ABSTRACT

Title

Prospective non-interventional study of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy

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Keywords

Advanced renal cell carcinoma, cabozantinib, dose modifications, dose interruptions, dose reductions, treatment discontinuations, real-life setting, pattern of use

Rationale and background

Renal cell carcinoma (RCC) is diagnosed in about 330,000 individuals worldwide each year and results in over 140,000 deaths [Ferlay et al, 2015]. Up to 30% of patients present with metastatic disease at initial diagnosis [Gupta et al, 2008]. In advanced stages, despite an increasing number of available systemic therapies such as immunotherapies, VEGF targeted therapies and mammalian target of rapamycin (mTOR) inhibitors for this malignancy, virtually all patients eventually relapse.

Cabometyx™ containing cabozantinib is indicated as monotherapy for advanced renal cell carcinoma as first line treatment of adult patients with intermediate or poor risk and in adults following prior VEGF-targeted therapy and in combination with nivolumab for the first line treatment of advanced renal cell carcinoma in adults.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor (TKI) with potent activity against MET, VEGF receptors (VEGFRs) and AXL as well as a number of other receptors of tyrosine kinases that have also been implicated in tumour pathobiology, including RET, KIT and FLT. Cabozantinib suppresses MET and VEGFR signalling, rapidly inducing apoptosis of endothelial and tumour cells, resulting in tumour regression in a variety of xenograft models [Sennino and McDonald, 2012; Yakes et al, 2011].

In the pivotal phase III METEOR study, treatment with cabozantinib was associated with a significant number of treatment-emergent adverse events (TEAEs) and a large majority of subjects required at least one dose modification (i.e. interruption or reduction) due to an adverse event (AE). In the real-world setting, the pattern of cabozantinib use and management of patients during treatment is largely unknown. The aim of this study was to understand the use of cabozantinib in real-life settings in terms of dose modifications due to AEs and thus to be able to identify if there were any prevalent practice patterns which would call for implementation of new measures to optimise the use of cabozantinib in RCC.

Research question and objectives

This prospective study aimed to understand the utilisation of cabozantinib in subjects with advanced RCC following prior VEGF-targeted therapy in real-life settings in terms of dose modifications due to AEs when used as a second line therapy or third and later line therapy. Other patterns of use of cabozantinib as indicated in the objectives were also studied.

Primary objective

- To describe the pattern of dose interruptions, reductions or discontinuations of cabozantinib due to AEs in clinical practice when used as a second or third and later line therapy.

Secondary objectives

- To describe the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings;
- To describe all treatment-emergent non-serious and serious AEs (SAEs);
- To describe the effectiveness of cabozantinib in RCC in real-life in terms of progression free survival (PFS) and best overall response (BOR);
- To describe the health care resource utilisation associated with the management of treatment related AEs during the treatment period (hospitalisation, surgical procedures, emergency room visits, intensive care unit stays, concomitant medications, physician visits and homecare visits by nurse, unplanned laboratory tests).

Study design

This was a prospective, international, multicentre, voluntary noninterventional post-authorisation safety study (PASS) conducted at 91 study centres in 11 European countries over a period of 4 years.

Setting

To avoid physician led selection bias, participating physicians were asked to include all successive eligible subjects except those who refused the collection of and/or access to their data until the required number of subjects were included in each of the two subgroups.

As the study sought to investigate the real-life management of patients in clinical practice, cabozantinib was administered as directed by the Investigator according to the study site's routine clinical practice and the Summary of Product Characteristics of Cabometyx™. There was no mandated schedule of assessments. Visits and evaluations were decided by the Investigator, based on local routine clinical practice. The Investigator then reported any data available for the applicable study assessments during a pre-defined data reporting period.

The length of follow-up was a maximum of 12 months per subject from treatment initiation.

Subjects and study size, including dropouts

The subjects fulfilling the following inclusion criteria were included, there were no exclusion criteria for this study.

