PASS INFORMATION

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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Joint PASS	No
Research question and objectives	The aim of this prospective study is 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 adverse event (AEs) when used as a second line therapy or third and later line therapy. Other patterns of use of cabozantinib are also described as listed in the study objectives. The aim of this report is to provide an interim analysis of data at a cut-off of three months follow-up for the first 340 subjects to complete, or be withdrawn, within the first three months of follow-up. The primary objective was 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. The secondary objectives were to describe: • the use of cabozantinib in subjects with advanced RCC treated in real-life clinical settings;

	• all treatment-emergent nonserious and serious AEs; • the effectiveness of cabozantinib in RCC in real-life in terms of progression free survival and best overall response; • 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).
Countries of study	Austria, Belgium, Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain and the United Kingdom
Author	PPD Ipsen Pharma 65, quai Georges Gorse 92100 Boulogne-Billancourt Paris, France

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Ipsen Pharma 65, quai Georges Gorse 92100 Boulogne-Billancourt Paris, France
MAH contact person	PPD PPD Ipsen Innovation 5 avenue du Canada 91940 Les Ulis France PPD

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

Date: 06 November 2020

Main author and affiliation: PPD Ipsen Pharma

Keywords

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

Rationale and background

Cabometyx™ (cabozantinib) tablets, a tyrosine kinase inhibitor (TKI), have been approved for the treatment of advanced RCC in treatment-naïve adults with intermediate or poor risk and in adults following prior VEGF-targeted therapy in the European Union, and for advanced RCC in the United States. In the pivotal Phase 3 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 is to understand the use of cabozantinib in real-life settings in terms of dose modifications due to AEs and thus be able to identify if there are any prevalent practice patterns which call for implementation of new measures to optimise the use of cabozantinib in RCC.

Research question and objectives

The aim of this prospective study is 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 are also described.

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 nonserious and serious AEs;
- To describe the effectiveness of cabozantinib in RCC in real-life in terms of progression free survival (PFS) and best overall response;
- 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 is a prospective, international, multicentre, non-interventional post-authorisation safety study (PASS) planned to be conducted at 100 study centres in 10 to 15 European countries over a period of 12 months.

The interim analysis, which the current report is based on, was carried out when at least 340 subjects completed, or were withdrawn within, the first three months of follow-up. This interim analysis was limited to the first three months of follow-up (maximum 105 days after first cabozantinib intake). The analysis was conducted so that preliminary results could be provided to local health authorities, where required. There will be no change in the study design or conduct based on the results of this interim analysis.

Setting

A total of 680 subjects were to be included in the study in countries where cabozantinib was marketed at the time of the study (Austria, Belgium, Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain and the United Kingdom). It was planned to include equal numbers of subjects receiving cabozantinib as a) second line therapy and b) third and later line therapy. 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 340 subjects were included in each of the two subgroups. The planned duration of the recruitment period was 24 months.

The length of follow-up was a maximum of 12 months per subject from treatment initiation, even if the subject continued to receive treatment with cabozantinib.

The interim analysis, which the current report is based on, was carried out when at least 340 subjects completed, or were withdrawn within, the first three months of follow-up.

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 Cabometyx™ Summary of Product Characteristics. 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 that was available for the applicable study assessments during a pre-defined data reporting period.

Subjects and study size, including dropouts

It was planned to include 680 subjects with the following inclusion criteria;

(1) Age ≥18 years old;

(2) Has a diagnosis of advanced RCC;

(3) Has received at least one prior VEGF-targeted therapy;

(4) For whom the treating physician has 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) Consents to participate in this non-interventional study.

The sample size was based on the primary endpoint; the proportion of subjects with dose modifications due to AEs based on the Investigator's decision. 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 that differs from the recommended regimen at initiation, a total of at least 680 subjects were required, 340 subjects in each subgroup.

The interim analysis was carried out when at least 340 subjects overall completed, or were withdrawn within, the first three months of follow-up.

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-ECGs (any abnormal clinically significant results recorded as AE/serious AE (SAE)), concomitant radiotherapies and surgeries.

