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2632P Second-line patterns and outcomes in 12,595 patients with advanced renal cancer in France: A nationwide cohort study

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Background: Current first-line treatment (L1) for advanced renal cancer (aRC) patients (pts) is based on several combinations (combo) of immune checkpoint blockers (IO: nivolumab [nivo], ipilimumab [ipi], pembrolizumab [pem]) and tyrosine kinase inhibitors (TKI: axitinib [axi], lenvatinib [len] and cabozantinib [cabo]). Outcomes of second-line treatment (L2) are unknown.

Methods: We included all aRC pts from the French national health insurance database (SNDS) who started L1 between 2019 and 2023. Primary outcome was overall survival (OS), defined as the time from L2 start to death or censoring. Treatment comparisons were performed with a Cox model using the inverse probability of treatment weights computed from a propensity score (PS).

Results: Between Jan 1, 2019, and Dec 31, 2023, 12,595 pts started L1, 2,588 (20.5%) with nivo-ipi, 3,459 (27.4%) with an IO-TKI combo and 3,998 (31.7%) with a TKI. Median (med) age was 66y [IQR 58-73], 9,251 (73.4%) pts were male and 7,933 (63.0%) started L1 within the first year of disease. Among pts treated with combo, med number of treatment lines was 2 [IQR 2-3], med time between L1 to L2 initiation was 9.2 mo (8.7-9.6) and 1,261 pts (20.9%) died before L2. Med follow up after L2 was 23.6 months (mo) (22.4-24.7). Among pts treated with combo, those treated in centers with $\geq$12 newly-treated pts/y had a better med OS from L1 (39.3 mo [36.6-42.5] vs 34.9 mo [31.6-37.9], p=0.002). Among pts treated with combo and who had a L2, 2,396 (89.5%) received cabo (from L1 to L5). After nivo-ipi, the most frequent L2 were cabo (n=876, 73.8%), axi (n=126, 10.6%) and sunitinib (sun) (n=101, 8.5%). Med OS were 17.1 mo (14.2-19.1) for cabo, 23.1 mo (17.2-32.3) for axi and 17.5 mo (13.2-21.7) for sun. After pem-axi (n=2,330), the most frequent L2 were cabo (n=844, 86.1%) and other TKI (sun or pazopanib [paz] or len, n=71, 7.2%). Med OS were 14.5 mo (12.8-16.1) for cabo and 19.2 mo (13.2-NA) for other TKI. After nivo-cabo (n=962), the most frequent L2 were axitinib (n=138, 55.0%) and other TKI (sun or paz or len, n=73, 29.0%). Med OS were 11.1 mo (8.4-NA) for axi and 7.6 mo (5.1-NA) for other TKI. No difference was found in PS analysis between L2 regimens.

Conclusions: This study presents a comprehensive description of L2 after a combo of IO or TKI in pts with aRC.

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2634P Remodelling of the tumor microenvironment by PD-1 blockade plus tyrosine kinase inhibitor in advanced renal cell carcinoma

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Background: The combination of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) has markedly improved clinical outcomes in advanced renal cell carcinoma (aRCC), yet therapeutic resistance remains a major challenge.

Methods: To elucidate the cellular and molecular mechanisms underlying treatment response and resistance, we conducted single-cell RNA sequencing (scRNA-seq) on 30 tumor samples from 18 aRCC patients treated at PLAGH, integrated with two public scRNA-seq aRCC datasets to yield 61 tumors across four groups (PreR, PreNR, PostR, PostNR). In total, 333,169 high-quality cells were profiled, revealing nine major cell types.

