on OS in mRCC patients treated with ICI-combination therapies. In ICI-combination therapy era, the role of CN still deserves attention. Research Sponsor: National Natural Science Foundation of China; 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University; Science and Technology Support Program of Sichuan Province; Clinical and Translational Medicine Research Project, Chinese Academy of Medical Sciences; Beijing Bethune Charitable Foundation; Beijing Bethune Charitable Foundation; Postdoctoral Research and Development Fund of West China Hospital of Sichuan University.

UNICAB: Cabozantinib in locally advanced or metastatic non-clear cell renal cell carcinoma post immunotherapy or in those unsuitable for immunotherapy (ANZUP 1802).

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Background: Rare variant non-clear cell renal cell cancer (nccRCC) have diverse biology and therapeutic response. Immune checkpoint immunotherapy (ICI) can benefit some people with nccRCC, but many experience progression. We sought to test cabozantinib (C) in people with nccRCC refractory to, or unsuitable for ICI. **Methods:** Eligible participants (pts) had advanced/metastatic nccRCC with good ECOG PS (<2) and either prior treatment with ICI or were unsuitable for ICI due to a contraindicating autoimmune disorder. Pts with urothelial or collecting duct tumour were excluded. Eligible pts started C at 60mg per day with dose modifications as required. Clinical cycles were 28 days and radiological assessment occurred 8-weekly for 12 months. Pts could then continue C via an access program. **Results:** 33 pts with nccRCC were recruited from Mar 2019 to Dec 2022. Recruitment was influenced by the COVID19 pandemic. Two pts were found ineligible (brain metastasis, concurrent CYP3A4 inducer). Pts tumour histology included papillary type 1 (10), chromophobe (7), papillary type 2 (4), Xp11 translocation (3) and other histologies (7). 24 pts had received prior ICI, mostly nivolumab alone (17) or anti-PD1-antibodies in combination with other agents (anti-CTLA4, anti-TIGIT). Median duration of therapy was 9 cycles. 17 pts ceased for unacceptable toxicity or disease progression and 12 pts completed the 12 months of treatment, with 2 remaining on trial treatment at time of analysis. A partial response was seen 7/31 (22%) pts overall, including 7/24 pts with prior ICI and 0/7 pts unsuitable for ICI. Median treatment duration was 7.5 cycles (range 2-12) in pts with prior ICI treatment, and 11 cycles (range 2-12) in pts unsuitable for ICI. 90% of pts required dose reduction, most often due to fatigue, hypertension, diarrhoea and hand-foot syndrome, with a mean C dose of 46mg/day. No new safety signals were observed. **Conclusions:** C is an active treatment for people with nccRCC previously treated with ICI, with similar toxicity to previous reports in other cancers. Pts unsuitable for ICI may have poorer outcomes for C therapy in nccRCC. Further follow-up will determine duration of response and overall survival. Clinical trial information: NCT03685448. Research Sponsor: IPSEN; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

Outcomes and prognostic factors of first-line combination of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) in *TFE3*-rearranged renal cell carcinoma.

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Background: Due to the rarity of TFE3-rearranged renal cell carcinoma (TFE3-rRCC) and the poor understanding of its underlying mechanisms, the clinical treatment landscape in TFE3-rRCC is largely undefined. Hence, the optimal therapy for TFE3-rRCC remains to be determined. The diversity of fusion partners leads to the high heterogeneity of TFE3-rRCC, yet no studies have compared responses of patients with different fusion partners to systemic treatment. **Methods:** Data were collected retrospectively from our institution. Patients with metastatic TFE3-rRCC were eligible. Kaplan-Meier survival analysis and univariate and multivariate analysis were performed to compare survival outcomes. RNA-seq was performed to determine fusion partners and explore the transcriptomic features. **Results:** A total of 38 patients with metastatic TFE3-rRCC were enrolled in this study. The fusion partners were identified in 33 (87%) patients. Patients receiving first-line ICI plus TKI had longer PFS than those not receiving first-line ICI plus TKI (median PFS: 11.5 vs. 5.1 months, P=0.098). Subgroup analysis demonstrated that patients with ASPSCR1-TFE3 fusion significantly benefited from ICI plus TKI (PFS HR: 0.068, 95% CI: 0.008-0.609, P=0.016), whereas no improvement in PFS was observed in patients with other fusions. Univariate and multivariate cox regression analysis further demonstrated that besides IMDC risk score, ASPSCR1-TFE3 fusion could also serve as an independent prognostic factor for PFS in patients receiving first-line ICI plus TKI. Among patients receiving ICI plus TKI, those with ASPSCR1-TFE3 fusion had longer PFS than those with other fusions (median PFS: not reached vs. 6.5 months, P=0.01). Transcriptomic data revealed that ASPSCR1-TFE3 fusion rearranged RCC harbored higher angiogenesis activity. Additionally, decreased infiltration of immunosuppressive M2-phenotype macrophages and Tregs was observed in tumors with ASPSCR1-TFE3 fusion. **Conclusions:** Metastatic TFE3-rearranged RCC patients with ASPSCR1-TFE3 fusion could benefit from ICI plus TKI. Higher angiogenesis activity and decreased infiltration of immunosuppressive cells were observed in tumors with ASPSCR1-TFE3 fusions, which may explain the clinical outcome. Research Sponsor: The Natural Science Foundation of China; China Postdoctoral Science Foundation; Research Foundation for the Postdoctoral Program of Sichuan University; 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University; Science and Technology Support Program of Sichuan Province; The Natural Science Foundation of Si Chuan Province; Natural Science Foundation of Sichuan Province; Post-Doctor Research Project, West China Hospital, Sichuan University.

An observational multicenter French study on unanswered questions in patients with advanced renal cell carcinoma (aRCC) treated with cabozantinib: OCTOPUS.

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Background: Real-world studies with cabozantinib in aRCC have investigated its effectiveness and tolerability in routine practice, but questions remain unanswered including: Activity of systemic therapies after progression on Cabozantinib, patterns of long-responders and use in elderly patients. **Methods:** OCTOPUS study (NCT05444933) is a retrospective study of all consecutive patients (pts) treated with cabozantinib 2nd line (2L) for aRCC from March 2018 to March 2021 in 26 French centers. Pre-defined analysis included: descriptive analysis of Cabozantinib 2L regimen, activity of subsequent line (defined by treatment duration), patterns of long-term responders (defined as duration of cabozantinib more than 12 months in patients with complete, partial response or stable disease); and in elderly pts (>75 years). **Results:** In total, 252 patients were included. Median age was 63 years (20-86), 84.1% had clear-cell histology. At Cabozantinib 2L initiation, among 69 patients with available IMDC score, IMDC risk was favorable/intermediate/poor in 13.0 %, 49.3% and 37.7 % of the cases, respectively. Patients had an ECOG PS of 1 (45.8%) or 2 (25.8%). Bone, liver and brain metastasis (mets), were present in 130 (52.0%), 69 (27.6%) and 34 (13.6%) patients, respectively. 102 (40.5%) pts had 3 or more mets sites and 167 (66.3%) pts had a prior nephrectomy. 154 (61.1%) pts were pretreated with a tyrosine kinase inhibitor (TKi) based regimen and 94 (37.3%) were pretreated with an immunotherapy (IO) based regimen. Results are reported in the table. 157 patients received a 3rd line (3L) treatment after cabozantinib: nivolumab (55.4%) or a VEGFR TKI (26.1%) including axitinib (85.4%). In this subgroup, the median duration of treatment (DOT) and median progression free survival (PFS) were respectively 8.2 months and 8.0 months, with a disease control rate (DCR) of 80.3 % for Cabozantinib 2L. **Conclusions:** We reported the pattern of use of Cabozantinib in RWE, highlighting feasibility in elderly and long-term exposure in long responders as well as subsequent therapy activity. Research Sponsor: None.

	n	DOT (months) median (95%CI)	PFS (months) median (95%CI)	DCR (%)
Overall population	252	**7.4** (6.1 - 8.5)	**6.9** (5.7-8.2)	**76.9**
Long responders	72	**19.3** (16.6 - 23.4)	**16.1** (14.3 – 18.6)	**100**
Elderly (>75 years)	37	**7.3** (4.8 – 10.9)	**5.7** (4.7 – 10.1)	**80.0**

Immune-related adverse events (irAEs) and the association with clinical outcomes in advanced genitourinary cancers treated with immunotherapy: A systematic review and meta-analysis.

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Background: The approval of several immune checkpoint inhibitors (ICIs) for the treatment of advanced genitourinary cancers has resulted in a significant revolution in the management of urological tumors. This study investigated the profile of the irAEs and evaluated the association between irAEs and clinical outcomes in the patients with advanced genitourinary cancers treated with ICIs. **Methods:** We conducted a comprehensive search of online databases up to April 2023 to identify eligible studies. We extracted the type, grade, and frequency of irAEs, the hazard ratios(HRs) and corresponding 95% confidence intervals (95%CIs) for overall survival (OS) and progression-free survival (PFS), raw data or the odds ratios (ORs) and corresponding 95% confidence intervals (95%CIs) for objective response rate (ORR) and disease control rate (DCR). RevMan5.3 software was used to calculate pooled results. **Results:** A total of 21 studies with 4779 patients were included. Of those, 13 studies investigated renal cell carcinoma (RCC), 6 studies investigated urothelial carcinoma (UC), and 2 investigated mixed population with RCC or UC. The pooled overall incidence was 29.0% (95%CI: 28.0%-30.0%) for any-grade irAEs in RCC and UC and 13.0% (95%CI: 11.0%-14.0%) for grade $\geq$3 irAEs. Furthermore, the HRs for OS and PFS in advanced genitourinary cancer patients with versus without irAEs were 0.45 (95%CI: 0.40-0.51, $p < 0.001$) and 0.41 (95%CI: 0.31-0.55, $p < 0.001$), respectively. The ORs for overall ORR and DCR in advanced genitourinary cancer patients with irAEs versus without irAEs were 3.65 (95%CI: 3.03-4.39, $p < 0.001$) and 4.19 (95%CI: 2.94-5.97, $p < 0.001$), respectively. In the subgroup analysis, we also observed a positive association between the occurrence of irAEs and improved treatment outcomes in UC and RCC, respectively. Specifically, patients with skin irAEs showed a better OS, patients with skin irAEs and thyroid disfunction were associated with better PFS. **Conclusions:** Our study provides a comprehensive overview of irAEs in advanced genitourinary cancers treated with immunotherapy. Our findings suggest that the occurrence of irAEs could be a favorable prognostic factor for advanced genitourinary cancer patients treated with ICIs. Research Sponsor: None.

Regulatory approvals for genitourinary (GU) cancer by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) over 20 years (2003-2023).

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Background: The past 2 decades has witnessed a transformation in the GU cancer therapy armamentarium. In this study, we analysed GU cancer therapy approvals (initial & supplemental) by the two largest global regulators (EMA and FDA) by evaluating approval timing, labels, biomarker requirements and drug withdrawal(s). **Methods:** A cross-sectional analysis of approved drugs and indications made for GU cancer medicines from each regulatory database from 2003-2023 was performed. We compared new approved therapies, indications and biomarker requirements. **Results:** The FDA approved 40 new therapies, corresponding to 57 indications, with 2 withdrawals. The EMA approved 33 new therapies, corresponding to 43 indications with 1 withdrawal. Overall, the FDA approved new GU cancer therapies 128 days earlier (table). In renal cell carcinoma (RCC), the FDA approved 14 new therapies across 18 indications, compared to 14 new therapies across 16 indications for the EMA. The FDA approved new RCC therapies 113 days earlier than the EMA. For concomitant approvals the FDA label was broader for 5 indications, more restrictive for 2 and equivocal for 9. In urothelial cancer (UC), the FDA approved 9 new therapies across 14 indications, compared to 7 new therapies across 7 indications for the EMA. The FDA approved new UC therapies 110 days earlier than the EMA. For concomitant approvals, the FDA label was broader for 4 indications and equivocal for 3. In prostate cancer (PC), the FDA approved 17 new therapies across 25 indications, compared to 12 new therapies across 20 indications for the EMA. The FDA approved new PC therapies 157 days earlier than the EMA. For concomitant approvals, the FDA label was broader for 2 indications and equivocal for 18. Across GU cancer, 8 therapies (both FDA and EMA) had biomarker-based eligibility with 3 notable differences in urothelial cancer: the EMA uniquely requires a PD-L1 combined positive score (CPS) $\geq$ 10 and PD-L1 $\geq$ 1% for pembrolizumab (platinum-ineligible) and Nivolumab (adjuvant), respectively. Although biomarker requirement was similar, the FDA has withdrawn atezolizumab in UC unlike the EMA. **Conclusions:** Over the past 20 years, there has been a substantial increase in new therapies to manage GU cancers. Patients in the US typically have access to more new therapies, earlier and across broader indications than those in Europe. However, a greater number of therapies are withdrawn after approval in the US. Biomarker-eligibility is broadly similar, with some discordance in UC. Research Sponsor: None.

	Median Delay (days) Between FDA and EMA Approval (IQR)	Withdrawn Therapies (regulator)
All	128.5 (66.75-279.5)	
RCC	113 (66.75-143)	
UC	110 (3.5-215)	Atezolizuamb (FDA) & Durvalumab (FDA)
PC	157 (39.5-279.5)	Sipuleucel-T (EMA: Manufacturer)

Outcomes of patients (pts) with advanced renal cell carcinoma (aRCC) treated with cabozantinib (CABO) after lenvatinib plus pembrolizumab (LEN+PEM).

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Background: LEN+PEM is an approved first-line therapy for aRCC. In the CLEAR study, it produced a 71% objective response rate (ORR), an 18% complete response rate, and improved progression-free survival (PFS) and overall survival (OS) compared to sunitinib. CABO is approved as second and later line therapy for aRCC. We explored the efficacy of CABO in pts with aRCC after treatment with LEN+PEM. **Methods:** This is a retrospective study of pts with aRCC who received CABO after LEN+PEM at our institution from 12/2019 to 8/2023. Demographics and clinical data were abstracted from the EMR. A blinded radiologist assessed tumor response using RECIST v1.1. We measured PFS, time on therapy (TOT) and OS from start date of CABO. **Results:** 22 pts were analyzed (Table 1). Median follow up was 7.7 months (mo); 11 pts received LEN+PEM on the HOPE 111 trial (NCT02501096). Among all 22 pts, 11 (50%) had a partial response (PR), 5 (22.7%) had stable disease (SD), and 6 (27.3%) had progressive disease (PD) on LEN+PEM. Median TOT with LEN+PEM was 7.4 mo (range: 1.8-29). 20 pts (90.9%) discontinued LEN+PEM due to PD, 1 pt (4.5%) due to fatigue, and 1 pt (4.5%) due to elevated liver enzymes. 17 pts received CABO right after LEN+PEM; 3 pts received 1 line and 2 pts received 2 lines of therapy before CABO after LEN+PEM. Of 19 pts with evaluable radiographic response on CABO, 1 pt had a PR (ORR 5.3%, PFS 16.1 mo) and 3 pts had SD for ≥6 mo. Median TOT with CABO was 4.3 mo (range: 0.2-18.2); 13 pts (59.1%) took CABO for ≥4 mo, 7 pts (31.8%) took it for ≥6 mo, of which 3pts receivedpalliative radiation andcontinued CABO therapy beyond PD. Median PFS and median OS with CABO were 4.1 mo (range: 1.2-16.1) and 8.1 mo (range: 0.8-22.5), respectively. At time of analysis, 4 pts were still taking CABO (3 SD, 1 not yet evaluated); 15 pts discontinued CABO: 12 for PD, 1 for Grade 3 hand-foot skin reaction, 1 per pt request, and 1 for transition to hospice; 3 pts died during CABO therapy (bowel obstruction [1], COVID-19 [1], cardiac arrest [1]). Adverse events attributed to CABO were consistent with published reports. **Conclusions:** In this cohort of heavily pretreated pts who received CABO after LEN+PEM, CABO demonstrated a modest clinical benefit in a minority of pts, underscoring the need to develop effective novel therapies for aRCC. Research Sponsor: None.

Characteristics at CABO initiation.	
Age at diagnosis	**54.8**
Median	**35.9-78.8**
(range)	
Age at start of CABO	**58.8**
Median	**39.2-81.0**
(range)	
Gender	
Male	17 (77.3)
PS	
0-1	17 (77.3)
Histology	
Clear Cell	20 (90.9)
Variant	2 (9.1)
Prior Nephrectomy	
None	9 (40.9)
Radical	13 (59.1)
IMDC risk	
Intermediate	16 (72.7)
Poor	6 (27.3)
Sites of Metastasis	Lung 19 (86.4), Nodal 17 (77.3), Bone 14 (63.6), Brain 8 (36.4), Liver 13 (59.1)
Median number of disease sites	4
(range)	1-7
Line of LEN+PEM	
1L	8 (36.4)
2L	7 (31.8)
3L+	7 (31.8)
Median number of therapies before CABO	2
(range)	1-6
Starting Dose	
20 mg	2 (9.1)
40 mg	14 (63.6)
60 mg	6 (27.3)

A phase 1 study of fianlimab (anti-LAG-3) in combination with cemiplimab (anti-PD-1) in patients with advanced ccRCC.

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Background: Concurrent blockade of lymphocyte-activation gene 3 (LAG-3) may enhance efficacy of anti–programmed cell death protein 1 (PD-1) therapies. We present safety and clinical activity data from a Phase 1 study in patients with clear cell renal cell carcinoma (ccRCC) treated with anti–LAG-3 (fianlimab) + anti–PD-1 (cemiplimab). **Methods:** Patients with advanced or metastatic ccRCC who had received no more than 2 previous regimens of anti-angiogenic therapy who were anti–PD-1/PD-L1-naïve (cohort 3) or anti–PD-1/L1-experienced with most recent dose within 3 months prior to screening (cohort 4) were eligible. All patients were to receive fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks for up to 24 months. Tumor measurements were performed by RECIST 1.1 every 6 weeks for 24 weeks, then every 9 weeks. **Results:** 15 patients (median age: 64 years) each in cohort 3 and 4 (total N=30) were enrolled and treated with fianlimab + cemiplimab as of 01 Nov 2022 data cutoff.For cohorts 3 and 4 respectively, 80% and 87% of patients were male, and 40% and 87% were White. All patients had prior cancer-related systemic therapy. 60% (9/15) and 93% (14/15) of patients in cohorts 3 and 4 had ≥2 lines of prior therapies, respectively. For cohorts 3 and 4, median treatment duration was 27 weeks and 18 weeks, and median follow-up was 13 months and 24 months, respectively. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 53% and 33% of patients in cohorts 3 and 4, respectively. Serious TEAEs occurred in 33% and 13% of patients in cohorts 3 and 4, respectively. Treatment-related TEAEs (TRAEs) were reported in 80% of patients in cohorts 3 and 60% of patients in cohort 4. The most common TRAEs (any grade) were rash (27%) and infusion related reaction (grade 1 and 2) (27%) in cohort 3 and fatigue (20%) in cohort 4. Grade ≥3 TRAEs occurred in 27% of patients in cohorts 3. Treatment was discontinued due to any TEAE in 3 patients in cohort 3 and 1 patient in cohort 4. In cohort 3, there was one death. The patient was a 79-year-old woman with a history of antiphospholipid syndrome who died from complications of biopsy-proven ischemic colitis attributed to study treatment. RECIST 1.1-based investigator-assessed objective response rate (ORR) was 20% (3 partial responses [PRs]) in cohort 3 and 7% (1 PR) in cohort 4. The disease control rate (DCR) was 60% and 73% in cohorts 3 and 4, respectively. Kaplan–Meier estimation of median progression-free survival was 4 months (95% confidence interval [CI], 1–10) in cohort 3 and 4 months (95% CI, 1–7) in cohort 4 patients. Duration of responses were 4, 7, and 26 months in 3 responders in cohort 3; and 6 months in one responder in cohort 4. **Conclusions:** Fianlimab + cemiplimab demonstrated promising signs of clinical activity with durable responses among patients with anti–PD-1/PD-L1-naïve (cohort 3) and anti–PD-1/L1-experienced (cohort 4), with an acceptable safety profile. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Final results of a phase I trial of HERV-E TCR transduced T cells for the treatment of HLA-A*11 patients with metastatic clear cell renal cell carcinoma (mccRCC).

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Background: Human endogenous retrovirus type E (HERV-E) is specifically expressed in ccRCC providing a safe target for T cell-based therapies. We investigated T cells transduced with a TCR targeting HERV-E (HERV-E T cells) for the treatment of mccRCC. **Methods:** This first-in-human study assessed the safety & efficacy of escalating doses of HERV-E T cells and manufacturing/clinical endpoints correlative analysis. HLA-A*11+ mccRCC patients (pts) were treated with a conditioning regimen, infusion of HERV-E T cells & IL-2. (NCT03354390). **Results:** Nineteen of185 pts tested were found to express HLA-A*11. 17 HLA-A*11 + pts enrolled on the study: 3 pts on each DL1-3 & 6 pts on DL4. 2 pts did not receive HERV-E T cells given disease progression during manufacturing period. Median age was 57 years. 86% received $\geq$ 3 prior systemic treatment (range 1-8). The manufacturing failure rate after first apheresis was 12% (n=2); both met target dose after second apheresis and repeat in vitro expansion. All HERV-E T cell products met release criteria for infusion including INF-γ production in response to HERV-E/HLA-A11-expressing tumor cells. Median HERV-E vector copy number (VCN) was 1.9. No dose-limiting toxicities (DLT), off-target toxicities or treatment-related deaths occurred. Pt#17 is on DLT monitoring period. 7 pts completed the planned 14 doses of IL-2 and all received at least 8 doses. Reasons for IL-2 discontinuation: hemodynamic (57%), cardiovascular (28%), pulmonary (28%), renal (14%) criteria & pts decision (14%). The best response was partial response in 7% & stable disease at least 8 weeks in 29% pts. HERV-E mRNA expression was detected in 5 primary & 9 metastatic specimens. HERV-E T cells were measurable in circulation post-dosing, with peak concentrations in the peripheral blood mononuclear compartment on day(D)+7. [DL1: 0.3 %, DL2: 1.2%, DL3: 0.5%, DL4: 12.3%]. Median HERV-E T cell VCN showed no correlation with HERV-E T cells peak concentration on D+4 & D+7. **Conclusions:** Proof of concept that HERV-T cells can induce tumor regression without evidence of causing off-target toxicities has been established by this trial. Infused HERV-E T cells were detectable transiently in vivo and induce effector cytokine production. Our initial results support the further development of HERV-E-directed therapies that focus on methods to improve in vivo persistence of TCR engineered T-cells and to target HERV-E antigens expressed on more commonly expressed HLA alleles. Research Sponsor: None.

Dynamics of selected serum cytokines.

