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CABOSEQ: The Effectiveness of Cabozantinib in Patients With Treatment Refractory Advanced Renal Cell Carcinoma: Results From the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

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In advanced kidney cancer, there is limited data to understand the efficacy of cabozantinib after contemporary first line therapy options. In a 346 patient real world database analysis we identified clinically meaningful activity of second line cabozantinib after all evaluated contemporary 1L therapies, including immune checkpoint blockade combination approaches.

Background : There are limited data evaluating the activity of cabozantinib (CABO) as second line (2L) therapy post standard of care ipilimumab-nivolumab (IPI-NIVO) or immuno-oncology(IO)/vascular endothelial growth factor inhibitor (VEGFi) combinations (IOVE). **Materials and Methods :** Using the IMDC database, we sought to identify the objective response rate, time to treatment failure (TTF) and overall survival (OS) of 2L CABO after IPI-NIVO, IOVE combinations, pazopanib or sunitinib (PAZ/SUN) or other first line (1L) therapies. Multivariable Cox regression, adjusted for underlying differences in IMDC groups, was used to compare differences in OS for 2L CABO based on preceding therapy. **Results :** Three hundred and forty-six patients received 2L CABO (78 post IPI NIVO, 46 post IOVE, 161 post PAZ/SUN, 61 post Other). Of the entire cohort, 12.6%, 62.6%, and 24.8% were IMDC favourable, intermediate, and poor risk, respectively. Patients that received 1L IPI-NIVO had a median OS of 21.4 (95% CI, 12.1 - NE [Not evaluable]) months compared to 15.7 (95% CI, 9.3 - NE) months in 1L IOVE and 20.7 (95% CI, 15.6 - 35.6) months in 1L PAZ/SUN, $P = .28$. Median TTF from the initiation of 2L CABO in the overall population was 7.6 (95% CI, 6.6 - 9.0) months. We were unable to detect a significant difference in 2L CABO OS based on type of 1L therapy received: 1L IPI-NIVO (reference group) vs. 1L IOVE HR 1.73 (95% CI, 0.83 - 3.62 $P = .14$), 1L PAZ/SUN 1.16 (95% CI, 0.67 - 2.00 $P = .60$), however given the retrospective observational nature of this work a lack of sufficient power may contribute to this. **Conclusion :** In a large real world dataset, we identified clinically meaningful activity of 2L CABO after all evaluated contemporary 1L therapies, irrespective of whether the 1L regimen included a VEGFi. These are real world benchmarks with which to counsel our patients.

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Introduction

Despite the therapeutic advances of combination first line (1L) IO therapies such as ipilimumab and nivolumab (IPI-NIVO)[1] or immuno-oncology(IO)/vascular endothelial growth factor inhibitor (VEGFi) combinations (IOVE (axitinib and avelumab, axitinib and pembrolizumab, cabozantinib and nivolumab, lenvatinib and pembrolizumab),[2-5] a majority of patients with metastatic renal cell carcinoma (mRCC) develop therapeutic resistance and require subsequent systemic anti-cancer therapies. In the phase 3 CheckMate 214 clinical trial, 54% of 1L IPI-NIVO patients received second line (2L) therapy, with 89 (30%) receiving cabozantinib.[6] Treatment patterns post IOVE are less well characterised due to shorter follow-up, but 35% of patients post 1L combination axitinib and pembrolizumab had already received 2L VEGFi directed therapy at a 30.6 median month follow-up.[7] Given the established inferior outcomes of approved anti-cancer therapies noted in the majority of real world vs. trial populations,[8] it is important to characterize drug activity in routine practice to clarify the relevance and reproducibility of trial data and inform practice regarding the optimum sequencing of therapies.