(1) Aged ≥18 years old;
(2) Had a diagnosis of advanced RCC;
(3) Had received at least one prior VEGF-targeted therapy;
(4) For whom the treating physician had decided to start treatment with cabozantinib tablets prior to inclusion;
(5) No previous exposure to cabozantinib prior to inclusion;
(6) Not concurrently involved in an interventional study;
(7) Consented to participate in this non-interventional study.

The sample size of the study was based on the primary endpoint, i.e. the proportion of subjects with dose modifications due to AEs based on the Investigator's decision (temporary interruption, dose reduction or discontinuation) assessed for each line of treatment (second line therapy or third and later line therapy). Based on the pivotal Phase 3 METEOR study, it was assumed 75% of subjects would require a dose modification. Therefore, a sample size of 289 subjects was calculated to be able to estimate a 2-sided 95% level of confidence of the dose modification proportion with a precision of ±5%. For a precision of at least 5% in each therapy line group, a minimum of 289 subjects were required in each subgroup. Assuming that up to 15% subjects

would start cabozantinib on a regimen different from the recommended regimen at initiation, a total of at least 680 subjects were required, 340 subjects in each subgroup.

Variables and data sources

Variables

- *Demographic characteristics*: age, gender, body height, tobacco use, occupational status, sick leave status.
- *Baseline characteristics*: presence of significant medical history, history and baseline characteristics of RCC, previous systemic treatment for RCC including surgery, baseline clinical parameters including Eastern Cooperative Oncology Group (ECOG) performance status, weight, height, blood pressure, electrocardiograms (ECGs), planned frequency of radiological assessments during cabozantinib treatment.
- *Cabozantinib pattern of use*: date of cabozantinib initiation, line of treatment, cabozantinib starting dose and schedule, date of the last dose of cabozantinib, any modification in the dose with date, concomitant radiotherapies, systemic therapy planned following cabozantinib discontinuation.
- *Effectiveness*: date of clinical and radiographic progression or death, overall response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or by other standard of care according to local routine clinical practice.
- *Health care resource utilisation during treatment with cabozantinib for treatment related AEs*: hospitalisation, surgical procedures, emergency room visits, intensive care unit stays, concomitant medications (initiation or change to manage AEs), physician visits and homecare visits by nurse, unplanned laboratory tests.
- *Safety*: serious and non-serious AEs, ECOG performance status, weight, blood pressure, clinically significant abnormalities observed for clinical laboratory tests and 12-lead ECGs (any abnormal clinically significant results recorded as AE/SAE), concomitant radiotherapies and surgeries.

Data sources

Data sources included medical records and work-up results.

Results

Subject disposition

A total of 689 subjects were included in the study in countries where cabozantinib was marketed at the time of the study (i.e. Austria, Belgium, Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain and the United Kingdom).

Of the 689 included subjects, eight failed screening and two died before the start of treatment. A total of 679 subjects were treated; 335 subjects received cabozantinib as a second line therapy and 343 subjects as a third and later line. One subject received cabozantinib as a first line therapy.

By the completion of the study, 455 subjects (67.0%) were withdrawn and 224 subjects (33.0%) completed the study. Overall, the most common reasons for withdrawal were progressive disease (222 subjects, 48.8%) and deaths (115 subjects, 25.3%) followed by AEs (57 subjects, 12.5%) and consent withdrawal (26 subjects, 5.7%).

All of the 679 subjects were included in the full analysis set (FAS) and Safety Populations and 433 subjects were included in the Primary Safety Population. A total of 246 subjects (36.2%) who did not start cabozantinib at the recommended dose of 60 mg daily were excluded from the Primary Safety Population.

Baseline disease characteristics

Demographics were similar between the two therapy line groups. Overall, the majority of subjects were male (496 subjects, 73.0%). The mean (standard deviation, SD) age was 65.6 (10.4) years with more than half of subjects aged ≥65 years (393 subjects, 57.9%). The countries whose centres contributed a higher number of subjects overall were France (174 subjects, 25.6%), Italy (159 subjects, 23.4%) and Spain (108 subjects, 15.9%).