Data sources

Data sources included medical records and work-up results.

Statistical methods

Primary endpoint

The primary endpoint was the proportion of subjects with dose modifications due to AEs based on the Investigator's decision (temporary interruption, dose reduction or discontinuation). Subjects were counted if at least one dose reduction or temporary interruption was observed and the primary reason for the reduction/temporary interruption was reported as an AE, or if cabozantinib was permanently interrupted and the subject discontinued from the study due to an AE.

Secondary endpoints

- *Description of the pattern of use of cabozantinib in real-life clinical settings*
  - Starting dose and schedule;
  - Duration of cabozantinib treatment;
  - Treatment line;
  - Dose reductions and reasons;
  - Treatment interruption and reasons;
  - Treatment discontinuation and reasons;

- Changes in the dose and schedule and reasons;
- Concomitant radiotherapies;
- Planned systemic therapy following cabozantinib discontinuation;
- Median time to first dose modification due to AEs based on the Investigator's decision (reduction, temporary interruption or discontinuation) together and for each component separately;
- Mean and median daily dose of cabozantinib received, and dose intensity (average daily dose compared to starting dose);
- Mean and median numbers of any dose modification (reduction, temporary interruption, increase or discontinuation);
- Median time to any first dose modification (reduction, temporary interruption, increase or discontinuation) together and for each component separately;
- Median time to end of treatment.

• *Effectiveness*
  - Overall best response per Investigator assessment (based on RECIST 1.1 as recommended or other standard of care);
  - Clinical and radiographic median PFS time (assessed by the Investigator based on RECIST 1.1 as recommended or other standard of care) defined as the time between the start date of cabozantinib and the date of progression or death;
  - Overall survival rate at the end of the study.

• *Description of health care resource utilisation associated with the management of treatment-related AEs (assessed by the Investigator as certain, probable, possible or unlikely) during the treatment period*
  - Number and duration of hospitalisations;
  - Number of surgical procedures;
  - Number of emergency room visits and intensive care unit stays;
  - Number of physician visits;
  - Number of homecare visits by nurse;
  - Concomitant medication (initiation or change to manage AEs);
  - Number of unplanned laboratory tests.

<u>Safety endpoints</u>

AEs, vital signs (systolic and diastolic blood pressure and weight) and ECOG performance status.

<u>Analysis sets</u>

- Included Population: all subjects who signed the informed consent form;
- Full Analysis Set (FAS): all included subjects who had taken at least one dose of cabozantinib;
- Safety Population: all included subjects who had taken at least one dose of cabozantinib and had a follow-up of safety;
- Primary Safety Population: all subjects from the Safety Population who started cabozantinib at the prescribed recommended dose (60 mg daily).

For the primary endpoint, the primary analysis was based on the Primary Safety Population and a supportive analysis was based on the Safety Population. For the secondary endpoints, the safety analysis was based on the Safety Population and the effectiveness analysis on the FAS population.

Statistical analysis

All analyses were primarily descriptive in nature. When appropriate, 2-sided 95% confidence intervals (CIs) were calculated based on the Clopper Pearson method. Continuous variables were summarised using mean, standard deviation (SD), minimum, median, maximum and 95% CIs for means when appropriate. Categorical nominal variables were summarised using frequency counts and percentages. Categorical ordinal variables were summarised using all the aforementioned descriptive statistics.

The median time to first dose modification due to AEs and median time to any first dose modification was analysed using the Kaplan-Meier (KM) survival analysis method. The median time, first and third quartiles and 95% CIs were estimated using KM product-limit estimation by therapy line group and total.

Results

Subject disposition

The interim analysis, which this report is based on, included the first 340 subjects in the study to complete, or be withdrawn within, the first three months of follow-up. This interim analysis was limited to the first three months of follow-up (maximum 105 days after first cabozantinib intake). These subjects were distributed across 78 active centres in 11 countries, predominantly France (83 subjects), Italy (78 subjects) and Spain (57 subjects). Two subjects were screening failures and one died before treatment start, 337 subjects received cabozantinib (146 as a second line and 191 subjects as a third or later line therapy), 72 subjects were withdrawn within the first three months of treatment and 265 subjects (118 in the second line and 147 in the third or later line group) were ongoing in the study. The most common reasons for withdrawal were death (27 subjects) and progressive disease (19 subjects) followed by AEs (10 subjects) and consent withdrawn by subject (9 subjects).