Cabozantinib is a tyrosine kinase inhibitor (TKI), with activity across the vascular endothelial growth factor (VEGF) receptor, rearranged during transfection (RET), mesenchymal epithelial transition factor (MET) and AXL.[9] Cabozantinib targets the oncogenic addiction of mRCC to neovascularisation. The phase 3 METEOR[10] and phase 2 CABOSUN[11] trials led to global regulatory approvals for cabozantinib in the 2L after prior VEGFi therapy, and 1L treatment landscapes respectively. However, these studies were largely undertaken prior to the establishment of 1L combination therapy as the standard of care. Despite the widespread use of cabozantinib across all lines of therapy in mRCC, there is a lack of data characterising the outcomes and treatment patterns associated with this agent post current standard of care 1L IO combination therapy.[12] Furthermore, 2L regulatory indications for cabozantinib worldwide are primarily limited to patients who had received prior VEGFi treatment, to reflect the inclusion criteria of METEOR.[10] In many jurisdictions, this restricts therapeutic use of cabozantinib to third line (3L) for patients who are treated with 1L IPI-NIVO and 2L VEGFi. Integration of cabozantinib into a shifting therapeutic paradigm requires real world evidence given the absence of randomised prospective data. In this context we interrogated the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) dataset of over 12,000 patients to examine outcomes in patients treated with 2L cabozantinib post contemporary 1L therapies including IPI-NIVO and IOVE.

Materials and Methods

Design

We utilized the IMDC dataset, a large multicentre observational cohort study, examining consecutive patients with mRCC at 40 centers across 14 countries. Each center has independent institutional review board approval. Data were collected between March 2007 and December 2021. A standardized template[13] was used to capture baseline demographic, histology, clinical, treatment, and outcome data. Patients were followed from the time of initiation of cabozantinib, until death or end of data collection. The IMDC captures data on patients treated with any systemic therapy for mRCC, with data collection and analyses undertaken retrospectively.

Patients were included if they received 2L cabozantinib monotherapy with no restrictions based on underlying histology. Patients may have ceased 1L therapy for any reason, including progression, toxicity or patient choice. Patients may have received cabozantinib as part of a clinical trial in the 2L setting. Patients with missing data regarding treatment duration or survival were excluded.

Endpoints

The primary endpoints of the study were time to treatment failure (TTF) and overall survival (OS) for patients treated with 2L cabozantinib, based on preceding type of 1L therapy. Secondary endpoints included real world, investigator assessed best overall imaging response (BOR) to 2L cabozantinib, as per RECIST v.1.1.[14] The objective response rate (ORR) was reported as the proportion of patients with a complete response (CR) or partial response (PR), in patients who were response evaluable. Response evaluable patients were defined as having receipt of baseline imaging and at least 1 set of imaging studies post initiation of cabozantinib.

