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Comparison of cabozantinib (CABO) versus sunitinib (SUN) following first-line (1L) nivolumab plus ipilimumab (NIVO+IPI) for metastatic renal cell carcinoma (mRCC): A target trial emulation using real-world data from the International mRCC Database Consortium (IMDC)

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Background

- The benefit of CABO in mRCC is well established post-tyrosine kinase inhibitor when compared to Everolimus, based on data from the METEOR trial[1].
- However, its comparative effectiveness vs SUN after 1L NIVO+IPI remains uncertain.

Objective

- Our aim was to estimate the effect of second-line (2L) CABO versus SUN within one year of discontinuing 1L NIVO+IPI on overall survival (OS).

Methods

Study population

- Patients (pts) from the IMDC with mRCC diagnosed after January 1, 2017 and undergoing 2L therapy with CABO or SUN were followed from initiation of 2L until death or last known contact.

Outcomes

- Primary outcome was OS, defined as time from initiation of 2L to death from any cause.
- Secondary outcomes included objective response rate (ORR) defined as partial or complete response as per RECIST 1.1 criteria and median time to treatment failure (TTF), defined as time from initiation of 2L to failure of 2L for any reason.

Statistical analysis

- A target trial emulation was designed, where application of randomized controlled trial (RCT) design principles were used to emulate a hypothetical open-label RCT using observational data from the IMDC.
- Inverse-probability of treatment weighting was used to adjust for hemoglobin, calcium, platelets, and neutrophils at 2L, Karnofsky performance score (KPS) at 2L, time from diagnosis to initiation of 2L, and response to 1L NIVO+IPI.
- Treatments were compared using adjusted Kaplan-Meier curves and adjusted hazard ratios (HR) from a Cox regression model.
- Missing data were addressed with multiple imputation by chained equations and E-values were used to assess the likelihood findings could be explained by residual confounding.

Results

Population

- 121 and 123 pts who received CABO and SUN after 1L NIVO+IPI were included.
- Only the best responses to 1L therapy and the proportion with a KPS < 80% at 2L differed significantly between CABO and SUN (p =0.006 and 0.002, respectively) (**Table 1**).

Outcomes

- The objective response rate among evaluable patients was 27% (21/79) for CABO vs 20% (18/89) for SUN (p=0.33).
- Median TTF was 8.5 (95% CI: 6.9-12.9) and 4.5 (95% CI 3.7-5.8) months for CABO and SUN (**Figure 2**).
- Median OS was 21.4 (95% CI 17.9–NA) months for CABO and 10.1 (95% CI 7.6–17.7) months for SUN (**Figure 1,** Adjusted HR 0.44 (95% CI: 0.22-0.86), p=0.02). This corresponds to an E-value of 2.91 suggesting a low likelihood of findings being due to residual confounding alone.
- The sensitivity analysis looking at the effect modification of the CABO vs. SUN effect based on response to 1L therapy is presented in **Figure 3**.

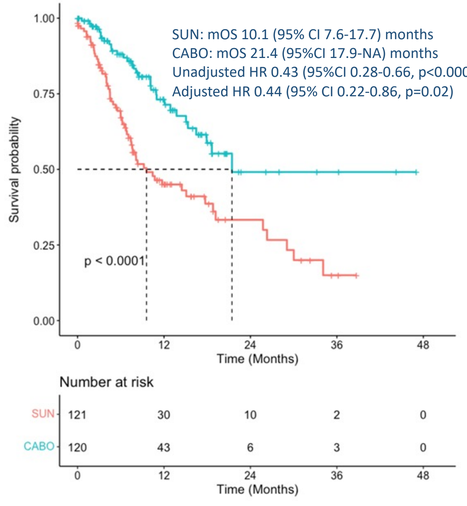
Limitations

- Potential selection bias as included patients discontinued 1L NIVO+IPI due to any reason. Exclusion of patients who started 2L more than 1 year after stopping NIVO+IPI helps address this bias.
- Imbalance in the proportion of patients with KPS <80 being higher in the SUN group, accounted for in the analysis with inverse-probability of treatment weighting.
- Missing data in the IMDC database, which may lead to residual confounding. A quantitative bias analysis was done to assess this limitation.

Conclusions

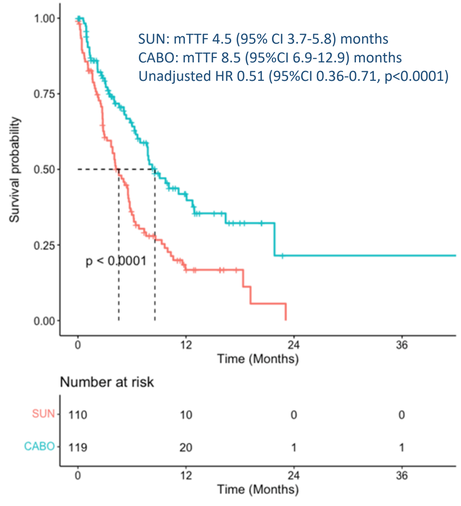
- In this real-world analysis, median OS after initiation of 2L CABO was 21.4 months, while it was 10.1 months after initiation of SUN, with an adjusted HR of 0.44 (95% CI 0.22-0.86).
- This provides evidence supporting CABO as a treatment option for mRCC following NIVO+IPI.