The majority of subjects (580 subjects, 85.7%) had clear cell RCC at diagnosis, the remaining subjects had non-clear cell RCC (97 subjects, 14.3%). Cancer histology at diagnosis was not reported for two subjects. The most common RCC stage at diagnosis was metastatic Stage IV (310 subjects, 46.4%). However, by the start of cabozantinib treatment, most of the subjects had progressed to metastatic Stage IV (664 subjects, 97.8%). The most common sites with at least one metastasis were lungs (408 subjects, 60.1%), lymph nodes (306 subjects, 45.1%) and bones (276 subjects, 40.6%).

In terms of baseline metastatic RCC prognosis, risk category was missing for almost 50% of the subjects (IMDC/Heng score missing for 303 subjects (44.6%) and MSKCC/Motzer score missing for 336 subjects (49.5%)). Of the subjects with available category for metastatic RCC prognosis at baseline, majority of the subjects were evaluated to be in the intermediate risk category according to both IMDC/Heng score (239 subjects, 63.6%)) and MSKCC/Motzer score (228 subjects, 66.5%). The study included 69 subjects (18.4%) under favourable risk category according to the IMDC/Heng score and 66 subjects (19.2%) according to the MSKCC/Motzer score. The study also included subjects under poor risk category (68 subjects (18.1%) as per the IMDC/Heng score and 49 subjects (14.3%) according to the MSKCC/Motzer score).

Overall, 281 subjects (41.4%) had a prior significant medical or surgical history. A large proportion of subjects had an ongoing significant medical or surgical history (539 subjects, 79.4%). The majority of subjects had prior nephrectomies (545 subjects, 80.3%) and most of the subjects had undergone a prior radical surgical procedure (497 subjects, 91.2%) with a curative intent (441 subjects, 80.9%).

In the third and later line group, the majority of subjects (258 subjects, 75.2%) had received two prior systemic therapies, a much smaller proportion of subjects had received three or more.

The TKIs (sunitinib and pazopanib) were commonly used prior first line systemic therapy in both groups while programmed death receptor-1 (PD1) inhibitor, nivolumab was the most commonly used second-line systemic therapy in the third and later line group (228 subjects, 66.5%).

The median time (range) since diagnosis in this study was 36.63 (1.9, 341.3) months. The time since diagnosis was 44.48 (5.4, 341.3) months for the third and later line group and 30.09 (1.9, 311.3) months for the second line group with considerable interindividual variability among subjects in both groups.

The median (range) study exposure was overall close to nine months (8.74 (0.0, 15.4) months) and was similar between the two therapy groups: 8.51 (0.2, 15.4) and 9.26 (0.0, 15.0) months in the second line group and third and later line group, respectively.

Primary endpoint

The primary endpoint was analysed on subjects in the Primary Safety Population, i.e. the subjects who started cabozantinib at the prescribed recommended dose of 60 mg daily.

Overall, 77.1% (95% CI: 72.9; 81.0) of subjects had a dose modification due to AEs. This was similar between the two therapy line groups; 76.4% (95% CI: 70.4; 81.6) versus 78.1% (95% CI: 71.6; 83.6) of the subjects in the second and third and later line groups, respectively.

The most common dose modifications due to AEs, observed in approximately half of the subjects in the Primary Safety Population were dose reduction (56.8% of subjects, 95% CI: 52.0; 61.5) and dose interruption (53.1% of subjects, 95% CI: 48.3; 57.9). The proportion of subjects with a dose reduction due to an AE was similar between the second and third and later line groups: 56.5% (95% CI: 50.0; 62.9) versus 57.1% (95% CI: 49.9; 64.2) of subjects, respectively. The proportion of subjects with a dose interruption due to an AE was also similar between the second and third and later line group: 53.2% (95% CI: 46.6; 59.7) versus 53.1% (95% CI: 45.8; 60.2) of subjects, respectively. Approximately a quarter of the subjects required dose discontinuation due to an AE (23.8% of subjects, 95%CI: 19.9; 28.1) with similar frequencies between the two therapy line groups: 22.8% (95%CI: 17.6; 28.7) of subjects in the second line group versus 25.0% (95%CI: 19.1; 31.7) of subjects in the third and later line group.