	IFNg	IL10	IL15	IL6	TNFa
Baseline	7.8 (3.9-2.9)	0.33 (0.2-0.3)	4.9 (4- 5.8)	6.1 (3.3-8.8)	3.3 (3.2-4.5)
D+4	325.8 (169.1-450.7)	10.31 (6.5-19.9)	102.8 (73.7-128.4)	34.6 (19.6-141.2)	10 (8.1-11.9)
D+7	146.4 (17.2-365.4)	18.38 (5.1-36.6)	23.5 (17.1-37.6)	19.9 (11.9-55)	13.1 (7.5-15.1)
D+14	5.2 (3.8-14.8)	1.46 (1.0-2.5)	14.5 (12.2-24.6)	9 (7-39.1)	4.7 (4.5-5.6)

Breaking boundaries: Exploring extended pembrolizumab in first-line treatment of renal cell carcinoma with axitinib-pembrolizumab combination.

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Background: The standard first-line treatment for metastatic renal cancer (mRCC) combines immune checkpoint- (ICI) and tyrosine kinase inhibitors (TKI). While TKI therapy continues until disease progression, ICI treatment is typically stopped after 24 months or 35 cycles, aligning with approval study criteria. However, in real-world practice, the decision to discontinue ICI therapy upon achieving a positive response can be distressing for both patients and healthcare providers; thus ICIs are not stopped. We conducted an initial analysis of prolonged pembrolizumab (Pem) use in axitinib-pembrolizumab (Axi-Pem) combination therapy to evaluate its effects and toxicity. **Methods:** We retrospectively analyzed data from mRCC patients treated with first-line Axi-Pem in 10 German tertiary care centers between 2019 and 2023. After completing 35 cycles or 24 months of Pem, patients were offered continued ICI therapy if positive response was assessed. We calculated objective response rate (ORR) and progression-free survival (PFS) from the treatment start to achievement of 36 therapy months. Adverse events (irAEs) were reported following CTCAE 5.0 criteria. **Results:** Out of 72 patients, 27 met strict eligibility criteria from the Keynote-426 study (NCT02853331), with a response at 24 months and continuous Pem therapy. Patients had a median age of 65.7 years (range: 34-84), and IMDC risk was favorable/intermediate/poor in 22.2%/55.5%/18.5%. Median follow-up was 33.2 months (range: 25.3-48.4). At the 36-mos landmark, median PFS was not reached (PFS 64.7%), ORR was 63.6%, with complete response, partial response, and stable disease observed in 9.1%(1)/54.5%(6)/9.1%(1) of cases, respectively. Permanent Pem discontinuation occurred due to progressive disease in two cases and complete response in one case. Another case led to Pem discontinuation due to immune-related toxicity. **Conclusions:** In our selected real-world patient cohort seeking prolonged ICI therapy, responders who received continuous Pem beyond 24 months achieve sustained efficacy in first-line treatment. Furthermore, the incidence of irAEs does not increase with prolonged exposure to ICI therapy. Additional results beyond the 36-month landmark are urgently needed to further support the clinical necessity and feasibility of ongoing ICI treatment in light of its impact on the overall financial burden of cancer care. Research Sponsor: None.

Lenvatinib plus everolimus (LenEve) in patients with pre-treated advanced renal cell carcinoma (mRCC): Real world evidence (Relevance).

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Background: The therapeutic armamentarium in mRCC underwent a rapid change during the recent past. LenEve, proved to be effective as subsequent treatment in mRCC in clinical trials.Here, we evaluate efficacy and safety in mRCC patients in a real-world setting. **Methods:** mRCC patients who started LenEve treatment between 08/2016 and 12/2021 at 6 tertiary German centers were retrospectively analyzed. Overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR), were evaluated per local investigator. Subgroup analyses by risk scores, previous therapies and initial dosing were performed. **Results:** Eighty-one patients were assessed: Median age was 61 years (range 42-80), 81.5% were males, ECOG score was 0 to 1 in 80.2%. Synchronous metastases were found in 39.5% of patients. The median number of treatment lines prior to LenEve was 3. Median treatment duration with LenEve was 6.1 months (range 0.2-29.2). The ORR, DCR, median OS and PFS was 28.4%, 61.7%, 11.3 months (95% CI 8.7-13.9) and 6.5 months (95% CI 5.4-7.6), respectively. Across patients with 0-2 compared to ≥3 previous therapeutic lines median PFS, OS and ORR were similar, as well as for patients with or without previous immunotherapy. Safety was manageable, with 6.2% of patients discontinuing treatment due to treatment related adverse events. **Conclusions:** High efficacy in second- and later-line in a heavily pre-treated real-world cohort of mRCC patients was demonstrated by LenEve, regardless of treatment line, IMDC risk group, initial dosing or previous treatment with immunotherapy. Research Sponsor: EISAI.

Pharmacodynamics and gene expression analysis of patients with renal cell carcinoma treated with combination nivolumab and TPST-1120 in a phase I clinical trial (NCT03829436).

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Background: TPST-1120 is a first-in-class, oral inhibitor of peroxisome proliferator-activated receptor (PPAR-α), a fatty-acid ligand-activated transcriptional factor that controls the expression of multiple genes involved in fatty acid oxidation (FAO), angiogenesis and inflammation. In a phase 1 open-label trial, TPST-1120 was administered as a single agent and in combination with nivolumab in multiple tumor types. Among the tumor types treated, 4 patients in the combination arm had Renal Cell Carcinoma (RCC). 2 of the patients experienced clinical and radiographic response confirmed by RECIST. On this study, we plan to further study the pharmacodynamic and radiographic changes in these patients with RCC to further understand signals to identify patients who may benefit from this treatment. **Methods:** Mutational analysis of ctDNA was assessed using the PredicineCARE assay (Predicine Inc.), and lipid analysis was performed by tandem mass spectrometry. Gene Expression changes were quantified using the nCounter PanCancer Iune Profiling Panel (Nanostring Inc.) supplemented with 30 PPAR-α target genes. The radiographic Analysis was performed with CT chest-abdomen-pelvis and response evaluated using RECIST criteria. **Results:** RCC patients with PR (2/4) confirmed by RECIST exhibit greater reductions in 6 PPAR-α regulated genes. They had an early increase in thrombospondin (TSP-1) level due to PPAR-α inhibition. An increase in long-chain fatty chain fatty acids was seen including circulating FFA, lysophosphorylcholine (LPC) or lysophosphorylethanolaine (LPE). They also had great reductions in 6 PPAR-α regulated genes including ACAD8, ACSL3, CPT2, FABP1, FABP3, HADHB. **Conclusions:** There is a paucity of treatment options for patients with stage IV RCC post anti-PD1 and anti-VEGF therapies. Novel therapies on this clinical scenario are needed. On this abstract we showed radiographic and pharmacodynamic data on patients with RCC who achieved a clinical partial response by RECIST on the phase I clinical trial TPST1120-001. The trial explored the se of a PPAR-α inhibitor in combination with Nivolumab. The pharmacodynamic data indicates that there is fatty acid oxidation perturbation and immune gene expression changes as potential biomarkers of clinical benefit. PI3K pathway or IDH mutations may indicating a signal that RCC patients may benefit from this combination therapy. Larger studies in the future may be designed to further explore the use of this combination in patients with RCC. Clinical trial information: NCT03829436. Research Sponsor: None.

Single institutional experience of neoadjuvant therapy prior to planned surgical resection for complex or locoregional renal cell carcinoma.

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Background: Cytoreduction via systemic neoadjuvant therapy is an emerging investigational strategy in localized renal cell carcinoma (RCC). We analyzed our single institutional experience with neoadjuvant therapy. **Methods:** ingle institutional retrospective analysis of patients with T2-T3N0M0 RCC. Patients received confirmatory biopsy for clear cell histology prior to receipt of systemic therapy and underwent radical (RN) or partial nephrectomy (RN). Neoadjuvant therapy consisted of tyrosine kinase inhibitor (TKI) or Immuno-oncology (IO) therapy and/or combination (TKI-IO). Neoadjuvant therapy was given prior to planned partial nephrectomy for complex renal mass with imperative indications for nephron preservation and prior to planned radical nephrectomy in setting of locoregional disease with possible adjacent organ or great vessel involvement where multiorgan system resection was risked. Primary outcome was percentage cytoreduction comparing pre-treatment and post treatment mass size. Secondary outcome included partial response (PR) rate as per RECIST criteria, negative surgical margins, and lack of major 30-day complications (Clavien ≥3). Comparative analysis was conducted for outcomes between groups for overall survival (OS), cancer specific survival (CSS), and progression free survival utilizing Kaplan Meier Analyses (KMA). **Results:** A total of 50 patients (33 TKI, 17 IO + TKI-IO) were analyzed (median follow up 31.1 months). Overall PR and cytoreduction rates were 18.0% and 4.2%. No differences in tumor size were noted (7.7 vs. 10.4 cm, p=0.08). There were no differences in % cytoreduction (12.2 vs. 11.8, p=0.13) and % PR (17.8% vs. 30.7%, p=0.73) between the groups. Overall, 18 patients and 30 patients underwent PN and RN, respectively. 30-day major complication rate was 28.0% and 20.5% was PSM rate. KMA revealed 3-year OS, CSS and PFS of 74%, 75%, and 14%. No differences were noted between TKI and IO/IO-combination groups for PFS (16.7% vs. 10.0%, p=0.45), CSS (70.9% vs. 93.3%, p=0.20), and OS (68.3% vs. 93.3%, p=0.06). **Conclusions:** Neoadjuvant therapy prior to surgery for complex and locoregional disease resulted in cytoreduction and was associated with acceptable safety, surgical quality, and short term oncological outcomes. Further investigation is requisite to delineate role of neoadjuvant therapy in localized RCC. Research Sponsor: None.

Upfront (uCN) vs. deferred (dCN) cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC): A systematic review and individual patient data (IPD) meta-analysis of 3323 patients.

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Background: Despite the well-established role of CN in the management of mRCC, the optimal timing of CN in regard to systemic therapy remains unclear. **Methods:** We systematically searched the MEDLINE, EMBASE, and Web of Science databases until August 26th, 2023, for studies comparing uCN and dCN and reconstructed overall survival (OS) IPD from their published Kaplan-Meier survival curves. We then performed one-stage and two-stage meta-analyses of OS, using parametric and non-parametric effect estimates. Landmark analyses using 6-month and 12-month cutoffs were used to account for immortal time bias. We also performed subgroup analyses according to MSKCC/IMDC risk and systemic therapy type. The risk of bias was assessed using the ROBINS-I and RoB2 tools. **Results:** We identified twelve studies (ten retrospective cohort and two randomized controlled trials) eligible for inclusion. Only two out of ten retrospective studies adjusted for immortal time bias and none of them appropriately adjusted for all predetermined confounding factors. A total of 3323 (2610 uCN and 713 dCN) patients were included in our analysis. Baseline characteristics, including age, gender, histology, IMDC/MSKCC risk score, and location of metastases were comparable between the two groups; the dCN group had more patients with ≥2 metastases (65.4% vs. 47.6%). Deferred CN was associated with superior OS in the one stage (HR: 0.75, 95% CI 0.67–0.84), 6-month landmark (HR: 0.74, 95% CI 0.65–0.84), 12-month landmark (HR: 0.78, 95% CI 0.68–0.91) and two-stage (HR: 0.69, 95% CI 0.58–0.84) meta-analyses. Similarly, dCN was associated with superior OS in the TKI-treated (HR: 0.61, 95% CI 0.51–0.74), ICI-treated (HR: 0.67, 95% CI 0.46–0.97), and intermediate IMDC/MSKCC risk (HR: 0.73, 95% CI: 0.55–0.97) subgroups. **Conclusions:** Deferred CN for the treatment of mRCC is associated with superior overall survival compared to uCN. Randomized studies are warranted to validate or refute these findings. Further studies to establish predictive models are needed to optimize selection of mRCC patients most likely to benefit from dCN. Research Sponsor: None.

Analysis	Outcome Measure	OS	95% CI	p-value
One-stage meta-analysis	HR	0.75	0.67–0.84	<0.001
One-stage meta-analysis (6-month landmark)	HR	0.74	0.65–0.84	<0.001
One-stage meta-analysis (12-month landmark)	HR	0.78	0.68–0.91	0.001
Two-stage meta-analysis	HR	0.69	0.58–0.84	<0.001
5-year life expectancy difference	Months	5.15	3.23–7.08	<0.001
5-year life expectancy ratio	Ratio	1.16	1.10–1.22	<0.001
TKI only (6-month landmark)	HR	0.61	0.51–0.74	<0.001
ICI only (6-month landmark)	HR	0.67	0.46–0.97	0.03
Intermediate IMDC/MSKCC risk (6-month landmark)	HR	0.73	0.55–0.97	0.03

Neutrophil extracellular traps in relation to efficacy of systemic therapy for metastatic renal cell carcinoma.

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Background: The efficacy of systemic therapy regimens, such as immune checkpoint inhibitors and tyrosine kinase inhibitors (IO-TKI) and targeted therapy, for metastatic clear cell renal cell carcinoma (ccRCC) remains unpredictable due to the lack of effective biomarkers. This study investigates the predictive value of neutrophil extracellular traps (NETs) in determining the efficacy of metastatic ccRCC. **Methods:** In this retrospective study, patients with metastatic ccRCC who received targeted drugs and IO-TKI were included. Immunofluorescence staining was utilized to quantify the levels of tissue NETs through cell counts of H3Cit(+) and MPO(+) cells. The correlation between NETs and clinicopathological features was analyzed, and the predictive value of NETs for drug efficacy and prognosis was assessed using Cox proportional hazard analysis. **Results:** A total of 183 patients with metastatic ccRCC were enrolled, including 150 patients who received TKIs and 33 patients who received IO-TKI. H3Cit and MPO were predominantly expressed in the nucleus and cytoplasm, respectively. The levels of NETs in tumor tissue were significantly higher than in para-tumor tissue ($p<0.001$). Increased levels of NETs in tumor tissue were associated with tumor N stage (p=0.02) and neutrophil-to-lymphocyte ratio (NLR) (p=0.02). In terms of predicting drug efficacy, a correlation between NETs levels and progression-free survival (PFS) was observed in the TKI with metachronous metastasis group (HR 1.73 [95% CI 1.02-2.91], log-rank p=0.037), while no correlation was observed in the targeted agent with synchronous metastasis group and IO-TKI group. Regarding overall survival (OS), activated NETs levels were associated with poor OS (HR 1.87 [95% CI 1.24-2.81], log-rank p=0.003). Cox analysis revealed that IMDC score (HR 1.462 [95% CI 1.030-2.075], p=0.033) and tumor tissue NETs level (HR 1.733 [95% CI 1.165-2.579], p=0.007) were independent prognostic risk factors for OS in patients with metastatic ccRCC. **Conclusions:** The active NETs level in tumor tissue can serve as a predictor of drug efficacy in patients with metastatic ccRCC who received targeted agents with metachronous metastasis. However, no significant correlation was observed in the IO-TKI group, and further investigation is required. Elevated levels of NETs in tumor tissue were also associated with poor prognosis in OS prediction. Research Sponsor: National Natural Science Foundation of China.

Serum IgG: A potential biomarker for predicting the efficacy of systemic therapy in metastatic renal cell carcinoma.

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Background: Immunotherapy-tyrosine kinase inhibitor (IO-TKI) and tyrosine kinase inhibitor (TKI) are the main treatment strategies that have significantly improved outcomes of metastatic renal cell carcinoma (mRCC) patients. However, there are no effective biomarkers available to predict the efficacy of these regimens. We aim to explore the predictive value of serum immunoglobulin G (IgG) in systemic treatment. **Methods:** The study consisted of 292 mRCC patients who received TKI or IO-TKI therapy. Serum IgG in the pre-treatment baseline, 1 month, and 3 months after systemic treatment were measured using the immunoturbidimetric method. The Wilcox test was used to compare baseline serum IgG levels and paired t-test was utilized to compare serum IgG levels between baseline and 3 months after treatment. Kaplan-Meier curve were used to evaluate the PFS and Cox proportional hazard regression analysis was conducted to identify independent determinant factors for PFS. **Results:** The baseline level of IgG was not associated with objective response rate (ORR) in the overall patient cohort. However, there was a significant decrease in IgG in patients achieving CR/PR and an increase in patients with SD/PD after 3 months of treatment ($p<0.05$). In the TKI cohort, the estimated 9-month PFS was significantly higher in the IgG-decrease group versus the IgG-increase group (HR 2.5, 95%CI 1.8-3.4, $p<0.001$). The results were similar in the IO-TKI cohort. The predictive value of alteration of IgG after 1-month treatment was demonstrated in terms of the estimated 9-month PFS (HR 1.5, 95%CI 1.0-2.3, $p=0{\cdot}048$). The ROC curve showed outstanding performance of alteration of serum IgG in predicting PFS. **Conclusions:** Alteration of serum IgG after systemic treatment is a reliable biomarker to predict the efficacy in mRCC patients. The change of IgG after 1-month treatment could serve as indicator of treatment efficacy and improve individualized drug selection. Further validation is warranted. Research Sponsor: None.

High expression of sialylated cancer-derived IgG and survival in metastatic clear cell renal cell carcinoma.

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Background: The treatment landscape of metastatic clear cell renal cell carcinoma (mccRCC) has evolved from cytokine regimens to targeted therapy, and now immunotherapy-based drug combinations over the past two decades. However, there is a lack of confirmed prognosis biomarkers for mccRCC patients. The International mRCC Database Consortium (IMDC) risk model is the most widely used effective biomarker for prognostication in mccRCC. Immunoglobulin G (IgG), well known as immune molecule secreted by B cells, has recently been detected in various types of cancer cells, named as cancer-derived IgG. Notably, it has been demonstrated that IgG derived from epithelial cancer cells displays unique N-glycosylation, which is highly sialylated (SIgG). In this study, we aimed to explore the expression of SIgG in mccRCC tissues using the monoclonal antibody RP215, and evaluated the correlation of SIgG expression level with clinicopathological factors and prognosis of mccRCC patients. **Methods:** A total of 179 mccRCC patients with complete clinicopathological information and survival data were enrolled. Tumor tissues were collected during surgery and fixed in 10% buffered formalin, embedded in paraffin. Tissue microarray slides were then constructed for immunohistochemistry (IHC). The primary end point was overall survival (OS), defined as the time from initiation of systemic treatment to death from any cause or last follow-up. **Results:** The results of IHC showed that SIgG was mainly expressed in the cell membrane and cytoplasm, and the high expression of SIgG was significant correlated with poor OS in mccRCC patients (HR = 2.281, $P < 0.001$). Moreover, based on multivariate Cox regression analysis, high SIgG expression was identified as an independent prognostic variable for OS in mccRCC patients (HR = 2.110, $P < 0.001$), as well as poor IMDC risk group (HR = 2.123, P = 0.018). The time-dependent ROC curve also suggested the promising prognostic value of SIgG expression, with a 5-year AUC of 0.679 for SIgG alone and 0.742 for SIgG combined with IMDC risk model. In addition, subgroup analyses were performed to further assess prognostic value of SIgG for mccRCC patients among groups based on IMDC risk group, metastatic site, and metastatic time. The prognostic value of SIgG was more marked in patients with intermediate (HR = 2.191, P = 0.019) and poor (HR = 2.111, P = 0.058) IMDC risk group, and lung metastasis (HR =1.970, P = 0.009). Notably, the prognostic value of SIgG was significant in both synchronous and metachronous metastasis patients. **Conclusions:** SIgG appears to be a reliable predictor for the outcome of mccRCC patients, and SIgG combined with IMDC risk model was a more effective prognostic model than IMDC risk group alone. Research Sponsor: None.

Monocyte to lymphocyte ratios and cancer-specific mortality for patients with renal cell carcinoma and inferior vena cava tumor thrombus.

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Background: Renal cell carcinoma (RCC) with inferior vena cava (IVC) tumor thrombus carries a poor prognosis and presents complex medical management to urologists. Long-term data examining RCC with IVC tumor thrombus is sparse. Specifically, markers predicting cancer-specific survival are lacking. Recently, immune cell markers in cancer, such as neutrophils, lymphocytes, and monocytes, have come into focus. These cell counts and/or ratios may provide a window into cancer-specific outcomes. The purpose of this study was to examine the use of immune cell ratios in patients with RCC and IVC tumor thrombus to predict survival outcomes through a collaboration project across North and South America. **Methods:** Patients were included in this study if they had a diagnosis of RCC with IVC tumor thrombus and underwent nephrectomy with IVC thrombectomy for their RCC. Data was reviewed and entered into a multi-institutional/continental database. Complete blood counts taken as close to the date prior to/date of surgery were used to calculate immune cell ratios. Neutrophil to (/) lymphocyte ratios were done by dividing patients' neutrophil cell count by their lymphocyte count. Monocyte/lymphocyte ratios were calculated in the same manner. Independent samples t-test was used to test for significance in cause of death post-operatively (RCC versus non-RCC cause) based on immune cell ratio. **Results:** There were 107 patients included in the study with long-term follow-up data (Mean: 2.6 years; Range: 0-16-years). Of all patients, 43/107 died by the end of the study, with 31/43 (72.1%) dying due to RCC and 12/43 (27.9%) from other causes. No difference existed in neutrophil/lymphocyte ratios based on cause of death (p=0.260). Monocyte/lymphocyte ratios were significantly lower in those who died from RCC relative to another cause (p=0.035). **Conclusions:** Immune cell ratios may have a role in predicting death from RCC. In our study, monocyte/lymphocyte ratios were significantly lower in patients who died from RCC compared to death from other reasons. Our results stem from a multi-continental/institutional study, and thus hold clinical utility as an increased focus is turned towards including diverse populations in research. Urologists may consider monocyte/lymphocyte ratios in the future when managing patients with RCC and an IVC thrombus. Research Sponsor: None.

Immune cell ratios and cause of death.

Variable	Death From RCC (standard dev.)	Death From Other Reason (standard dev.)	P-value
Neutrophil/Lymphocyte	3.3 (1.4)	4.2 (2.2)	0.260
Monocyte/Lymphocyte	0.39 (0.13)	0.56 (0.2)	0.035

Note: P-values are comparing immune cell ratios based on cause of death. Standard deviations are in parentheses.

Hypoxia-inducible factor-2 alpha (HIF-2α) target activation and clinical outcomes in 942 patients with clear cell renal cell carcinoma.

