Cabozantinib real-world effectiveness in the 1st- through 4th-line settings for the treatment of metastatic renal cell carcinoma (mRCC): Results from the International mRCC Database Consortium (IMDC)

Chun Loo Gan[1], Shaan Dudani[1], J. Connor Wells[1], Frede Donskov[2], Sumanta K Pal[3], Nazli Dizman[3], Nityam Rathi[4], Benoit Beuselinck[5], Flora Yan[6], Aly-Khan A. Lalani[7], Aaron Hansen[8], Bernadett Szabados[9], Guillermo de Velasco[10], Ben Tran[11], Jae Lyun Lee[12], Ulka N Vaishampayan[13], Georg A. Bjarnason[14], Mathushan Subasri[15], Toni K. Choueiri[16], Daniel Y.C. Heng[1,*]

[1]Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [2]Aarhus University Hospital, Aarhus, Denmark; [3]City of Hope Comprehensive Cancer Center, Duarte, CA; [4]Huntsman Cancer Hospital, Salt Lake City, Utah; [5]University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [6]University of Texas Southwestern Medical Center, Dallas, Texas; [7]Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; [8]Princess Margaret Cancer Centre, Toronto, ON, Canada; [9]Queen Mary University of London, Barts Cancer Institute, London, UK; [10]University Hospital 12 de Octubre, Madrid, Spain; [11]Personalised Oncology Division, Walter and Eliza Hall Institute of Medical Research; Peter MacCallum Cancer Center, Parkville, Victoria, Australia; [12]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [13]Barbara Ann Karmanos Cancer Institute, Detroit, Michigan; [14]Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; [15]London Ontario Health Sciences Centre; [16]Dana-Farber Cancer Institute/Brigham and Women's Hospital/Harvard Medical School, Boston, MA

Background

- Cabozantinib is approved for metastatic renal cell carcinoma (mRCC) based on the METEOR and CABOSUN trials.
- Real-world effectiveness and dosing patterns of cabozantinib are not well characterized over different lines of therapy and post immuno-oncology (IO) combination therapies.
- The need for dose reduction in TKIs (a surrogate for toxicity and adequate drug exposure) is associated with improved outcome[1,2] but this has not been investigated with cabozantinib.
- We describe the efficacy and dosing patterns of cabozantinib in the first- (1L), second- (2L), third- (3L), and fourth-line (4L) settings.

Methods

- Using the IMDC dataset, we identified all patients treated with cabozantinib between 2011 and 2019.
- Outcome measures of interest were:
  - Objective response rate (ORR), Time to treatment failure (TTF), Overall survival (OS)
  - Impact of the need for dose reduction on TTF and OS
- Multivariable Cox regression analysis was performed to control for imbalances in IMDC risk factors.

Results

413 patients with mRCC treated with cabozantinib were identified.

- Patient characteristics are reported in Table 1.
- The treatment outcomes and dose patterns are shown in Table 2 and 3, respectively. The ORR for all patients was 27% (81/304).
- Overall, 50% (129/258) of patients required dose reduction.
- The TTF and OS were significantly longer for patients who required dose reduction, compared to those who did not (see Figure 1).
- Median time to dose reduction was 1.2 months.

Table 1: Baseline characteristics and IMDC risk factors

	1st line (N=34)	2nd line (N=143)	3rd line (N=142)	4th line (N=94)
Age, median (IQR)	62 (57-70)	57 (49-64)	56 (50-63)	57 (50-64)
Male	88% (30/34)	80% (115/143)	77% (109/142)	78% (73/94)
Clear cell histology	44% (10/23)	82% (85/104)	75% (88/118)	87% (65/75)
Sarcomatoid histology	14% (3/21)	20% (20/98)	19% (21/109)	6% (4/71)
Prior nephrectomy	74% (25/34)	76% (109/143)	87% (124/142)	88% (83/94)
Liver metastases	9% (3/34)	17% (24/143)	18% (25/143)	16% (15/94)
Bone metastases	27% (9/34)	39% (55/143)	30% (43/143)	26% (24/94)
Lung metastases	59% (20/34)	67% (96/143)	70% (100/143)	69% (65/94)
Brain metastases	6% (2/34)	4% (5/143)	7% (10/143)	2% (2/94)
IMDC risk groups				
Favourable	14% (4/29)	12% (13/107)	11% (11/98)	9% (6/69)
Intermediate	41% (12/29)	64% (68/107)	59% (58/98)	49% (34/69)
Poor	45% (13/29)	24% (26/107)	30% (29/98)	42% (29/69)
IMDC risk factors at time of initiation of cabozantinib				
KPS <80%	29% (9/31)	21% (25/122)	31% (40/129)	40% (35/88)
Diagnosis to therapy <1 yr	70% (23/33)	73% (105/143)	51% (73/142)	49% (46/94)
Calcium > ULN	7% (2/31)	6% (7/122)	13% (14/107)	20% (14/71)
Hemoglobin < LLN	58% (18/31)	59% (76/130)	65% (82/126)	70% (59/84)
Neutrophils > ULN	19% (6/31)	12% (15/129)	23% (27/120)	23% (18/80)
Platelets > ULN	16% (5/31)	8% (10/130)	18% (22/124)	24% (20/83)