In the Primary Safety Population, nearly than two-thirds of the subjects had a dose modification due to an AE considered as related to cabozantinib (70.2% of subjects, 95% CI: 65.7; 74.5) with similar frequencies between the two therapy line groups: 69.2% (95% CI: 62.9; 75.0) and 71.4% (95% CI: 64.6; 77.6) of subjects in the second line and third and later line groups, respectively.

A supportive analysis performed on the subjects who started cabozantinib at 40 mg/day (N=221) showed that dose modifications due to AE were numerically lower in these subjects (70.6%, 95% CI: 64.1; 76.5) than those starting at 60 mg/day. The proportion of subjects requiring dose reductions was also numerically lower in this subgroup (43.9%, 95% CI: 37.2; 50.7) than those who started at 60 mg/day.

The results of the supportive analysis on the Safety Population (N=679, subjects who had taken at least one dose of cabozantinib) were generally consistent with the results of primary analysis.

<u>Secondary endpoint - Pattern of use of cabozantinib in real-life clinical settings (Safety Population)</u>

- *Dose and duration of treatment*

- Majority of the subjects were either treated with cabozantinib as a second (335 subjects, 49.3%) or third line (257 subjects, 37.8%) therapy. Fewer subjects were treated with cabozantinib as a fourth or later line therapy (86 subjects, 12.7%). Of all the subjects, only one received cabozantinib as first line therapy.
- Of 679 subjects, 433 (64.0%) started cabozantinib treatment at the recommended dose of 60 mg/day. Of these, more subjects started cabozantinib as second line therapy (237 subjects, 54.7%) than as third and later line therapy (196 subjects, 45.3%).
- Of 679 subjects, 221 (32.5%) started cabozantinib treatment at a dose of 40 mg/day. Among these subjects, 58.8% (130 of 221 subjects) started in the third and later line and 40.7% (90 of 221 subjects) started in the second line.
- Very few subjects started cabozantinib treatment at 20 mg/day (2.7% of subjects) or other dose (1.0% of subjects).
- The subjects were treated with a median (range) average daily dose of 40.0 (7.8; 60.0) mg/day which was similar between the two groups: 40.7 (17.0; 60.0) mg/day in the second line group and 39.2 (7.8; 60.0) mg/day in the third and later line group.

- Among the subjects previously treated with nivolumab in the Safety Population, majority of the subjects (285 of 296 subjects, 96.3%) started cabozantinib treatment as third and later line therapy. Around half of the subjects in the third and later line group (56.5%) started cabozantinib treatment at the recommended dose of 60 mg/day (161 of 285 subjects). Around 39.0% of the subjects in the third and later line group started cabozantinib treatment at a dose of 40 mg/day (111 of 285 subjects). Very few subjects started cabozantinib treatment at 20 mg/day or other dose. The overall median (range) average daily dose in this subgroup of subjects previously treated with nivolumab was 39.9 (13.8; 60.0) mg/day and overall mean (SD) dose intensity was 0.789 (0.238).