Of the 340 subjects included, 337 were included in the FAS and Safety Population and 217 in the Primary Safety Population.

Baseline disease characteristics

In the FAS, disease characteristics at baseline were similar between the two therapy line groups. Overall, the vast majority had clear cell RCC at diagnosis (83.7% of subjects, the remaining 16.3% of subjects had non-clear cell RCC), the most common RCC stage at diagnosis was metastatic Stage IV (45.8% of subjects) with the majority progressing to metastatic Stage IV by the start of cabozantinib treatment (96.4% of subjects). The most common site for at least one metastasis was the lungs, bones and lymph nodes (57.3%, 42.1% and 40.7% of subjects, respectively). Most subjects were of intermediate risk for metastatic RCC prognosis according to both the International Metastatic RCC Database Consortium/Heng (62.2% of subjects) and Memorial Sloan Kettering Cancer Center/Motzer (68.0% of subjects) scoring system. The median (range) time since diagnosis was longer for the third or later line than the second line group; 48.30 (5.4, 341.3) vs. 32.33 (1.9, 234.8) months, with considerable individual variation among subjects for both groups.

As the interim analysis was limited to the first three months of follow-up, the median (range) study exposure overall was close to three months (2.79 (0.0, 3.9) months) and similar between the two therapy line groups.

Primary endpoint

In the Primary Safety Population (N=217, primary analysis population), more than half of subjects had a dose modification due to an AE (65.4% of subjects, 95% CI: 58.7; 71.7). This was similar between the two therapy line groups; 64.2% (95% CI: 54.3; 73.2) and 66.7% (95% CI: 57.1; 75.3) of subjects in the second and third or later line groups, respectively.

The most common type of dose modification due to an AE overall was a dose reduction (45.6% of subjects, 95% CI: 38.9; 52.5) or a dose interruption (44.7% of subjects, 95% CI: 38.0; 51.6). The proportion of subjects with a dose reduction due to an AE was numerically larger in the third or later line than the second line group; 51.4% (95% CI: 41.7; 61.0) vs. 39.6% (95% CI: 30.3; 49.6) of subjects. The proportion of subjects with a dose interruption due to an AE was similar between the second and third or later line group; 43.4% (95% CI: 33.8; 53.4) and 45.9% (95% CI: 36.4; 55.7) of subjects, respectively.

The proportion of subjects overall with a dose discontinuation due to an AE within the first three months of treatment was small (10.6% of subjects, 95%CI: 6.8; 15.5). This was numerically larger in the third or later line than the second line group; 13.5% (95%CI: 7.8; 21.3) vs. 7.5% (95%CI: 3.3; 14.3) of subjects.

The results of the supportive analysis on the Safety Population (N=337) were generally consistent with the primary analysis.

More than half of subjects overall had a dose modification due to an AE related to cabozantinib (59.9% of subjects, 95% CI: 53.1; 66.5) (secondary analysis). This was similar between the two therapy line groups; 58.5% (95% CI: 48.5; 68.0) and 61.3% (95% CI: 51.5; 70.4) of subjects in the second and third or later line groups, respectively. Results were similar for the Safety Population.

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

- *Dose and duration of treatment*
  - The majority of subjects were either on cabozantinib as a second (43.3% of subjects) or third line (40.4% of subjects) therapy. Fewer subjects were on cabozantinib as a fourth or later line therapy (16.3% of subjects).
  - Overall, more than half of subjects started cabozantinib treatment at the recommended dose of 60 mg/day (64.4% of subjects). A numerically larger proportion of subjects started at 60 mg/day in the second than in the third or later line group (72.6% vs. 58.1% of subjects, respectively). A third of subjects started cabozantinib treatment at 40 mg/day (32.3% of subjects) with a numerically larger proportion of subjects starting at this dose in the third or later than in the second line group (37.7% vs. 25.3% of subjects, respectively).