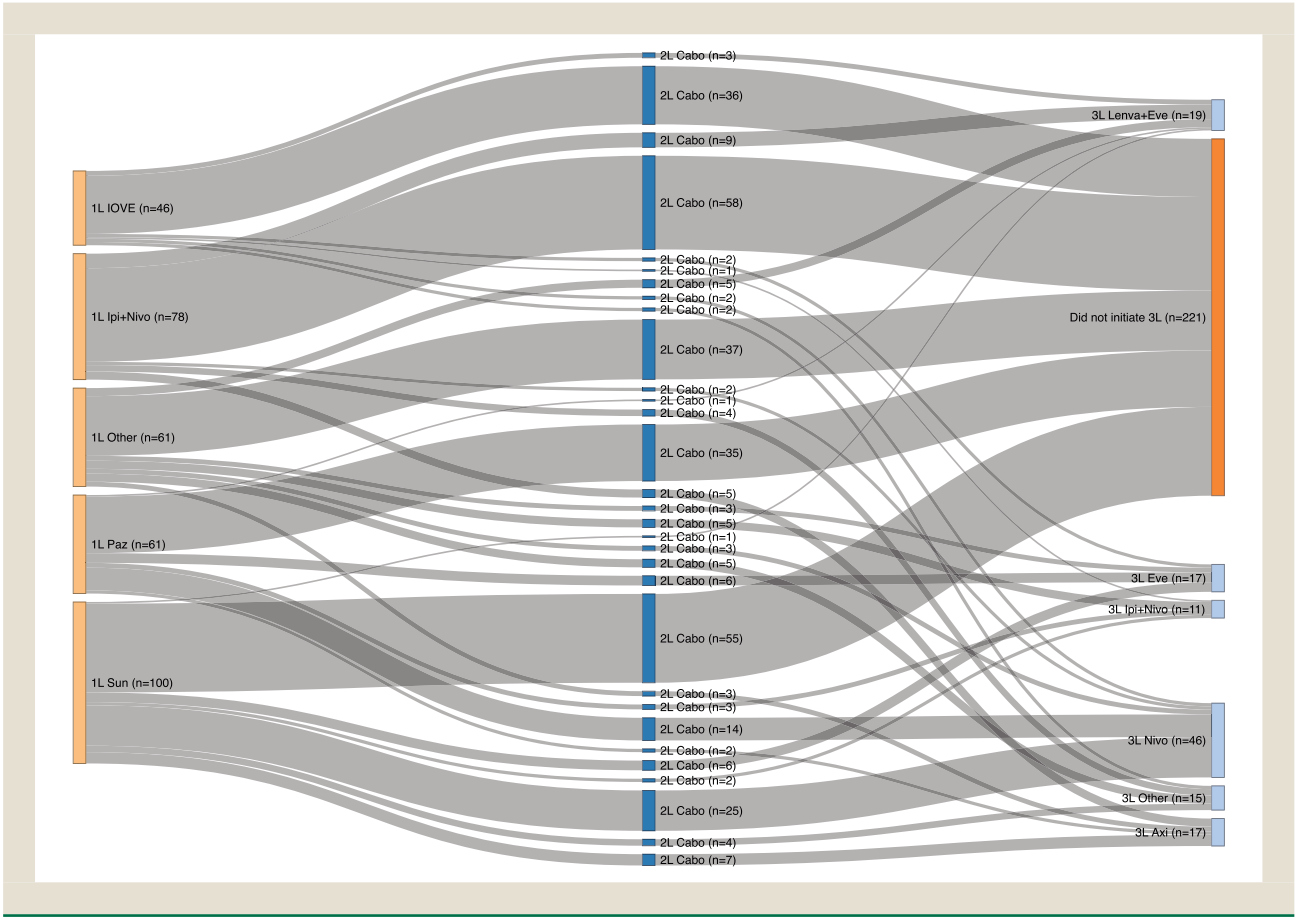
Statistical Analysis

Baseline demographic and clinical characteristics were described using percentages (%) for categorical variables and means with (standard deviation) for continuous variables. Chi-squared tests were used for comparisons of categorical variables and ANOVA for continuous variables. Absolute standardized differences comparing baseline characteristics according to preceding line of therapy were calculated.[15] No formal calculations of sample size or statistical power were performed given the observational nature of this cohort analysis. Data analysis is descriptive in nature.

TTF was defined as the time from commencement of 2L cabozantinib until treatment discontinuation, death, or censored last follow-up. OS was defined as the time from commencement of 2L cabozantinib to death or censored last follow up. The Kaplan Meier method was used to describe TTF and OS.

A multivariable Cox regression analysis, adjusted for underlying differences in baseline IMDC risk groups, was used to compare differences in OS and TTF between 2L cabozantinib patients treated with 1L IPI-NIVO, 1L IOVE, 1L pazopanib/sunitinib (PAZ/SUN) and 1L Other. IMDC risk factors have been described previously.[13] Analyses were conducted using R (v 4.1.0), with 2 sided tests and a significance level of ≤ 0.05. The median observation time was used to estimate the median follow-up.

Figure 1 Sankey diagram outlining treatment patterns for patients receiving second line(2L) cabozantinib.



Results

Baseline Characteristics

Three hundred and forty-six patients received 2L cabozantinib (13 missing due to incomplete survival data). The flow chart used to define the final analyzed population is outlined in the CONSORT diagram in Supplementary Figure 1. The Sankey diagram in Figure 1 outlines the treatment sequences of all patients that received 2L cabozantinib. Of patients that received 2L cabozantinib, 63.8% (221/346), did not receive any 3L therapy.

Of those that received 2L cabozantinib (Table 1), 78 were post 1L IPI NIVO, 46 post 1L IOVE, 161 post 1L PAZ/SUN, and 61 post 1L Other. Other 1L therapies included experimental or nonregulatory body approved combinations such as Atezolizumab/Bevacizumab, n = 24 or single agent anti-PD-1 agents nivolumab or pembrolizumab, n = 15. Of the entire cohort, 12.6%, 62.6%, and 24.8% were IMDC favourable, intermediate, and poor risk, respectively. 83.6% had clear cell histology, 18.5% had a sarcomatoid component and 38.3% had bone metastasis at diagnosis.

