Cabozantinib associated with concomitant radiotherapy or a bone-targeted agent (multimodal approach, results from the CABOREAL study *post hoc* analysis)

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Marine Gross-Goupil,[a] Aude Fléchon,[b] Loïc Mourey,[c] Delphine Topart,[d] Gwenaëlle Gravis,[e] Stéphane Oudard,[f] Jean M Tourani,[g] Lionnel Geoffrois,[h] Emeline Meriaux,[i] Antoine Thiery-Vuillemin,[j] Philippe Barthélémy,[k] Sylvain Ladoire,[l] Brigitte Laguerre,[m] Laetitia Zara,[n] Valérie Perrot,[n] Bernard Escudier,[o] Laurence Albiges[o]

[a]Hôpital Saint-André, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [b]Centre Léon Bérard, Lyon, France; [c]IUCT-Oncopôle Institut Claudius Regaud, Toulouse, France; [d]Centre Hospitalier Universitaire de Montpellier, Montpellier, France; [e]Institut Paoli-Calmettes, Marseille, France; [f]Hôpital Européen Georges Pompidou, Paris, France; [g]Poitiers Teaching Hospital, Poitiers, France; [h]Institut de Cancérologie de Lorraine, Vandœuvre-Lès-Nancy, France; [i]Centre François Baclesse, Caen, France; [j]University Hospital Jean Minjoz, Besançon, France; [k]Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [l]Center GF Leclerc, Dijon Cedex, France; [m]Centre Eugène Marquis, Rennes, France; [n]Ipsen, Boulogne-Billancourt, France; [o]Gustave Roussy, Université Paris-Saclay, Villejuif, France

Background

- Radiotherapy may also help to control pain associated with advanced and metastatic cancer, particularly bone metastasis.[1]
- Cabozantinib is approved as monotherapy in Europe for the treatment of advanced renal cell carcinoma in treatment-naive adults with intermediate or poor risk, or following prior vascular endothelial growth factor-targeted therapy.[2]
- Bone is a common site of tumour cell spread in metastatic renal cell carcinoma (mRCC). Bone metastasis is present in approximately one-third of patients at diagnosis and develops in a further one-third of patients during the course of their disease.[3,4]
- Bone metastasis is associated with poor prognosis in patients with mRCC receiving targeted treatment such as cabozantinib, and patients may therefore benefit from concomitant bone-targeted agents (cBTA).[5]
- The CABOREAL study (ClinicalTrials.gov identifier NCT03744585) examined real-world use of cabozantinib in the largest unselected population to date of patients with mRCC.[6]

Objective

- The aim of this study was to report the use and activity of cabozantinib in the subgroup of patients from CABOREAL who received concomitant radiotherapy (cRT) or cBTA.

Methods

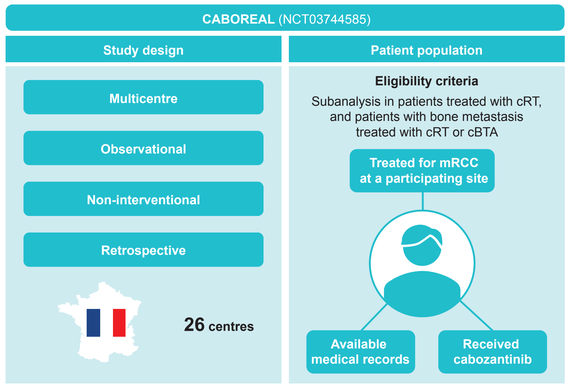
Study design

- CABOREAL was a multicentre, observational, non-interventional, retrospective study involving 26 centres in France (**Figure 1**).
- The study included patients who received cabozantinib treatment for mRCC via the French Early Access Program (from 12 September 2016 until the official licensing on 19 February 2018).

Patient population

- Patients were eligible for inclusion if they:
  - had been treated for mRCC at one of the participating sites via the French Early Access Program
  - had received at least one dose of cabozantinib
  - had available medical records.

Figure 1. Overview of study methods



cBTA, concomitant bone-targeted agents; cRT, concomitant radiotherapy; mRCC, metastatic renal cell carcinoma.