Results: Immune landscape analyses showed increased T cells in responders and neutrophils enrichment in non-responders. Predictive and therapeutic index analyses confirmed T cells as positive predictors and neutrophils as adverse factors. Among six neutrophil subtypes, a $VEGFA^{+}CEACAM1^{+}$ subset (Neu_06_VEGFA) was enriched in non-responders and exhibited immunosuppressive and angiogenic features, and high expression of checkpoint ligands LGALS3 and CEACAM1. T cell profiling revealed terminal exhaustion and increased Tregs in non-responders, with high checkpoint receptors expression indicating convergent suppression from myeloid and lymphoid compartments. We further identified SAA^{+}tumor cells as key drivers of resistance. These cells were enriched in non-responders and promoted Neu_06_VEGFA expansion via SAA—FPR and TGFβ—TGFBR signaling, leading to upregulation of CEACAM1 on neutrophils. Spatial and functional analyses revealed close interaction between SAA^{+} tumor cells and $CEACAM1^{+}$ neutrophils, correlating with $CD8^{+}$ T cell dysfunction. Targeting either SAA or CEACAM1 in vivo reprogrammed the tumor microenvironment, reduced neutrophil-mediated suppression, restored $CD8^{+}$ T cell activity, and enhanced ICI plus TKI efficacy.

Conclusions: In summary, we identify a tumor—myeloid—T cell axis driving drug resistance in aRCC, wherein SAA^{+} tumor cells promote the expansion of $CEACAM1^{+}$ neutrophils that impair T cell function. Targeting this pathway represents a promising approach to overcome resistance to immunotherapy.

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2635P Optimal treatment duration in metastatic renal cell carcinoma patients responding to immune checkpoint inhibitors: Should we treat beyond two years?

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Background: Immune checkpoint inhibitors (ICPIs) can lead to long-lasting responses in metastatic renal cell carcinoma (mRCC). Optimal treatment duration in these patients is unknown. Prolonged treatment can lead to late toxicity, burden for day clinics and financial toxicity.

Methods: This multicenter retrospective study included mRCC patients responding to ipilimumab/nivolumab in first line or nivolumab in later lines, who were treated for at least 21 months and did not stop for toxicity. Progression-free survival (PFS), overall survival (OS), and cancer-specific survival (CSS) were modeled non-parametrically and semi-parametrically. The effect of elective ICPI discontinuation between 21-25 months on PFS was assessed by a causal inference approach using artificial censoring along with inverse probability of censoring weighting.

Results: Ninety-five patients from 18 Belgian centers were followed up for a median of 62.1 (95% CI 57.3-67.5) months. Fifty-four (56.8%) patients received ipilimumab/nivolumab, whereas 41 (43.2%) received nivolumab, for a median treatment duration of 33.8 (95% CI 28.5-39.6) months. Fifteen (15.8%) patients electively discontinued their ICPI between 21-25 months. They had more often a metachronous metastatic pattern (P=0.048) and a complete response (P=0.045). Their 3-year survival rates after discontinuation were 57.1% (95% CI 34.3-95.1) for PFS, 67.5% (95% CI 37.0-100.0) for OS, and 90.0% (95% CI 73.2-100.0) for CSS. Elective ICPI stop between 21-25 months did not significantly impact the hazard for progression/death (adjusted HR 1.08, 95% CI 0.64-1.84, P=0.766).

Conclusions: Among mRCC patients responding to ICPI, elective therapy discontinuation approximately 24 months after initiation does not appear to compromise survival outcomes compared to continuing therapy.

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2636P Patient perceptions of cure in metastatic renal cell carcinoma

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Background: Patient surveys consistently show that the most important treatment outcome for patients with metastatic renal cell carcinoma (mRCC) is a cure. Yet, little is known about how patients interpret and define the term in the context of their disease.

Methods: A survey to assess perceptions of "cure" was developed by KCCure in collaboration with medical experts and distributed from 09/2024 to 10/2024 through patient communities, mailing lists, websites, and social media.