Comparing baseline characteristics of patients that received 2L cabozantinib, by 1L therapy, there were no statistically significant differences based on variables such as age at initiation of cabozantinib, gender, sites of metastases or sarcomatoid differentiation. Imbalances in IMDC risk were noted, as expected based on regulatory approvals, with significantly more IMDC poor risk patients treated with 1L IPI-NIVO (37.5% vs. 17.1% IOVE vs. 22.9% 1L PAZ/SUN P= .028). Significantly fewer non- clear cell patients received 1L IOVE (10.8%) or 1L IPI-NIVO (8.5%) vs. 1L PAZ/SUN (15.9%), P = .004, but due to the low absolute numbers in this subgroup it was not used as an adjustment factor in the subsequent Cox regression.

Time to Event Endpoints

Median observation time for OS from initiation of 2L cabozantinib was 9.5 months. Table 2 outlines the noted TTE endpoints and ORR for patients receiving 2L cabozantinib. Figure 2A presents the OS curves, and median OS (95% CI) for the overall population of patients receiving 2L cabozantinib. Median OS was 18.1 (95% CI, 15.4-24.1) months. Figure 2B outlines the OS curves in 2L cabozantinib stratified by type of 1L therapy, alongside log rank P values. The median OS for 2L cabozantinib, if patients received 1L IPI-NIVO was 21.4 (95%

Table 1 Baseline Characteristics of Patients Treated with 2L Cabozantinib

Variable	Overall	1L IOVE	1L Ipi + Nivo	1L Other	1L Paz/Sun	*P* value	Absolute Standardized Difference
N	346	46	78	61	161		
Age at Diagnosis of mRCC, Years (mean (SD))	60.04 (11.11)	59.40 (8.29)	58.94 (11.25)	59.67 (12.65)	60.91 (11.16)	.582	0.095
Age at Start of 2L Cabo, Years (mean (SD))	61.78 (11.29)	61.32 (8.25)	59.75 (11.23)	61.48 (12.90)	63.02 (11.36)	.208	0.151
Men (%)	272 (78.6)	33 (71.7)	64 (82.1)	50 (82.0)	125 (77.6)	.505	0.141
Liver Met at Diagnosis (%)	65 (19.5)	8 (18.2)	16 (21.9)	11 (18.3)	30 (19.2)	.944	0.051
Bone Met at Diagnosis (%)	130 (38.3)	16 (36.4)	31 (40.3)	24 (39.3)	59 (37.6)	.968	0.046
Brain Met at Diagnosis (%)	18 (5.4)	2 (4.5)	7 (9.6)	1 (1.7)	8 (5.1)	.238	0.184
Sarcomatoid (%)	46 (18.5)	5 (13.2)	12 (22.2)	15 (30.0)	14 (13.1)	.053	0.25
NonClear Cell (%)	48 (16.4)	4 (10.8)	6 (8.5)	18 (31.0)	20 (15.9)	.004	0.321
IMDC Score (%)						.028	0.371
Favourable	35 (12.6)	10 (24.4)	3 (4.7)	7 (12.7)	15 (12.7)		
Intermediate	174 (62.6)	24 (58.5)	37 (57.8)	37 (67.3)	76 (64.4)		
Poor	69 (24.8)	7 (17.1)	24 (37.5)	11 (20.0)	27 (22.9)		
Karnofsky Score < 80% (%)	32 (9.2)	3 (6.5)	10 (12.8)	4 (6.6)	15 (9.3)	.548	0.124
Calcium > ULN (%)	29 (8.4)	4 (8.7)	12 (15.4)	6 (9.8)	7 (4.3)	.036	0.197
Hemoglobin < LLN (%)	147 (42.5)	14 (30.4)	41 (52.6)	24 (39.3)	68 (42.2)	.101	0.238
Platelets > ULN (%)	47 (13.6)	5 (10.9)	15 (19.2)	8 (13.1)	19 (11.8)	.415	0.124
Neutrophil > ULN (%)	41 (11.8)	4 (8.7)	10 (12.8)	8 (13.1)	19 (11.8)	.896	0.076
Diagnosis to systemic tx less than one year (%)	230 (66.5)	27 (58.7)	67 (85.9)	40 (65.6)	96 (59.6)	<.001	0.338
Objective Response Rate in 1L (%)	77 (23.8)	18 (39.1)	10 (13.5)	13 (23.2)	36 (24.5)	.016	0.307
1L Systemic Tx (%)						<.001	
1L IOVE	46 (13.3)	46 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)		
1L Ipi+Nivo	78 (22.5)	0 (0.0)	78 (100.0)	0 (0.0)	0 (0.0)		
1L Other	61 (17.6)	0 (0.0)	0 (0.0)	61 (100.0)	0 (0.0)		
1L PAZ	61 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	61 (37.9)		
1L SUN	100 (28.9)	0 (0.0)	0 (0.0)	0 (0.0)	100 (62.1)		