Table 1. Baseline characteristics and treatment history

	All patients		Patients with bone metastasis			
	+ cRT (n = 85)	− cRT (n = 325)	+ cRT (n = 62)[a]	− cRT (n = 172)	+ cBTA (n = 35)	− cBTA (n = 194)
Age, years, median (range)	63.0 (36.0–82.0)	64.0 (22.0–92.0)	62.0 (38.0–82.0)	64.0 (23.0–92.0)	63.0 (42.0–81.0)	63.0 (23.0–92.0)
ECOG PS score, n (%)						
< 2	50 (59.5)	197 (61.0)	33 (54.1)	94 (54.7)	16 (45.7)	106 (54.9)
≥ 2	34 (40.5)	126 (39.0)	28 (45.9)	78 (45.3)	19 (54.3)	87 (45.1)
Missing	1	2	1	0	0	1
Clear-cell histology, n (%)	79 (92.9)	271 (83.6)	59 (95.2)	146 (84.9)	31 (88.6)	170 (87.6)
Missing	0	1	0	0	0	0
Number of metastatic sites, n (%)						
1	7 (8.2)	28 (8.6)	5 (8.1)	7 (4.1)	2 (5.7)	10 (5.2)
2	17 (20.0)	102 (31.4)	13 (21.0)	45 (26.2)	11 (31.4)	44 (22.7)
3	38 (44.7)	110 (33.8)	28 (45.2)	55 (32.0)	13 (37.1)	68 (35.1)
≥ 4	23 (27.1)	85 (26.2)	16 (25.8)	65 (37.8)	9 (25.7)	72 (37.1)
Missing	0	1	0	0	0	0
Number of previous treatment lines, n (%)						
0	0	3 (0.9)	0	2 (1.2)	0	2 (1.0)
1	21 (24.7)	80 (24.6)	15 (24.2)	45 (26.2)	11 (31.4)	49 (25.3)
2	27 (31.8)	110 (33.8)	21 (33.9)	58 (33.7)	16 (45.7)	60 (30.9)
3	20 (23.5)	62 (19.1)	14 (22.6)	33 (19.2)	3 (8.6)	42 (21.6)
≥ 4	17 (20.0)	70 (21.5)	12 (19.4)	34 (19.8)	5 (14.3)	41 (21.1)
Previous nephrectomy, n (%)						
Yes	77 (90.6)	274 (84.3)	57 (91.9)	141 (82.0)	28 (80.0)	165 (85.1)

[a]Includes five patients who did not have bone metastasis at cabozantinib initiation. Percentages are subject to rounding.
cBTA, concomitant bone-targeted agents; cRT, concomitant radiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Cabozantinib exposure and patterns of use

	All patients		Patients with bone metastasis			
	+ cRT (n = 85)	− cRT (n = 325)	+ cRT (n = 62)	− cRT (n = 172)	+ cBTA (n = 35)	− cBTA (n = 194)
Dose at initiation, % (95% CI)						
60 mg	75.3 (64.7–84.0)	69.8 (64.4–74.7)	75.8 (63.3–85.8)	69.0 (61.5–75.8)	68.6 (50.7–83.1)	71.0 (64.0–77.3)
40 mg	23.5 (15.0–34.0)	27.5 (22.7–32.7)	22.6 (12.9–35.0)	28.1 (21.5–35.4)	28.6 (14.6–46.3)	26.4 (20.4–33.2)
20 mg	1.2 (0.0–6.4)	2.2 (0.9–4.4)	1.6 (0.0–8.7)	2.3 (0.6–5.9)	2.9 (0.1–14.9)	2.1 (0.6–5.2)
Other	0	0.6 (0.1–2.2)	0	0.6 (0.0–3.2)	0	0.5 (0.0–2.9)
Missing	0	1	0	1	0	1
Treatment duration, months, median (range)	10.9 (0.6–29.1)	6.5 (0.1–28.0)	10.7 (1.0–29.1)	5.7 (0.1–27.8)	8.2 (1.1–22.7)	6.9 (0.1–29.0)
Average daily dose, mg, median (range)	37.9 (17.8–60.0)	40.0 (13.9–60.0)	40.2 (17.8–60.0)	40.1 (13.9–60.0)	36.7 (13.9–60.0)	40.5 (14.9–60.0)
Dose modification, % (95% CI)	61.2 (50.0–71.6)	58.0 (52.4–63.5)	56.5 (43.3–69.0)	53.8 (46.0–61.4)	68.6 (50.7–83.1)	51.8 (44.5–59.0)
Dose reduction, % (95% CI)	58.8 (47.6–69.4)	56.5 (50.9–62.0)	53.2 (40.1–66.0)	52.6 (44.9–60.3)	65.7 (47.8–80.9)	50.3 (43.0–57.5)
Alternative dosing schedule,[a] % (95% CI)	20.0 (12.1–30.1)	14.5 (10.9–18.8)	19.4 (10.4–31.4)	11.1 (6.8–16.8)	5.7 (0.7–19.2)	14.5 (9.9–20.3)

[a]Modification of dosing frequency without change in dose. Percentages are subject to rounding.
cBTA, concomitant bone-targeted agents; CI, confidence interval; cRT, concomitant radiotherapy.

