22 March 2018
EMA/235286/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: CABOMETYX

International non-proprietary name: cabozantinib

Procedure No. EMEA/H/C/004163/II/0003

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ATA	adequate tumor assessment
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
CTEP	Cancer Therapy Evaluation Program
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society of Medical Oncology
Hgb	hemoglobin
HIF	hypoxia-inducible factor
HR	hazard ratio
IC_{50}	inhibitory concentration
IFN-α	interferon-alfa
IHC	immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
IRC	Independent Radiology Committee
ITT	intent-to-treat
KPS	Karnofsky performance status
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance image
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NE	not estimable
NPACT	nonprotocol anticancer therapy
ORR	objective response rate
OS	overall survival
PD	progressive disease

PD-1 programmed death receptor-1 (PD-1)PFS progression-free survival

PR partial response

qd once daily

QoL quality of life

RCC renal cell carcinoma

RECIST Response Evaluation Criteria in Solid Tumors

RTK receptor tyrosine kinase

SAP statistical analysis plan

SD stable disease (or standard deviation)

sNPACT systemic non-protocol anticancer therapy

TKI tyrosine kinase inhibitor

UE unable to evaluate

ULN upper limits of normal

VEGF(R) vascular endothelial growth factor (receptor)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Ipsen Pharma submitted to the European Medicines Agency on 28 August 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include for the treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk per IMDC criteria' for CABOMETYX; as a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add a warning on dose reductions and dose interruptions and to update the safety information. The final report of the randomised phase II study comparing cabozantinib with commercially supplied sunitinib in subjects with previously untreated locally advanced or metastatic renal cell carcinoma (study A031203) is submitted in support of this application. The Package Leaflet is updated accordingly. The risk management plan (version 3.0) is also submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to make some editorial changes in the product information.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Submission date	28 August 2017
Start of procedure:	16 September 2017
CHMP Rapporteur Assessment Report	10 November 2017
CHMP Co-Rapporteur Assessment Report	10 November 2017
PRAC Rapporteur Assessment Report	17 November 2017
PRAC members comments	22 November 2017
Updated PRAC Rapporteur Assessment Report	27 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2017
Request for supplementary information (RSI)	14 December 2017
CHMP Rapporteur Assessment Report	19 February 2018
PRAC Rapporteur Assessment Report	20 February 2018
PRAC members comments	28 February 2018
Updated PRAC Rapporteur Assessment Report	1 March 2018
PRAC Outcome	8 March 2018
CHMP members comments	12 March 2018
Updated CHMP Rapporteur Assessment Report	14 March 2018
Opinion	22 March 2018

2. Scientific discussion

2.1. Introduction

Kidney cancer is diagnosed in 340 000 individuals worldwide (North America 64 000, Europe 115 000) each year and results in 140 000 deaths annually (North America 17 000, Europe 50 000)[1]. The incidence has generally increased in recent years[2]. Renal cell carcinoma accounts for approximately 90% of kidney cancer cases. Approximately 75% of RCCs are clear cell tumors (Lopez-Beltran et al 2006).

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
[2] Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 2015;67(3):519-30.

Many patients present with advanced or unresectable disease at initial diagnosis, and up to 30% of patients eventually relapse following surgical management of initially localized disease[3]. The median overall survival for patients with advanced RCC ranges from about 8 months (poor risk score) to 4 years (favourable risk score). The extent and location of tumour metastases in patients with advanced RCC contribute to significant morbidity. Metastatic symptoms include airway obstruction, venous thromboembolism, bone pain, skeletal related events (SREs), and hypercalcemia. In addition, paraneoplastic syndromes (hypertension and disorders of the endocrine, hepatic, and neuromuscular system impact quality of life of patients with advanced RCC[4]. Prognostic factors for survival in patients with advanced RCC have been described including the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria[5] on the basis of clinical pretreatment characteristics. Factors associated with a shorter survival were low Karnofsky performance status (KPS), low hemoglobin level, and high corrected serum calcium. A subsequent IMDC model developed for advanced RCC patients[6, 7] and was validated and has become well-established. It includes the following three additional risk factors: time from initial diagnosis to initiation of therapy of < 1 year, high absolute neutrophil count, and high platelet count.

Information on prognosis from the ESMO guidelines (see table below) shows that poor risk patients have a considerably shorter life expectancy than intermediate risk patients:

Table 1: Median overall survival estimates in first- and second-line according to the IMDC risk groups

Number of risk factors	Risk category	First-line [8] median OS (months)	Second-line [9] median OS (months)
0	Favourable	43.2	35.3
1–2	Intermediate	22.5	16.6
3–6	Unfavourable	7.8	5.4

IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma.