• *Dose modifications for any reason*

- Overall, majority of the subjects had a dose modification for any reason (637 subjects, 93.8%). The proportion of the subjects requiring a dose modification was similar between the second and third and later line groups (94.6% and 93.3% of subjects, respectively).
- Mean (SD) number of dose modifications for any reason experienced by the overall subjects was 2.7 (2.3). Mean (SD) number of dose modifications in the second and third and later line groups during follow-up was 2.5 (1.9) and 3.0 (2.6), respectively, and the median (range) number was 2.0 (1, 10) and 2.0 (1, 20), respectively.
- Of all the subjects, 395 (58.2%) had at least one dose/treatment modification which involved either a dose reduction or a dose increase.
- Of all the subjects, 384 (56.6%) had at least one dose reduction for any reason which was similar between the second and third and later line groups (56.1% and 57.1% of subjects, respectively). The most common reason for a dose reduction in both groups were AEs, mainly diarrhoea, Palmar plantar erythrodysaesthesia syndrome, asthenia, decreased appetite and fatigue. Of these, 366 subjects (53.9% of all the subjects) had a dose reduction independent of their dosing schedule. Only 56 subjects (8.2%) overall had a dose schedule change independent of a dose change. This was similar between the second and third and later line therapy groups.
- At least one dose increase for any reason was reported for 81 subjects (11.9%). This was numerically higher in the subjects in the third and later line group (14.0%) than in the second line group (9.9%). Dose increases occurred mainly for subjects on a dose of cabozantinib below the recommended dose of 60 mg/day and primarily due to previous treatment interruption or dose reduction.
- At least one treatment interruption for any reason was reported for 396 subjects (58.3%). The proportion of subjects with a treatment interruption was higher in the third and later line than in the second line group (61.2% versus 55.5% of subjects, respectively). The most common reason for a treatment interruption in both groups was an AE. The median (range) duration of interruption was comparable between the second and third and later line groups: 21.0 (2.0; 123.0) and 19.5 (1.0; 225.0) days, respectively.
- Of the 679 subjects, 437 (64.4%) discontinued treatment. Treatment discontinuation was similar between the second and third and later line groups (65.4% and 63.6% of subjects, respectively). The most common reasons of treatment discontinuation were disease progression (197 subjects, 45.1%) and AEs (171 subjects, 39.1%).

• *Time to first dose modification*

- The overall median time to first dose modification due to AE was 60.0 (95% CI: 57.0; 68.0) days. Median time to first dose modification due to AE was

longer for subjects in the second line group than for those in the third and later line group: 68.0 (95% CI: 58.0; 84.0) and 56.0 (95% CI: 49.0; 61.0) days, respectively.

- The median time to first dose modification for any reason overall was 51.0 (95% CI: 45.0; 56.0) days. Median time to first dose modification for any reason was longer for subjects in the second line group than for those in the third and later line group; 57.0 (95% CI: 52.0; 62.0) and 44.0 (95% CI: 39.0; 50.0) days, respectively.

• *Concomitant radiotherapies*

- Concomitant radiotherapies were reported for 70 subjects (10.3%) with similar proportion between the second and third and later line groups. Of these subjects, the majority (61 of 70 subjects, 87.1%) had only one concomitant radiotherapy at any site, mostly bone (47 of 70 subjects, 67.1%), in both the therapy groups.

• *Planned systemic therapies following cabozantinib discontinuation*

- Of the 437 subjects who discontinued cabozantinib treatment, nearly half of the subjects (206 subjects, 47.1%) had subsequent systemic therapies planned with a higher proportion of the subjects in second line group (120 of 219 subjects, 54.8%) than in the third and later line group (86 of 218 subjects, 39.4%). In the second line group, the most common subsequent systemic therapy was nivolumab (97 of 120 subjects, 80.8%) whilst in the third and later line group, the most common subsequent systemic therapies were axitinib (23 of 86 subjects, 26.7%), everolimus (17 of 86 subjects, 19.8%), nivolumab (14 of 86 subjects, 16.3%) and other antineoplastic agents (14 of 86 subjects, 16.3%).

<u>Secondary endpoint – Effectiveness of cabozantinib in RCC in real-life setting (FAS Population)</u>

• *Overall response rate (ORR) as per RECIST 1.1*

- In the 313 evaluable subjects, as per RECIST 1.1, an ORR of 31.3% (95% CI: 26.2; 36.8) was reported. The ORR was higher in the third and later line group than in the second line group: 40.9% (95% CI: 33.1; 49.1) versus 22.0% (95% CI: 15.8; 29.3) of subjects, respectively.