Other = Patients that received 1L Atezolizumab/Bevacizumab; n=24 or single agent anti-PD-1 agents nivolumab or pembrolizumab, n=15
Acronyms – 1L= 1st line; IOVE = Immuno-oncology/vascular endothelial growth factor receptor combination; Paz = pazopanib; SUN = sunitinib

CI, 12.1 - NE [Not evaluable]) months compared to a median OS of 15.7 (95% CI, 9.3 - Not evaluable) months in 1L IOVE, 20.7 (95% CI, 15.6 - 35.6) months in 1L PAZ/SUN and 14.3 (95% CI, 10.5 - 28.8) months in 1L Other, $P = .28$. 1 year OS was broadly similar when examined by type of 1L therapy: 66.6% post 1L IPI-NIVO, 54.3% post 1L IOVE, 65.6% post 1L PAZ/SUN and 56.5% post 1L Other.

TTF from the initiation of 2L cabozantinib in the overall population is described in Figure 2C, with a median TTF of 7.6 (95% CI, 6.6 - 9.0) months in the overall population. The median TTF stratified by 1L therapy is outlined in Figure 2D with similar times to event endpoints noted post 1L IPI-NIVO 6.9 (95% CI, 6.1 - Not evaluable) months, 1L IOVE 5.7 (95% CI, 4.4 - Not evaluable) months, 1L PAZ/SUN 8.2 (95% CI, 7.3 - 10.8) and 1L Other 6.8 (95% CI, 5.0 - 17.9- 10) months, logrank $P = .67$.

In our multivariable IMDC risk group adjusted regression analysis, we were unable to detect a significant difference in OS in 2L cabozantinib treated patients based on their type of 1L therapy. No difference was found when 1L IPI-NIVO (reference group) was compared with 1L IOVE: a nonsignificant HR of 1.73 (0.83 - 3.62 $P = .14$). In a further sensitivity analysis, when other common 1L approaches such as 1L PAZ/SUN were compared to 1L IPI-NIVO, again no statistically significant difference in OS was identified 1.16 (0.67 - 2.00 $P = .60$), or with indeed any other 1L approach: 1L Other HR 1.32 (0.71 - 2.45 $P = .37$).

Similarly, no statistical difference was detected, when the TTF of patients that received 2L CABO was analysed by type of 1L therapy: 1L IPI-NIVO (reference group) vs. 1L IOVE HR 1.62 (0.89 - 2.95 $P = .11$), 1L PAZ/SUN 1.11 (0.70 - 1.76 $P = .65$) or 1L Other HR 1.16 (0.68 - 1.96 $P = 0.59$).

Best Overall Response

Of 2L CABO patients, 77.4% (268/346) of were response evaluable, please refer to the CONSORT diagram in Supplementary Figure 1, for further information on patient selection. Broadly ORR in 2L was similar irrespective of 1L therapy received, 26.4% post 1L IPI-NIVO vs. 32.5% post 1L IOVE vs. 25.2% post 1L PAZ/SUN vs. 20.8% post 1L other. A numerically higher percentage of patients experienced primary progressive disease as best response to 2L cabozantinib post 1L PAZ/SUN (30.6%), compared to 1L Other (24.5%) 1L IOVE (17.5%) and 1L IPI-NIVO (9.4%).