Renal cell carcinoma is usually resistant to chemotherapy and current therapies in treatment-naïve patients with locally advanced or metastatic RCC are anti-angiogenic drugs that target VEGF (ie, bevacizumab) and VEGFRs (ie, sunitinib, pazopanib), temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, which is usually reserved for RCC patients with poor-risk disease[8]. The median PFS ranges from 8 to 11 months for treatment-naïve patients receiving sunitinib or pazopanib[9, 10, 11, 12]. In

[3] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Kidney Cancer Version 2.2017. October 31, 2016.
[4] Cella D, Escudier B, Tannir NM, Powles T, Donskov F, Peltola K et al. Quality of life in the Phase 3 METEOR trial of cabozantinib vs everolimus for advanced renal cell carcinoma. Presented at the 41st European Society for Medical Oncology conference; 2016 Oct 7-11; Copenhagen, Denmark. Poster 816P, Abstract 3390.
[5] Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol. 2004;22:454-463.
[6] Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicentre study. J Clin Oncol. 2009;27(34):5794-9.
[7] Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14(2):141-8.
[8] Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271-81.
[9] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24.

the above registrational studies for sunitinib and pazopanib, treatment-naïve patients of any risk category (favorable-, intermediate-, and poor-risk) were enrolled. A retrospective analysis of the registrational Phase 3 trial of sunitinib vs IFN-α trial in treatment-naïve subjects[13] showed differences in median PFS in the sunitinib arm by IMDC risk category (favourable 16.0 months; intermediate 10.7 months; poor 2.5 months). The registrational study Phase 3 trial of temsirolimus included only treatment-naïve patients with intermediate- or poor-risk disease per MSKCC criteria. In the temsirolimus arm the median PFS was 5.5 months and the median OS was 10.9 months[14].

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of renal cell carcinoma (2016) presents an algorithm for systemic treatment in mRCC with a clear cell component (Figure 1). According to the algorithm, sunitinib is the recommended first-line treatment of clear cell RCC for patients with good or intermediate risk, while temsirolimus is the first choice in patients with poor risk, however, with sunitinib as a "reasonable alternative".

[10] Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-8.
[11] Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31.
[12] McDermott DF, Atkins MB, Motzer RJ, Rini BI, Escudier BJ, Fong L, et al. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). J Clin Oncol. 2017;35(6 Suppl):Abstract 431.
[13] Rini BI, Hutson TE, Figlin RA, Lechuga M, Valota O, Serfass L, M et al. Sunitinib in patients with metastatic renal cell carcinoma: Clinical outcome according to IMDC risk group. J Clin Oncol 2017;35(15 Suppl):Abstract 4584.
[14] Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271-81.

