Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Prior systemic therapies to cabozantinib

Prior treatment	Total population (N = 88) N (%)[1]
≥ 1 VEGFR TKI agent	68 (77)
Sunitinib	49 (56)
Pazopanib	25 (28)
Axitinib	20 (23)
Temsirolimus	4 (5)
Everolimus	11 (12.5)
Anti PD-1	48 (55)
Nivolumab + Ipilimumab	20 (23)
ICI + anti- VEGF(R)	5 (6)

Abbreviations: ICI: Immune Checkpoint Inhibitor;

[1]Patients may have received more than 1 prior therapy

eTable 2. Antitumor activity of cabozantinib according to baseline characteristics

	Cohort A[1]		Cohort B[2]	
	N = 31	Intracranial response rate	N = 53	Intracranial response rate
Number of brain metastases				
-1	6	3 (50%)	12	3 (25%)
-2	7	4 (57%)	17	9 (53%)
-≥3	17	9 (53%)	24	13 (54%)
- unknown	1	1		
Prior brain-directed therapy				
-No	11	8 (73%)	2	2 (100%)
-Yes	20	9 (45%)	51	23 (45%)
IMDC risk group				
-Favorable	7	4 (57%)	4	2 (50%)
-Intermediate	12	10 (83%)	30	13 (43%)
-Poor	12	3 (25%)	18	10 (56%)
- Unknown	-	-	1	0

Abbreviations: TTF: Time to treatment failure; OS: Overall Survival

[1] Evidence of radiological intracranial progressive disease at baseline (prior brain-directed local therapy was allowed if radiological confirmation of intracranial progression before starting cabozantinib).

[2] Patients with stable brain metastases at cabozantinib initiation or patients with progressing BM concomitantly treated by brain-directed local therapy. Concomitant brain-directed local therapy was defined as any brain-directed local therapy within two months prior to cabozantinib initiation.

eTable 3. Overall incidence of adverse events considered related to cabozantinib

	Treatment population (N= 88)							
Adverse Events	**Overall**		**Grade 1-2**		**Grade 3-4**		**Unknown grade**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
No. of subjects with any events	**81**	**92**	**79**	**90**	**15**	**17**	**6**	**7**
Fatigue	68	77	59	67	6	7	3	3
Diarrhea	40	46	39	44	1	1	-	-
Palmar-plantar erythrodysesthesia	28	32	26	30	2	2	-	-
Nausea	27	31	23	23	1	1	3	3
Mucositis	25	28	20	26	4	5	1	1
Hypertension	22	25	20	23	-	-	2	2
Vomiting	14	16	12	14	1	1	1	1
Transaminitis	10	11	9	10	-	-	1	1
Hypothyroidism	5	6	5	6	-	-	-	-
Thrombocytopenia	4	5	2	2	2	2	-	-
Dyspnea	4	5	3	3	-	-	1	1
Proteinuria	3	3	1	1	1	1	1	1
Neutropenia	1	1	-	-	1	1	-	-

Data are n (%). Includes adverse events after the date of first dose and including 30 days after the date of last dose of cabozantinib. Patients with multiple occurrences of the same toxicity were counted only once at the maximum grade. No grade 5 adverse events were reported.

eFigure. Gadolinium enhanced brain magnetic resonance imaging of one patient in cohort A (no history of brain radiotherapy). Left cerebellum metastasis measured 7 mm at baseline, 4 mm at 12 week follow-up representing partial response