Table 2 Clinical Outcomes for Patients that Received 2L CABO

	Median TTF months (95% CI)	Median OS months (95% CI)	1 Year Treatment Failure Free	1 Year OS	Objective Response Rate	Progressive Disease
CABO post 1L ALL N = 346	7.59 (6.61 - 8.98)	18.12 (15.42 - 24.10)	34.3%	63.5%	26.2% 70/268	20.1%54/268
CABO post 1L IPI-NIVO N = 78	6.90 (6.05 - NE)	21.44 (12.07 - NE)	34.1%	66.6%	26.4% 14/53 (1.9% CR)	9.4% 5/53
CABO post 1L IOVE N = 46	5.72 (4.41 - NE)	15.68 (9.27 - NE)	26.8%	54.3%	32.5% 13/40 (0% CR)	17.5% 7/40
CABO post 1L PAZ/SUN N = 161	8.22 (7.33 - 10.82)	20.74 (15.58 - 35.64)	36.8%	65.6%	25.2% 37/147 (1.3% CR)	30.6% 45/147
CABO post 1L OTHER N = 61	6.84 (5.03 - 17.92)	14.30 (10.49 - 28.77)	32.1%	56.5%	20.8% 11/53	24.5% 13/53
CABO post 1L VEGFi METEOR[10]		21.4 (18.7 - NE)		73%	17%	14%

Acronyms – CABO= cabozantinib; VEGFi= Vascular endothelial growth factor receptor inhibitor; TTF= Time to treatment failure; OS= Overall survival; CI= confidence interval; 2L= Second line

Discussion

This dataset is the largest examination of the activity of 2L cabozantinib in a real world context. Accepting the limitations of comparing real world to clinical trial data, TTE and real world imaging endpoints from our study are similar to that of the pivotal METEOR[10] experience, as outlined in Table 2, with a numerically identical median OS of 21.4 months post 1L IPI-NIVO presented herein and observed post 1L VEGFi inhibition in METEOR.

Because METEOR, the sands have rapidly shifted, with 1L IO combination therapies becoming firmly established in the treatment paradigm for the majority of patients.[16] No patients in METEOR were treated with 1L IPI-NIVO or 1L IOVE and thus real world, observational approaches are critical to identifying the role of cabozantinib in appropriate sequencing of treatments in mRCC. With 124 patients receiving preceding contemporary standard of care IO combination therapy in this dataset, these findings represent a current, relevant outline of cabozantinib activity.