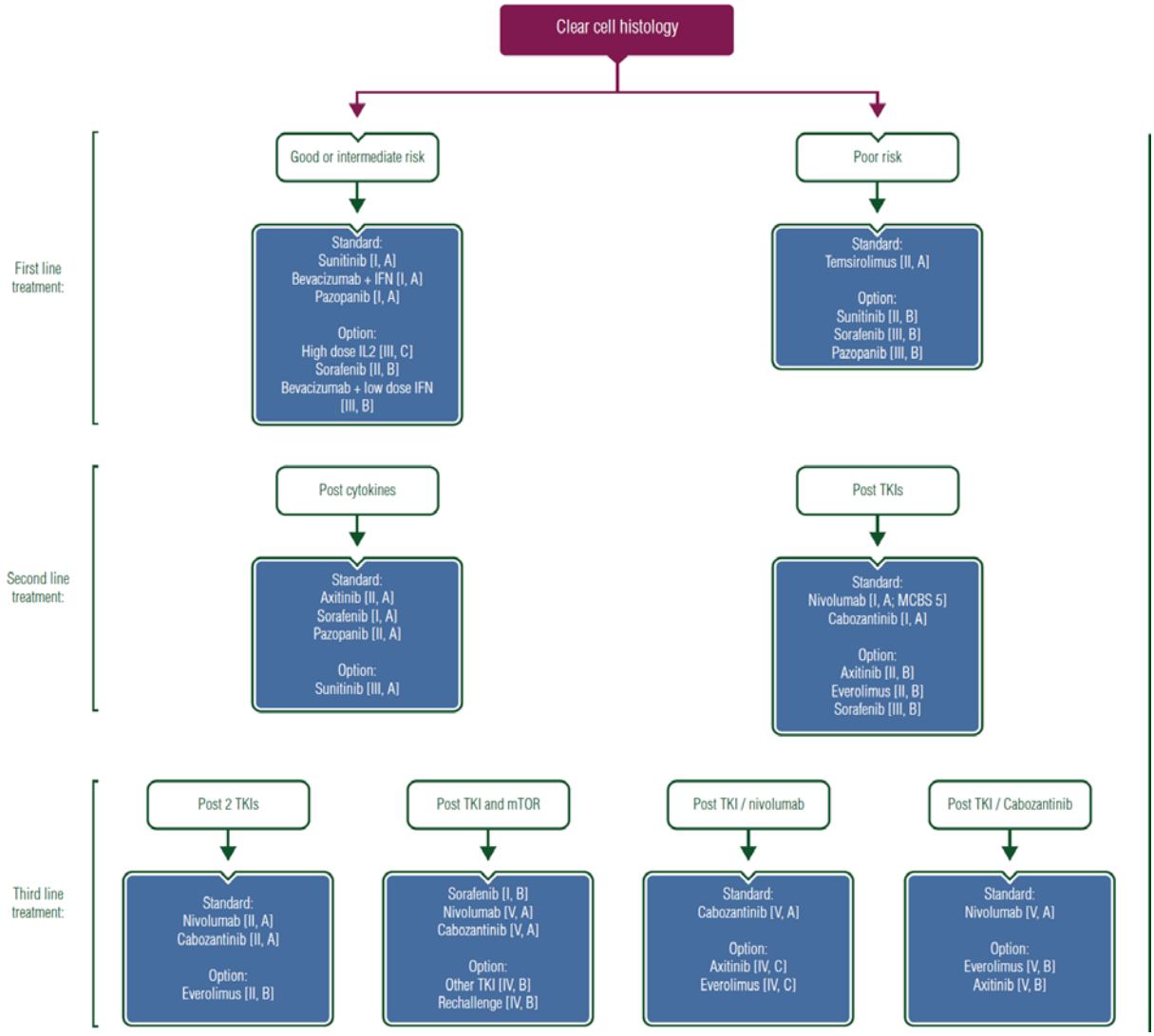


Figure 1: ESMO Algorithm for systemic treatment in mRCC
mRCC, metastatic renal cell carcinoma; IFN, interferon; IL2, interleukin 2; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; MCBS, ESMO Magnitude of Clinical Benefit Scale v1.0.

Despite advances in the treatment of RCC over the past decade, the vast majority of patients acquire resistance to targeted therapy as evidenced by disease progression. In addition, approximately 25% of treatment-naïve patients are a priori resistant to VEGF-targeted therapy and derive no clinical benefit[15]. Therefore, an unmet need remains for treatments that will prolong time to progression and improve survival.

Cabozantinib is a multi-targeted small inhibitor tyrosine kinases. Cabozantinib has shown inhibition against several RTKs known to influence tumor growth, metastasis, and angiogenesis, including MET, VEGFR2, and AXL. The initial marketing authorisation for cabozantinib (Cabometyx) was based on a phase 3 trial (METEOR) of cabozantinib vs everolimus in patients with advanced RCC after prior anti-angiogenic therapy. Median PFS by independent radiology committee (IRC) review was 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm (HR 0.58 [95% CI: 0.45, 0.74]; p<0.0001). Median OS was 21.4 months in the cabozantinib arm vs 16.5 months in the everolimus arm (HR 0.66

[15] Heng DY, Mackenzie MJ, Vaishampayan UN, Bjarnason GA, Knox JJ, Tan MH et al. Primary anti-vascular endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma: clinical characteristics, risk factors, and subsequent therapy. Ann Oncol. 2012;23(6):1549-55.

[95% CI: 0.53, 0.83]; p=0.0003). Clinical benefit of cabozantinib was demonstrated across risk categories (by Memorial Sloan Kettering Cancer Center model): the HRs for PFS were 0.47 (favourable), 0.48 (intermediate), and 0.67 (poor); the corresponding HRs for OS were 0.70, 0.65, and 0.74[16] .

The MAH now proposes to extend the indication to treatment-naïve patients. They have applied for the following indication:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk per IMDC criteria.

The application is based on Study A031203, a Phase 2, randomized, open-label study of previously untreated metastatic RCC (mRCC) subjects conducted to compare cabozantinib vs sunitinib cabozantinib vs sunitinib[17]. The study population consisted of untreated RCC subjects who were intermediate- or poor-risk per the IMDC criteria. Focus was directed toward subjects in these risk groups because the intermediate-/poor-risk groups comprise 80% of all subjects with RCC[7].

The agreed indication was as follows:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC):

- in treatment-naïve adults with intermediate or poor risk (see section 5.1)

- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

The applied Type II variation concerns extension of indication to include treatment of advanced renal cell carcinoma in treatment-naïve adults with intermediate or poor risk per IMDC criteria. With the initial MAA, an ERA was submitted based on the prevalence of RCC, leading to a $PEC_{SURFACE\ WATER}$ -value above 0.01 µg/L. In the course of the MA procedure, a refined penetration factor (F_{pen}) was provided based on a justified estimate of prevalence for advanced RCC, including both first-line treatment and following prior vascular endothelial growth factor (VEGF)-targeted therapy. This led to a refined $PEC_{SURFACE\ WATER}$ value below 0.01 µg/L. The final study report for the aqueous exposure bioaccumulation test with the bluegill (study ID 750A-102) has been provided, confirming that the bioconcentration factors (BCF) for whole fish tissue were well below the threshold values of 2000 or 5000. Thus, cabozantinib is not a PBT substance. Consequently, cabozantinib is not expected to pose a risk to the environment.

Table 2: Environmental risk assessment

Substance (INN/Invented Name): Cabozantinib (S)-malate			
CAS-number (if available): 1140909-48-3			
PBT screening		Result	**Conclusion**

[16] Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917-27.

[17] Hackshaw MD, Holmes M, Lankford M, Thomas M, Ogbonnaya A, Eaddy M. Prescribing Preferences in the First-Line Treatment for Patients With Metastatic Renal Cell Carcinoma in the United States. Clin Genitourin Cancer. 2016;14(5):e479-e487.