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Background: *Von Hippel Lindau* (*VHL*) gene function is uniformly lost in clear cell renal cell carcinoma (ccRCC) with consequent accumulation of hypoxia inducible factor 2 alpha (HIF-2α). HIF-2α inhibitors have entered the clinical arena as a new class of agents, alone and in combinations. While *VHL* loss is thought to result in broad increase of HIF-2α activity, preclinical data suggests that HIF-2α target activation varies across patients. Xenograft response to HIF-2α inhibition helped define an RNA-based HIF-2α target signature (SIG) comprising 277 genes downregulated with treatment (Courtney et al. CCR 2020). We applied this signature in our analysis of two large cohorts. **Methods:** Retrospective analyses were conducted using two cohorts: 533 tumors from the Cancer Genome Atlas Project (TCGA) with emphasis on early-stage disease and 409 archival tumors collected from patients receiving pazopanib or sunitinib on the phase 3 COMPARZ trial in metastatic RCC. Using single-sample gene set enrichment analysis (ssGSEA), enrichment scores were calculated for HIF-2α-SIG and a previously validated 6 gene tumor angiogenesis SIG (McDermott et al. Nat Med 2020). Individual patients were classified as "high" vs "low" for each (enrichment scores $<$ vs $\geq$ median). We tested associations of HIF-2α and angiogenesis scores with overall survival (OS) using the Kaplan Meier Method and log-rank comparison. **Results:** In the TCGA cohort, patients with "high" HIF-2α-SIG had inferior median OS compared to those with "low" levels (69 months [95% CI 53-117] vs 'not reached', log-rank $p<0.0001$). In the metastatic COMPARZ cohort, "high" HIF-2α-SIG associated adversely with median OS (27 months [95% CI 21-32] vs 36 months [95% CI 28-not reached], log-rank p=0.0240) while angiogenesis scores associated favorably. In both cohorts the majority of HIF-2α "high" patients categorized "low" for angiogenesis and vice versa. Associations amongst HIF-2α-SIG, angiogenesis-SIG, and OS are summarized below (Table). **Conclusions:** HIF-2α target activation was adversely associated with survival in early and late stage ccRCC while angiogenesis scores correlated favorably. HIF-2α targets other than VEGF appear to have clinical impact and should be explored. HIF-2α-SIG may prove helpful for clinical development of targeted HIF-2α inhibitors and deserves further study. Research Sponsor: None.

Associations of HIF-2α and angiogenesis score with overall survival.

				Median OS		
		Median OS	Log-rank	Angio Low	Angio High	Log-rank
TCGA N = 533	**HIF-2α Low**	Not Reached N = 265	P<0.0001	Not Reached N = 96	Not Reached N = 170	P<0.0001
	HIF-2α High	69 months N = 267		56 months N = 170	117 months N = 97	
COMPARZ N = 409	**HIF-2α Low**	36 months N = 204	P=0.0240	23 months N = 98	Not Reached N = 106	P=0.0005
	HIF-2α High	27 months N = 205		27 months N = 108	27 months N = 97	

Peripheral blood cell counts as biomarkers of clinical benefit in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC) receiving immune checkpoint inhibitor (ICI) combination (combo) therapies.

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Background: Numerous combos of ICIs and Tyrosine Kinase Inhibitors (TKIs) have received approval for the management of mccRCC. Specific peripheral blood cell counts reflect inflammation and impact anti-tumor immunity, and here we investigated their role as biomarkers of clinical benefit to ICI combos in RCC. **Methods:** We performed a retrospective study of 179 mccRCC patients treated with ICI combos ≥ 4 weeks (2013-2023), where we examined baseline and 6-week post-treatment Neutrophil to Lymphocyte ratio (NLR), Red cell Distribution Width (RDW), and eosinophil values. We categorized these values as High (H) or Low (L) based on baseline medians. Our analysis included objective response rate (ORR), overall survival (OS), progression-free survival (PFS), and time to next treatment (TNT). Kaplan-Meier methods and the log-rank test were used to evaluate time from start of ICI combos to the event of interest. **Results:** Our analysis included 111 eligible ICI-naïve mccRCC patients median age 63, 76% male. IMDC risk scores categorized 22% as favorable, 53% intermediate, and 25% poor risk. Treatment included 50 (45%) patients on ICI+ICI combos with a median therapy duration of 6.3 months, and 61 (55%) on ICI+TKI with a median duration of 8.8 months. In the ICI+ICI group, median OS was 28.2 months (95% CI 20.7-38.4), PFS 5.5 months (95% CI 3.7-7.8), and TNT 12.7 months (95% CI 7.4-20.4). In the ICI+TKI group, median OS was 21.7 months (95% CI 17.1-25.4), PFS 7.4 months (95% CI 5.6-11.1), and TNT 12.5 months (95% CI 9.7-16.4). The ORR was 38% in the ICI+ICI group, and 56% in the ICI+TKI group (p=0.062). No differences were seen with NLR. In the ICI+ICI group, higher baseline RDW levels were correlated with a shorter TNT, while higher eosinophil levels at week 6 were correlated with longer PFS and TNT (significant results highlighted in the table below). **Conclusions:** Eosinophil levels and RDW are potentially readily available biomarkers in the clinic for predicting and monitoring ICI combo treatment outcomes in mccRCC patients. Validation of these results in larger cohorts is warranted. Research Sponsor: None.

Outcome	ICI + ICI RDW at baseline	ICI + ICI Eosinophils at 6 weeks (H vs. L) (HR (95% CI)	ICI + TKI Eosinophils at 6 weeks
OS	-	-	p=0.02 3.4 (1.2-9.5)
PFS	-	p=0.0145 2.8 (1.23-6.58)	-
TNT	p=0.0044 0.35 (0.17-0.72)	p=0.018 3.58 (1.6-8.0)	-

Significance of CD73/adenosine receptor 2 (A2aR) and immune microenvironmental status in renal cell carcinoma with sarcomatoid changes and rhabdoid features.

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Background: One of the most aggressive forms among the kidney cancer is sarcomatoid and rhabdoid (S/R) renal cell carcinoma (RCC). There is still no effective treatment, and new therapies are needed. In this study, we focused on CD73 and A2aR, which regulate Treg involved in immune escape, and examined them clinicopathologically. **Methods:** We reviewed a total 1390 formalin-fixed, paraffin-embedded specimens of surgically resected RCC between 1989 and 2016. We detected 60 cases of RCC with sarcomatoid changes and rhabdoid features. We performed immunohistochemistry of CD73, A2aR, PD-L1, and CD8. We attempted to examine clinicopathological significance of CD73- and A2aR- positive RCC with S/R RCCs. The relationship between clinical and pathological features was evaluated using Wilcoxon's rank sum and Fisher's exact tests. A Cox proportional hazards regression model was used for multivariate analysis. Both PFS and OS were analyzed by using the Kaplan-Meier method and compared by the Wilcoxon's rank test. All statistically significances were defined as $P<0.05$. **Results:** High-grade components were sarcomatoid changes (31 cases, 51.7%), rhabdoid features (16 cases, 21.7%), and both sarcomatoid and rhabdoid (13 cases, 21.7%). CD73 expression in the high-grade component was observed in 41 cases (68.3%), and A2aR expression was observed in 27 cases (45%). Significant differences among cMstage and high-grade components, sarcomatoid and rhabdoid, are detected in A2aR positive cases, respectively (p=0.0368, 0.0396, 0.0187). The univariate analysis showed a significantly poorer OS for patients whose tumors expressed CD73 and A2aR (P = 0.0109 and $P < .0001$). To validate this finding further, a multivariate analysis was performed using the Cox proportional hazards model). The results indicated that A2aR expression (P = 0.0206) and pTstage (P = 0.0433) were independent markers for unfavorable prognosis in S/R RCCs. CD73 and A2aR expressions were significantly related to poor PFS (P = 0.0395, P = 0.0043, respectively). CD73 and A2aR expressions were significantly related to poor OS (P = 0.0188, $P < .0001$, respectively). **Conclusions:** CD73 and A2aR expression correlated with the poorest prognosis group among S/R RCCs, indicating that the use of inhibitors against them in combination with conventional therapies may improve prognosis. Research Sponsor: JSPS KAKENHI.

Tumor-infiltrating CD163-positive macrophages and clinical outcomes to first-line nivolumab therapy in patients with advanced clear cell renal cell carcinoma (ccRCC) enrolled in the HCRN GU16-260 trial.

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Background: There is evidence that intratumoral myeloid cell infiltration can modulate response to immune checkpoint inhibitors in some tumor types, but its role in ccRCC remains unclear. Here, we investigated the role of tumor-infiltrating CD163-positive macrophages as a determinant of clinical outcome to anti-PD-1 therapy in patients (pts) with advanced ccRCC treated with first-line nivolumab therapy as part of the HCRN GU16-260 clinical trial. **Methods:** Primary tumor tissues from pts with ccRCC (n= 67) were analyzed by multiparametric immunofluorescence (IF). Image analysis algorithms were used to assess the density of CD163-positive cells (dCD163) in tumor areas with high CD8+ T cell-infiltrates. In addition, dCD163 was also assessed in randomly selected tumor areas. Log-transformed densities were correlated with objective response rate (ORR) and progression-free survival (PFS) using Cox proportional hazards and binary logistic (modeling odds of attaining objective response) regression analysis, respectively. Alpha level was set *a priori* at 5% (2-sided). The functional form of CD163 for the PFS endpoint was obtained using a smoothed martingale residual plot. **Results:** Analysis of dCD163, assessed in high-CD8+ cell tumor areas and measured as a continuous variable, showed a positive association with ORR (OR= 2.21, p= 0.002) and PFS (HR= 0.77, p= 0.028). However, visual inspection of the dCD163 functional form plot for PFS revealed a threshold effect at the raw (log-transformed) value of 262.5 (5.6) cell/mm^2. Similar to the entire cohort, in patients with dCD163 below this threshold (n= 54), dCD163 was positively associated with PFS (HR= 0.61, p$<$.001). In contrast, in patients with dCD163 above this threshold (n=13), results suggested the presence of a negative association between dCD163 and PFS (HR= 1.36, p= 0.726). Of note, similar findings were obtained by analyzing dCD163 assessed in random tumor areas. **Conclusions:** Levels of tumor-infiltrating CD163-positive macrophages are associated with improved clinical outcomes to first-line nivolumab in pts with advanced ccRCC up to a density threshold, above which an association with poor outcomes is noted. Further investigations into the role of tumor-infiltrating myeloid cells in predicting outcomes to anti-PD-1-based therapies are ongoing. Clinical trial information: NCT05403541. Research Sponsor: DOD.

Detection of sarcomatoid renal cell carcinoma using plasma cell-free DNA methylation.

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Background: Sarcomatoid differentiation (SD) in renal cell carcinoma (RCC) is associated with poor survival and heightened response to immune checkpoint blockade. Detection of SD can be challenging due to spatial heterogeneity and sampling error. Herein, we introduce a novel tissue–informed epigenomic approach to noninvasively identify sarcomatoid differentiation in patients with RCC from cell-free DNA (cfDNA) using <1mL of plasma. **Methods:** Methylated immunoprecipitation and high-throughput sequencing (MeDIP-seq) was performed on pathologically reviewed clear cell RCC frozen tissue samples with and without SD (sarcomatoid-RCC and epithelioid-RCC, resp.) collected at the Dana-Farber Cancer Institute. Differentially methylated regions (DMRs) between sarcomatoid and epithelioid subtypes were identified using DESeq2 (false discovery rate of $q < 0.01$). Then, MeDIP-seq was performed on cell-free DNA (cfMeDIP-seq) from patients with sarc-RCC and epi-RCC. A Sarcomatoid Methylation Score (SMS) was derived for each sample by aggregating the methylated cfDNA signal at tissue-derived sarcomatoid-enriched DMRs (sarc-DMRs), while normalizing to signal at epithelioid-enriched DMRs (epi-DMRs). Scores were compared between the two groups using a Wilcoxon rank-sum test. A classifier was built to distinguish sarc-RCC from epi-RCC based on SMS and its performance was evaluated using the area under the receiver operating characteristic (AUROC) curve. **Results:** We identified 32,086 DMRs between 9 sarc-RCC and 10 epi-RCC tissue samples at a false discovery rate of $q < 0.01$, among which We selected 16,083 DMRs that are enriched in sarcomatoid vs. epithelioid. We generated high-quality cfMeDIP-seq profiles from plasma of 46 patients, 13 with sarc-RCC and 33 with epi-RCC. SMS were significantly higher in sarc-RCC vs. epi-RCC plasma samples ($p = 6.7\times10^{-8}$). These scores achieved an AUROC curve of 0.95 for classifying patients with sarc-RCC from patients with epi-RCC. **Conclusions:** We present the first proof of concept study for the detection of sarcomatoid differentiation in RCC based on tissue-informed assessment of DNA methylation signals in cfDNA using <1mL of plasma. This approach could overcome the challenges of spatial heterogeneity and sampling error that make identification of sarc-RCC difficult. More generally, it establishes a paradigm for identifying histologic subtypes of cancer based on their epigenomic correlates from cfDNA, with possible therapeutic implications in real-time. Research Sponsor: None.

Fanconi anemia complementation group C (*FANCC*) gene association with hereditary and sporadic renal tumors (RT).

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Background: Inactivating genomic alterations (GA) of *FANCC* gene are associated with genomic instability, DNA cross-linking, and homologous DNA repair deficiency (HRD). *FANCC* GA are most frequently associated with colon, lung, breast, and prostate cancers (0.5% frequency) with germline *FANCC* mutations linked to familial breast cancer. *FANCC* GA have been rarely associated with RT and are not currently linked to any hereditary renal cancer predisposition syndromes. We evaluated the incidence of *FANCC* GA and other genomic features across cancer types. **Methods:** 463,546 clinically advanced cancers (CAC) underwent hybrid capture-based comprehensive genomic profiling using the FDA-approved F1CDx assay to detect all classes of GA. MSI status, tumor mutation burden (TMB), gLOH, prediction of germline status, genomic ancestry, and genomic signature were determined with algorithm-based analysis. PD-L1 expression was tested by IHC (Dako 22C3 tumor proportional score; low positive (LP) 1-49%). **Results:** 1,993 (0.43%) CAC featured *FANCC* GA. 27 of these *FANCC*-mutated tumors (20 male, mean age 57) were RT (0.35% of 7,668 RT): 13 clear cell, 3 sarcomatoid, 3 urothelial, 3 chromophobe, 2 squamous cell, 2 medullary renal carcinomas (RCC), and 1 Wilm's tumor. The primary tumor was sequenced in 9 cases and a metastatic site in 18 (5 lymph node, 4 soft tissue, 3 brain, 2 liver, 1 each lung, adrenal, eye, bone). Only 1 of 25 tested *FANCC*-mutated RT was MSI-high. The mean TMB was 5.7 mut/Mb while the median TMB was 2.5 mut/Mb, and 4 cases (15%) featured TMB ≥10 mut/Mb. 2 of 4 *FANCC*-mutated RT that were tested for PD-L1 were LP. The mean gLOH was 7.5%. Genomic ancestry evaluation revealed 21 EUR, 4 AFR, and 2 AMR patients. Genomic signature could be assessed in 5 cases: 4 were MMR deficient. The *FANCC* mutations included inactivating short variant mutations in 24 cases (10 nonsense, 10 frameshift, 2 non-frame and 2 splice-site mutations) and 3 truncating rearrangements (*FANCC*:*SUSD3*,*FANCC*:*FANCC*, *FANCC*:*C20orf24*). Interestingly, 14 (52%) of the *FANCC*-mutated RT were predicted to be germline. Additional GA in the *FANCC*-mutated RT included *VHL*, *TP53*, *CDKN2A*, *ARID1A*, *PBRM1*, *TERT*, *PTEN*, and *SETD2*. **Conclusions:** Somatic and germline mutations in *FANCC* occur in an exceedingly small subset of clinically advanced RT but at similar rate to other cancers. RT with inactivated *FANCC* do not appear to have a different GA landscape from RT with wild-type *FANCC*. The high frequency of predicted germline status during somatic testing with *FANCC* alterations suggests the importance of further workup with confirmatory germline testing as it may affect counseling for other family members. Limitations of this study include lack of clinical and therapy data annotation. Research Sponsor: None.

Malignant epithelioid angiomyolipoma (eAML)/PEComa of the kidney: A genomic landscape study.

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Background: While renal AML is generally a benign tumor, malignant eAML is a rare form of renal malignancy of uncertain histogenesis featuring variable prognosis. Consequently, most series are limited in small sample sizes and lack comprehensive genomic analysis. We sought to survey the genomic landscape in malignant renal eAML and identify potential therapeutic targets. **Methods:** After reviewing our database containing over 400,000 advanced cancer samples we identified 34 cases of malignant eAML. Comprehensive genomic profiling (CGP) was performed using a hybrid capture technique to assess all classes of genomic alterations (GA). MSI status, gLOH, genomic ancestry and gene signatures were determined by CGP. TMB was measured in mutations/megabase of sequenced DNA. PD-L1 positivity was determined by IHC using the DAKO 22C3 tumor cell proportional score (0% = negative; 1-49% = low positive). **Results:** The primary malignant eAML was used for CGP in 14/34 (41.2%) and a metastatic site biopsy was used in 20 (58.8%) cases (10 liver, 3 lung, 4 retroperitoneum, 2 peritoneum and 1 psoas muscle). There were 19 (55.9%) female patients and a mean age of 60 years (median 53 years). In a subset 17 of cases when either MART1, MelanA or HMB45 IHC staining was performed all cases were positive for at least 1 marker. There were no MSI-high cases. The mean and median TMB was 1.6 mutations/Mb. Of the 4 malignant eAML cases tested, 3 (75%) were negative and 1 (25%) case was low PD-L1 expression positive. 25 (73.5%) of the cases featured short variant mutations in the *TSC2* gene while the other 9 (26.5%) were *TSC2* mutation negative. 4 (11.8%) of the malignant eAML featured germline GA in the *MUTYH*, *CD36*, *FLCN*, and *FANCC* genes of uncertain roles in the development of the disease. There were no *TSC2* germline GA. Other GA were mostly not currently targetable and included the tumor suppressors *TP53* at 29.4%, *CDKN2A/B* at 14.7%, *ATRX* at 11.8%, and *RB1* at 8.8%. Aside from the frequent *TSC2* alterations, other GA potentially implicating MTOR inhibitor use include GA in *PTEN* at 5.9% and *NF2* at 2.9%. Additionally, *BRCA1* was altered in 2.9% of cases, suggesting the possible utility of a PARP inhibitor. In a 28 case subset, the mean gLOH was 6.3% (range 0% to 37.9%) with 3 cases (10.7%) featuring a gLOH of $>$ 16%. 26 (76.5%) of these patients were of EUR ancestry, 5 (14.7%) of AMR ancestry and 3 (8.8%) of AFR ancestry. No specific genomic signature characterized the malignant eAML cases. **Conclusions:** Renal malignant eAML, also known as malignant PEComa of the kidney, is an exceedingly rare malignant tumor. Our CGP identified that the majority of cases exhibit non-germline *TSC2* mutations. Interestingly, other germline alterations were found in 4/34 cases which are of unknown significance. While there may be limited opportunities for targeted or immunotherapies aside from MTOR inhibition, CGP analysis may still provide guidance into identification of potential therapeutic targets. Research Sponsor: None.

Association of microbial metabolism of tryptophan with resistance to immune checkpoint (ICB) therapy in renal cell cancer (RCC).

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Background: Metastatic RCC has a poor prognosis. Despite improvement in treatment outcomes with ICB and targeted therapy, many patients fail to respond to first line therapy and durable responses remain elusive. The tryptophan metabolite kynurenine, an agonist of the immunosuppressive aryl hydrocarbon receptor (AhR), is associated with resistance to ICB. However, IDO (Indole 2,3 dioxygenase) blockers which inhibit tryptophan metabolism to kynurenine failed to show benefit in clinical trials, suggesting the presence of alternate AhR activation. We hypothesize that microbial metabolism of tryptophan to indole metabolites may be associated with AhR activation and ICB resistance. **Methods:** We prospectively collected paired stool and blood samples of treatment naïve metastatic RCC patients, treated with ICB +/- Tyrosine kinase inhibitors (TKI) at treatment initiation and at time of first response assessment (12+/-3 weeks). We evaluated stool metagenomics and untargeted stool and plasma metabolomics among responders (R) and non-responders (NR). We focused on kynurenine/tryptophan and indoles/tryptophan ratio to evaluate differential host and microbial metabolism of tryptophan. A responder was classified as progression free survival (PFS) greater than 6 months. We also performed global metabolomics on tumor and plasma of germ-free (GF) & specific pathogen free (SPF) mice to identify microbial & host metabolites. **Results:** Among 120 patients accrued, baseline paired samples were analyzed from 99 patients, 39 were treated with combination ICB, while 60 patients were treated with ICB + TKI. Median follow up was 15 months. 65% of patients had PFS $>$ 6 months. Using unpaired t test comparing baseline relative abundance of metabolites between R vs NR - plasma Kynurenine/tryptophan ratio was significantly higher in NR vs R, at baseline and at 3 months (baseline-0.042 vs 0.01, p=0.01, 3 months-0.058 vs 0.02, p=0.02). Microbial metabolites of Tryptophan -Indole pyruvic acid (IPA), Indole carboxylic acid (IcA), and Indole acetaldehyde (IAAld) were differentially associated with ICB resistance and was significantly higher in NR (IcA: 8.0 vs 5.2, p=0.03; IPA: 82.4 vs 64.9, p=0.01; IAAld: 78.7 vs 64.6, p=0.03). We also noted differential enrichment of microbial KEGG enzymes associated with IPA, IAAld and IcA production in the stool of NR patients compared to R. Microbial origin of these metablites was confirmed by its absence in tumor of GF mice. **Conclusions:** This is first study in metastatic RCC which shows the association of indoles (microbial metabolites of tryptophan) with resistance to ICB. These indoles are known to be potent AhR agonists and are associated with immunosuppression suggesting that microbial metabolism of tryptophan may represent a novel pathway for ICB resistance in RCC patients. Research Sponsor: None.

Endogenous retrovirus expression and its impact on tumor-infiltrating immune cells in papillary renal cell carcinoma.

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Background: Endogenous retroviruses (ERVs) represent 5-8% of the human genome, and their expression in cancer cells correlates with response to immunotherapy in clear cell renal cell carcinoma (ccRCC). Whether this association also exists in papillary renal cell carcinoma (PRCC) is unknown. Studying ERV expression in PRCC and its impact on the tumor microenvironment (TME) may help elucidate its role in PRCC response to immunotherapy. **Methods:** We quantified ERV expression on human PRCC tissue samples using real-time quantitative PCR (RT-qPCR). ERV4700 was selected due its correlation with response to immunotherapy when expressed in ccRCC. In addition, we stained matched human FFPE tissue with 31 antibodies using multiplex immunohistochemistry (mxIHC) to investigate the TME. Using mxIHC protein expression levels, we generated a probabilistic cell classification algorithm to quantify immune cells. We investigated associations between ERV expression data, clinicopathologic variables, and immune cell proportions in the tumor samples using linear regression. **Results:** We performed ERV expression and mxIHC analysis on 104 PRCC nephrectomy samples from 1997-2016. After quality control, 78 unique patient tumor samples had results from both pipelines. Median patient age was 65 (IQR 56-71), 74.4% were male, and Fuhrman grade was 1 in 3.9%, 2 in 5.9%, 3 in 50.0%, and 4 in 9.0% of patients. Over a median follow-up of 3.03 years (IQR 0.61-6.99 years), 11.5% had recurrence after definitive local therapy, and 7.7% had an RCC-related death. Increased ERV expression correlated with increasing Fuhrman grade ($r = 0.057$, $p < 0.001$), but not with disease recurrence or RCC-related death. Increased ERV expression was also associated with an increased TME proportion of cytotoxic T cells, memory T cells, and CD20+ B cells, and with a decreased TME proportion of macrophages (see Table 1). **Conclusions:** Higher expression of ERV4700 correlates with increased proportions of cytotoxic T cells in the TME of PRCC samples. Given its association with immunotherapy response in ccRCC, further studies are warranted to study ERV expression as a prognostic and predictive biomarker in PRCC. Research Sponsor: Department of Defense Kidney Cancer Research Program.