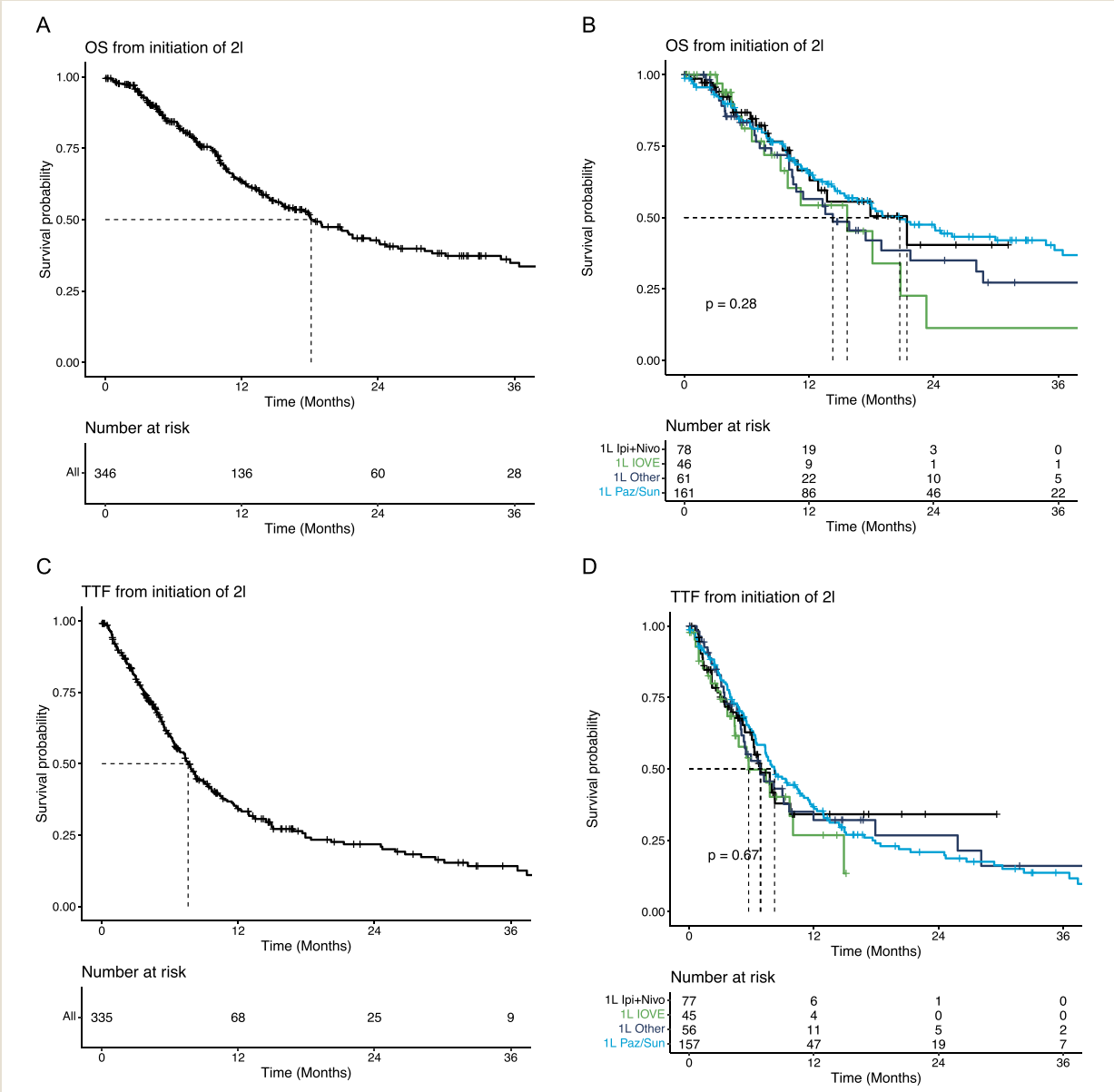
With clinically meaningful TTE data, similar ORR, overlapping TTF and OS curves and no significant differences detected on adjusted multivariable Cox regression, there is comparable activity of 2L cabozantinib irrespective of preceding 1L therapy. Major regulatory labels for cabozantinib, such as the European Medicines Agency[17] and Health Canada[18] limit the treatment refractory monotherapy indication to VEGFi experienced patients only, with no comment on cabozantinib sequencing post 1L IO combination approaches. Access to subsequent therapies is important in improving outcomes for patients living with cancer. This is emphasized by the 63.8% of patients that received no 3L therapy post 2L cabozantinib. Given the number of post IO combination patients included, this work can give confidence to clinicians that cabozantinib has activity following 1L contemporary IO combinations, irrespective of whether a VEGFRi is included. The recent introduction of 1L IOVE combinations speaks to the instability of those survival curves after the respective medians are reached. There remain many unanswered questions re: the optimum sequence of therapies post progression with 1L combination therapies and until randomized trials such as CONTACT-03[19] read out, real world analyses of large cohorts remain relevant to inform practice.

Data outlining cabozantinib activity post 1L IO combination therapies is limited to primarily real world analyses[12,20] and posthoc subgroup analyses of pivotal trials.[21] Prospective data outlining cabozantinib activity is sparse, and includes the phase II, nonrandomised BREAKPOINT trial, in a 1L IO combination experienced population, which was recently presented in abstract form.[22] Forty-eight evaluable patients received a median of 10 cycles of cabozantinib, with a 43% response rate. A median progression free survival of 9.3 months alongside a 34% >= grade 3 adverse event rate outlined the promising role of this agent in a contemporary setting. Similarly, the phase 3 randomized CANTATA trial, which compared a glutaminase inhibitor telaglenastat + cazobanitnib vs placebo + cabozantinib, outlined the activity of cabozantinib in an IPI-NIVO experienced population. An exploratory pre-specified analysis of the post IPI-NIVO subgroup found a median PFS of 9.2 months, with an ORR of 37%. Of note, the addition of the glutaminase inhibitor did not improve efficacy of cabozantinib.[23]

A relevant examination of the activity of cabozantinib in contemporary real world practice was outlined by *McGregor et al.*[20] Eighty-six IO experienced patients, with a higher number of median treatment lines, 2, and increased incidence of poorer prognostic features at baseline such as 52.3% bone metastases had a short median OS of 13.1 months. A 2-centre retrospective experience of 2L VEGFi-TKI cohort post 1L IO containing therapy (excluding IOVE) identified 19 patients receiving 2L cabozantinib. The notable robust cabozantinib activity described in that cohort, with a median progression free survival of 15.2 months (7.9 - NE), 74% OS at 1 year and 47% ORR may be related to the requirement to have clear cell histology exclusively, or the fact that all patients received their IO 1L therapy in a trial setting, implying a higher probability of improved outcomes, given that established favourable prognostic risk factor.[24]