Bioaccumulation potential- log K_{ow}	OECD 123	Log Dow = 3.88 (a pH 5) Log Dow = 5.15 (at pH 7.4)			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Log Dow = 5.15 (at pH 7.4)			Potentially B
	BCF	BCF KgL= 719/ 745 L/kg			not B
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$ refined (prevalence)	0.00126	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(N)
Phase II b Studies					
Study type	***Test protocol***	***Endpoint***	***value***	***Unit***	***Remarks***
Bioaccumulation	OECD 305	BCF SSL = 2 BCF KgL=	246/ 312 719/ 745 (conc.: 0.83 and 9.1 µg/L)	L/kg	%lipids: 5% SSL: steady state, lipid corr. KgL: kinetic, growth and lipid corrected

2.2.2. Discussion on non-clinical aspects

The MAH did not provide non-clinical data to support this indication, which is considered acceptable by the CHMP. The MAH submitted the final study report for the aqueous exposure bioaccumulation test with the bluegill (study ID 750A-102) for the ERA. Considering the above data, cabozantinib is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application suggests that there will be an increase in patient exposure to the product with the indication in the treatment of naïve patients with RCC. However, the ERA assessment in the initial marketing authorisation was conservative since the analysis captured the whole of the RCC population. Therefore, although there will be an increase in the use of the product in practice, the new analyses suggests that it is not expected to lead to a significant increase in environmental exposure further to the use of cabozantinib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the

community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study (Phase)	Study Report	Proposed Role of Study in Application		Number of Subjects	
		Efficacy	Safety	Experimental Arm	Comparator Arm
A031203 (CABOSUN) (Phase 2)	Full CSR, Primary analysis	√	√	Cabozantinib 60 mg: 79 RCC (efficacy) 78 RCC (safety)	Sunitinib 50 mg: 78 RCC (efficacy) 72 RCC (safety)

2.4. Clinical efficacy

2.4.1. Main study(ies)

Title of the study: Study A031203. Randomized Phase II study comparing cabozantinib with commercially supplied sunitinib in subjects with previously untreated locally advanced or metastatic renal cell carcinoma

Methods

Study participants

Main Eligibility Criteria:

- Was ≥ 18 years of age
- Had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2
- Histologic documentation: RCC with some component of clear cell histology. Histologic documentation of metastatic disease was not required.
- Locally advanced (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to stage IV RCC, according to American Joint Committee on Cancer [AJCC] staging).
- Had an intermediate (1-2 risk factors) or poor risk (≥ 3 risk factors), per the IMDC Criteria[6]. Subjects therefore had to have one or more of the following six factors:
    - Time from diagnosis of RCC to systemic treatment (ie, initiation of A031203 protocol
    - treatment) < 1 year
    - Hemoglobin (Hgb) < lower limit of normal (LLN)
    - Corrected calcium > upper limit of normal (ULN)
    - Karnofsky Performance Status (KPS) < 80%
    - Neutrophil count > ULN
    - Platelet count > ULN
- Had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria ie, lesions that could be accurately measured in at least one dimension (longest diameter recorded) as ≥ 2 cm with conventional techniques or as ≥ 1 cm with spiral computed tomography (CT) scan.
- Must not have had a major surgical procedure or significant traumatic injury within 6 weeks prior to study registration (randomization), or must have fully recovered from any such procedure.

(Subjects who had had a nephrectomy could have been enrolled 4 weeks after surgery providing that there were no wound-healing complications.)

- No active brain metastases; subjects with treated, stable brain metastases for at least 3 months were eligible.

- Prior Treatment
  - No prior systemic treatment for RCC (supportive therapies such as bisphosphonates or denosumab were permitted)
  - Must not have had a major surgical procedure or significant traumatic injury within 6 weeks prior to study registration (randomization), or must have fully recovered from any such procedure. (Subjects who had
  - had a nephrectomy could have been enrolled 4 weeks after surgery providing that there were
  - no wound-healing complications.)
- No chronic concomitant treatment with strong cytochrome P450 (CYP) 3A4 inducers or inhibitors. Subjects could not have received a strong CYP3A4 inducer within 12 days prior to registration nor a strong CYP3A4 inhibitor within 7 days prior to registration.

- Radiation
  - to the brain, thoracic cavity, abdomen, or pelvis had to be completed at least 90 days before registration;
  - to bone had to be completed at least 14 days before registration;
  - to other sites had to be completed at least 28 days before registration
  - In all cases, there had to be complete recovery and no ongoing complications from prior radiation therapy.

Treatments

Subjects were treated with one of the following regimens:

- Cabozantinib treatment arm: oral cabozantinib (60 mg) once-daily (qd) (as tablets)
- Sunitinib treatment arm: oral sunitinib (50 mg) qd for 4 weeks (as capsules) followed by a 2-week rest per cycle (approved dosing regimen from the registrational Phase 3 sunitinib study[9]

One cycle was defined as 6 weeks in duration for each treatment arm.

Cabozantinib was to be taken orally on an empty stomach following a 2-hour fast and subjects continued to fast for 1 hour after each dose.

Sunitinib was administered without regard to meals.

Subjects who had a complete response (CR), partial response (PR), or stable disease (SD) continued treatment at the highest tolerable dose until the appearance of disease progression or unacceptable toxicity. Subjects who had disease progression were to receive a minimum of 2 cycles of therapy, but any subject with rapid disease progression was removed from treatment.