Data analysis

- In this subanalysis, data on treatment duration, dosing regimen, and overall survival (OS) were summarized for the following groups, based on concomitant therapy.
  - Cabozantinib with cRT versus no cRT in all patients.
  - Cabozantinib with cRT versus no cRT in patients with bone metastasis.
  - Cabozantinib with cBTA versus no cBTA in patients with bone metastasis.
- Descriptive analyses were conducted.
- The Wilcoxon–Mann–Whitney test was used to compare the duration of treatment between groups.

Results

Baseline characteristics

- Of 410 patients treated with cabozantinib during the study, 85 received cRT; of these patients with cRT, 24.7% received cabozantinib as second-line therapy, 31.8% as third-line therapy, and 43.5% as fourth-line therapy and beyond. In addition, 73 (85.9%) of 85 patients with cRT did not require cabozantinib dose interruption.
- In total, 229 patients had bone metastasis, 35 of whom received cBTA (denosumab or bisphosphonates).
- Baseline characteristics and treatment history according to concomitant therapy are summarized in **Table 1**.

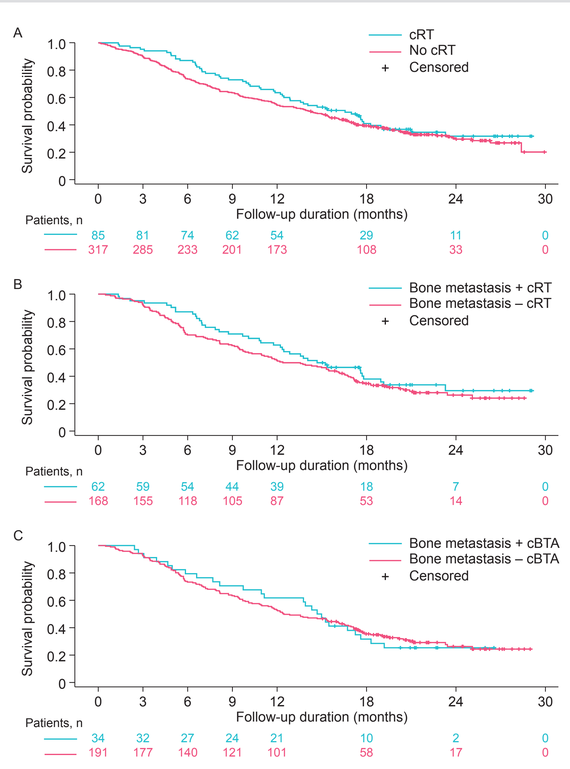
Cabozantinib treatment patterns

- Cabozantinib exposure and patterns of use are summarized in **Table 2**.
- The median (range) durations of treatment were as follows.
  - In patients treated with cRT versus those with no cRT: 10.9 (0.6–29.1) months versus 6.5 (0.1–28.0) months ($p < 0.001$).
  - In patients with bone metastasis treated with cRT versus those with no cRT: 10.7 (1.0–29.1) months versus 5.7 (0.1–27.8) months ($p < 0.001$).
  - In patients with bone metastasis treated with cBTA versus those with no cBTA: 8.2 (1.1–22.7) months versus 6.9 (0.1–29.0) months (not significant).

Overall survival

- In patients treated with cRT versus those with no cRT (**Figure 2A**):
  - median (95% confidence interval [CI]) OS was 16.6 (12.4–19.0) months versus 14.2 (11.8–16.1) months
  - OS rate at 24 months was 31.7% versus 29.5%.
- In patients with bone metastasis treated with cRT versus those with no cRT (**Figure 2B**):
  - median (95% CI) OS was 15.0 (11.8–19.0) months versus 13.0 (9.9–16.2) months
  - OS rate at 24 months was 29.7% versus 26.4%.
- In patients with bone metastasis treated with cBTA versus those with no cBTA (**Figure 2C**):
  - median (95% CI) OS was 14.8 (9.7–17.6) months versus 12.5 (10.8–16.2) months
  - OS rate at 24 months was 25.3% versus 26.2%.

Figure 2. Overall survival following cabozantinib initiation, by concomitant therapy



cBTA, concomitant bone-targeted agents; cRT, concomitant radiotherapy.