TME cell proportion associations with log ERV expression.

Immune Cell Type	Correlation (r)	*P*-value
Cytotoxic T cells	0.19	<0.001*
Helper T cells	0.07	0.214
Regulatory T cells	-0.04	0.532
Memory T cells	0.18	0.001*
Macrophages	-0.12	0.030*
NK cells	-0.06	0.279
CD20+ B cells	0.12	0.035*

*p<0.05.

Topological heterogeneity of genomic and immunologic effects from combination immunotherapy treatment in the neoadjuvant setting for renal cell carcinoma (RCC).

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Background: We present a multi-regional genomic analysis of tumor from a phase 1b clinical trial of perioperative durvalumab (D) and tremelimumab (T) in patients (pts) with high-risk RCC. Genomic & transcriptomic analyses were performed on nephrectomy samples post neoadjuvant therapy to assess genomic/immunologic impact of combinatorial D+T therapy compared to D alone. **Methods:** Post-treatment nephrectomy samples were regionally sampled at 4 locations: non-tumor, tumor distant, tumor near, and tumor center. RNA-sequencing was performed on all 4 regions and utilized on a per patient basis to identify regional tumor microenvironment alterations compared to normal kidney. Whole exome sequencing was performed on tumor center. **Results:** 29 pts enrolled in the trial. 15 were included in the analysis; 5 received neoadjuvant D and 10 received D+T. 60 multi-regional specimens were analyzed; each patient's own normal kidney tissue served as their baseline. There were significant transcriptional differences in D+T compared to D alone (Table). While many of these genes overlapped between treatment arms, the amplitude of differentially expressed genes (i.e., differences between normal and tumor tissue) were greater in the D+T arm, particularly among immune related genes, such as CD8A, CXCL9, CXCL13 and PRAME. Enhanced immune activity was confirmed by immune deconvolution analyses showing broad regional immune infiltration of lymphocytes, including $CD8^+$ T cells, in D+T, which was not detected in D alone. Further comparison of mutational profiles within this cohort showed that D+T treatment resulted in increased clonality compared to D. **Conclusions:** These data highlight the potential differential genomic/immunologic impact of combination immunotherapy vs single agent across tumor topology. It also demonstrates the utility of pt specific comparisons and a multiregional sampling approach. D+T treatment resulted in enhanced immune activity in RCC tumors and activation of anti-tumor processes above and beyond D alone. This design increases power & biological interpretation of small pt cohorts and allows additional insight into enhanced activation of the immune system with D+T. Summary of transcriptomic comparisons within D & D+T cohorts per region where $p < 0.05$ was used as selection criteria along with positive & negative log fold change. Pathway analysis performed using Hallmarked pathways based on differentially expressed genes, and Celltype deconvolution via ssGSEA ($p<0.05$). Research Sponsor: None.

	Downregulated Genes	Upregulated Genes	Downregulated Pathways	Upregulated Pathways	Decreased Cell Types	Increased Cell Types
TC vs NK (D)	1248	527	0	0	0	0
TD vs NK (D)	1228	622	0	0	0	0
TN vs NK (D)	1109	453	0	0	0	0
TC vs NK (D +T)	2752	1745	8	18	0	8
TD vs NK (D +T)	2815	2251	8	20	0	13
TN vs NK (D +T)	2411	1873	7	20	0	11

TC = tumor center; TD = tumor distant; TN = tumor near; NK = normal kidney.

Prognostic value of circulating tumor DNA fraction (TF) for patients with metastatic renal cell carcinoma (mRCC).

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Background: Risk stratification, based on the IMDC classification, is central to treatment decisions for patients with mRCC. The strongest prognostic feature in the original validation was the clinical assessment of patient frailty through performance status (PS). Although inexpensive and ubiquitous, clinical features such as PS are prone to degrees of subjectivity and considerable variation in assessment from practitioner to practitioner. Recent work (Reichert et al. 2022, Annals of Oncology) observed that TF levels around the initiation of new treatment were prognostic independently of standard clinical features including ECOG PS, in advanced/metastatic lung, breast, prostate, and colorectal cancers, but has not yet been investigated in mRCC. **Methods:** This study used a cohort of patients in the de-identified nationwide, U.S. based Flatiron Health-Foundation Medicine renal cell clinico-genomic database, which originated from approximately 280 US cancer clinics (~800 sites of care), who underwent genomic testing as part of routine care. TF estimation on FoundationOne Liquid CDx was based on a composite algorithm incorporating multiple factors including aneuploidy and variant allele frequency of canonical alterations. Clinical characteristics, laboratory and treatment data were captured from the electronic health record. Real-world progression-free survival (rwPFS) and overall survival (rwOS) were evaluated by TF level. **Results:** 45 patients with mRCC and liquid biopsy testing had TF assessments within 90 days of start of new treatment. Patients with TF≥1% (15 of 45) had younger median age (58y vs. 66y, $p = 0.041$) and higher prevalence of calcium levels above upper limit of normal (46% vs. 4%, $p < 0.001$). Higher TF (≥1%) was associated with less favorable rwPFS (hazard ratio (HR) 1.41, 0.70-2.82, p=0.34) and rwOS (HR 2.54, 1.08-5.96, p=0.033). In the 15 patients with TF ≥1%, we observed detection of known pathogenic genomic alterations in *VHL* (7/15, 47%), *SETD2* (4/15, 27%), *PBRM1* (4/15, 27%), *BAP1* (3/15, 20%). **Conclusions:** In this initial cohort study, ctDNA TF shows prognostic significance in mRCC with potential to inform expected longevity of patients. Liquid biopsy detects alterations characteristic of mRCC genomics, supporting its utility to identify drivers and potential targetable alterations. Risk stratification based entirely upon algorithmic determination independent of human interpretation has the potential to improve risk stratification in mRCC and improve treatment decisions. Expansion of our cohort and survival data maturation will allow for evaluation of whether TF may be a useful addition to the established IMDC clinical classification and improve risk stratification and treatment assignment. Research Sponsor: Foundation Medicine Inc.

Association between β3-adrenergic receptor agonist use and risk of kidney cancer among patients with overactive bladder.

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Background: New aspects of β3-AR have been recently described with overexpression in cancers. Although post-authorization safety study of mirabegron, the first approved β3-AR agonist for overactive bladder (OAB), found no association between mirabegron use and risk of overall cancer, subgroup analysis revealed that some malignancies were significantly associated with β3-AR agonist use. This study aimed to examine whether cumulative β3-AR agonist use is associated with a higher risk of kidney cancer and demonstrate underlying mechanisms of β3-AR agonist through murine model. **Methods:** This nationwide population cohort study included newly diagnosed OAB patients who initiated their OAB medications between 2015 and 2020. In pulmonary metastatic orthotopic murine mRCC model, primary tumor weight and number of lung nodules were measured and evaluation of browning of perinephric fat (PF) and tumor immune microenvironment (TIME) was performed and compared between β3-AR agonist and vehicle treatment groups. **Results:** Among a total of 3,728,929 patients, 7,437 (0.2%) developed kidney cancer after starting OAB medications. There was an increased risk of kidney cancer among β3-AR agonist users (hazard ratio (HR)=1.514, 95% confidence interval (CI) 1.418–1.615) compared to anticholinergic users. The incidence of kidney cancer was also significantly increased with an increase in the cumulative dose of mirabegron (adjusted HR (aHR)=1.221 (1.104-1.351) for 30-180 cDDDs (cumulative defined daily doses), aHR=1.413 (1.281-1.558) for >181 cDDDs) compared to low-dose cDDDs (<30 cDDDs)). The β3-AR agonist treated mice demonstrated significantly higher primary tumor burden and lung metastasis with increased mitosis in cancer cells and browning of PF. Immunofluorescence analysis demonstrated that β3-AR agonist modulate TIME by increasing both myeloid-derived suppressor cells and regulatory T cells. **Conclusions:** This is the first study to demonstrate the association of kidney cancer and β3-AR agonist both in murine and human studies. By showing that the β3-AR agonist not only increases PF browning but also induces immune tolerance which eventually increases the initiation and progression of kidney cancer, we suggest β3-AR as the potential therapeutic target for novel anti-neoplastic approaches. Research Sponsor: Korea Health Industry Development Institute; National Research Foundation of Korea; Korean Urological Oncology Society; Yonsei University College of Medicine; Foundation for Korean Urological Association.

Effect of cytoreductive nephrectomy on the efficacy of immunotherapy in metastatic renal cell carcinoma by decreasing IL-6 to modulate tumor-associated macrophage and myeloid-derived suppressor cell.

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Background: Although the contemporary role of cytoreductive nephrectomy (CN) has been significantly downsized, the role of CN in immuno-oncology era still remains. Since the efficacy of immune checkpoint inhibitor (ICI) is limited, the role of CN in combination with ICI from the perspective tumor immune microenvironment (TIME) was evaluated using murine models and hypothesized that interleukin 6 (IL-6) blockade would enhance the efficacy of ICI therapy. **Methods:** Low- and high-tumor burden pulmonary metastatic orthotopic murine mRCC models have been developed. Antibodies targeting PD-1, CTLA-4, and IL-6 were systemically injected through the peritoneum. Renca implanted kidney was removed in the CN performed group and the timing of CN was differentiated according to the upfront and deferred CN group. The remodeling of the TIME was analyzed by flow cytometry, immunofluorescence analysis, and measurement of cytokines. **Results:** Upfront CN group demonstrated significantly better survival outcomes compared to deferred CN group in low-tumor burden models, while significantly longer survival was reported in deferred CN group compared to upfront CN group in high-tumor burden models. CN modulate IL-6 levels which act as a negative regulator of myeloid-derived stem cells (MDSCs) and M2 tumor-associated macrophage (TAM). The blockade of IL-6 activated CD8+ T-cell accumulation and led to decreased expression of MDSCs and M2 TAM, which is similar to the effects on TIME by CN combined with ICI therapy. **Conclusions:** This study is the first animal study to demonstrate the role of CN in combination with ICI. CN decreases the production of the cytokine IL-6, increasing the anti-cancer immunity TIME through modulation of MDSC and M2 TAM. Our study provides a research basis for the significant role of IL-6 in tumor regression and highlights a novel target to improve the efficacy of immunotherapy. Research Sponsor: Korea Health Industry Development Institute; Korean Urological Oncology Society; Yonsei University College of Medicine.

Preclinical testing of a novel PD-L1 inhibitor for the treatment of renal cell carcinoma.

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Background: Immune checkpoint inhibitors (ICI) targeting PD-1/PD-L1 axis has revolutionized the therapeutic landscape of patients with advanced and locally advanced renal cell carcinoma (RCC). However, complete response rates remain low and there is a need for novel therapeutic options for ICI-resistant and refractory RCC. Our group has generated a novel humanized anti-PD-L1 antibody, called H1A, that induces PD-L1 degradation preventing not only its interaction with PD-1 but also inhibiting pro-tumorigenic intracellular signaling. In this study, we compared the antitumor activity of H1A with FDA-approved ICI using patient-derived immune cells and humanized mouse tumor models. **Methods:** In vivo antitumor activity of H1A and atezolizumab (ATZ) was compared in three humanized PD-1/PD-L1 mouse tumor models with different immunogenicity (E0771:high, MC38:moderate, B16-F10:poor). Peripheral blood mononuclear cells (PBMC) were isolated from 14 RCC patients undergoing with nephrectomy. PBMC were treated with H1A, nivolumab (NIV), atezolizumab (ATZ) and pembrolizumab (PEM) to evaluate their efficacy in inducing tumor cell death in an ex-vivo cytotoxicity assay. Mass cytometry was employed to determine the impact of H1A and atezolizumab on the PBMC profile. **Results:** MC38 tumors showed moderate response to both H1A and ATZ which was abrogated by CD8 T cell depletion. In E0771 tumors, higher percentage of complete responders was observed with H1A compared to ATZ and E0771 rechallenge revealed memory antitumor immunity with complete rejection of tumors. Patient-derived PBMC treated with H1A showed superior tumor cell killing compared to NIV, PEM and ATZ ($p<0.01$). While H1A treatment of PBMC induced expansion of effector NK and CD8 T cells ($GZMB^+$ T-bet^+), ATZ treatment led to enrichment of Tregs ($CD25^+$,$Foxp3^+$) expressing inhibitory markers PD-1 and LAG-3. **Conclusions:** H1A demonstrated superior antitumor activity compared to FDA-approved ICI which lays the ground for clinical testing of H1A as a next-generation immune checkpoint inhibitor for the treatment of renal cell carcinoma. Research Sponsor: NIH; Mayo Clinic Cancer Center; Fonds de Recherche du Quebec-Sante.

Multi-omic characterization of acquired resistance to immune checkpoint inhibitors in patients with metastatic renal cell carcinoma.

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Background: While immune checkpoint inhibitors (ICI) have improved outcomes in patients (pts) with metastatic renal cell carcinoma (mRCC), acquired resistance (ARX) is commonly encountered. We aimed to characterize the genomic and transcriptomic correlates underlying ARX in ICI-treated mRCC patients. **Methods:** We identified pts with mRCC at Dana-Farber Cancer Institute and Fox Chase Cancer Center, treated with ICI-based regimens who had an initial response to therapy followed by disease progression. Tissue samples from the primary tumors or metastases were collected before ICI treatment and after ARX from a treatment-emergent escape lesion. Whole exome sequencing (WES) and bulk RNA-sequencing (RNA-seq) were performed. Somatic mutations were called using the Cancer Genome Analysis pipeline. Differential gene expression analysis (DGE) was run using DESeq2, followed by gene set enrichment analysis (GSEA). Immune cell fractions were estimated using CIBERSORTx. Cell fraction and tertiary lymphoid structures (TLS) scores were compared between post and pre-ARX samples using the Wilcoxon test. **Results:** A total of 41 samples (n=23 pre-ARX and n=18 post-ARX) were collected from 14 unique patients. After quality control, WES and RNA-seq data were available for 27 samples (14 pre-ARX and 13 post-ARX) and 9 samples (3 pre-ARX and 6 post-ARX), respectively. No discernable enrichment of gene mutations was detected in the post-ARX setting compared to the pre-ARX. DGE identified 61 downregulated immunoglobulin genes in the post-ARX setting. GSEA revealed significant depletion of pathways associated with B-cell and T-cell function in post-ARX samples (all adjusted $p<0.05$). Similarly, a trend towards decreased naïve B cell and CD8+ T cell fractions was observed in the post-ARX setting ($p=0.17$ for both). Three previously reported TLS-associated expression signatures were depleted in the post-ARX samples compared to pre-ARX ($p=0.015$, $p=0.065$ and $p=0.065$, respectively). Immunohistochemistry assessment of 3 samples from one pt using ant-CD3 and CD20 antibodies confirmed the presence of TLS in the pre-ARX sample and their absence in two different post-ARX samples. **Conclusions:** In our cohort of pts with mRCC, no gene mutations were implicated as drivers of ARX. However, ARX was associated with downregulation of B-cell signaling and humoral mediated immunity, as well as absence of TLS. Ongoing efforts are in progress to include more samples. Research Sponsor: None.

Evolution of the functionality of microbial communities in patients with metastatic renal cell carcinoma (mRCC) receiving cabozantinib (cabo)/nivolumab (nivo) with or without CBM588: A randomized clinical trial.

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Background: Our team has previously demonstrated in two prospective studies that the live bacterial product CBM588 may enhance clinical outcomes in patients with mRCC (Ebrahimi et al ASCO 2023, Dizman et al Nature Med 2022). In the current study, we sought to determine if gut microbial functionality is associated with clinical outcomes in patients with mRCC treated with cabo/nivo with or without CBM588. **Methods:** Pts ≥18 yrs old with histologically verified (clear-cell, papillary, or sarcomatoid component) mRCC and no prior systemic therapy for metastatic disease were enrolled and randomized 1:2 to receive either cabo/nivo at the standard dose/schedule alone or with CBM588 dosed at 80mg PO BID. Whole metagenome sequencing was performed on stool specimens collected at baseline and week 12 of treatment. Taxonomic profiling was conducted using MetaPhlAn 4, and functional profiling was performed using HUMAnN 3. HUMAnN 3 annotates open reading frames and provides highly accurate information on metabolic pathways and other molecular functions from metagenomic or metatranscriptomic sequencing data. The ANCOM-BC was used to detect the taxonomic/genetic features with differential abundance between two time-points within the same treatment arm. **Results:** A total of 30 (20:10 M:F) pts were enrolled with a median age of 65 (36-84). 5 pts (17%) had sarcomatoid features, and 2 pts (7%) had predominant papillary histology. Objective response was achieved in 20% and 65% of the pts in the cabo/nivo and cabo/nivo/CBM588 arm, respectively. Significant changes in 9 metabolic pathways (1 upregulation, 8 downregulation) in the control arm and 7 metabolic pathways (2 upregulation, 5 with downregulation) in the experimental arm were identified. Superpathways of biosynthesis of different forms of menaquinole, a reversible redox component of the electron transfer chain, were depleted with cabo/nivo treatment. In contrast, the biosynthesis of menaquinol-8 and 1,4 dihydroxy-6-naphthoate (an intermediate of the menaquinone pathway) were upregulated in cabo/nivo/CBM588 arm. **Conclusions:** Our interrogation of metabolic dynamics and pathways in patients receiving CBM588 suggests key differences in biosynthesis pathways of menaquinone between control and experimental arms. Menaquinones (vitamin K2 derivatives) have been previously reported to induce apoptosis in many cancer cell types and also increase the objective response rate to sorafenib in patients with hepatocellular carcinoma. Our findings provide mechanistic evidence for the effect of the addition of CBM588 to cabo/nivo on gut microbiome function and the resultant improvement in clinical outcomes in mRCC, potentially through enhancing the enteric production of vitamin K2. Clinical trial information: NCT05122546. Research Sponsor: Exelixis.

Tumor characteristics associated with detectable circulating tumor DNA pre-operatively in patients with renal masses suspicious for RCC.

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Background: Understanding the specific tumor characteristics associated with detectable ctDNA in the blood of patients with renal cell carcinoma (RCC) is critical to informing future studies seeking to establish the clinical utility of such testing. We characterized pathological and clinical characteristics associated with ctDNA detected preoperatively in patients with renal masses suspicious of RCC. **Methods:** Using our single institution prospectively maintained database, we identified consecutive patients who underwent partial or radical nephrectomy for non-metastatic suspected RCC (stages cT1b-cT3) during 2022-2023. Included were patients who had undergone tumor-informed ctDNA testing using the commercial Signatera assay (Natera). Baseline characteristics, pathology results, imaging study results, and oncological treatment and follow-up data were collected from the electronic medical records. ctDNA results were collected through the Natera portal. Study findings were reported using descriptive statistics. A p-value of <0.05 was considered statistically significant. R programming language version 4.3 was used for all statistical analyses. **Results:** A total of 54 patients with a median age of 63 years (IQR 51-71) were included in the study. Twenty-one (39%) were women. The median follow-up time was 4 months (range: 1-21 months). Among the 54 patients, 27 (50%) had detectable ctDNA pre-operatively Post-operative results were available for 33 patients, and 3 (9%) had detectable tDNA (of those 2 had Inferior vena cava involvement). The first patient developed metastatic disease. The two other patients are receiving adjuvant immunotherapy. Analysis of 50 patients with solely malignant RCC revealed that patients with detectable versus undetectable ctDNA were older 67 vs. 54 years (p=0.03), had a higher pathological stage (p= 0.002), larger tumors (7.2 vs. 4.7 cm, p = 0.004), and higher pathological grade (grade 3-4 vs. grade 1-2; p=0.035) (Table 1). All the patients with renal vein or inferior vena cava involvement had detectable ctDNA (n=8). **Conclusions:** In our cohort, preoperative ctDNA was detectable in 50% of patients with suspected clinically localized RCC. Detectable ctDNA preoperatively correlated with clinically relevant features. The ability of preoperative ctDNA to predict re-currence and survival in patients with clinically localized RCC warrants further evaluation. Research Sponsor: None.

		Negative ctDNA (n=24)	Positive ctDNA (n=26)	p
Age (median [IQR])		54 [49, 66]	67 [58, 74]	0.028
Histological Subtype (%)	Clear cell	17 (70.8)	21 (80.8)	0.122
	Papillary	1 (4.2)	4 (15.4)	
	Clear Cell Papillary	2 (8.3)	0 (0)	
	Chromophobe	4 (16.7)	1 (3.8)	
Histological Grade (%)	Low (1-2)	16 (80)	12 (48)	0.035
	High (3-4)	4 (20)	13 (52)	
Lymphovascular Invasion (%)		0 (0)	5 (19.2)	0.051
Sarcomatoid Features (%)		0 (0)	3 (11.5)	0.236
Necrosis Detected (%)		4 (16.7)	8 (30.8)	0.327

Clinicopathological features and transcriptomic profiles of MED15-TFE3-rearranged renal cell carcinoma: A retrospective study of 14 cases.

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Background: TFE3-rearranged renal cell carcinoma (TFE3-rRCC) is a rare type of RCCs with various fusion types and heterogeneous clinicopathological features. MED15-TFE3 is a fusion that usually present as an extensive cystic mass with low malignant potential. We sought to summarize the clinicopathological, transcriptomic characteristics and survival outcome in MED15-TFE3-rRCC patients. **Methods:** All 14 cases were collected retrospectively fromSichuan University West China Hospital from 8/2011 to now. Diagnosis of MED15-TFE3 fusion was confirmed by fluorescence in situ hybridization and RNA sequencing. The clinicopathological features and follow-up data were collected for further analysis. The tumor transcriptomic profiles were analyzed by Gene Set Enrichment Analysis (GSEA), Gene Ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis via R tool. **Results:** The median age was 43.5 years (range, 22 to 70). Majority of the cases were female (10/14). 8 patients (57.1%) underwent radical nephrectomy, 1 patient received cytoreductive surgery, and 5 patients (35.7%) received partial nephrectomy. At initial diagnosis, most cases (10/14) were localized disease, while 2 patients had regional lymph nodes metastasis, and 1 patient had distant metastasis (bone). For the patients without distant metastasis (n=13), 2 patients developed metastasis (liver, lung, abdominal, in situ) with disease-free survival of 11.4 and 29.0 months. As for the pathological features, 10 (71.4%) of thesamples presentedcystic morphologically, and other 4 (28.6%) were papillary. 10 (71.4%) were in G2 by ISUP score. For metastatic patients, 3 received first-line therapy (1 axitinib, 1 axitinib + sintilimab, 1 sunitinib), 2 received second-line therapy (1 axitinib + sintilimab, 1 axitinib + toripalimab), 1 received third-line therapy (axitinib + toripalimab + everolimus). They are still under follow-up. GSEA analysis illustrated that compared to paraneoplastic tissue, apical surface, bile acid metabolism, KRAS signaling, Xenobiotic Metabolism, and estrogen response were upregulated in tumor. For the patients with distant metastases, the transcriptomic analysis revealed that organelle fission, nuclear division, mitotic nuclear division, and chromosome segregation were significantly upregulated, which may be associated with tumor metastasis. The overall immune cell infiltration was comparable in metastatic patients and non-metastatic patients. However, the expression level of type 17 T helper cell, B cells, plasmacytoid dendritic cell, and activated dendritic cell were significantly different. **Conclusions:** MED15-TFE3 rRCC mainly present low-grade cystic renal neoplasm with favorable prognosis. For metastatic MED15-TFE3 rRCC, there is no standard therapy. And the transcriptomic evidence may provide insights for future research. Research Sponsor: None.