Crossover between treatment arms was not prescribed by the protocol. Subsequent non-protocol therapy was documented.

Table 3 summarizes the dose levels used in this study and the dose reductions allowed for unacceptable toxicity. Doses may have been modified at any time.

Table 3: Dose reductions

Study Treatment	Starting Dose	First Dose-Level Reduction (-1)	Second Dose-Level Reduction (-2)
Cabozantinib	60 mg	40 mg	20 mg
Sunitinib	50 mg	37.5 mg	25 mg

No dose reductions were allowed below dose level -2 (20 mg cabozantinib and 25 mg sunitinib). If further dose reductions were required, study treatment was discontinued. Doses were not to be re-escalated once reduced.

If dosing with sunitinib or cabozantinib was interrupted for more than 6 weeks, subjects were to be discontinued from protocol treatment.

Objectives

The primary objective was to determine if subjects with renal cancer treated with cabozantinib had improved progression-free survival (PFS) compared with subjects treated with sunitinib.

The secondary objectives were:

- To determine whether the response rate of subjects with renal cancer treated with cabozantinib was higher when compared with subjects treated with sunitinib.
- To determine whether subjects with renal cancer treated with cabozantinib had improved overall survival (OS) when compared with subjects treated with sunitinib.

Companion Sub-Study (A031203-ST1):

- To determine whether renal cancer subjects with high hepatocyte growth factor receptor protein (MET) expression by immunohistochemistry (IHC) had improvement in PFS compared with subjects with low MET expression on both arms of this study.

Outcomes / endpoints

Primary endpoint

The primary efficacy endpoint is duration of progression-free survival (PFS). Duration of PFS is defined as the time from randomization to the earlier of the following events: disease progression as determined per RECIST 1.1 or death due to any cause.

Tumour assessments of the chest/abdomen/pelvis (CAP) were performed in all subjects at registration/randomization (baseline) and every 12 weeks (± 10 days) after randomization while on study treatment. Post-treatment assessments continued every 12 weeks until progression or until 5 years after randomization, whichever came first. A CT scan of the chest was preferable although lesions on chest X-ray were acceptable when clearly defined and surrounded by aerated lung. The abdomen/pelvis scan was performed by CT (or MRI). The same method of assessment was to be used to characterize each identified and reported lesion at baseline and during follow-up. An MRI (or CT) scan of the brain was performed in all subjects at baseline. After randomization, MRI (or CT) scans of the brain were performed (only if the baseline brain scan was indicative of metastases or signs or symptoms of brain metastases subsequently developed) on the same schedule as the CAP scans.

Subjects who had a complete response (CR), partial response (PR), or stable disease (SD) continued treatment at the highest tolerable dose until the appearance of disease progression or unacceptable toxicity.

Subjects who had disease progression were to receive a minimum of 2 cycles of therapy, but any subject with rapid disease progression was removed from treatment and details (ie, tumour measurements) were documented. After progression, subjects were followed every 6 months until death or 5 years after registration (randomization) for survival and second malignancy.

Protocol-specified radiographic tumour assessments were evaluated per RECIST (v1.1; Eisenhauer et al 2009) by the Investigator. For the purposes of this submission, a blinded, central review of radiographic images to determine PFS and response rates per RECIST v1.1 was conducted retrospectively by an IRC. The IRC (MedQIA, Los Angeles, CA) comprised board-certified radiologists who determined radiographic response and progression following randomization. To minimize the potential introduction of bias, these individuals did not have any direct contact with the study site personnel or subjects.

Secondary endpoints

The secondary endpoints were OS (time from randomization to death from any cause) and ORR (proportion of subjects at the time of data cut-off with a best overall response of CR or PR per RECIST 1.1 which was confirmed at a subsequent visit $\geq$ 28 days later). To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessment not less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6-8 weeks.

Sample size

The study was designed by the Alliance to provide 85% power for an event-driven analysis of PFS to test the null hypothesis of no difference in PFS vs. an alternative hypothesis that the HR ($\lambda_{cabozantinib}/\lambda_{sunitinib}$) is 0.67 (assuming a median PFS time in the sunitinib arm of 8 months vs 12 months in the cabozantinib arm) with a 1-sided type I error rate=0.12. The calculation was based on the COMPARZ RCC pazopanib vs sunitinib trial, which enrolled treatment-naïve subjects, but took into account that Study A031203 enrolled only intermediate- and poor-risk subjects, while the COMPARZ study also included patients with favourable risk status (25%).

Assuming an accrual rate of 5.8 subjects/month over a 24-month enrollment period, follow-up of 20 months after closure to randomization for the PFS endpoint, that PFS follows an exponential distribution, and allowing for 7% ineligibility rate: 123 events were required and the total sample size was 150 subjects.

Randomisation

Subjects were randomized 1:1 to treatment with either cabozantinib or sunitinib.

Subject enrolment was facilitated using the web-based Oncology Patient Enrolment Network (OPEN) registration system. Site staff used OPEN to enrol all subjects to this study. This system is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrolment, initializes the subject in the Medidata Rave database. The OPEN system provided the site with a confirmation of registration (randomization) and treatment information.