Conclusions

- Previously reported findings[7] from CABOREAL showed a median OS of 14.4 months in the overall population and 13.7 months in patients with bone metastasis, a population known to have a poor prognosis in mRCC.[5]
- In this subanalysis of data from the largest (N = 410) real-world study to date of cabozantinib in patients with mRCC, the use of cRT was associated with a longer duration of cabozantinib treatment in the second- and third-line setting or beyond than no cRT, suggestive of an enhanced management strategy.
- Similar trends were observed for the use of cRT and cBTA in patients with bone metastasis.
- These findings suggest that a multimodal approach using cRT and cBTA alongside cabozantinib may represent a beneficial management strategy for patients with mRCC.

Abbreviations

cBTA, concomitant bone-targeted agents; CI, confidence interval; cRT, concomitant radiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mRCC, metastatic renal cell carcinoma; OS, overall survival.

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Author contributions All authors have contributed to study conception/design, drafting of the publication or revising it critically for scientific accuracy and important intellectual content, and final approval of the publication.

Disclosures MG-G: honoraria (self), advisory board and travel/accommodation/expenses – AstraZeneca, Bristol Myers Squibb, Ipsen, MSD, Novartis, Pfizer, Roche. **AF:** honoraria (self) and travel/accommodation/expenses – Bristol Myers Squibb, Ipsen, Merck, Pfizer. **LM:** honoraria (self) and travel/accommodation/expenses – Astellas, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, MSD, Pfizer, Sanofi; advisory/consultancy – Astellas, Bristol Myers Squibb, Janssen, Sanofi. **DT:** expert testimony (self and institution) – Astellas; invited speaker (self and institution) – Bristol Myers Squibb; invited speaker (institution) – Sanofi; advisory board (self and institution) – Janssen. **GG:** funding (institution) – Janssen; invited speaker (institution) – Amgen, Astellas, Bristol Myers Squibb, Janssen, MSD, Sanofi; advisory board (institution) – AAA Pharma, Alliance, Bristol Myers Squibb, Janssen, Merck-Pfizer, Pfizer; principal investigator (PI)/co-ordinating PI (institution) – Bristol Myers Squibb; travel/accommodation/expenses – Bristol Myers Squibb, Janssen, Sanofi. **SO:** research grant/funding (institution) – AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Janssen, Pfizer, Sanofi; advisory board, honoraria (self) and travel/accommodation/expenses – Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Janssen, Merck, Novartis, Pfizer, Sanofi. **JMT:** nothing to disclose. **LG:** advisory board (self) – Bristol Myers Squibb, Ipsen, Merck, MSD, Pfizer; invited speaker (self) – Ipsen. **EM:** nothing to disclose. **ATV:** honoraria and consulting/advisory role – Astellas, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi; research funding – Pfizer; travel/accommodation/expenses – Astellas, AstraZeneca, Ipsen, Janssen, MSD, Roche/Genentech. **PB:** honoraria – Seagen; advisory/consultancy role – Amgen, Astellas, Bristol Myers Squibb, EUSA Pharma, Ipsen, Janssen Cilag, MSD, Novartis, Pfizer, Roche, Sanofi; travel/accommodation/expenses – Astellas, Bristol Myers Squibb, Ipsen, Janssen, MSD, Pfizer, Roche, Sanofi. **SL:** research grant/funding (institution) – Novartis; expert testimony (self) – Astellas, Bristol Myers Squibb, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi; travel/accommodation/expenses – Astellas, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, Novartis, Pfizer, Sanofi. **BL:** honoraria (self) – Astellas, AstraZeneca, Ipsen, Janssen, MSD, Pfizer, Roche; travel/accommodation/expenses – Bristol Myers Squibb, Novartis, Pfizer. **LZ:** full-/part-time employment and shareholder/stockholder/stock options – Ipsen. **VP:** full-/part-time employment and shareholder/stockholder/stock options – Ipsen. **BE:** advisory board (self) – Aveo, Bristol Myers Squibb, Eisai, Ipsen, Pfizer. **LA:** honoraria (institution) and advisory/consultancy role (institution) – Astellas, AstraZeneca, Bellerophon, Bristol Myers Squibb, Corvus Pharmaceuticals, Ipsen, Janssen, Merck & Co., MSD, Novartis, Pfizer, Springer Healthcare; research grant/funding (institution) – Bristol Myers Squibb.

Acknowledgements The authors thank all patients involved in the study, as well as their caregivers, care team, investigators, and research staff in participating institutions.

Medical writing support The authors thank David Gothard (PhD) of Oxford PharmaGenesis, Oxford, UK, for providing medical writing support, which was industry sponsored in accordance with Good Publication Practice (GPP3) guidelines.

For further information, please send your question(s) to Marine Gross-Goupil (**marine.gross-goupil@chu-bordeaux.fr**).

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Presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2021 | Virtual format | 16–21 September 2021

This study was sponsored by Ipsen