• *ORR as per other standard of care*

- In the 242 evaluable subjects, as assessed by other standard of care, in the FAS Population, the proportion of subjects with ORR was 39.5% (95% CI: 33.3; 46.0). The ORR was higher in the third and later line group than in the second line group: 48.0% (95% CI: 39.1; 57.1) versus 30.4% (95% CI: 22.2; 39.7) of subjects, respectively.

• *ORR as per whatever the method*

- The ORR based on whatever the method of assessment analysed the subjects with no radiological assessment in two ways; such subjects were either not included in the analysis or were included as non-responders if the reason for cabozantinib discontinuation was “death”, “adverse event” or “disease progression” (subjects with reason of discontinuation other than mentioned above were not considered).
- The analysis excluding the subjects with no radiological assessment, included 555 subjects and reported an ORR of 34.9% (95% CI: 30.9; 39.0). The ORR was higher in the third and later line group than in the second line group: 44.1% (95% CI: 38.2; 50.1) versus 25.5% (95% CI: 20.5; 31.1) of subjects, respectively.
- The analysis considering the subjects with no radiological assessment as non-responders (90 subjects of 645) reported an ORR of 30.0% (95% CI: 26.5; 33.7) which was higher

in the third and later line group than in the second line group: 38.0% (95% CI: 32.7; 43.5) versus 21.9% (95% CI: 17.5; 26.9) of subjects, respectively.

- These analyses in subgroups showed worst effectiveness in subjects with presence of bone metastases, the subjects in poor risk group and subjects with non-clear cell RCC where the ORR was numerically higher in the third and later line group than in the second line group.

• *Progression Free Survival*

- The median duration of PFS, as assessed by RECIST 1.1, was 8.7 (95% CI: 7.9; 9.7) months in the overall subjects. The median duration of PFS was 9.2 (95% CI: 8.0; 10.9) months in the subjects in the third and later line group, marginally higher than 8.1 (95% CI: 6.3; 9.4) months in the second line group.
- The median duration of PFS, as assessed by other standard of care, was marginally lower (7.8 (95% CI: 6.5; 8.8) months) than the PFS assessed by RECIST 1.1. The median PFS in the subjects in the second line group and the third and later line group was 7.0 (95% CI: 5.4; 8.8) months and 8.1 (95% CI: 6.5; 9.6) months, respectively.
- The median duration of PFS, assessed as whatever the method, was 8.3 (95% CI: 7.4; 8.8) months. The median PFS in the second line group and in the third and later line group was 7.8 (95% CI: 6.3; 8.7) months and 8.7 (95% CI: 7.6; 9.6) months, respectively.

• *Overall Survival Rate*

- Overall, the proportion of surviving subjects at 4 months, 8 months and 12 months was 90%, 81% and 74%, respectively.
- The estimates of the proportion of surviving subjects in the second line therapy group was 90% at 4 months, 82% at 8 months and 76% at 12 months.
- In the third and later line therapy group, 89%, 80% and 72% of the subjects were surviving at 4 months, 8 months and at 12 months, respectively.

<u>Secondary endpoint – Healthcare resource utilisation associated with the management of treatment-related AEs (Safety Population)</u>

• *Hospitalisations, Surgical Procedures and Visits*

- Around 39.6% of the subjects in the Safety Population were hospitalised at least once during the study with equal rate between the two therapy line groups. The mean (SD) number of hospitalisations per subject was 1.5 (0.9) for a mean (SD) duration of 13.9 (13.9) days.
- Overall, 16.6% of the subjects had emergency room visits and 3.5% had intensive care unit (ICU) stays. The visits were similar between the two therapy line groups.
- Unplanned physician and oncology specialist visits were numerically higher in the subjects in the third and later line therapy group than in the subjects in second line therapy group.