Results: Out of 1,167 respondents, 492 mRCC patients who had received systemic therapy were included. Sixty-five percent were female, with a median age of 58.7 years. Most (83%) were from the United States, 7% from Europe, 5% from Canada and 3% from Australia, 2% from Asia. 42% were on first line treatment, 30% second line, 13% third line, and 15% in fourth or later line. When asked how doctors described their disease, only 1% were told they were cured, 3.7% "not yet cured," 41% that their disease was incurable or terminal, and in 38.5% of patients, the word "cure" wasn't used. When patients self-described their situation, only 2% said they were cured, 46% said incurable, 29.3% not yet cured, and 23% chose "other." When asked what percentage of mRCC patients they believe can be cured, 58% believed it was 10% or fewer, with more than one-quarter (28%) who responded none could be cured. When asked to share their feelings about use of the word cure, 40% responded negatively to the term "cure," calling it "reckless" or "dangerous," while another 40% expressed caution. Only 10% reacted positively. When asked how long a patient must be disease-free to be told they are cured, 63% of respondents said "never" for metastatic patients, and 25% said doctors should never use the term for any patient, regardless of stage.

Conclusions: Despite wanting curative outcomes, patients remain skeptical that cures are possible with current therapies. These findings underscore a widespread distrust of the term "cure", rooted in both personal experience and perceived medical reality. Awareness of patient perceptions and fears can help shape discussions with medical professionals, enhance communication, and support more successful pathways to developing curative treatments.

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2637P Survival outcomes based on the number of cycles of Ipilimumab in patients (pts) in the US with metastatic clear cell renal cell carcinoma (mccRCC) treated with first-line (1L) Ipilimumab (Ipi) plus Nivolumab (Nivo)

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Background: Ipi + Nivo combination is a standard 1L treatment for mccRCC, with overall survival (OS) reaching ~53 months in the CheckMate-214 trial [PMID: 39098455]. However, real-world data on outcomes in pts who receive less than four cycles of Ipi remain limited. Herein, we aimed to assess survival outcomes based on the number of Ipi cycles received and the receipt of Nivo maintenance.

Methods: This retrospective study used the nationwide Flatiron Health electronic health record (EHR) derived deidentified database. Eligibility: Pts diagnosed with mccRCC, IMDC risk score poor or intermediate, and receiving 1L Ipi + Nivo (≤4 cycles of Ipi). Pts who initiated 1L Ipi + Nivo within 3 months of the data cut-off date were excluded. The primary exposures were the number of Ipi + Nivo cycles and receipt of Nivo maintenance. Primary outcomes were time to next treatment (TTNT) and OS.

Results: Of 955 pts who initiated therapy between 6/20/2016 and 8/2/2024, 91 (9.5%) received 1 cycle of Ipi, 125 (13.1%) received 2 cycles, 134 (14%) received 3 cycles, and 605 (63.4%) received 4 cycles. Among those, 598 (62.6%) received Nivo maintenance and 357 (37.4%) did not. Median TTNT and OS gradually improved with the increasing number of Ipi cycles and the receipt of Nivo maintenance.

Table: 2637P Median TTNT and OS (months) by the number of Ipi cycles and Nivo maintenance

Ipi + Nivo cycles	Nivo maintenance	N (%)	Median TTNT (mo) (95% CI)	Median OS (mo) (95% CI)	Receipt of 2L, n (%)
1	Yes	14 (15)	10 (5.7 — -)	46 (23 — -)	9 (64)
	No	77 (85)	1.3 (1.2 — 2.1)	1.5 (1.2 — 2.4)	10 (13)
2	Yes	22 (18)	11 (3.1 — -)	- (13 — -)	9 (41)
	No	103 (82)	2.2 (1.9 — 2.8)	4 (3 — 11)	35 (34)
3	Yes	52 (39)	11 (8.9 — 18)	50 (23 — -)	32 (62)
	No	82 (61)	2.8 (2.6 — 3.5)	13 (4.3 — 24)	38 (46)
4	Yes	510 (84)	18 (15 — 23)	52 (44 — 62)	240 (47)
	No	95 (16)	3.7 (3.5 — 4.6)	15 (9.2 — 26)	55 (58)

Conclusions: In this large real-world analysis, a higher number of Ipi cycles was associated with improved survival outcomes in pts who received 1L Ipi + Nivo. These data may guide treatment decisions and pt counseling in the clinic. Limitations include retrospective study, real-world data, and immortal time bias.

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