Randomization was stratified by the following factors as assessed by the Investigator:

- **Bone metastases at baseline**

  a) yes

  b) no

- **IMDC risk categories:**

  a) Intermediate (1-2 risk factors)

  b) Poor (3 or more risk factors)

In order to meet the IMDC risk category criteria, subjects had to have one or more of the following six factors:

- Time from diagnosis of RCC to systemic treatment < 1 year
- KPS score < 80%
- Hgb < 13 g/dL (< 130 g/L) for males and < 11.5 g/dL (< 115 g/L) in females
- Neutrophil count > upper limit of normal (ULN)
- Platelets > ULN
- Corrected calcium > ULN

Blinding (masking)

This was an open-label study. Study subjects, site personnel, and study teams at the Alliance had access to the actual randomized treatment assignment and the nature of the study treatment actually received. Exelixis had no access to any data before the Alliance completed their initial analysis of the study. Data review during the conduct of the study was conducted on unblinded data; however, a blinded, central review of radiographic images was conducted retrospectively by an IRC as an additional step to the protocol specified evaluation of PFS and response rates by the Investigator. The IRC reviewed all available radiographic images and was blinded to treatment identity and to clinical data that could have led to inadvertent unblinding. Treatment assigned and treatment received were excluded from the data review output unless necessary to conduct the review.

Statistical methods

Alliance censoring rules

The analysis cut-off date is the date of the 123rd event. Subjects who experienced an event after this cut date or those who did not experience an event were right censored as of the date of their last tumour assessment available on or before the cut date. Subjects with no post-baseline tumour assessments were censored at date of randomization.

Use of subsequent anticancer therapy or missing radiologic image data were not reasons for censoring progression per Alliance censoring rules.

Exelixis analyses

The SAP produced by Exelixis used the following censoring rules outlined in the FDA document 'Guidance for Industry-Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007':

- Subjects who receive non-protocol systemic anticancer treatment (NPACT) after randomization and before experiencing an event will be right censored at the date of the last adequate tumour assessment (ATA) on or prior to the date of initiation of NPACT.
- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cut-off will be right censored on the date of their last ATA prior to the cut-off date.
- Subjects who experience an interval corresponding to 2 or more consecutive scheduled tumour assessments (operationally defined as an interval > 178 days) without an ATA immediately followed by an event will be right censored on the date of their most-recent ATA prior to the missing/inadequate assessments. However, if such an interval is immediately followed by an ATA with an overall response of SD, PR, or CR, this will be deemed sufficient clinical evidence that progression did not occur during the period of missing data and the missing evaluations will be ignored.

The application of FDA-recommended censoring rules for PFS necessarily reduces the number of events available for analysis. To increase the number of events that would be included in such analyses the data cut-off for radiographic endpoints was extended to September 15, 2016 (database extract January 13, 2017; the latest date for which OS data were available). The median time of follow-up at that data cut-off was 25.0 months.

PFS analyses

The date of the 123rd PFS event varies depending upon the source of RECIST evaluation (investigator or IRC) and the nature of censoring rules applied (Alliance or FDA-recommended). According to the SAP, if a given combination of RECIST evaluation and censoring rules yields < 123 PFS events the analysis cut-off date is 15 September 2016 (the date of last scans available for independent evaluation).

The Exelixis SAP describes the following PFS analyses to be performed:

- Investigator-determined PFS (progression per RECIST 1.1 as determined by the investigator, or death):
    - Using the censoring rules per the Alliance group (PFS1)
    - Investigator-determined PFS with implementation of FDA-recommended censoring rules (PFS2)
- Inclusion of clinical outcomes (“clinical claims”) as events (PFS3-4)
- Aligning radiographic progression dates with the planned assessment schedule (“uniform dates”) to address the potential for inconsistent imaging frequency between arms (PFS5-6)
- Radiographic progression per independent radiology committee (IRC) review (when data are available):
    - By Alliance and FDA-recommended censoring rules (PFS7-8)
    - With “uniform dates” adjustment (PFS9-10)

To explore the effect of potentially informative censoring on investigator assessments, four sensitivity analyses (PFS21-24) based on the rules per PFS2 analyses will be conducted in the ITT population by reclassifying subjects censored for potentially informative reasons as events differentially between the treatment arms in various patterns.

When IRC data are available, these analyses will be repeated as PFS81-PFS84 by reclassifying censored subjects per the PFS8 definition.

All efficacy analyses will be conducted amongst all subjects in the ITT population. Hypothesis testing between the two treatment arms will be performed using the stratified logrank test. Two-sided p-values will be presented. The stratification factors are those used to stratify the randomization. Unstratified results will also be provided.

The median duration of PFS and the associated 95% confidence interval for each treatment arm will be estimated using the Kaplan-Meier method. The stratified and unstratified HRs and the corresponding 95% confidence intervals will be estimated using a Cox regression model.

Interim analysis

A single interim futility analysis of PFS was conducted by the Alliance at the 50% information fraction. The criterion for futility was not met. The study therefore continued to the primary endpoint analysis. Following the interim analysis, the DSMB recommended at the 07 November 2014 meeting that the trial continue without change.