There are a number of limitations to this work that should be considered. It may be contested that a HR of 1.73 (95% CI, 0.83-3.62 $P = .14$) for OS in 2L cabozantinib patients treated with IOVE vs IPI-NIVO (reference) is potentially clinically meaningful, if not statistically significant. The large confidence intervals in our regression analysis suggests a potential lack of statistical power to make such descriptive

Figure 2 A – Overall survival from time of initiation of 2L cabozantinib in the overall population B - Overall survival from time of initiation of 2Lcabozantinib by type of first line(1L) therapy received C – Time to treatment failure from time of initiation of 2Lcabozantinib in the overall population D - Time to treatment failure from time of initiation of 2Lcabozantinib by type of 1Ltherapy received.



comparisons. Furthermore, an inability to identify statistical difference between outcomes based on varying preceding lines of treatment does not necessarily imply equivalence, given the nature of this observational data. Mature follow up and future accrual will help clarify any interaction for activity of 2L cabozantinib in terms of OS by type of 1L therapy received. There are a number of treatment selection biases in deciding 1L therapy in mRCC that may not have been captured in our analysis, supported by the low prevalence of patients with a Karnofsky Performance Status of <80 (9.2%) in our cohort, compared to other real world experiences of 2L VEGFRi in mRCC.[25] However, our work reflects a real world, multi-national, academic and community centre experience and this increases the relevance and replicability of this data. Our lack of dosing information and toxicity data also limit this work given the established exposure-response relationship for cabozantinib.[12]

This data adds to the body of work supporting the role of VEGFi TKI in later lines of therapy. Given the multiple active agents in mRCC, further randomized prospective trials are required to elucidate optimum treatment sequencing, either as a single agent or in novel

combinations.[19,26] Until then, large, international collaborative approaches such as this work are critical in clarifying the relative place in the paradigm of various agents, including cabozantinib.

Conclusion

This study provides outcome benchmarks for 2L cabozantinib in a contemporary setting. These TTE and imaging endpoints can be utilised by clinicians in patient counselling when sequencing treatments in the contemporary post IO combination therapy era. There is clinically relevant activity of 2L cabozantinib irrespective of 1L therapy received.

Clinical Practice Points

- There are limited data evaluating the activity of cabozantinib (CABO) as second line (2L) therapy post standard of care ipilimumab-nivolumab (IPI-NIVO) or immuno-oncology(IO)/vascular endothelial growth factor inhibitor (VEGFi) combinations (IOVE).
- Using the IMDC database, we sought to identify the objective response rate, time to treatment failure (TTF) and overall survival (OS) of 2L CABO after IPI-NIVO, IOVE combinations, pazopanib or sunitinib (PAZ/SUN) or other 1L therapies.
- In a large real world dataset, we identified clinically meaningful activity of 2L CABO after all evaluated contemporary 1L therapies. We were unable to detect a significant difference in 2L CABO OS based on type of 1L therapy received: 1L IPI-NIVO (reference group) vs. 1L IOVE HR 1.73 (95% CI, 0.83 - 3.62 $P = .14$), 1L PAZ/SUN 1.16 (0.67 - 2.00 $P = .60$).
- Given the number of post IO combination patients included, this work can give confidence to clinicians that cabozantinib has activity following 1L contemporary IO combination, irrespective of whether a VEGFRi is included. This data adds to the body of work supporting the role of VEGFi TKI in later lines of therapy. Given the multiple active agents in metastatic renal cell carcinoma, further randomized prospective trials are required to elucidate optimum treatment sequencing, either as a single agent, or in novel combination. Until then, large, international collaborative approaches such as this work are critical in clarifying the relative place in the paradigm of various agents, including cabozantinib.

Author Contributions

Ethics consent has been provided by each IMDC participating site. A provincial state-wide Alberta ethics (Health Research Ethics Board of Alberta) has provided overseeing ethics approval for the IMDC. Data analysis and statistical code utilised can be made available on reasonable request, Conceptualisation, VN DH, Methodology, VN DH DB DB WC, Investigation, VN CW BM CL AS RM LM SP FD BB MO LL TP BS TC DH DB DB WC, Writing Original & Review, VN DH DB DB WC, Supervision, DH

Disclosure

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.07.008.

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