PD-L1 expression and its prognostic value in metastatic papillary renal cell carcinoma: Results from a GETUG multicenter retrospective cohort.

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Background: Papillary renal cell carcinoma (pRCC) is a rare and aggressive cancer with no specifically established therapeutic strategy in the metastatic setting. Combinations of tyrosine kinase and immune checkpoint inhibitors are a promising option. We aimed to study the immune landscape of metastatic pRCC, and its associations with angiogenesis pathways expressions, to search for potential therapeutic targets. **Methods:** The expression of immune markers (PD-L1, PD-1, PD-L2, LAG-3) and angiogenic pathways (CAIX, c-MET), was analyzed by immunohistochemistry on 75 metastatic pRCC retrieved from a retrospective multicenter GETUG cohort. Our primary endpoint was to evaluate the prognostic impact on overall survival (OS) of PD-L1 expression in metastatic pRCC. Secondary endpoints were to describe the expression of the other immune markers and of angiogenic pathways and to estimate the associations between the expression of PD-L1 and the expressions of the other markers or angiogenic pathways. **Results:** In median, patients were 61 years old at metastatic diagnosis. Concerning their first-line metastatic treatment, 67 (89%) had received Sunitinib, and 8 (11%) had received Everolimus. The Karnofsky Performance Score at treatment initiation was $\geq$ 80 for 62 (83%) patients. Overall, 25.3% of tumors were PD-L1 positive. PD-L2 was more frequently expressed (45.3%), PD-1 and LAG-3 were positive in 17.3% both. Concerning the angiogenic markers, CAIX was expressed in 46.7% of tumors, c-MET in 41.3%. None of these markers were significantly associated with PD-L1 expression. 64% (48/75) expressed at least one immune marker, and 40% (30/75) were "double-positive", as they expressed both immune and angiogenic markers. In univariate analysis, OS was significantly shorter for patients with PD-L1 positive pRCC (HR=3.3; 95%CI=1.3-8.6; p=0.01). A multivariate analysis confirmed a significant association between PD-L1 expression and shorter survival (HR=5.4; 95%CI=1.4-20.9; p=0.01). **Conclusions:** These results reinforce clinical data on the expected benefit of immunotherapy in metastatic pRCC treatment, as PD-L1 expression is a factor of poor prognosis in our multicenter cohort. Research Sponsor: None.

Glutamine metabolism and VEGF analysis to elucidate and overcome the mechanism of tyrosine kinase inhibitor resistance in renal cell carcinoma.

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Background: Clinical practices have demonstrated improvements in prognosis of patients with advanced renal cell carcinoma (RCC) by combination therapies with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors. However, TKI-resistance is inevitable which hinders further improvement in prognosis. In our previous study, we reported regulating glutamine metabolism could bring about re-sensitivity to Sunitinib (Su) in Su-resistant Renal cell Carcinoma (RCC) cells. However, the mechanism of re-sensitivity and whether it applies to other tyrosine kinase inhibitors (TKIs) has been still unknown. **Methods:** We established Su and Cabozantinib (Cabo) -resistant cells in 3 RCC cell lines (786-O, Caki-1 and ACHN). We analyzed the activity of glutamine metabolism and VEGF pathway, before and after TKI-resistant、furthermore, conducted antitumor effect in vitro and vivo studies to evaluate re-sensitivity to TKI and relationship between VEGF signaling and regulating glutamine metabolism. **Results:** In all TKI-resistant cells, the overexpression of glutamine metabolism and VEGF signaling were observed. In vitro and vivo study using Su, the regulating glutaminolysis resulted in 40-74% cell-killing effect in 3 Su-resistant cell lines. Whereas the regulating glutaminolysis also resulted in 35-55% cell-killing effect in 3 Cabo-resistant cell lines. Although the antitumor effect was observed in only 786-O among Su-sensitive cells, it was not observed among Cabo-sensitive cells. Moreover, antitumor effect of regulating glutamine metabolism is more remarkable in vivo. When conducting immunostaining of CD31 to evaluate vascular endothelium, angiogenesis was significantly inhibited by regulating glutamine metabolism.Evaluating VEGF signaling in RT-PCR, VEGFR2 expression and VEGF signaling were downregulated, and PTEN upregulated by suppressing glutamine metabolism. **Conclusions:** By evaluating glutamate metabolism with VEGF analysis in TKI-resistant RCC cells, we have come to understand a part of the phenomenon of re-sensitivity to TKIs. The inhibition of VEGF signaling and its consequent impact on the tumor microenvironment by regulating glutamine metabolism, are considered to be the mechanisms causing re-sensitivity to TKIs in TKI-resistant cells.We could use TKIs more effectively by regulating glutaminolysis to improve prognosis in advanced RCC patients. Research Sponsor: None.

Identification of a novel prognostic gene signature in a clear cell renal cell carcinoma (ccRCC) population using an integrated multi-study single-cell RNAseq dataset.

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Background: Clear cell renal cell carcinoma (ccRCC) is a highly heterogeneous disease with varying prognoses and treatment responses. Understanding the underlying molecular determinants of this diversity is key to tailoring effective treatment strategies for each patient (pt). Here, we leveraged single−cell RNA sequencing (scRNA−seq) data to assess intra−tumoral diversity and its impact on pt prognosis. **Methods:** scRNA−seq raw data from five published studies were processed with Seurat's standard workflow and integrated to remove biases using Harmony. We then re−analyzed the malignant cell cluster, defined by CA9, NDUFA4L2, and IGFBP3 expression, at a higher resolution. The resulting tumor cell sub−clusters were subjected to differentially expressed gene (DEG) and gene ontology (GO) enrichment analyses. A signature based on all DEGs with a fold change > 1.25 was applied on TCGA−KIRC cohort using single−sample gene set enrichment analysis and then correlated with relapse−free survival (RFS) and overall survival (OS) by Kaplan−Meier and multivariate Cox analyses. **Results:** We integrated scRNA−seq data from 50 samples from 44 pt's (40% T3−4, mean age 75, 10% females). A total of 288K cells were classified into 19 clusters. The tumor cluster was re−analyzed and three biologically distinct tumor cell sub−clusters (labeled MC_1, MC_2, and MC_3) were identified, each with unique molecular markers. GO analysis showed enrichment in genes associated with iron sequestration, oxidative phosphorylation, and apoptotic signaling, respectively. In the KIRC cohort, a 23−DEG signature from MC_2 strongly correlated with RFS (HR 0.49; 95% CI 0.35−0.67 $p < 0.001$; 5-RFS: 74% vs. 54%) and OS (HR 0.44; 95% CI 0.33−0.60 $p < 0.001$; 5-OS: 75% vs. 51%) and was independent of other clinical variables in the multivariate analysis (Table 1). Moreover, this signature identified a subset of T1−T2 tumors (47.8%) with low risk of relapse (HR 0.38; 95% CI 0.19−0.78, $p = 0.008$; 5-RFS: 92% vs. 80%) and longer OS (HR 0.35; 95% CI 0.20−0.62 $p < 0.001$; 5-RFS: 90% vs. 68%). **Conclusions:** We have identified three distinct tumor cell sub−populations in an integrated scRNA−seq database, each characterized by unique transcriptomic profiles. A gene expression signature based on the MC_2 sub−cluster was prognostic in the TCGA dataset and may help in identifying patients with a higher risk of relapse and candidates to adjuvant therapy. Research Sponsor: None.

Multivariate analysis results.

Variable (Reference)	RFS HR (p-value)	OS HR (p-value)
MC_2 − Mid (Low)	0.62 (0.015)	0.63 (0.009)
MC_2 − Hi (Low)	0.48 (0.001)	0.40 (0.001)
Grade (1-2):	−	−
· **3**	1.41 (0.109)	1.18 (0.400)
· **4**	2.45 (< 0.001)	1.52 (0.082)
Sarcomatoid (No)	1.12 (0.671)	1.89 (0.015)
Necrosis (No)	0.77 (0.299)	1.37 (0.154)
Stage (I):	−	−
· **II**	2.25 (0.015)	1.13 (0.693)
· **III**	3.94 (< 0.001)	2.04 (0.001)
· **IV**	14.11 (< 0.001)	4.73 (< 0.001)

The immune characteristic analysis of BAP1 mutated clear cell renal cell carcinoma.

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Background: Commonly mutated genes in clear cell renal cell carcinoma include VHL, PBRM1, and BAP1. Although the detection rate of BAP1 mutations in RCC is not high, from an evolutionary perspective. BAP1 mutated renal cell carcinoma tends to have clinical features of higher malignancy, faster disease progression, and poor efficacy of classic drug treatments. Therefore, this study uses our center and TCGA database to analyze the correlation between transcriptome, immune cell infiltration, immune checkpoint expression and other characteristics and the efficacy of immune checkpoint inhibitor-based treatment in patients with BAP1 mutated renal cell carcinoma. **Methods:** 1. The correlation between the expression of immune-related factors CD4, CD8 and immune checkpoints PD-L1, LAG3 and BAP1 RNA and the expression difference between wild and mutant groups were analyzed through the TCGA database. 2. Collect BAP1 mutant and wild-type patients retrospectively, and verify the expression of CD4, CD8, PD-L1 and LAG3 by immunohistochemistry. 3. The enrichment analysis of the signaling pathway was carried out after the intersection of TCGA and the differential genes of the center. 4. To analyze the clinical curative effect difference between BAP1 wild-type and mutant advanced RCC patients receiving target immunotherapy. **Results:** The TCGA data confirmed that there was no difference in the expression of PD-L1 RNA between the two groups (P=0.5); while there was a significant difference in the expression of LAG-3 RNA, which was higher in the BAP1 mutant type than in the wild type (P=0.023); 24 cases of BAP1 wild-type ccRCC specimens available in the gene detection database of our center were selected, and the results of immunohistochemistry suggested that there were differences in the expression of LAG3 (p=0.009) between the BAP1 wild-type and mutant types, while PD There was no significant difference in the expression of -L1 (p=0.157). The transcriptome data enrichment analysis results of TCGA and our center database showed that BAP1 was closely related to cytokine signaling, cAMP signaling pathway and immune response signals in the tumor immune microenvironment. In terms of clinical efficacy, the PFS time of BAP1 wild-type RCC patients receiving ICI combined with TKI therapy was significantly longer than that of BAP1 mutant patients (median follow-up time: 23.93 months; median PFS: 24.63 vs. 11.73 months, HR: 0.304, 95%CI: 0.070-1.324, p=0.025). **Conclusions:** This study found that BAP1 and cytokines, cAMP pathway and immune inflammation-related pathways were significantly enriched at the transcriptome level. IHC results suggested that LAG3 was more highly expressed in patients with BAP1 mutation. Clinical treatment analysis found that PD-1 inhibitor-based immune combination therapy is not effective for patients with BAP1 mutations. In summary, LAG3 may be a potential therapeutic target in the future for patients with BAP1-mutated RCC. Research Sponsor: None.

Development and validation of a tumor tissue based multivariate biomarker for predicting angiogenesis inhibitor clinical benefit in renal cell carcinoma (RCC).

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Background: Angiogenesis inhibitors, including vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), are standard of care therapy (alone and in combination) for several advanced cancers, including RCC. There is an unmet need for a biomarker to identify patients with RCC most likely to benefit from VEGFR TKIs to guide individualized treatment decision making. Hence, we sought to develop and validate a biomarker for predicting single-agent systemic VEGFR TKI benefit in patients with RCC. **Methods:** Candidate biomarkers were selected by co-expression patterns in VEGFR TKI sensitive/resistant tumor types from pan-solid tumor TCGA expression profiling data and the literature. The angiogenesis inhibitor treatment response score (Angio TRS) was developed as a multivariate expression-based algorithm from RNA-based quantitative transcriptional profiling (qTP) performed in parallel with clinical FFPE tumor based comprehensive genomic profiling, with the Angio TRS High/Low threshold set at the median of clear cell RCC samples. The locked Angio TRS (and High/Low status) was then validated in a cohort of adult RCC patients treated with a systemic line of single agent VEGFR TKI therapy within a prospective observational trial; group outcomes (by time to next therapy [TTNT]) were compared by univariate analysis, Cox proportional hazards modeling (adjusting for age, biologic sex, histology, nuclear grade [incorporating sarcomatoid features], therapy line, and TKI type), and unadjusted Kaplan Meier analysis. Laboratory information for IMDC risk group status was not available. **Results:** Across 3,721 solid tumor tissue samples, median Angio TRS was highest in known VEGFR TKI sensitive tumors (RCC, thyroid carcinoma, sarcoma). Angio TRS was then validated in a separate cohort of 86 patients with RCC treated with single agent systemic VEGFR TKI (median follow-up 29.2 months; 76% male, 77% clear cell, 14% with sarcomatoid features, 84% 1st line, and 71% treated with sunitinib, pazopanib or axitinib); 52% of patients were Angio TRS High. By univariate analysis, Angio TRS status (p=0.008) and nuclear grade 4 (with or without sarcomatoid features; p=0.06 & 0.07) were most significantly associated with VEGFR TKI TTNT; by multivariate analysis, only Angio TRS status was significantly associated with TTNT (High vs. Low median TTNT 15.8 vs. 5.6 months, adjusted hazard ratio 0.46, p=0.012). **Conclusions:** Angio TRS is a multivariate expression-based algorithm performed on FFPE tumor tissue, validated to be prognostic of clinical outcome for patients with RCC treated with single agent VEGFR TKI when controlling for clinical factors. Angio TRS may support individualized treatment decision making in patients with advanced RCC. Additional independent validation in a cohort of Kaiser Permanente patients will be presented. Clinical trial information: NCT03061305. Research Sponsor: Strata Oncology.

Increased spatial coupling of integrin and collagen IV in the immunoresistant clear cell renal cell carcinoma tumor microenvironment.

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Background: Immunotherapy (IO) has improved response rates for patients with advanced clear cell renal cell carcinoma (ccRCC), but most will develop resistance. We sought to utilize cellular-level spatial transcriptomics in the IO naïve and IO exposed settings to better understand IO resistance in ccRCC tumor immune microenvironment (TIME). **Methods:** Tissue was obtained from primary ccRCC kidney tumors. Matched tumor and stromal fields of view (FOV) were included for analysis. Spatial molecular imaging (SMI) was obtained for three tissue microarrays using Nanostring's CosMx platform. Cells were phenotyped using Insitutype and the Kidney Cell Atlas as a reference. T cells and macrophages were further subtyped using subclustering and differential gene expression. Tumor cells were phenotyped using differential gene expression of proximal tubule cells with high VEGF expression and a LASSO regression model. Cell abundance and clustering by phenotype were then analyzed by treatment status. Clustering of all cell types was quantified using univariate Ripley's K. Radii between 9 and 90um were visually compared to identify an appropriate search distance; a final radius of 27um was selected. Spatial gene set enrichment (GSE) analysis followed by a post hoc spatial analysis of associated transcripts from select enriched gene sets were performed. Global Moran's I test was used to quantify spatial autocorrelation of ligand-receptor (LR) pairs. Multiplex immunofluorescence (mIF) validation testing was performed using antibody markers against proteins from significant LR pairs in the autocorrelation analysis. Analysis was performed in R using the spatialTIME and sfdep packages. **Results:** 15 IO naïve and 6 IO treated patients were evaluated. Compared to IO naive tumors, IO exposed tumors harbored more CD8+ T cells and neutrophils in the stromal FOVs ($p < 0.001$ for both), and more non-classical monocytes in the tumor FOV ($p = 0.002$). No univariate clustering changes were seen following IO. On spatial GSE, the endothelial to mesenchymal (EMT) pathway was enriched and two associated LR transcript pairs were significantly autocorrelated; *COL4A1* (gene for collagen IV) and *ITGAV* (gene for integrin αv-subunit) in the stroma ($p=0.024$). Expression of these genes were highest amongst fibroblasts and tumor cells. On mIF validation testing, integrin αv positive cells were more abundant in the IO exposed samples compared to IO naïve samples ($p=0.004$). Potential therapeutics that target this pathway have not yet been tested in ccRCC. **Conclusions:** We found a shift in the abundance of immune cells in the ccRCC TIME following IO treatment. Additionally, we saw significant autocorrelation of two transcripts associated with the EMT pathway, *ITGAV* and *COL4A1*, amongst fibroblasts and tumor cells. Increased abundance of integrin αv positive cells was confirmed on mIF validation testing. Research Sponsor: 2023 Moffitt Team Science-Miles for Moffitt Award and the Cancer Center Support Grant.

Therapeutic targeting of metabolic dysfunction by amino acid restriction and alternate day fasting in renal cell carcinoma models.

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Background: The use of immunotherapies and targeted drugs has significantly improved the clinical outcome of kidney cancer patients. However, the inevitable long-term toxicities and development of drug resistance remain a critical challenge for advanced clear cell and non-clear cell renal cell carcinoma (RCC) patients thus highlighting the need for novel therapeutic strategies. Large-scale metabolomic data have associated metabolic alterations with the pathogenesis and progression of RCC. As diet has been reported to potentially modulate tumor metabolism, dietary interventions represent an innovative strategy to treat metabolically dysregulated tumors. However, the biological basis of the success of dietary interventions is unknown, representing a critical roadblock in the use of dietary restrictions in patients. In this study, we investigated the role of amino acid (AA) restriction and alternate day fasting in metabolic and energy dynamics in preclinical models of clear cell and translocation RCC with the overall goal of expanding the understanding of metabolism's role in tumor progression and response to therapies. **Methods:** Seahorse, immunofluorescence, metabolomics, transcriptomics, genetic silencing, and pharmacological inhibition were utilized to assess the mechanisms underlying nutrient utilization and metabolic dysfunction in RCC. Patient-derived organoids and murine xenograft models were used to demonstrate the impact of dietary interventions and targeted therapies **Results:** Our data suggests that oxidative-phosphorylation is the main source of tumor-derived ATP in a subset of ccRCC cells but in all the tRCC cells assessed. AA restriction was associated with decreased oxidative phosphorylation in RCC models with baseline elevated mitochondrial function. Similarly, RCC models with a more glycolytic phenotype had decreased glycolytic function and reduced tumor burden in response to fasting conditions. The results from combining dietary interventions and targeted therapies are ongoing and will be presented. **Conclusions:** Our data suggests that oxidative-phosphorylation is the main source of tumor-derived ATP in a subset of ccRCC cells but in all the tRCC cells assessed. AA restriction was associated with decreased oxidative phosphorylation in RCC models with baseline elevated mitochondrial function. Similarly, RCC models with a more glycolytic phenotype had decreased glycolytic function and reduced tumor burden in response to fasting conditions. The results from combining dietary interventions and targeted therapies are ongoing and will be presented. Research Sponsor: None.

IL-6 and PIM1 expression in renal cell carcinoma.

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Background: Renal cell carcinoma (RCC) is a top ten malignancy in the U.S. Overexpression of the proviral integration site for moloney murine leukemia virus 1 (PIM1) kinase is associated with poor clinical outcomes in RCC patients. PIM1 is a constitutively active serine/threonine kinase promoting cell proliferation, apoptosis resistance, invasion, and migration. The mechanisms underlying PIM1 expression and its function in RCC are not fully delineated. IL-6 is a pleiotropic cytokine that activates the JAK/STAT signaling cascade. High serum IL-6 levels are associated with the poor prognosis of RCC patients and may contribute to RCC invasion and metastasis. STAT3/5 binds directly to the PIM1 promoter inducing PIM1 expression. An IL-6/STAT3/PIM1 axis exists in pancreatic and breast cancer. We previously reported that PIM1 is overexpressed in a panel of human RCC cell lines relative to renal proximal tubule epithelial cells. We also identified that RCC cells secrete IL-6. Our prior studies suggest that differential expression of PIM1 may be linked to autocrine IL-6 signaling. We thus hypothesize that an IL-6/JAK/STAT pathway regulates the expression of PIM1 in RCC. **Methods:** Retrospective review of DNA (592-gene or whole exome) and RNA (whole transcriptome) NGS data from real-world patient samples profiled at a CLIA-certified lab (Caris Life Sciences). Pathway analysis of differentially expressed genes was assessed using GSEA. Overall survival was calculated from insurance claims data. To understand how IL-6 signaling through the JAK/STAT pathway may regulate PIM1 expression in RCC cells, we examined whether IL-6 blockade using anti-IL-6 antibody or tocilizumab, would modulate PIM1 expression. Similarly, we assessed whether ruxolitinib, and LLL12, a STAT3 inhibitor could regulate PIM1 expression. **Results:** Transcriptome analyses show that *PIM1* expression is significantly increased in metastatic RCC relative to primary RCC. Survival curves demonstrate that *PIM1* overexpression is associated with decreased overall survival for RCC patients, independent of treatment received. *IL-6* expression was up to 6.5-fold higher in RCC patients with *PIM1* overexpression. In RCC cell lines, IL-6 blockade through either anti-IL-6 antibody or tocilizumab was sufficient to decrease PIM1 protein levels. Treatment with ruxolitinib leads to a dose and time-dependent decrease in PIM1 levels. Incubation with a STAT3 inhibitor also resulted in decreased PIM1 levels in RCC cells. **Conclusions:** These results suggest that differential expression of PIM1 in RCC may be linked to autocrine IL-6 signaling. Furthermore, poor survival in *PIM1*-overexpressing RCC patients is independent of treatment received, and therefore necessitates use of targeted therapies against this axis. Multiple FDA-approved agents are available that target this pathway. Further investigation is required to determine the efficacy of these agents in pre-clinical models and clinical trials. Research Sponsor: Kidney Cancer Association; National Institutes of Health; Brown University.

Spatial analysis of the tumor immune microenvironment in papillary renal cell carcinoma.

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Background: Spatial analysis of the tumor immune microenvironment (TIME) has yet to be explored in papillary renal cell carcinoma (pRCC). We utilized multiplex immunofluorescence (mIF) and spatial transcriptomics using spatial molecular imaging (SMI) to evaluate TIME properties in pRCC and contrasted these results with clear cell RCC (ccRCC). **Methods:** Tumor specimens were obtained from localized RCC tumors. mIF was performed on regions of interest (ROIs) selected from matched compartments from tumor, stroma, and tumor/stromal subsets of the interface. Two antibody panels were used for markers against T cells and B cells/ macrophages. Marker abundance and clustering differences between pRCC and ccRCC were evaluated across ROIs. Select markers were also explored across pathologic tumor staging in pRCC. The SMI platform used for validation utilized probes against 959 transcripts. Cells were phenotyped using InSituType using the Kidney Cell Atlas as a reference. Cell clustering was quantified by univariate and bivariate Ripley's K using the spatialTIME package in R. **Results:** mIF was performed on 1178 ROIs from 16 pRCC tumors and 70 ccRCC tumors. Compared to ccRCC, pRCC immune cell abundance was statistically lower amongst many T cell types and M2-like macrophages (Figure). M1-like macrophages were the only cell line seen at higher levels in interface compartments only. Increased macrophage clustering was observed in pRCC, including doubly positive M2-like macrophages in interface compartments (p=0.001 and 0.007). Higher abundance of CD8+ and FOXP3+ T cells in pRCC was associated with worse clinical stage, but no trend was seen with marker clustering. Four ROIs from 2 pRCC patients underwent SMI validation. On SMI of the tumor compartment, T cells were clustered with other T cells, B cells, and M1 macrophages. **Conclusions:** Compared to ccRCC, pRCC has fewer T cells and macrophages but more macrophage clustering. Using spatial transcriptomics, we found significant clustering between T cells, macrophages, and B cells in pRCC. Research Sponsor: 2023 Moffitt Team Science-Miles for Moffitt Award and the Cancer Center Support Grant.