Multiplicity

No adjustments were made for multiple analyses.

Overall survival and Objective response rate

The key secondary efficacy endpoints for this study are ORR and duration of OS. Formal hypothesis testing was not planned for key secondary efficacy endpoints and p-values are presented without adjustment for multiple endpoints.

The ORR is defined as the proportion of subjects with the best overall response of complete response (CR) or partial response (PR) as assessed per RECIST 1.1, which is confirmed by a subsequent visit ≥ 28 days later. Key analysis of ORR are performed with the same data cut-off as the corresponding PFS analysis, using all subjects in the ITT population. Subjects who do not have any post-baseline tumour assessments are counted as non-responders. Two-sided p-values were generated using the Fisher's exact test. Analysis using the Cochran-Mantel-Haenszel method to adjust for the randomization stratification factors arealso presented.

A summary of BOR includes:

- The count and proportion of subjects with best overall response of CR, PR, SD, PD and unable-to-evaluate (UE). Reasons for UE will be provided.
- Point estimates of ORR with confidence intervals calculated using exact methods
- The difference in response rates between the two treatment arms and associated
- confidence intervals
- The odds ratio and corresponding p-value

Analyses are provided for both investigator-determined response and response per IRC (when data are available). Waterfall plots showing best percentage change in target lesion size as assessed by the investigator and IRC are also presented for each treatment group using the ITT population.

Overall survival is defined as the time from date of randomization to date of death due to any cause. All data available as of 13Jan2017 were considered for the analyses of OS. For subjects who are alive at the time of data cut-off or are permanently lost to follow-up, duration of OS are right censored at the earlier of the following: date the subject withdrew consent from all follow-up, data cut-off date, or the date the subject was last known to be alive.

OS (months) = (date of death or censoring – date of randomization + 1)/30.4375

The statistical methods employed for the analyses of OS are the same as those described for the analyses of primary endpoint of PFS (Kaplan-Meier, Cox regression).

Duration of Objective Response (DOR)

Duration of objective response, defined as the time from the tumour assessment that first documents PR or CR that is subsequently confirmed at least 28 days later until the date of documented radiographic progression, per RECIST 1.1. Only subjects with confirmed CR or PR are included in this analysis.

Duration of objective response (months) = (earliest date of progression, death or censoring – date of first documented objective response + 1)/30.4375

The duration of objective response will be analysed per statistical methods described above. Analysis per investigator and IRC is presented using the following 2 censoring rules (Alliance group and FDA guidance).

Subgroups for Efficacy Analyses

The following subgroup analyses were performed to further examine the robustness of the findings in this study. Forest plots are presented for the subgroup analyses. The analysis of OS, ORR, PFS per investigator using Alliance and FDA censoring rules and PFS per IRC per FDA censoring rules were repeated in each of the following subgroups:

- Age (< 65 years, ≥ 65 years)
- Gender (female, male)
- Race (White, Other)
- ECOG performance status (0, 1, 2)
- Bone metastases at baseline-stratification factor at randomization (Yes, No)
- Heng Criteria – stratification factor at randomization (Intermediate [1-2], Poor [3-6])
- cMET status (Positive, Negative, Missing)