• *Concomitant Medications for Adverse Events*

- Majority of the subjects received concomitant medications for the management of adverse events (582 of 679 subjects, 85.7%). The proportion of the subjects receiving concomitant medications was marginally higher in the third and later line group (298 of 343 subjects, 86.9%) than in the second line group (283 of 335 subjects, 84.5%). The concomitant medications from the therapeutic classes of antidiarrheals (212 of 679 subjects, 31.2%), analgesics (200 of 679 subjects, 29.5%), systemic antibacterials

(168 of 679 subjects, 24.7%), thyroid therapy (144 of 679 subjects, 21.2%) and systemic corticosteroids (121 of 679 subjects, 17.8%) were commonly used for the management of adverse events.

• *Unplanned Laboratory Tests*

- Unplanned laboratory tests were performed for 113 of 679 subjects (16.6%). The proportion of the subjects with at least one unplanned laboratory tests was higher in the third and later line group (70 of 343 subjects, 20.4%) than in the second line group (43 of 335 subjects, 12.8%).

Safety (Safety Population)

• *All TEAEs*

- Overall, 5309 TEAEs were reported by 651 (95.9%) subjects. The proportion of subjects with a TEAE was similar between the two treatment line groups; 2376 TEAEs were reported by 320 (95.5%) subjects in the second line group and 2929 TEAEs by 330 (96.2%) subjects in the third and later line group.
- The TEAEs were mostly mild (Grade 1; 2610 TEAEs in 528 subjects, 77.8%) or moderate (Grade 2; 1811 TEAEs in 534 subjects, 78.6%) in intensity. Of the remaining TEAEs, a large proportion were severe (Grade 3; 633 TEAEs in 322 subjects, 47.4%), several were life-threatening or disabling (Grade 4; 51 TEAEs in 46 subjects, 6.8%) and several led to death (Grade 5; 133 TEAEs in 129 subjects, 19.0%).
- The most common TEAEs overall, also the most common in the two therapy line groups, were diarrhoea, decreased appetite, Palmar-plantar erythrodysaesthesia syndrome, asthenia, hypertension, fatigue, nausea and weight decrease.
- Commonly reported TEAEs of Grade 3 intensity were diarrhoea, hypertension, Palmar-plantar erythrodysaesthesia syndrome, asthenia, fatigue, decreased appetite, weight decrease and nausea.
- Grade 4 intensity TEAEs were not frequent and included single occurrences of different PTs under metabolism and nutrition disorders, gastrointestinal disorders and infections and infestations. Among the most of the commonly reported TEAEs with cabozantinib, Grade 4 intensity TEAEs were only reported for diarrhoea and hypertension in one subject each in the second line group.

• *Treatment-related TEAEs*

- Majority of the TEAEs were considered related to study treatment; 3592 related TEAEs were reported in 614 (90.4%) subjects. The proportion of subjects with a treatment-related TEAE was similar between the two therapy line groups. A total of 1650 treatment-related TEAEs were reported in 301 (89.9%) subjects in the second line group and 1942 treatment-related TEAEs were reported in 313 (91.3%) subjects in the third and later line group. The most common related TEAEs overall, also the most common in the two therapy line groups, were diarrhoea, decreased appetite, Palmar-plantar erythrodysaesthesia syndrome, asthenia, hypertension, fatigue, nausea, hypothyroidism, mucosal inflammation, weight decrease, stomatitis, dysgeusia and vomiting.
- Related TEAEs were mostly mild (Grade 1; 1853 TEAEs in 483 subjects, 71.1%) or moderate (Grade 2; 1301 TEAEs in 477 subjects, 70.3%) in intensity, a large proportion were severe (Grade 3; 373 TEAEs in 237 subjects, 34.9%), a few were life-threatening or disabling (Grade 4; 21 TEAEs in 18 subjects, 2.7%) and a few led to death (Grade 5; 16 TEAEs in 13 subjects, 1.9%). This was similar between the two therapy line groups.