Figure 1: Unadjusted OS from initiation of 2L for patients treated with CABO and SUN



Abbreviations: OS: Overall survival ; 2L: Second-line ; CABO: Cabozantinib ; SUN: Sunitinib.

Figure 2: Unadjusted TTF from initiation of 2L for patients treated with CABO and SUN



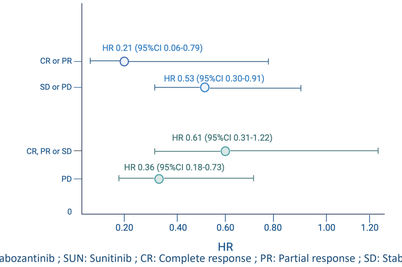
Abbreviations: TTF: Time to treatment failure ; 2L: Second-line ; CABO: Cabozantinib ; SUN: Sunitinib.

Table 1 : Characteristics of patients initiating 2L CABO and SUN

	Overall (n=244)	CABO (n = 121)	SUN (n = 123)	P-value
Mean age (SD)*	60.8 (10.2)	61.6 (11.03)	60.6 (9.27)	0.16
Male	184/244 (75.4)	90/121 (74.4)	94/123 (76.4)	0.82
Non-clear cell histology	24/173 (13.9)	14/110 (12.7)	10/63 (15.9)	0.73
Sarcomatoid	31/147 (21.1)	15/86 (17.4)	16/61 (26.2)	0.28
KPS < 80%*	53/164 (32.3)	18/86 (20.9)	35/78 (44.9)	**0.002**
Time from diagnosis to treatment < 1 year	196/242 (81.0)	100/121 (82.6)	96/121 (79.3)	0.62
Hemoglobin < LLN*	143/215 (66.5)	69/106 (65.1)	74/109 (67.9)	0.77
Neutrophils > ULN*	46/211 (21.8)	23/103 (22.3)	23/108 (21.3)	0.99
Platelets > ULN*	40/216 (18.5)	16/107 (15.0)	24/109 (22.0)	0.25
Calcium > ULN*	15/196 (7.7)	6/99 (6.1)	9/97 (9.3)	0.56
Brain Met at Diagnosis (%)	18/239 (7.5)	11/116 (9.5)	7/123 (5.7)	0.387
Liver Met at Diagnosis (%)	48/239 (20.1)	23/116 (19.8)	25/123 (20.3)	1.000
Bone Met at Diagnosis (%)	108/243 (44.4)	52/120 (43.3)	56/123 (45.5)	0.830
Nephrectomy (%)	135/244 (55.3)	64/121 (52.9)	71/123 (57.7)	0.529
Discontinued 1L due to Toxicity (%)	63/198 (31.8)	28/107 (26.2)	35/91 (38.5)	0.090
Best response to 1L (%)				**0.006**
CR or PR	36/218 (16.5)	16/111 (14.4)	20/107 (18.7)	
PD	115/218 (52.8)	50/111 (45.0)	65/107 (60.7)	
SD	67/218 (30.7)	45/111 (40.5)	22/107 (20.6)	
Time on 1L, months (SD)	5.11 (5.82)	5.71 (6.20)	4.51 (5.38)	0.109
Time from 1L to 2L, months (SD)	2.49 (4.04)	2.12 (3.85)	2.85 (4.20)	0.162
IMDC Score 1L (%)				0.930
Favorable	14/210 (6.7)	7/103 (6.8)	7/107 (6.5)	
Intermediate	124/210 (59.0)	62/103 (60.2)	62/107 (57.9)	
Poor	72/210 (34.3)	34/103 (33.0)	38/107 (35.5)	

Abbreviations : 2L: Second-line ; CABO: Cabozantinib ; SUN: Sunitinib ; KPS: Karnofsky performance scale ; LLN: Lower limit of normal ; ULN: Upper limit of normal ; Met: Metastasis ; 1L : First-line ; CR: Complete response ; PR: Partial response ; PD: Progressive disease ; SD: Stable disease ; IMDC: International mRCC database consortium. * : At 1L initiation.

Figure 3: Effect modification of CABO vs SUN impact based on response to 1L therapy



Abbreviations: CABO: Cabozantinib ; SUN: Sunitinib ; CR: Complete response ; PR: Partial response ; SD: Stable disease ; PD: Progressive disease

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1: Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, Hammers HJ, Donskov F, Roth BJ, Peltola K, Lee JL, Heng DYC, Schmidinger M, Agarwal N, Sternberg CN, McDermott DF, Aftab DT, Hessel C, Scheffold C, Schwab G, Hutson TE, Pal S, Motzer RJ; METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016 Jul;17(7):917-927.

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