    Very few subjects started cabozantinib treatment at 20 mg/day (1.8% of subjects) or 'other' dose (60 mg every other day or unknown frequency) (1.5% of subjects).
  - As the interim analysis was limited to the first three months of follow-up, the mean (SD) duration of treatment overall was close to three months (3.05 (0.85) months) and was similar between the two therapy line groups.
  - The overall mean (SD) average daily dose was 44.03 (12.78) mg/day and was numerically larger in the second (46.55 (11.92) mg/day) than in the third or later (42.10 (13.11) mg/day) line group. This was similar between the two therapy line groups. Results were similar for the Primary Safety Population.

- *Dose modifications for any reason*
  - Overall, the majority of subjects had a dose modification (dose reduction, interruption or discontinuation) for any reason (74.8% of subjects). This was similar between the second and third or later line groups. The results were similar for the Primary Safety Population.
  - The mean (SD) number of dose modifications (reduction, increase, interruption or discontinuations) for any reason experienced by the Safety Population was 1.9 (1.2), and the median (range) number was 2.0 (1, 9). This was similar between the two therapy line groups.
  - The most common type of dose/treatment modification overall for any reason was a treatment interruption (49.9% of subjects) followed by a dose reduction (43.9% of subjects). A comparatively smaller proportion of subjects discontinued treatment (20.5%) and few had a dose increase (6.2%). The proportion of subjects with a treatment interruption was numerically larger in the third or later line than the second line group, whereas for all other dose modification types, it was similar between the two therapy line groups.
  - Dose increases occurred mainly for subjects on a dose of cabozantinib below the recommended dose of 60 mg/day, i.e. of the 21 subjects with a dose increase, 16 had a starting dose of 40 mg/day. All except one had their dose increased to 60 mg/day, presumably as the lower dose was well tolerated. Of these subjects, 7 stayed at 60 mg/day whereas 8 had their dose eventually reduced to 40 mg/day again. The remaining subjects with dose increases, either started at a dose below 40 mg/day and were increased to 40 or 60 mg/day or started at 60 mg/day, had an initial dose reduction then an increase. No subjects had a dose increase to above 60 mg/day.
  - Overall mean (SD) total treatment interruption was 18.99 (14.83) days which was similar between the two therapy line groups.
  - The most common reason for a treatment interruption and dose reduction was an AE in both therapy line groups (>84%). For treatment discontinuation, in the second line group the most common reason was equally AEs (42.3%) or disease progression (46.2%), whereas in the third or later line group, the most common reason was an AE (55.8%). The most common reason for a dose increase was treatment resuming.
  - Results were similar for the Primary Safety Population.
- *Time to first dose modification*
  - The overall median time to first dose modification due to an AE was 59.0 (95% CI: 53.0, 71.0) days. This was longer for subjects in the second line group than for those in the third or later line group; 70.0 (95% CI: 56.0, 99.0) and 53.0 (95% CI: 44.0, 64.0) days, respectively.
  - The overall median time to any first dose modification was 45.0 (95% CI: 40.0, 53.0) days. This was longer for subjects in the second line group than for those in the third or later line group; 55.0 (95% CI: 45.0, 62.0) and 39.0 (95% CI: 35.0, 46.0) days, respectively.
- *Concomitant radiotherapies*
  - Overall, only 20 subjects (5.9%) had at least one concomitant radiotherapy and they were equally distributed between the second and third or later line groups

(10 subjects in both). The majority of subjects had only one concomitant radiotherapy at any site in the second and third or later line therapy groups (10 and 8 subjects, respectively) and the most common site was the bones in both groups (9 and 7 subjects, respectively).

- *Planned systemic therapies following cabozantinib discontinuation*
  - Of the 72 subjects who discontinued cabozantinib, 13 subjects (18.1%) had systemic therapies planned once cabozantinib was discontinued. They were equally distributed between the second and third or later line groups (6 and 7 subjects, respectively). For the second line group, the most common type of systemic therapy was nivolumab (5 subjects) whilst for the third or later line therapy, the most common type was axitinib and everolimus (both 2 subjects).