Development of AB-2100, an autologous integrated circuit T (ICT) cell therapy targeting CA9 intended for the treatment of ccRCC.

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Background: Relapsed/refractory clear cell renal cell carcinoma (ccRCC) progressing after treatment with CPI and VEGF inhibitor remains an area of unmet need. We have developed AB-2100, an autologous, integrated circuit T (ICT) cell engineered to include three new features: a sequential "AND" logic gate that requires the IO presence of two antigens in the tumor microenvironment (TME) to trigger T cell killing; a shRNA-miR module to enhance resistance to suppressive TME via constitutive knockdown of FAS and TGFBR2; and a constitutive synthetic pathway activator (SPA) that increases STAT3 signaling for enhanced T cell cytotoxicity and expansion. **Methods:** A previous clinical study of CA9-specific CAR-T cell therapy was limited by on-target, off-tumor toxicity. To overcome this, AB-2100 includes a sequential "AND" logic gate that consists of a priming receptor (PrimeR) targeting PSMA, and a CA9-targeted CAR that is upregulated upon PrimeR engagement with PSMA expressed on the tumor neovasculature. A series of assays were performed to assess the specificity and potency of AB-2100: dual-antigen specificity of the logic gate was assessed in vitro and in vivo against CA9+ and PSMA+CA9+ tumors; vascular priming was modeled by co-culturing AB-2100 cells with PSMA-expressing endothelial cells and CA9+ tumor cells; a FAS cross-linking assay was conducted to assess the impact of FAS knockdown; the enhanced anti-tumor activity conferred by TGFBR2 shRNA and SPA modules were assessed in a 786-O xenograft model; and AB-2100 potency was measured in a subcutaneous renal A498 xenograft. **Results:** AB-2100 selectively kills tumors that express both CA9 and PSMA, and not tumors that express CA9 alone, as assessed by in vitro cytotoxicity against single or dual antigen expressing tumor cell lines and by a dual flank xenograft model. Furthermore, we confirmed that co-culture with PSMA-expressing endothelial cells was sufficient to upregulate CA9 CAR expression and enable tumor cell killing. Finally, AB-2100 containing both shRNA-miR and SPA modules demonstrated enhanced anti-tumor activity in xenograft RCC models. **Conclusions:** These data demonstrate that AB-2100 selectively targets tumors co-expressing PSMA and CA9, and can overcome multiple suppressive mechanisms in the TME. These results support the evaluation of AB-2100 in the clinic for the treatment of advanced or metastatic ccRCC. Research Sponsor: None.

Development and application of a precision cell-free DNA (cfDNA) minimal residual disease (MRD) test to enable optimized treatment selection in patients with genitourinary (GU) cancers.

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Background: By predicting those most likely to relapse, cfDNA-based MRD testing has potential clinical utility for adjuvant therapy decision making. Ideally, MRD would be paired with validated treatment selection testing to enable precision adjuvant therapy. Herein we report the development and application of a combined personalized MRD and treatment selection test to patients with GU cancer. **Methods:** Patients with clinically localized solid tumors undergoing definitive therapy were enrolled on a prospective trial (NCT05082701) where precision MRD testing was performed with standard imaging-based disease recurrence monitoring. StrataMRD was performed on 2 tubes of peripheral blood through assessment of 1-12 personalized tracer mutations identified via tumor tissue profiling by Strata Select, which also provides validated genomic profiling, and angiogenesis inhibitor and immunotherapy treatment response scores (Angio TRS and IRS, respectively). Patients with GU cancers and valid StrataMRD results from at least one time point were eligible for this analysis. Tissue biomarkers were compared vs. 792 patients with advanced GU cancers tested by the same tissue platform. **Results:** A total of 49 patients with GU cancers who underwent definitive surgery and had at least one valid cfDNA based MRD test were eligible (*Table). The median age was 64 years, 92% of patients were male, and 49% of patients were stage I or II (vs. 51% stage III); patients underwent initial MRD testing at a median of 11 weeks after surgery and a median of 3 MRD tests have been performed per patient. Overall, 4/49 (8.2%) patients had an initial MRD+ test, and 8/49 (16.3%) had a MRD+ test at any time point (4 converted from MRD- to MRD+). Patient level MRD sensitivity and specificity in the evaluable cohort (with concurrent or subsequent imaging) was 100% (6 MRD+ / 6 recurrences) and 100% (24 MRD- / 24 not recurred), respectively. In this cohort, 34% and 52% of the renal cell carcinoma (RCC) patients were IRS- and Angio TRS-High, respectively, compared to 29% and 50%, respectively, of patients with advanced RCC undergoing similar tissue testing. Similarly, 15%, and 14% of the patients with bladder or other GU cancers were IRS-High, respectively, compared to 27% and 13% of those with advanced bladder or other GU cancers, respectively. **Conclusions:** Personalized cfDNA based MRD testing had high sensitivity and specificity vs. routine imaging for detecting disease recurrence in patients with GU cancers. Combined tumor testing with validated angiogenesis inhibitor and immunotherapy treatment selection biomarkers enables individualized adjuvant therapy decision making. Clinical trial information: NCT05082701. Research Sponsor: Strata Oncology.

MRD by tumor type.

Tumor Type	n (%)	Initial MRD+	Any MRD+
Kidney	29 (59%)	0 (0%)	1 (3%)
Bladder	13 (27%)	3 (23%)	5 (38%)
Penile	4 (8%)	1 (25%)	2 (50%)
Testis	2 (4%)	0 (0%)	0 (0%)
Prostate	1 (2%)	0 (0%)	0 (0%)

Dynamic profiling in patients with metastatic clear cell renal cell carcinoma (mRCC) undergoing first-line treatment with cabozantinib: A sub-exploratory analysis from CABOPRE trial.

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Background: RCC is a heterogeneous disease with variable responses to systemic therapy. Tumor microenvironment (TME) and mi-RNA expression has been associated with prognosis in RCC, but its predictive role based on treatment remains uncertain. CABOPRE (EudraCT 2018-001201-93) was a multicentre, single-arm, phase II trial investigating perioperative cabozantinib (cabo) in mRCC patients with intermediate/poor IMDC prognosis. Primary objective was to assess overall response rate (ORR). Between December 2018 and December 2020, 15 patients were included and evaluable for ORR. Partial response was achieved in 4 patients (26%), stable disease in 10 patients (66%), and 1 progressed (6%). Cytoreductive nephrectomy was performed in 11 patients (73%). Updated overall survival at 2 years was 60%. In this work, we analysed the change expression differences of selective mi-RNAs in plasma and TME previous before and after 12 first weeks of perioperatory cabo. **Methods:** Plasma samples were used for RNA purification using Plasma miRNEasy System from Thermofisher Scientific. Nanostring platform, Human v3 miRNA Assay cartridge from nanostring and by bioinformatics' analyses using Nsolver software for miRNA discovery and using TaqMan Advance miRNA System (Applied Biosystems) for validation. TME (tumor and stroma cell) was analysed with Tissue microarray using Digital Spatial Profiler (DSP) on a subset of 12 paired samples (treatment-naïve/ 12 weeks post-cabo). We used GeoMx DSP platform (Nanostring) and GeoMx RNA immune pathways Panel .Data obtained was analysed using a GeoMx Analysis Suite 2.3. **Results:** Differentially Expressed miRNAs: We identified 9 miRNAs with significant differential expression when comparing samples before and after treatment (6 downregulated and 3 upregulated). Efficacy Association: In our discovery cohort, 6 miRNAs were differentially expressed between responder cabo patients. These miRNAs were further validated. miR-150-5p (Up), miR-590-5p (Up), and miR-31-5p (Down) displayed particularly promising performance in responder patients. Microenviromental Dynamics: DSP analysis revealed differential expression profiles related to immune and angiogenesis processes depending on cabo response. **Conclusions:** After 2 years of follow-up, our data demonstrates the feasibility and safety of perioperative cabo in mRCC. Molecular analysis reveals 3 specific mi-RNAS whose expression patterns correlated with cabo responses, potentially serving as predictive biomarkers. Additionally, DSP analysis underscores the substantial microenvironmental heterogeneity within kidney cancer, highlighting its complex nature. These findings collectively contribute to our understanding of mRCC management, offering promising avenues for personalized treatment approaches. Research Sponsor: None.

Oncogenic fusions in renal cell carcinoma.

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Background: Detecting actionable or diagnostic fusions in solid tumors may significantly alter clinical decisions, including therapy selection. Some fusions have matched drugs approved for use in the patient's cancer, or in another cancer. Others have published evidence of benefit with particular drugs but are not included in guidelines, and some may represent an inclusion criterion for clinical trials. While diagnostic fusions may not have associated therapies, they are cancer-defining and can lead to re-classification of tumors. Here we describe actionable and diagnostic fusions we have observed in renal cell carcinoma (RCC). **Methods:** Tumor samples from patients diagnosed with RCC were analyzed using the OncoExTra assay, which identifies somatic mutations and gene fusions through tumor-normal, whole-exome DNA and whole-transcriptome RNA sequencing. All actionable fusions, defined as those with associated FDA-approved targeted therapies in any cancer type, those that made patients eligible for an active clinical trial, or those with evidence in guidelines or the literature for possible matched therapies in any cancer, are detectable using this assay. We examined samples from patients with RCC who had the OncoExtra assay performed between May 2018 and Mar 2023 and identified both actionable and diagnostic fusions. **Results:** Among 389 tumor samples from patients diagnosed with RCC, there were 11 (2.8%) actionable and 1 (0.3%) diagnostic fusion identified. The actionable fusions included 6 (1.5%) *TFE3*, 1 (0.3%) *ALK*, 1 (0.3%) *EGFR*, 1 (0.3%) *ERBB4*, 1 (0.3%) *YAP* and 1 (0.3%) *FGFR2*, and the diagnostic fusion was *NAB2/STAT6*. The 6 *TFE3* oncogene fusions involved 4 different partner genes (*PRCC* was the partner in 3 fusions). *ALK*, *EGFR*, *ERBB* and *FGFR* fusions are found across a variety of cancers, and all have matched FDA-approved drug therapies in at least one cancer type. For example, *ALK* fusions, including the observed *EML4/ALK* fusion, which is common in non-small cell lung cancer, have several matched ALK-inhibitor therapies. *TFE3* (transcription factor binding to *IGHM* enhancer 3) gene fusions are a diagnostic genomic alteration in microphthalmia-associated transcription factor (MiT) translocation RCC, which is a rare but aggressive subtype of RCC. While *TFE3* fusions do not have FDA-approved matched therapies in any cancer, they are known to result in PIK3K/AKT/mTOR and MET activation, suggesting inhibitors of these pathways may be considered in these patients. The *NAB2/STAT6* diagnostic fusion is characteristic of solitary fibrous tumors, suggesting that the patient likely had this kind of tumor. **Conclusions:** Whole-transcriptome sequencing allowed the identification of actionable fusions with the potential to affect clinical decisions regarding therapy in 2.8% of RCC patient tumors. In addition, one patient was found to have a fusion that is characteristic of a solitary fibrous tumor, demonstrating the power of genomic profiling to aid diagnosis. Research Sponsor: Exact Sciences.

Cellular and molecular determinants of limited anti-tumor immunity in chromophobe renal carcinoma (ChRCC).

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Background: ChRCC is a rare form of kidney cancer with a poor prognosis in the metastatic setting, in part due to very limited responses to immune checkpoint inhibitors (ICIs), as compared to clear cell RCC (ccRCC). The mechanisms underlying the poor response of ChRCC to ICIs remain largely uncharacterized. We therefore investigated at the single-cell resolution the cellular and molecular determinants of anti-tumor immunity in ChRCC. **Methods:** ChRCC samples with matched normal kidney specimens were evaluated using single-cell RNA (scRNA-seq) and single-cell T-cell receptor (scTCR-seq) sequencing. Similar data (scRNA-seq and scTCR-seq) was obtained for ccRCC samples (Braun DA. et al., 2021). T cell clonotypes were inferred and classified into their degree of expansion (poorly, moderately and highly expanded). Diversity metrics (normalized Shannon's entropy) were calculated. Using a previously described methodology (Young M.D. et al., 2018), the cell of origin (COi) of ChRCC was inferred from scRNA-seq data of normal kidney samples, followed by differential gene expression (DGE) and pathway analysis (DPA) between the putative COi and ChRCC cells to identify potential mediators of diminished immune responses. Immunohistochemistry (IHC) of ChRCC and ccRCC samples was used to assess CD8+ and PD-1+ immune cell populations. **Results:** Analysis of the scTCR-seq data identified a higher proportion of poorly expanded clonotypes in ChRCC as compared to ccRCC ($p=0.05$), along with a lower proportion of highly expanded clonotypes ($p=0.07$). Normalized (Shannon's) entropy was found to be higher in ChRCC versus ccRCC ($p<0.05$). Analysis of annotated scRNA-seq data identified a lower proportion of CD8+ and CD4+ T-cells among immune cells in ChRCC vs. ccRCC (44.6 vs. 9.6% and 12.3 vs. 3.2%, respectively). DGE between ChRCC and its putative COi (alpha-intercalated cell) showed a lower expression of HLA class I genes in ChRCC ($p<0.05$). DPA showed a marked downregulation of antigen presentation and protein processing pathways in ChRCC ($p<0.05$). IHC analysis showed a markedly low infiltration of CD8+ and PD-1+ immune populations in ChRCC, as compared to ccRCC. **Conclusions:** ChRCC cells have marked downregulation of HLA class I genes and antigen processing pathways related to their COi. Additionally, ChRCC tumors have poor infiltration of T-cells, which show a low degree of clonal expansion. These mechanisms may help to explain the limited anti-tumor immunity and ultimately, the poor response to ICIs seen among patients with ChRCC. Research Sponsor: None.

Circulating tumor DNA in the surveillance of patients with oligometastatic renal cell carcinoma treated with stereotactic ablative radiation.

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Background: Oligometastatic renal cell carcinoma (oRCC) patients receiving stereotactic ablative radiation (SAbR) are in need of effective biomarkers beyond imaging to identify those most likely to fail rapidly and therefore would benefit from systemic therapy. Detection of minimal residual disease (MRD) using circulating tumor (ctDNA) is a promising tool to guide decisions in the management of solid tumors. Herein, we investigate the utility of longitudinal ctDNA monitoring to identify high-risk patients. **Methods:** Patients with oRCC on surveillance after previous SAbR were enrolled in a prospective registry study and longitudinal quantitative ctDNA testing were performed using a tumor-informed commercial ctDNA assay (Signatera). Disease progression was assessed using standard-of-care clinical / radiographic exams and compared to the ctDNA levels that were obtained within the median 32.5 days (IQR 18.5-59) of radiographic exams. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated. **Results:** The cohort encompassed 17 patients with oRCC (16/17 metachronous >1 year after nephrectomy) who underwent 42 ctDNA measurements between September 2022 and August 2023 with a median of 3 (range 2-6) ctDNA time points per patient. Median follow up after start of ctDNA monitoring was 10.3 months. Seven patients developed radiographic progression at new sites including 6 who received additional SAbR and one who started systemic therapy with interleukin-2. At most recent follow up, 13/17 patients had no radiographic evidence of disease. Out of the 42 ctDNA time points, 11 had detectable ctDNA and 17 had clinical/radiographically detectable metastasis. The sensitivity, specificity, PPV, and NPV were calculated to be 64.7%, 100.0%, 100.0%, and 80.6% respectively. Out of 6 patients who underwent had ctDNA testing on SAbR, 5 had undetectable levels and the only patient that had detectable ctDNA levels showed a robust decline in ctDNA levels post SAbR. In the interleukin-2 treated patient, detectable levels of ctDNA became undetectable post treatment which also correlated with a complete radiographic response. **Conclusions:** This study highlights the utility of ctDNA as a prognostic biomarker in the surveillance of oRCC patients who were previously treated with SAbR. A high SPE and PPV suggests that rising ctDNA levels may harbinger radiographic progression requiring systemic therapy intervention. A larger study is warranted to further validate the findings of this study and to optimally integrate ctDNA kinetics to direct subsequent treatment choices for the oRCC patients. Research Sponsor: None.

Initial screening efforts for the OPTIC RCC trial.

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Background: OPTIC RCC (NCT05361720) uses RNA sequencing (seq) of tumor tissue to assign therapy in front-line metastatic clear cell renal cell carcinoma (mccRCC) patients. The operational characteristics of tumor tissue procurement, sequencing, cluster assignment and start of therapy are presented. **Methods:** Patients diagnosed with mccRCC without prior systemic therapy are eligible for enrollment. RNAseq of primary and/or metastatic tumor tissue is performed by Tempus (Chicago, IL) and data analyzed via an automated cloud-based informatics tool. **Results:** Twenty-three patients have been screened. Twelve patients (52%) had both primary and metastatic tumors submitted for RNAseq, 4 (17%) had primary only, and 7 (30%) had only metastatic tumor available. Three patients (13%) failed screening because no tumors passed RNAseq quality control (QC). When possible, patients were assigned to clusters based on data from metastatic tumor (15/20, 75%). However, 5/20 (25%) of patients were assigned to clusters based on primary tumor sequencing data because the metastatic tumor was not available or failed QC. Eight patients (40%) were assigned to cluster 1/2, 7 (35%) were assigned to cluster 4/5, and 5 (25%) were assigned to cluster 3/6/7. Primary tumors were more likely to be assigned to cluster 1/2 (12/14, 86%) than metastatic tumors (5/10, 50%) ($p<0.01$, Fisher's exact test). Of the 9 pts with both primary and metastatic RNAseq, 5 patients had discordant tumor clusters (primary cluster 1/2 and metastatic cluster 4/5 or 3/6/7); 4 patients with concordant tumor clusters (both cluster 1/2). The mean time from consent to cluster assignment was 32 days (SD +/- 18), though this improved over time. Ten patients have started therapy. **Conclusions:** Patients with mccRCC can be enrolled on clinical trials that utilize tissue-based RNA sequencing biomarkers. Accrual and analysis correlating cluster assignment with treatment response are ongoing. This trial is funded by the DOD Kidney Cancer Research Program (W81XWH-22-1-1033). Clinical trial information: NCT05361720. Research Sponsor: Department of Defense.

The distribution of mutations across tumor size in ccRCC and their prognostic importance in small masses.

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Background: Substantial efforts have been made to delineate mutational pathways to progression in ccRCC and the prognostic importance of key mutations, yet the distribution of these mutations across tumor size remains unknown. We hypothesized that *VHL* and PBRM, as more truncal mutations, would be roughly equally prevalent across tumor sizes, while mutations associated with aggressive disease - *SETD2*, *BAP1*, and *CDKN2a* copy-number loss - would be predominantly observed in larger tumors. We further hypothesized that *SETD2*, *BAP1*, and *CDKN2a* copy-number loss mutations, when present in smaller (≤7 cm) ccRCC tumors, would portend worse prognosis. **Methods:** We assessed a combined cohort of 333 ccRCC tumors from TCGA-KIRC and TRACERx Renal for the distribution of mutations across tumor size. Logistic regression was used to model the presence of each mutation against tumor size. We assessed a subset of 194 tumors ≤7cm for associations of key mutations with clinical outcomes while controlling for size. In small masses, logistic regression was used to model the presence of metastatic disease and invasive disease, and Cox proportional hazards was used to model overall survival, against *SETD2*, *BAP1*, *CDKN2a* copy-number loss, and tumor size. **Results:** On logistic regression an increase in one centimeter of tumor size was associated with *SETD2*, *BAP1*, and *CDKN2a* loss at odds ratios of 1.16, 1.11, 1.19 ($p<0.05$); whereas no significant association was observed between tumor size and both *VHL* and *PBRM1* (p=0.18, p=0.65). Among 194 tumors ≤7 cm, *SETD2* and *CDKN2a* loss were associated with metastatic disease at odds ratios of 3.86 and 3.84 ($p<0.05$); *CDKN2a* loss was associated with worse overall survival at hazard ratio 2.19 ($p<0.05$), all while controlling for tumor size. **Conclusions:** *SETD2* mutations, *BAP1* mutations, and *CDKN2a* copy-number loss are rare in small ccRCC and are increasingly common in larger tumors, whereas *VHL* and *PBRM1* are fairly evenly distributed across tumor sizes. In tumors≤7 cm,*SETD2* mutation and *CDKN2a* loss were associated with metastatic disease and *CDKN2a* loss was associated with worse overall survival. SETD2 mutations and CDKN2a loss may help risk stratify ccRCC in biopsied and resected tumors. Research Sponsor: None.

Percentage of ccRCC tumors with key mutations at different tumor sizes.

Cohort:	TCGA (n=227)			TRACERx (n=106)			Combined (n=333)		
Tumor Size	≤4 cm	>4-≤7 cm	> 7 cm	≤4 cm	>4-≤7 cm	> 7 cm	≤4 cm	>4-≤7 cm	> 7 cm
N	53	95	79	22	24	60	75	119	139
VHL - % (n)	58% (31)	61% (58)	48% (38)	73% (16)	88% (21)	67% (40)	63% (47)	66% (79)	56% (78)
PBRM1 – % (n)	28% (15)	37% (35)	32% (25)	50% (11)	50% (12)	50% (30)	35% (26)	39% (47)	40% (55)
SETD2* – % (n)	6% (3)	16% (15)	11% (9)	14% (3)	21% (5)	37% (22)	8% (6)	17% (20)	22% (31)
BAP1* – % (n)	6% (3)	7% (7)	15% (12)	5% (1)	21% (5)	27% (16)	5% (4)	10% (12)	20% (28)
CDKN2a Loss* – % (n)	8% (4)	17% (16)	18% (14)	32% (7)	38% (9)	75% (45)	15% (11)	21% (25)	42% (59)

*$p < 0.05$ for size positively associated with presence of mutation on logistic regression.

Association of transitional gradient from clear cell to sarcomatoid renal cell carcinoma with macrophage/tumor cell crosstalk.