KPS = Karnofsky performance status; ULN = upper limit of normal; LLN = lower limit of normal

Figure 1: Effect of the need for dose reduction due to toxicity on TTF and OS

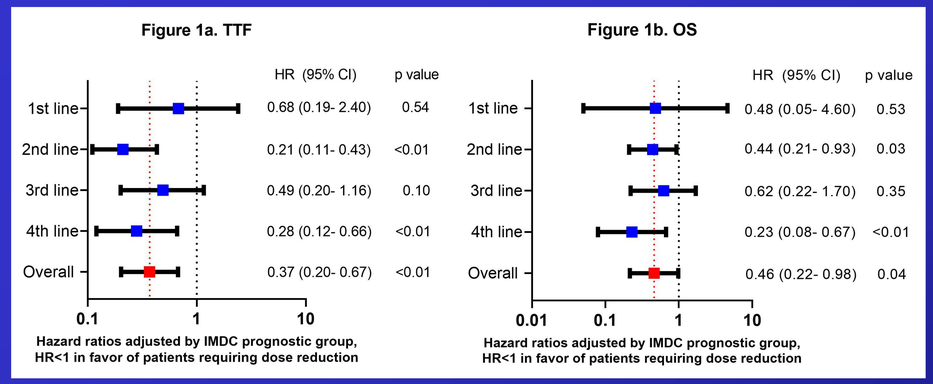

Table 2: 1L to 4L treatment outcomes

	1st line	2nd line	3rd line	4th line	Post 1st line IO Combos
ORR	32% (9/28)	26% (28/109)	25% (25/102)	29% (19/65)	22% (5/23)
Best response					
CR	0% (0/28)	1% (1/109)	0% (0/102)	2% (1/65)	0% (0/23)
PR	32% (9/28)	25% (27/109)	25% (25/102)	28% (18/65)	22% (5/23)
SD	50% (14/28)	52% (57/109)	48% (49/102)	49% (32/65)	57% (13/23)
PD	18% (5/28)	22% (24/109)	28% (28/102)	22% (14/65)	21% (5/23)
TTF (mo) (95% CI)	8.3 (4.6-6.0)	7.3 (5.5-8.2)	7.0 (5.0-9.4)	8.0 (5.6-10.4)	5.4 (4.4-5.8)
Median OS (mo) (95% CI)	30.7 (5.8-36.8)	17.8 (11.9-23.3)	12.6 (9.3-21.7)	14.9 (10.2-21.7)	17.4 (4.8-23.3)

IO Combos include Ipilimumab/Nivolumab (n=5) and various PD(L)1 + VEGF inhibitor combinations (n=18); CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; CI = confidence interval

Table 3: Dose patterns of cabozantinib across 1L to 4L

	1st line	2nd line	3rd line	4th line
Median final daily dose for patients who had dose reduction	40mg	40mg	40mg	40mg
Average daily dose	36.6mg	37.8mg	34.8mg	34.7mg
Percentage of patients discontinued treatment due to toxicities	32% (7/22)	16% (14/85)	26% (17/65)	30% (11/37)

Conclusions

- The ORR and TTF of cabozantinib were maintained from the 1L to 4L therapy settings.
- Dose reduction rates were similar to those in clinical trials.
- Dose reduction due to toxicity was associated with improved TTF and OS. This contributes to mounting evidence that TKI toxicity is associated with better outcomes and that toxicity is a surrogate of adequate drug exposure, as has been prospectively studied for sunitinib and axitinib[3,4].
- Cabozantinib has clinical activity after 1L IO combination agents with an ORR of 22%, TTF 5.4 months and OS of 17.4 months.

References

1. Parmar A, Bjarnason G. Individualization of Dose and Schedule Based On Toxicity for Oral VEGF Drugs in Kidney Cancer. *Kidney Cancer.* 2019;3:213-225.
2. Sternberg CN, Motzer RJ, Hutson TE, et al. COMPARZ Post Hoc Analysis: Characterizing Pazopanib Responders With Advanced Renal Cell Carcinoma. *Clin Genitourin Cancer.* 2019;17(6):425-435 e424.
3. Bjarnason GA, Knox JJ, Kollmannsberger CK, et al. The efficacy and safety of sunitinib given on an individualised schedule as first-line therapy for metastatic renal cell carcinoma: A phase 2 clinical trial. *Eur J Cancer.* 2019;108:69-77.
4. Ornstein MC, Pal SK, Wood LS, et al. Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2019;20(10):1386-1394.

Correspondence to: Daniel YC Heng MD MPH FRCPC, Tom Baker Cancer Centre, Calgary, Alberta, Canada. **Daniel.Heng@ahs.ca** **@DrDanielHeng**