- *TEAEs leading to dose modifications*

- Of the 5309 TEAEs in 651 subjects, 1478 TEAEs in 510 subjects needed a dose modification. Thus around 27.8% of all TEAEs were associated with dose modification. The proportion of the TEAEs associated with dose modification was similar between the two therapy line groups (28.8% in the second line group and 27.0% in the third and later line group). The most common TEAEs associated with a dose modification were diarrhoea, Palmar-plantar erythrodysaesthesia syndrome, asthenia, decreased appetite, fatigue, nausea, vomiting, mucosal inflammation, stomatitis, hypertension, weight decrease, hypothyroidism, abdominal pain, dysgeusia and general physical health deterioration.
- Of 1478 TEAEs associated with a dose modification, temporary interruption of cabozantinib treatment was required to manage 942 TEAEs (63.7%) while dose reduction was required for 783 TEAEs (53.0%).
- Of all the TEAEs, 286 (approximately 5.4%) required treatment discontinuation of cabozantinib to manage the TEAEs in 171 subjects (25.2%).

- *Serious TEAEs*

- Overall, 556 serious TEAEs were reported by 313 (46.1%) subjects of which 180 serious TEAEs were considered related to treatment in 124 (18.3%) subjects. The proportion of subjects reporting a serious TEAE, irrespective of whether related or not, was similar between the two therapy line groups. Serious TEAEs reported in ≥5 subjects were general physical health deterioration, disease progression, pneumonia, pulmonary embolism, dyspnoea, diarrhoea, pleural effusion, pyrexia, death, sepsis, asthenia, respiratory failure, vomiting, arthralgia, cardiac failure, anaemia, hypothyroidism, hypomagnesaemia, condition aggravated, COVID-19 and lower respiratory tract infection.

- *SAEs leading to death*

- Overall, 133 fatal SAEs were reported for 129 (19.0%) subjects in the study. Of these, 32 fatal SAEs of disease progression in 32 subjects (4.7%) and 26 fatal SAEs of general physical health deterioration in 26 subjects (3.8%) were reported. Among the subjects with disease progression as the primary reason of death, two subjects in the third and later line group also had other fatal SAEs; one subject had dyspnoea while the other had acute kidney injury and multiple organ dysfunction syndrome. Other fatal SAEs reported in more than 1 subject were death (8 subjects), respiratory failure and condition aggravated (5 subjects each), pulmonary embolism (4 subjects), pneumonia, sepsis, and malignant neoplasm progression (3 subjects each), asthenia, multiple organ dysfunction syndrome, sudden death, pleural effusion, intestinal obstruction and acute kidney injury (2 subjects each). The remaining fatal SAEs were reported in 1 subject each. Majority of the fatal SAEs were judged by the investigators to be not related to the study treatment. However, SAEs such as gastric obstruction, pulmonary embolism, pneumonia, increased transaminase were deemed to be possibly related to the study treatment. Few events of pancytopenia and pulmonary embolism were considered as probably related. Some of the deaths and disease progressions were also considered possibly related to the study treatment.

Discussion

Cabozantinib in second or later lines of therapy was efficient and manageable in a real-world setting. Although the majority of subjects required a dose reduction or temporary dose interruption due to an AE, the rate of treatment discontinuations due to AEs was low. No noteworthy differences were noted between the two treatment line groups when considering the proportion of subjects experiencing TEAEs, related-TEAEs, serious TEAEs and the intensity of TEAEs

The practice of monitoring for TEAEs and managing them by reducing the dose or temporarily interrupting treatment could optimise the use of cabozantinib in RCC.

Overall, the safety profile of cabozantinib in this study was consistent with the known safety profile of cabozantinib. No new safety signal was identified.

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Names and Affiliations of Principal Investigators

Principal Investigator	A Principal Investigator at each site was responsible for the conduct of the study at that site.
Coordinating Investigator:	PPD