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Background: Sarcomatoid de-differentiation in renal cell carcinoma (sRCC) leads to aggressive tumors that are uniquely responsive to adjuvant immunotherapy. sRCC is thought to arise by an epithelial to mesenchymal transition (EMT) of the parental tumor, most commonly clear cell RCC (ccRCC). However, factors that drive sRCC are unknown and no biomarkers exist to predict the transition. Furthermore, the immune microenvironment in sRCC is not well understood and may provide additional therapeutic targets. Here, we use spatial biology and in vitro studies to explore EMT/immune cell crosstalk in sRCC. **Methods:** Single cell spatial transcriptomics was performed on a human sRCC specimen via the NanoString CosMx platform and semi-supervised clustering referenced to scRNAseq data was used to identify a spatial transition from ccRCC to sRCC. Segmented bulk spatial transcriptomics was performed on 4 sRCC specimens, mapping the CosMx cell signatures. Multiplex immunofluorescent staining (mIF) was performed on 29 sRCC specimens. In vitro work was performed using 3 RCC cell lines and THP-1 derived macrophages to explore mechanisms between cell types and genes of interest. **Results:** Single cell spatial transcriptomic data revealed a ccRCC population, 2 sRCC cell types, and a novel transitional cell type along the EMT continuum and spatially between ccRCC and sRCC. These signatures were mapped onto segmented bulk spatial transcriptomic data confirming the same spatial transition pattern in 4 sRCC specimens. Importantly, matched H&E shows the transitional cell type present in areas histologically defined as ccRCC, demonstrating molecular evidence of transition towards sRCC prior to histologic changes. Cell to cell distance analysis and mIF in 29 sRCC specimens revealed a strong correlation of M2 macrophages with the transition and sRCC cell types. CCL20, a factor known to assist in macrophage recruitment was upregulated on transition cells and in vitro led to polarization to an M2-like phenotype. FZD4 was the highest fold changed gene lost from the ccRCC to transitional cells and knockdown of FZD4 in vitro led to EMT in RCC cells. In vitro culture of RCC cells with M2 macrophages led to CCL20 upregulation and loss of FZD4. The TCGA KIRC database was used to validate the ability to identify the transition signature in ccRCC and its association with poorer disease specific survival. **Conclusions:** We report the first detection of a transitional cell type along the de-differentiation pathway from ccRCC to sRCC. This cell type is detectable in areas histologically defined as ccRCC, demonstrating strong potential as a transcriptional biomarker to inform adjuvant immunotherapy. We show that CCL20 on tumor cells leads to macrophage recruitment and polarization, resulting in FZD4 loss and CCL20 upregulation, which induce EMT and propagates a vicious cycle of EMT/macrophage crosstalk in sRCC. Research Sponsor: None.

Diversity among editorial boards of genitourinary oncology journals.

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Background: Several studies have evaluated the ethnic and gender diversity among editorial boards of academic journals in science and medicine, and revealed disparities among representation of historically underrepresented groups. However, the diversity among editorial boards in the field of genitourinary oncology remains unclear. **Methods:** Using the master journal list from Clarivate, we identified academic journals with a dedicated or primary focus in genitourinary cancers. We then identified the list of editorial board members on each journal's website. We evaluated economic diversity based off each editor's country of origin, and classified countries as high income based off World Bank listing for the 2024 fiscal year. We confirmed gender from each editor's self-reported gender on his or her academic profile. **Results:** We identified 7 journals with a focus in genitourinary cancers. Among these journals, a total of 485 editor positions were identified, with 397 men (81.86%) and 80 women (16.49%). The gender of 8 individuals (1.65%) could not be confirmed. 28 editors (5.77%) were from countries not identified as high-income countries per World Bank criteria. **Conclusions:** There are disparities in country of origin among editors of genitourinary oncology journals, with a small proportion of editors originating from countries classified as middle- or low-income. Research Sponsor: None.

Gender and country of origin representation among editorial boards of genitourinary oncology journals.

Total Editor Positions	Male editors	Female editors	Unknown gender	Originating from high-income country	Originating from middle- or low-Income country
485	397	80	8	457 (United States, Canada, United Kingdom, Italy, Spain, Denmark, Israel, Oman, Singapore, South Korea, Germany, Netherlands, Japan, Australia, Sweden, Switzerland, Chile, Hong Kong, Belgium, Greece, Austria, Slovakia)	28 (China, India, Turkey, Ghana, Russia, Pakistan, Brazil, Bulgaria, Serbia, Morocco)

Network meta-analysis (NMA) to assess comparative efficacy of lenvatinib plus pembrolizumab compared with other first-line treatments for management of advanced renal cell carcinoma (aRCC).

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Background: The CLEAR trial showed statistically significant improvements in overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and complete response (CR) in subjects treated with lenvatinib plus pembrolizumab (L+P) vs. sunitinib. We conducted an indirect treatment comparison to investigate the comparative efficacy of L+P vs. other first-line (1L) treatments in aRCC. **Methods:** A systematic literature review identified 24 randomized controlled trials evaluating 22 interventions in 1L treatments for aRCC. Bayesian NMAs were conducted to evaluate comparative efficacy outcomes for intention to treat (ITT) and the intermediate-/poor risk population, based on the CLEAR trial final data cutoff (31st Jul 2022). **Results:** L+P had a >70% probability of providing greater OS benefit than 8 of the 12 comparators; the benefit was statistically significant against 2 treatments (interferon α-2a: hazard ratio [HR] 0.65; 95% credible interval [CrI] 0.48–0.88 and sunitinib: 0.79; 0.63–0.99). For PFS (assessed under United States Food and Drug Administration censoring rules), L+P showed a >75% probability of providing greater benefit over all available comparators, including numerical, but not statistically significant advantage over immunoncology (IO) therapies nivolumab+ipilimumab (N+I), avelumab+axitinib (A+A), nivolumab+cabozantinib (N+C) and pembrolizumab + axitinib (P+A). The benefit was significant for 13 out of 18 comparators—relative efficacy estimates ranged from HR=0.18 (95% CrI 0.08–0.40) for placebo to HR=0.51 (95% CrI 0.29–0.89) for atezolizumab + bevacizumab. For response outcomes, L+P demonstrated >90% probability of greater ORR compared with all available comparators; the benefit was statistically significant against 9 of 12 comparators—the relative odds ratio ranged from 1.85 (95% CrI 1.22–2.81) for P+A to 38.47 (95% CrI 11.94–180.19) for placebo. L+P showed statistically significant ORR benefit against IO therapies N+I and P+A, and numerical, but not statistically significant advantage over A+A and N+C. Greater than 80% probability of CR benefit was observed across 13 of 14 comparators, with statistical significance achieved against 8 comparators. L+P showed numerical, but not statistically significant advantage over all IO comparators. Comparison of the ITT population and intermediate-/poor subgroup results indicated that the benefit of L+P on PFS against comparators seen in the ITT population was generally maintained in the subgroup for those comparisons that were still feasible. **Conclusions:** The NMA results show that combination therapy with L+P provides a comparable OS, and a trend of improvement in PFS and response outcomes, compared with most current global standard of care IO therapies for treatment-naïve patients with aRCC. Research Sponsor: Eisai Inc.

Using automated machine learning to detect kidney anomalies.

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Background: Artificial Intelligence (AI) in Urology has been used for many conditions including benign prostatic hyperplasia (BPH), urological oncology, and kidney transplant. Many computer models use algorithms that may be intricate for urologists to implement, but automated machine learning (AML) can be used to create simple models. Here we expand the use of AI and AML in image detection of kidney tumors, stones, and unremarkable kidney from computed tomography (CT) using Google Vertex AI, a machine learning platform that allows for the building, training, and deployment of models. **Methods:** Google Vertex AI machine learning system was trained to perform image detection. CT Kidney images were taken from publicly available data from Kaggle, an online database and machine learning platform. Images are from multiple hospitals in Dhaka, Bangladesh. 300 CT Kidney Images were uploaded on Google Vertex AI: 100 tumors, 100 stone, and 100 normal. 240 images were used to train the model, 30 for validation, and a final 30 images for assessing the accuracy of predictions after the training phase. To comprehensively evaluate our model, CT kidney images from the Cedars Sinai Medical Center were employed for further testing. All training images lacked annotations and were solely classified as normal, stone, or tumor. **Results:** True positivity rate for image detection during model training was 100% for tumors, stones, and normal CTs. We further tested accuracy using Cedars Sinai patient images, using 10 tumors, 10 stones, and 5 normal. The accuracy of the AI prediction was 80%, 70%, and 100%, respectively. **Conclusions:** Artificial Intelligence can be useful in interpreting urological imaging even in a minimally trained system. A model such as ours may allow for rapid identification and labeling of renal masses, kidney stones, and normal studies with moderate fidelity. Further training of this model may increase accuracy. Research Sponsor: None.

Safety and efficacy of surgery in renal cell carcinoma with supradiaphragmatic tumor thrombus involving cardiac procedures.

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Background: Invasion of the IVC is a unique feature of RCC. Tumor extension into the supradiaphragmatic IVC carries high morbidity and mortality attributable to surgical complexity. It is unclear whether safety and efficacy have been shown to warrant cytoreductive surgery for metastatic RCC with concomitant thrombus. We present outcomes of cytoreductive and non-cytoreductive radical nephrectomy (RN) with supradiaphragmatic tumor thrombectomy (TT) involving cardiac surgery. **Methods:** We reviewed our nephrectomy database for patients with RCC and supradiaphragmatic tumor thrombus. RN with TT was performed by a single team from urology, surgical oncology and cardiothoracic surgery. Rank Sum for numerical and chi-square for categorical variables were used to test for differences between cytoreductive and non-cytoreductive RN. Kaplan Meier curves estimated cancer-specific survival (CSS) and overall survival (OS). **Results:** From 2006-2023, 43 patients underwent RN with supradiaphragmatic TT. The tableindicates notable clinical and surgical features. No patient participated in a related clinical trial perioperatively. No case required circulatory arrest. One patient required temporary dialysis and later passed from multi-organ failure. 5-year CSS was 12% vs. 78% (p=0.007) and OS was 11% vs. 53% (p=0.044) for cytoreductive and non-cytoreductive surgery respectively. **Conclusions:** RN with supradiaphragmatic TT is safe with durable treatment response in patients with non-mRCC. Although safety of cytoreductive RN is comparable, further investigation into the role of neoadjuvant therapy is recommended. Research Sponsor: None.

Clinical and surgical features of patients undergoing RN with supradiaphragmatic TT.

Variable	Non-cytoreductive (n=24; %)	Cytoreductive (n=19; %)	p-value
Age* (years)	67 (63-72)	61 (56-66)	**0.048**
BMI* (kg/m^2)	28.1 (22.7-32.9)	25.8 (23.5-31.2)	0.493
Male	15 (62.5)	9 (47.4)	0.321
Race			
White	16 (66.7)	15 (79)	0.273
Black	7 (29.2)	2 (10.5)	
Other	1 (4.2)	2 (10.5)	
HTN	21 (87.5)	11 (57.9)	**0.027**
DM	14 (58.3)	3 (15.8)	**0.005**
ECOG PS 1+	4 (16.7)	4 (21)	0.524
Neoadjuvant	2 (8.3)	1 (5.3)	0.695
Tumor size* (cm)	9.7 (6.9-12.9)	9.7 (6.7-13.0)	0.951
Operative Time* (min)	433 (309-517)	426 (361-590)	0.388
Level of Proximal IVC Clamp			
Bypass	13 (54.2)	8 (42.1)	0.719
Intrapericardial	4 (16.7)	5 (20.9)	
Extrapericardial	7 (29.1)	6 (37)	
IVC Clamp Time* (min)	33 (20-35)	28 (26-40)	0.714
Cardiac Bypass Time* (min)	80 (57-93)	61 (34-92)	0.515
Renal Vein Clamp Time* (min)	26 (20-34)	34 (19-45)	0.706
Porta Hepatis Clamp Time* (min)	13 (7-31)	6 (5-30)	0.644
Vasopressor Drip			
Intraop only	11 (45.8)	8 (47.1)	0.469
Intraop to PACU/ICU	13 (54.2)	8 (47.1)	
EBL* (mL)	1150 (700-2500)	2500 (1000-5950)	0.066
Units pRBC*	6 (3-8)	6 (4-11)	0.407
LOS* (days)	10 (7-14)	14 (8-22)	0.142
ICU LOS* (days)	3 (0-4)	4 (2-8)	0.157
Clavien 3+ Complications	10 (41.7)	11 (57.9)	0.227
Readmission	3 (13.6)	6 (33.3)	0.138

*(median, IQR).

TPS485 Trials in Progress Poster Session

International multicenter real-world registry for patients with metastatic renal cell carcinoma: Meet-URO 33 study (REGAL study).

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Background: Nowadays, different systemic treatments are available for the first-line setting of metastatic renal cell carcinoma (mRCC). Immuno-combinations are the standard first-line therapy in all mRCC patients regardless the IMDC risk category, even though TKI monotherapy is still a therapeutic option in selected patients. However, comparisons between the different first-line treatment strategies are lacking and few real-world data are available in this setting. For these reasons, the regimen choice represents an important issue in clinical practice and the optimal treatment sequence remains unclear. **Methods:** The Meet-URO 33 (REGAL) study is a multicentric prospective observational study enrolling mRCC patients treated with first-line systemic therapy according to clinical practice in a real-world setting. A retrospective cohort of mRCC patients who received first-line systemic therapy from 1st of January 2021 will also be included. The study includes 84 Italian centers and a study amendment will be submitted to include about 10 European centers. The Meet-URO 33 study aims to provide a large-scale real-world database on mRCC patients and the primary objective is to identify potential prognostic and predictive factors that could help guide the treatment choice. Secondary objectives include the comparison between treatment strategies in first-line and subsequent lines according to response and survival outcomes and toxicity profile; the assessment of the correlation between the clinical and tumor characteristics and the choice of the first line of treatment; the assessment of the prognostic performance of the Meet-URO score compared with the IMDC score. Moreover, given the registry nature of the study, further studies will be planned subsequently, both on the entire cohort (e.g. genomic analyses and artificial intelligence) and particular subgroups (e.g. poor-risk category, elderly, non-clear cell histology) to answer as many clinical questions as possible. The descriptive statistics will be used to summarize the clinical characteristics of patients and the distribution of prognostic factors. All time-to-event endpoints (PFS, OS) will be analyzed using the Kaplan-Meier method, the restricted mean survival time (RMST) and the Cox proportional hazard regression model. The binary endpoints (ORR, DCR) will be analyzed through relative frequencies and logistic regression. For all the comparisons between treatments, all causal inference techniques such as propensity scores and marginal structural models will be used. All the steps for a correct target trial emulation strategy will be followed to avoid potential biases deriving from the observational nature of the study. In particular, in comparing the different treatments, the principles of emulating a clinical trial will be applied, developing appropriate ad hoc protocols for each planned comparison. Clinical trial information: CESC IOV 2023-78. Research Sponsor: None.

A phase I/II, open label, single arm study on safety, tolerability and anti-tumour effiacy of orellanine treatment in patients with metastatic clear-cell or papillary renal cell carcinoma.

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Background: Poisoning by the mushroom "deadly webcap"(Cortinarius sp.) causes irreversible kidney damage but there are no known effects on other organs. The fungal toxin, orellanine, selectively targets proximal tubular cells in rats and in humans by disturbing the cell metabolism causing decreased protein synthesis and apoptosis. Clear cell and papillary renal cell carcinoma (RCC) originate from proximal tubule cells. Orellanine induced concentration-dependent decline in viability in RCC cell lines and in primary cultures from human clear cell and papillary RCC. Orellanine induced apoptosis and tumour shrinkage in RCC(SKRC-17) transplanted to rats on peritoneal dialysis and the tumours become necrotic with almost no viable tissue. Based on these data a drug has been developed based on chemically synthesized orellanine (www.oncorena.com). **Methods:** The primary objectives of this study are to evaluate the safety and tolerability and to determine the maximum tolerable dose (MTD) of orellanine in patients with metastatic clear cell or papillary RCC and end stage renal disease who are on chronic haemodialysis and who have failed standard of care treatment. The secondary objectives are to study the pharmacokinetic (PK)profile of orellanine and to assess the efficacy of orellanine in treating these patients with respect to objective response (OR). Exploratory objectives are to access progression free and overall survival (PFS and OS) and to conduct analysis of circulating tumour specific DNA in the blood. Serum will be collected for unspecific future research which may include sequencing or genomic analyses. Orellanine will be given intravenously once monthly. A total of 6 to 20 patients will be enrolled in a dose escalation phase to determine MTD or a dose causing complete response (CR). An independent Data Review Committee (DRC) will access cumulative data and provide recommendations and decisions for every change in dose level. Once MTD has been determined up to 20 patients will be treated in a dose expansion phase to better characterize safety, tolerability and primary efficacy. CT/MRI will occur every 4 weeks (Q4W) during dose escalation phase and Q8W during the dose expansion phase. Enrollment has started and since the occurrence of end stage renal disease in patients with metastatic RCC is uncommon, patients in this first in man study are recruited both from western Europe and north America. The study is performed in the Centre for Clinical Cancer Studies (CKC) at Karolinska University Hospital, Stockholm, Sweden Reference: Lisa Buvall et. al. Orellanine specifically targets renal cell carcinoma.Oncotarget. 2017; 8:91085-91098. https://doi.org/10.18632/oncotarget.19555. Clinical trial information: NCT05287945. Research Sponsor: None.

TPS487 Trials in Progress Poster Session

Strategic treatment pause of first-line immune checkpoint inhibitor + VEGFR-tyrosine kinase inhibitor in patients with good or intermediate risk metastatic renal cell carcinoma (mRCC) in response at 1 year of treatment (SPICI-GETUG R05): A non-inferiority randomized clinical trial.

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Background: Treatment of mRCC consists of combination of either Immune Checkpoint Inhibitor (ICI)-Tyrosine Kinase Inhibitor (TKI) for all IMDC prognosis group, or ICI-ICI for intermediate and unfavorable IMDC groups. Treatments are maintained until disease progression or toxicity for a total duration of 2 years for ICI, in routine. Acceptability and feasibility of treatment pause of the TKI, with no detrimental effect on efficacy were reported in the prospective STAR trial. The good-risk population is characterized by prolonged survival, close to that reported in the intermediate risk population group with a single adverse prognostic factor. Therefore, a pause of ICI-TKI could improve quality of life, safety, and total cost of care without detrimental impact on oncologic outcomes. **Methods:** This non-inferiority, randomized, open-label, multicenter, parallel-group trial (NCT05219318) aims to compare treatment pause versus treatment continuation in good or intermediate risk mRCC patients with only one prognostic factor and a confirmed objective response (complete or partial) at 12 months of treatment with ICI-TKI. 372 patients (186 in France) will be recruited in tertiary hospitals and randomized in a 1:1 ratio with stratification by center, prognostic group (good/intermediate) and response (complete/partial). The primary objective is to test the non-inferiority of treatment pause versus continuation, with the estimation of the difference in 12-month progression rate after randomization, and its one-sided 97.5% confidence interval. The non-inferiority margin is set at 15%. An interim safety data monitoring at 6 months after randomization of the first third of participants (i.e. 60 per arm) will check progression rate after treatment pause. A formal interim futility analysis will be performed when 50% of the study sample reaches the primary outcome time point, using a Bayesian predictive power stopping rule and a futility threshold set at 20%. Secondary objectives are overall safety and tolerability, health-related quality of life, anxiety and depression, quality-adjusted survival, 2-year overall and progression-free survival. Others objectives include progression patterns (site, known lesions, or/and new lesions), subsequent treatment (type, efficacy), in the experimental arm. In France, healthcare resource utilization and costs at 12 months will be compared. The first participant was randomized in January 2023. 27 centers in France were selected and are gradually/progressively opening. The opening of European centers is being planned. Health Ministry and National Cancer Institute Funds. Clinical trial information: NCT05219318. Research Sponsor: Hospital Program of Clinical Research.

TPS488 Trials in Progress Poster Session

Neoadjuvant pembrolizumab (PEMBRO) and axitinib (AXI) in renal cell carcinoma with associated inferior vena cava tumor thrombus (NEOPAX).

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Background: Renal cell carcinoma (RCC) has a biologic propensity for vascular invasion leading to a venous tumor thrombus (VTT) in the renal vein or inferior vena cava (IVC) in up to 25% of cases. RCC with VTT is a poor prognostic factor for cancer-related mortality. Additionally, depending on the tumor burden and extent of the tumor thrombus (TT), patients can become symptomatic from the VTT, affecting patients' quality of life. The current standard of care for RCC with an IVC TT is to undergo a radical nephrectomy with an IVC thrombectomy which may be associated with high surgical morbidity and mortality. We hypothesize that the combination of PEMBRO and AXI given in the neoadjuvant setting will decrease the IVC TT burden. The KEYNOTE-426 trial evaluated the combination of PEMBRO and AXI in the metastatic setting which showed an objective response rate of 59.3%. Thus, it is reasonable to consider a response in the overall burden of disease, inclusive of the VTT. This decrease in size of the VTT can potentially lead to decreased surgical complications, improve patient-related outcomes, and improve progression-free survival (PFS) and overall survival (OS). **Methods:** This single-center, open-label, single-arm phase II trial is enrolling patients with clear cell RCC that demonstrate IVC TT. The primary endpoint is the IVC TT response (change in size) after neoadjuvant PEMBRO and AXI. The extent of IVC TT will be measured by the Mayo classification and cross-sectional dimensions. Secondary endpoints include surgical complications/ morbidity per Clavien-Dindo classification, 1-year PFS, 1-year OS, and safety of PEMBRO and AXI. Correlative analysis of pre and post operative tumor samples will also be performed. Patients will receive the combination of PEMBRO 200 mg intravenously and AXI 5 mg orally twice daily every 21 days for 4 cycles. A radiographic assessment will be performed at baseline and after up to 12 weeks (4 cycles) of therapy to evaluate the primary endpoint of IVC TT response. Patients will undergo a definitive surgery per treating urologist within 2 weeks (+/- 7 days) after this evaluation. Patients will have at least cT3b tumor with or without lymph node or distant metastases and a biopsy confirming a component of clear cell RCC. The study will include patients who are candidates for upfront surgery as determined by their treating urologist. A Simon's two-stage design will be utilized with the first stage enrolling 9 subjects. If there are zero responses, the trial will be stopped. If there are 3 or more patients that are not able to undergo surgery due to treatment-related adverse events, enrollment will be paused. If neither of these occur, we will enroll 8 additional subjects, rejecting the null hypothesis of an IVC response in only 5% of patients if we observe at least 3 of 17 patients with a measured reduction from baseline size of the TT. Clinical trial information: NCT05969496. Research Sponsor: None.

TPS489 Trials in Progress Poster Session

Phase III randomized trial of stereotactic ablative radiotherapy (SAbR) for oligometastatic advanced renal carcinoma (EA8211-SOAR).