Secondary endpoint – Effectiveness of cabozantinib in RCC in real-life setting (FAS)

- *Overall best response*
  - Of the evaluable 133 subjects assessed by RECIST 1.1, most had a partial response or stable disease. No subjects had a complete response.
  - Approximately a third of subjects overall had a partial response (30.8% of subjects, 95% CI: 23.1; 39.4). A numerically larger proportion of subjects had a partial response in the third or later than in the second line group; 36.1% (95% CI: 25.1; 48.3) vs. 24.6% (95% CI: 14.5; 37.3) of subjects, respectively.
  - The overall response rate (the proportion of subjects achieving complete or partial response as best overall response relative to the total number of evaluable subjects) for all subjects was the same as the proportion of subjects with a partial response.
  - Approximately half of subjects had stable disease (53.4% of subjects, 95% CI: 44.5; 62.1). A numerically larger proportion of subjects had stable disease in the second than in the third or later line group; 59.0% (95% CI: 45.7; 71.4) vs. 48.6% (95% CI: 36.7; 60.7) of subjects, respectively.
- *Deaths*
  - Overall, 30 subjects (8.9%) (95% CI: 6.1; 12.5) died during the three-month follow-up period. The number of deaths was rather similar between the second and third or later line groups; 12 subjects (8.2%) (95% CI: 4.3; 13.9) and 18 subjects (9.4%) (95% CI: 5.7; 14.5), respectively.
  - The most common primary reason for death was disease progression in both the second and third or later line groups (7 (4.8%) and 12 (6.3%) subjects, respectively) followed by an SAE (3 (2.1%) and 6 (3.1%) subjects, respectively). Disease progression was also reported as an SAE in this study. See the safety section for specific reasons of death.

Secondary endpoint – Healthcare resource utilisation associated with the management of treatment-related AEs

- These data are not presented in the current report as very limited data are available regarding the use of health care resources to manage treatment-related AEs.

Safety (Safety Population)

- *All TEAEs*
  - Almost all subjects in the Safety Population experienced a TEAE; 1902 TEAEs reported by 312 (92.6%) subjects. The proportion of subjects with a TEAE was rather similar between the two treatment line groups; 757 TEAEs reported by

132 (90.4%) subjects in the second line group and 1145 TEAEs by 180 (94.2%) subjects in the third or later line group.

- The most common TEAEs overall, also the most common in the two therapy line groups, were diarrhoea, palmar-plantar erythrodysaesthesia syndrome, asthenia, fatigue, decreased appetite and nausea.
- TEAEs were mostly mild (Grade 1; 958 TEAEs in 250 subjects, 74.2%) or moderate (Grade 2; 632 TEAEs in 245 subjects, 72.7%) in intensity, a large proportion were severe (Grade 3; 241 TEAEs in 126 subjects, 37.4%), several were life-threatening or disabling (Grade 4; 19 TEAEs in 18 subjects, 5.3%) and several led to death (Grade 5; 30 TEAEs in 29 subjects, 8.6%). This was similar between the two therapy line groups.

• *Treatment-related TEAEs*

- The majority of TEAEs were considered related to study treatment; 1390 related TEAEs were reported by 290 (86.1%) subjects. The proportion of subjects with a treatment-related TEAE was numerically lower in the second line than in the third or later line group; 564 treatment-related TEAEs reported by 122 (83.6%) subjects vs. 826 treatment-related TEAEs by 168 (88.0%) subjects, respectively.
- The most common related TEAEs overall, also the most common in the two therapy line groups, were diarrhoea, palmar-plantar erythrodysaesthesia syndrome, asthenia, fatigue, nausea, hypertension, decreased appetite, mucosal inflammation, stomatitis and dysgeusia.
- Related TEAEs were mostly mild (Grade 1; 711 TEAEs in 218 subjects, 64.7%) or moderate (Grade 2; 477 TEAEs in 217 subjects, 64.4%) in intensity, a large proportion were severe (Grade 3; 171 TEAEs in 105 subjects, 31.2%), a few were life-threatening or disabling (Grade 4; 6 TEAEs in 5 subjects, 1.5%) and a few led to death (Grade 5; 6 TEAEs in 6 subjects, 1.8%). This was similar between the two therapy line groups.