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Background: Optimal strategies for managing oligometastatic renal cell carcinoma (RCC) are unclear. While systemic therapy is the accepted standard, Stereotactic Ablative Radiation (SAbR) is a promising alternative based on retrospective and limited prospective data[1–3]. SAbR may spare patients from systemic therapy toxicity, but progression of occult micrometastasis remains a concern. This prospective ECOG-ACRIN phase 3 randomized trial will compare SAbR to systemic therapy for oligometastatic RCC. Co-primary endpoints are overall survival (OS) and toxicity. **Methods:** Patients with RCC (any histology except for sarcomatoid) with an ECOG performance 0-2, International Metastatic RCC Database Consortium (IMDC) favorable and intermediate-risk, and 2-5 extracranial metastases are eligible. The exclusion criteria include prior systemic therapy (except for adjuvant therapy) and brain metastases. Patients with intact primary are eligible after definitive treatment of the primary site. Stratification factors include 1) number of metastases (2-3 vs 4-5), 2) histology (clear cell vs non-clear cell), 3) IMDC (0 vs 1-2), 4) prior adjuvant systemic therapy (yes vs no), and 5) time from treatment of primary disease (<1yr vs >1yr). Patients will be randomized to up front systemic therapy (the type of systemic therapy will be chosen at the discretion of the investigator) versus SAbR (and additional SAbR of up to a total of 6 metastasis while disease remains amenable) followed by systemic therapy. Co-primary endpoints are OS and toxicity (≥grade 3). Target accrual goal is 472 patients which will provide 85% power to test non-inferiority in OS from a non-inferiority hybrid design, assuming a null hazard ratio of 1.24 and alternative hazard ratio of 0.85. If it is concluded that SAbR arm has non-inferior OS, superiority in toxicity will be tested. Secondary endpoints include health-related quality of life (QOL) as measured with NFKSI-19 and EQ-5D-5L and progression free survival (PFS). Exploratory endpoints include PFS of 1st line systemic therapy, local control with SAbR and cost-effectiveness. The trial has been open for enrollment since September 2023. References: 1. Hannan R, Christensen M, Christie A, et al: Stereotactic Ablative Radiation for Systemic Therapy-naïve Oligometastatic Kidney Cancer. Eur Urol Oncol, 2022; 2. Zhang Y, Schoenhals J, Christie A, et al: Stereotactic Ablative Radiation Therapy (SAbR) Used to Defer Systemic Therapy in Oligometastatic Renal Cell Cancer. Int J Radiat Oncol Biol Phys 105:367-375, 2019; 3. Tang C, Msaouel P, Hara K, et al: Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial. Lancet Oncol, 2021. Clinical trial information: NCT05863351. Research Sponsor: US National Institute of Health.

TPS490 Trials in Progress Poster Session

The role of cytoreductive nephrectomy in metastatic renal cell carcinoma in immune-oncology era (SEVURO-CN): A study protocol for a multi-center, prospective, randomized trial.

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Background: The role of cytoreductive nephrectomy (CN) in the treatment of metastatic renal cell carcinoma (mRCC) remains unclear in the immuno-oncology (IO) era. The results of two randomized trials, CARMENA and SURTIME, questioned the role and timing of CN. However, despite the latest advances in the systemic treatment of mRCC, previous trials have only used targeted therapy, and no studies have fully investigated the role of CN in immune checkpoint inhibitor (CPI) settings, and there is an urgent need for future studies to better define the role and timing of CN. **Methods:** This study is an open-label, multi-center, parallel, prospective, randomized, interventional clinical study to evaluate the efficacy of CN in combination with CPIs in mRCC patients with International mRCC Database Consortium (IMDC) intermediate- and poor-risk. Synchronous mRCC patients with ≤3 IMDC risk features will be randomly allocated to three groups (1, upfront CN; 2, deferred CN; and 3, systemic therapy (ST) only). For ST, the nivolumab plus ipilimumab combination regimen, one of the standard regimens for intermediate- and poor-risk mRCC, is chosen. The primary endpoint is overall survival. The secondary endpoints are progression-free survival, objective response rate, number of participants with treatment-related adverse events, and number of participants with surgical morbidity. We will analyze the genetic mutation profiles of the tumor tissue, circulating tumor DNA, urine tumor DNA, and tumor-infiltrating lymphocytes. The gut and urine microbial communities will be analyzed. The study will begin in 2023 and will enroll 40 patients. Clinical trial information: NCT05753839. Research Sponsor: National Research Foundation of Korea.

TPS491 Trials in Progress Poster Session

Combination nivolumab and ipilimumab with and without camu camu in first-line treatment of metastatic renal cell carcinoma (mRCC).

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Background: Combination immune checkpoint inhibition (ICI) with ipilimumab and nivolumab (ipi/nivo) is an established first-line treatment for patients (pts) with intermediate and poor-risk mRCC. CheckMate214 demonstrated a survival advantage with ipi/nivo over sunitinib; unfortunately, 20% of cases developed primary progression to immunotherapy. Recent data suggest that the gut microbiome is key in modulating clinical responses and immune-related toxicities. Therefore, modulating the gut microbiome is a novel adjunct strategy to dual ICI in mRCC. Our group has previously proven that the addition of a live bacterial product (CBM588) enhances clinical responses in pts with mRCC treated with ICI, and the combination of ICI (Dizman *et al.*, 2022) or with a tyrosine kinase inhibitor (Ebrahimi *et al.*, 2023). Camu camu (*Myrciaria dubia*) is a comestible berry characterized by a polyphenol-rich nutritional profile. In extract form, it is rich in castalagin, which appears to have probiotic properties. In mouse tumor models, camu camu increased the abundance of fecal *Ruminococcus* spp. when combined with ICI (Messaoudene *et al.*, 2022). This shift in the gut microbiome composition was associated with stronger CD8+ T-cell and CD4+ Th1-dependent antitumor responses. Camu camu and ICI reestablished the efficacy of anti-PD1 therapy, reducing tumor size compared to ICI alone. This pilot study aims to identify the biological effect of camu camu with ipi/nivo in pts with mRCC.
Methods: This is an investigator-initiated, randomized, open-label, single-center trial comparing camu camu with ipi/nivo versus ipi/nivo alone in pts with treatment-naïve mRCC. Eligibility criteria include pts $\geq$ 18 year old, PS 0-1, histological confirmation of clear-cell RCC with or without a sarcomatoid component, intermediate or poor risk per IMDC, no prior systemic treatment and measurable disease,. 30 pts will be enrolled and randomized in a 2:1 fashion, favoring the study arm. Pts will be treated with camu camu at 1500 mg PO daily, in with ipi/nivo at standard dosing. Pts will be followed monthly. Treatment will be continued until progression (RECIST v1.1) or toxicity. The primary endpoint is change in the abundance of *Ruminococcus* spp. in the stool from baseline to week 12 of therapy. We have 80% power to detect a 1 SD difference between the mean change detected in the two groups using a two-group T-test with a one-sided type I error of 0.05. Secondary endpoints include overall response rate, progression-free survival, safety, effect on gut microbiome diversity and function, comparison of the proportion of circulating cytokines and chemokines from baseline to week 12, and changes in the abundance of metabolic pathways and fungal microbiome profile. Response will be assessed by CT after the first 12 weeks of therapy and every 12 weeks, thereafter. The study is currently open to enrollment. Clinical trial information: NCT06049576. Research Sponsor: None.

TPS492 Trials in Progress Poster Session

Advanced renal cell cancer combination immunotherapy clinical trial (ARCITECT; HCRN GU 22-587).

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Background: First-line treatment for patients with metastatic clear cell renal cell carcinoma (mccRCC) often includes an anti-PD1 inhibitor in combination with either an anti-CTLA inhibitor (IO/IO) or a VEGF receptor tyrosine kinase inhibitor (TKI) (IO/TKI). Although some patients treated with nivolumab/ipilimumab (Nivo/Ipi) (IO/IO) experience durable responses leading to treatment free intervals, over two-thirds experience disease progression. Resistance to Nivo (anti-PD1) monotherapy has been associated with increased presence of a subpopulation of Tregs in the tumor microenvironment. Botensilimab (Bot) is an IO agent that leverages novel FcyR-associated mechanisms of action to enhance T cell priming, deplete intratumoral Tregs and enhance myeloid activation. Combination botensilimab/balstilimab (Bot/Bal) (anti-CTLA/anti-PD1) has shown impressive anti-tumor activity in diseases where Nivo/Ipi has shown little to no efficacy. **Methods:** ARCITECT is a phase II, multicenter study evaluating the efficacy and safety of Bot/Bal relative to Nivo/Ipi. Patients with mccRCC (favorable, intermediate, or poor risk), no prior systemic therapy (including adjuvant or neoadjuvant), and at least one measurable lesion as defined by RECIST 1.1 are eligible for enrollment. 120 patients will be randomized in a 2:1 fashion to Arm A (Bot/Bal induction followed by Bal maintenance) or Arm B (Nivo/Ipi induction followed by Nivo maintenance) each for a maximum of 2 years. Stratification factors include IMDC risk groups and sarcomatoid histology. The primary endpoint is overall response rate (ORR) per RECIST 1.1. We hypothesize that Bot/Bal will lead to a superior ORR (55%) relative to Nivo/Ipi (40%). This trial has $>$ 90% power to detect the alternative hypothesis while maintaining a one-sided significance level of not more than 0.10 using the exact binomial. The study will be monitored for early stopping in favor of the null hypothesis based on a Simon's two stage design. In the first stage, 69 patients will be enrolled (Arm A:46 and Arm B:23). If at the end of the first stage, Arm A has either at least 18/42 (42.8%) of eligible patients responding or an ORR at least numerically equivalent to that for eligible patients in Arm B, then the trial will progress to the second stage. The primary endpoint will be met if there are 38/80 responders (ORR $>$ 47.5%) in Arm A. Key secondary endpoints include landmark progression-free survival, treatment-free survival and rates of immune-related adverse events. Correlative studies will explore immune and molecular predictors of response and resistance to IO/IO in tumor and blood. Clinical trial information: NCT05928806. Research Sponsor: None.

TPS493 Trials in Progress Poster Session

SWOG S2200 (PAPMET2): A phase II randomized trial of cabozantinib with or without atezolizumab in patients with advanced papillary renal cell carcinoma (PRCC).

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Background: The role of immune therapy is not established in PRCC. The S1500 (PAPMET) clinical trial established single agent cabozantinib as the standard of care for PRCC (PMID 33592176) with a median progression free survival (PFS) of 9.0 months compared to 5.6 months with sunitinib. Trials have shown activity of PD-(L)1 antagonists as monotherapy (PMID 33529058) or in combination with targeted therapy (PMID 34491815). In a single arm study of cabozantinib/nivolumab the median PFS was 12.5 months (PMID 35298296). There are no prior randomized studies of immune therapy in PRCC. Single arm trials often overestimate the true effect size (PMID 31218346), highlighting the unmet clinical need for a randomized clinical trial in PRCC. We hypothesize that the combination will have higher clinical activity than single agent cabozantinib. **Methods:** This is a prospective randomized phase II clinical trial conducted through the NCTN and led by SWOG. The primary endpoint is a comparison of PFS between cabozantinib and cabozantinib/atezolizumab. Secondary endpoints include comparison of objective response rate, overall survival and safety. Patients are treated with cabozantinib 60mg/day versus cabozantinib 60mg/day + atezolizumab 1200 mg q3 weeks. 200 patients will be enrolled and randomized 1:1. Key inclusion criteria include a pathologic confirmation of PRCC; presence of metastasis; 0-1 prior systemic lines of therapy for metastatic disease; and measurable disease as defined by RECIST 1.1 criteria. Prior treatment with adjuvant pembrolizumab is allowed if completed greater than 6 months before enrollment. Key exclusion criteria include clinically significant autoimmune disease; ongoing use of strong CYP3A4 inhibitors, strong CYP3A4 inducers. Planned correlatives include stool microbiome testing and genomic/transcriptomic analysis from blood and baseline tissue assays. Clinical trial information: NCT05411081. Research Sponsor: NIH/NCI grant awards: U10CA180888 and U10CA180819; Genentech, Inc (a member of the Roche Group), and Exelixis Inc.

TPS494 Trials in Progress Poster Session

Phase II study of axitinib intensification compared to nivolumab alone after induction with ipilimumab plus nivolumab in patients with mRCC without previous complete response (AxIn study).

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Background: The combination of nivolumab plus ipilimumab (N+I) is able to increase the overall survival (OS), progression free survival (PFS) and overall response rate (ORR) compared to sunitinib in patients (pts) with metastatic renal cell carcinoma (mRCC) at intermediate or poor prognosis. However, the rate of pts with partial response to N+I (32%) is lower of that reported with the combination of axitinib plus pembrolizumab (51%). Moreover, analysis of outcome based on the depth of response strongly suggests a connection between response and survival. This study aims at investigating the efficacy of an intensified strategy with axitinib added to nivolumab in mRCC pts without complete response at the end of N+I induction. **Methods:** AxIn study (NCT05817903) is a randomized, open-label, multicenter, phase 2 trial evaluating in mRCC pts who completed induction with N+I without complete response or progressive disease, whether the intensification of therapy by adding axitinib to the standard nivolumab can increase the response rate and improve the survival compared to nivolumab alone. Eligible pts with partial response or stable disease after completion of N+I induction as first-line therapy, without any toxicity $\geq$ G2, and candidates to maintenance nivolumab as per standard clinical practice will be randomized 1:1 to intensification of therapy with axitinib in addition to nivolumab (Arm A) or nivolumab alone (Arm B). The primary endpoint is to assess the ORR of pts treated with the intensification of axitinib plus nivolumab compared to the standard of care of nivolumab monotherapy. Secondary endpoints include PFS, OS, depth of response, duration of response, quality of life, and safety. Exploratory biomarkers analysis will be performed. The trial is actively recruiting. Clinical trial information: NCT05817903. Research Sponsor: Pfizer.

TPS495 **Trials in Progress Poster Session**

Efficacy of perioperative pembrolizumab treatment in patients with resectable metastases from kidney cancer: The PE-PE study.

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Background: Radical metastasectomy and other local treatment strategies (including definitive radiotherapy, RT) can be carried out instead of systemic therapies for selected metastatic renal cell carcinoma (mRCC) patients (pts) with the aim of healing the patient even in an advanced disease stage. Recent data suggests a potential benefit from perioperative immunotherapy with immune checkpoint inhibitors (ICIs), as shown by the significant efficacy of adjuvant pembrolizumab in the M1 NED subgroup of the KEYNOTE-564 trial. Moreover, important activity of a short course of pembrolizumab has been demonstrated also in oligometastatic mRCC pts in combination with stereotactic ablative RT in the RAPPORT study. To date, no randomized trial has evaluated the concomitant use of pembrolizumab with surgery or definitive RT in mRCC compared to local therapy alone, which is the aim of our study. **Methods:** PE-PE study (NCT05578664) is a randomized, open-label, multicenter, phase 2 study evaluating the efficacy of pembrolizumab in delaying tumor progression in pts with oligometastatic mRCC who are candidates for radical surgery and/or definitive RT of the metastases. Eligible pts should have undergone previous nephrectomy and have maximum three metastases considered eligible for radical metastasis directed therapy (MDT; either metastasectomy or RT) and new disease must have appeared within 5 years from prior nephrectomy or metastasectomy. Pts will be randomized 2:1 to receive pembrolizumab at flat dose of 400 mg every six weeks for a total of 9 cycles (one year of therapy) and MDT from day 21 to day 42 of the cycle 1 (ARM A); or MDT alone within 42 days from randomization (ARM B). The primary endpoint is to assess the relapse free survival (RFS) defined as the length of time from randomization to the appearance of radiological progression in pts who receive pembrolizumab compared to those who do not. Secondary endpoints include: distant RFS (defined as the time from randomization to the appearance of distant metastases other those treated with surgery or RT), overall survival, and safety. Exploratory biomarkers analysis will be performed. The trial is actively recruiting. Clinical trial information: NCT05578664. Research Sponsor: MSD.

Phase 1b/2 study of combination ^{177}Lu girentuximab plus cabozantinib and nivolumab in treatment naive patients with advanced clear cell RCC.

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Background: Complete response (CR) is still a rare event in patients with advanced clear cell renal cell carcinoma (ccRCC). The combination of nivolumab plus cabozantinib was recently approved for the first-line treatment of ccRCC based on the CheckMate 9ER phase 3 study demonstrating improved progression-free survival (PFS) & objective response rate (ORR) in comparison to sunitinib. However, the CR rate was only 9%. Since the anti-tumor effects of immune checkpoint inhibitors are dependent on the presence of activated tumor-infiltrating T cells, drugs that could synergize with T cells' anti-tumor activity can allow us to improve CR rates. Activation of the cGAS-STING pathway which is induced by radiation-induced DNA damage, is one promising mechanism that has been investigated. Many studies have shown that radiation treatment augments immune checkpoint inhibition. However, it is not always possible to radiate all metastatic lesions. Therefore, targeted peptide receptor radionuclide therapies, have been developed by conjugating radioisotopes to receptor binding analogs targeting specific cancer cell surface proteins, thereby delivering targeted radiation to cancer cells in the body with minimal damage to surrounding healthy cells. ^{177}Lu girentuximab is the first antibody-radioisotope designed for ccRCC, targeting carbonic anhydrase 9-expressing cells, which includes > 90% of ccRCC. It has been tested in metastatic ccRCC as a single agent & shown to be safe and effective in stabilizing disease in 57% of pts. In this study, we hypothesize ^{177}Lu girentuximab-induced DNA damage will potentiate the STING pathway, and this activation will synergize with nivolumab and cabozantinib to promote trafficking and infiltration of activated T cells to tumors and achieve higher CR rates. **Methods:** Up to 100 patients with treatment na'i"ve, biopsy-proven ccRCC with adequate organ/marrow function with 1 evaluable lesion by RECIST 1.1 will be enrolled. A 5-patient safety lead-in will evaluate myelosuppression. Ongoing safety, & futility monitoring will employ a Bayesian approach. The sample size was chosen for reasonable operating characteristics to distinguish a CR rate (primary endpoint) of 18% as better than 9% using a beta(0.09, 0.91) prior. Secondary endpoints are ORR, PFS by RECIST 1.1, and overall survival. ^{177}Lu-girentuximab 1480 MBq/m^2 (61% of single agent MTD) will be administered every 12 weeks for up to 3 cycles. Starting with the 2nd cycle, nivolumab & cabozantinib will be added at standard dose. To explore the effects of the treatment on inducing activated T cell infiltration, patients will undergo pre/post-treatment PET scan with [18F]F-AraG radiotracer as well as biopsies for single cell, spatial transcriptomics and proteomics studies. Clinical trial information: NCT05239533. Research Sponsor: None.

TPS497 Trials in Progress Poster Session

A multi-center, open-label phase II study of lenvatinib plus pembrolizumab (LEAP) in patients with renal cell carcinoma with brain metastasis previously treated with immune checkpoint blockade.

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Background: Brain metastasis incidence has historically ranged from 2%-15%, whereas modern series post-immunotherapy (IO) have found incidences as high as 29%. Despite the revolution of the RCC treatment landscape with the discovery of targeted therapy and IO agents, treating RCC patients with brain metastasis remains challenging. Our snRNA-seq studies showed that brain metastases have a unique immunosuppressive environment with a layer of neuronal regulation, which is targetable by inhibiting FGFR2. Moreover, neuronal cells have proliferative signaling on tumor cells through FGFR4 signaling, which is targetable by a multi-target tyrosine kinase inhibitor of VEGFR, FGFR1-4, PDGFR and other receptors. Additionally, Keynote-146 showed efficacy of pembrolizumab+lenvatinib on extracranial metastasis sites in patients who progressed on immunotherapy alone. Based on these findings we hypothesize that pembrolizumab+lenvatinib can modulate the immunosuppressive brain metastasis microenvironment and is safe and effective in patients with renal cell carcinoma (RCC) and brain metastasis who were previously treated with immune checkpoint blockade. **Methods:** This is a multi-center, open-label phase II study evaluating the efficacy and safety of pembrolizumab+Lenvatinib in patients with RCC and untreated brain metastasis who were previously treated with immune checkpoint blockade. The study will implement a Bayesian design with 40 patients, with futility monitoring based on a null hypothesis median intracranial progression free survival (icPFS) of 4.8 months with a target improvement of median PFS equal to 8.7 months. Pembrolizumab (200 mg IV Q3W) and lenvatinib (20 mg PO QD) will be administered in 21-day cycles for a maximum of 24 months (or 35 cycles) in the absence of disease progression or until unacceptable toxicity, death, withdrawal of consent, or discontinuation from the study treatment for any other reason. The primary endpoint is icPFS as assessed by Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) criteria. The key secondary endpoints are intracranial objective response rate (ORR) of non-irradiated measurable (tumor diameter 0.5-3.0 cm on magnetic resonance imaging (MRI)) brain metastases and distant brain failure rate defined by the recurrence of new brain metastases outside of the radiation field, as assessed by RANO-BM, and overall survival (OS). Other secondary endpoints are safety, extracranial ORR, extracranial PFS, as assessed by the RECIST 1.1 and iRECIST. Exploratory analyses will include evaluation of tissue, blood-based and cerebrospinal fluid immune-related correlates, identification of imaging characteristics of treatment, evaluation of the neurological and cognitive function, seizure reduction, steroid, and opiate pain medication. Clinical trial information: N/A. Research Sponsor: Merck.

TPS498 **Trials in Progress Poster Session**

Multiomics approach for patient stratification and novel target identification in metastatic clear cell renal carcinoma (Meet-URO 31).

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Background: The choice of the best treatment in first line metastatic clear-cell renal cell carcinoma (mccRCC) patients is becoming an issue, since no biomarkers are available to guide the treatment allocation strategy. Recently there has been a great deal of interest in Artificial Intelligence (AI) systems and their ability to process heterogeneous data for both classification and prediction purposes. An additional fields of interest in genitourinary oncology are also liquid biopsy and radiomics. Non-invasive liquid biopsy methods are able to detect and characterize circulating cell-free DNA (cfDNA), extracellular vesicles (EV) associated RNAs and circulating tumor cells (CTCs) and to allow longitudinal evaluation of tumor evolution whereas radiomics may provide a novel approach to develop predictive tools by correlating imaging features to tumor characteristics including histology, tumor grade, genetic patterns and molecular phenotypes, as well as clinical outcomes. We hypothesize that AI can be used to integrate data obtained from radiomics, genomic and transcriptomic analysis of CT scan, neoplastic tissues and circulating cell-free DNA or microvescicle-associated RNA with the purpose of defining an optimal allocation strategy for patients with mccRCC undergoing first-line therapy and identifying novel targets in mccRCC. **Methods:** This is a multicenter Italian prospective translational study evaluating transriptomic, genomics and radiomics in treatment-naïve advanced ccRCC patients. Subjects will be screened to identify a total of 100 patients eligible for the study, candidate to receive first-line treatment as per investigator's choice according to clinical practice. Tumoral tissue, plasma samples and radiological exams will be collected at baseline, at 3 months, at the time of first radiological evaluation and at disease progression (PD) to provide a comprehensive molecular profile and radiomic features extrapolation, respectively. AI systems will be used to build a genomic-radiomic profile of patients to correlate to treatment response. The planned sample size of 100 patients will allow an exploratory analysis of the prognostic and predictive performance of the "multiomic" classifier, to be subsequently validated in a larger expansion cohort of patients. Through the above research we are confident to provide proof of concept that AI is able to combine the information from genomics, transcriptomic and radiomics to provide an opportunity for a molecularly driven patients' stratification, aiming to choose the ideal first-line systemic treatment for each patient. Enrollment has already begun and the trial has enrolled 15 of the planned 100 patients. Clinical trial information: NCT05782400. Research Sponsor: AIRC (Italian Associacion for Cancer Research).