• *TEAEs leading to dose modifications*

- TEAEs led to temporary interruption of cabozantinib treatment in 141 (41.8%) subjects, dose reduction in 131 (38.9%) subjects and treatment discontinuation in 35 (10.4%) subjects. For all dose modifications, the proportion of subjects was numerically larger in the third or later line group than in the second line group.
- The most common TEAEs for both temporary treatment interruptions and dose reductions overall, also the most common in the two therapy line groups, were diarrhoea, asthenia, palmar-plantar erythrodysaesthesia syndrome, mucosal inflammation, fatigue, decreased appetite, vomiting and stomatitis. In addition, for temporary interruptions, nausea and hypertension were common TEAEs. The majority of TEAEs leading to a discontinuation were reported in only 1 or 2 subjects overall; those reported in >2 subjects were asthenia and palmar-plantar erythrodysaesthesia syndrome.

• *Serious TEAEs*

- 173 serious TEAEs were reported by 112 (33.2%) subjects, of these, 79 serious TEAEs were considered related to treatment in 59 (17.5%) subjects. The proportion of subjects reporting a serious TEAE or serious related TEAE was similar between the two therapy line groups. The majority of serious TEAEs were

reported in 1 or 2 subjects overall; those reported in >2 subjects were general physical health deterioration, disease progression, pyrexia, diarrhoea, vomiting, dyspnoea, pulmonary embolism, respiratory failure, sepsis, pneumonia and hyperthyroidism.

- Three additional SAEs reported by 3 subjects in the Safety Population occurred before the start of cabozantinib treatment: dyspnoea, haemoptysis and cholangitis.

• *SAEs leading to deaths*

- 30 SAEs led to the death of 29 (8.6%) subjects; 12 SAEs in 11 (7.5%) subjects and 18 SAEs in 18 (9.4%) subjects in the second and third or later line group, respectively.
- Overall, the most common SAEs leading to death were disease progression (7 subjects, 2.1%) followed by general physical health deterioration (6 subjects, 1.8%). Of these subjects, one subject reported two SAEs leading to death: general physical health deterioration and septic shock. The other SAEs leading to death were pneumonia, sepsis, intestinal obstruction and respiratory failure (in 2 subjects each) and asthenia, death, sudden death, pancytopenia, cardiac failure congestive, metastases to central nervous system, depressed level of consciousness and acute kidney injury (in 1 subject each).
- The events of unexplained death and pancytopenia (reported in 1 subject each) were reported as probably treatment-related and the event of pneumonia (in 1 of the 2 subjects reporting pneumonia) was reported as possibly treatment-related. All other deaths were considered not treatment-related or unassessable (sepsis, intestinal obstruction and respiratory failure in 1 subject each of the 2 subjects reporting each event).

Discussion

Cabozantinib use in subjects with advanced RCC following prior VEGF-targeted therapy in a 'real-world' setting led to TEAEs that were characteristic of those observed with other TKIs in RCC subjects and were generally manageable by modifying the dose of cabozantinib. Most subjects required a dose reduction or temporary treatment interruption due to an AE, however, the rate of treatment discontinuations due to AEs within the first three months of treatment was low. 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.

Cabozantinib was better tolerated when used as a second line therapy than a third or later line therapy; a numerically larger proportion of subjects in the third or later line group required a dose reduction, temporary interruption or discontinued cabozantinib due to an AE (entire Safety population) than in the second line group. The rate of discontinuations in the third or later line, bearing in mind that this interim analysis was for the first three months of treatment only, were still comparatively low. Otherwise, there was no noteworthy difference between the two therapy line groups when considering the proportion of subjects experiencing TEAEs, related-TEAEs, serious TEAEs, TEAEs leading to death and the intensity of TEAEs.