Results

Participant flow

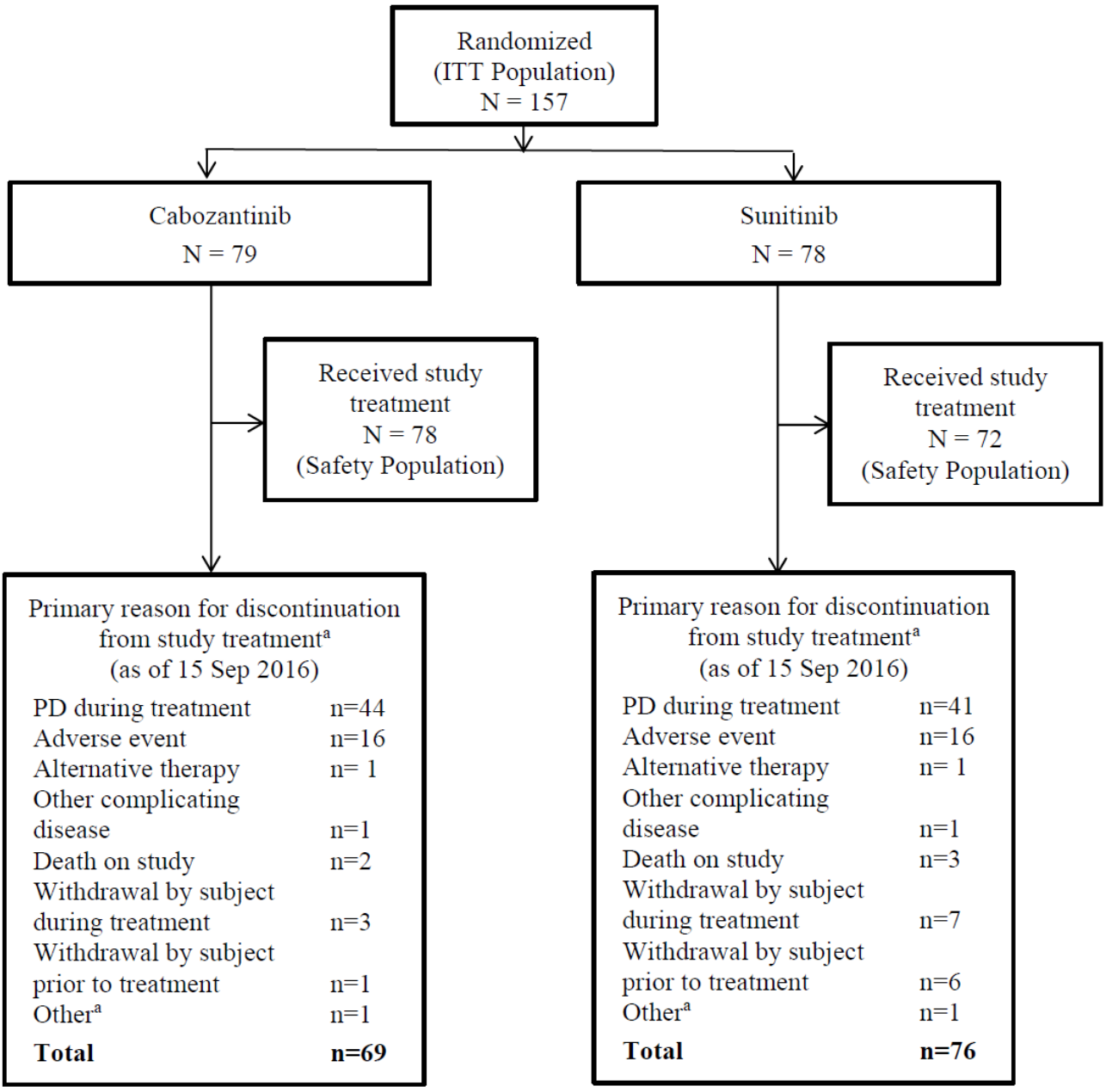


Figure 2: Flow Chart of Subject Disposition as of 15 September 2016 (ITT Population)

Disposition results based on the PFS endpoint cut-off date (11 April 2016), previously reported by the Alliance were similar to those of the 15 September 2016 cut-off date. As of 11 April 2016, 66 patients (84%) in the cabozantinib arm and 76 patients (97%) in the sunitinib arm had discontinued study treatment[18].

Disposition results based on the OS database cut-off date (13 January 2017) were similar to those of the 15 September 2016 cut-off date. As of 13 January 2017, 71 patients (90%) in the cabozantinib arm and 76 patients (97%) in the sunitinib arm had discontinued study treatment.

As of 15 September 2016, 40 patients in the cabozantinib arm (51%) and 29 patients in the sunitinib arm were in survival follow-up.

[18] Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol. 2017;35 (6):591-597.

Recruitment

Study Period: 15 July 2013 (first subject enrolled) – 13 January 2017 (data cut-off date for overall survival).

All 77 sites in the study were located in the United States.

Conduct of the study

Overall survival analyses were conducted with the most mature OS data available from the Alliance (through a cut-off date of 13 January 2017). The cut-off dates for the key efficacy endpoints are provided in Table 4.

Table 4: Data Cut-off Dates for Primary and Secondary Efficacy Endpoints

Endpoint	Study A031203	Database cutoff dates
Primary	**PFS** by RECIST (The original assessment was determined by the Investigator. A retrospective determination was performed per IRC.)	**Alliance: 11 April 2016** **CSR: 15 September 2016**
Secondary	**OS**	**Alliance: 15 September 2016** **CSR: 13 January 2017**
Secondary	**ORR** by RECIST (The original assessment was determined by the Investigator. A retrospective determination was performed per IRC.)	**Alliance: 01 August 2016** **CSR: 15 September 2016**

There were 8 amendments to the Original Protocol. With the exception of the introduction of retrospective IRC data collection in the most recent Protocol Update 8 (21. Oct. 2016), none of the protocol updates had a substantial impact on the collection or analysis of the study's primary or secondary objectives. Most of the protocol changes were clarifications, and mainly affected the safety evaluation.

SAP

A SAP was not prospectively developed by the Alliance. The Exelixis SAP, which was developed after release of the Alliance results, describes statistical analyses that Exelixis conducted retrospectively to meet the requirements of a regulatory submission, including the full set of prior history, baseline, demographics, study treatment, safety, and efficacy summaries required for an ICH-compliant study report. Further, although the Alliance protocol employed 1-sided p-values, for consistency with Exelixis-sponsored pivotal study reports, all p-values presented are 2-sided unless otherwise specified. The Exelixis SAP v1 was approved on 31 May 2017, prior to the receipt of IRC results. The protocol did not feature IRC review of radiographic images until Update 8 (21. Oct. 2016), after the date of the original Alliance analysis (11. April 2016). The Exelixis SAP specifies analyses of the IRC data.

The protocol did not implement event and censoring definitions for primary PFS analysis, nor were sensitivity analyses included to address the potential for bias arising from inconsistent imaging schedules or informative censoring. The Exelixis SAP specified a set of PFS analyses consistent with FDA guidance (see Statistical methods).

Protocol deviations

Subjects were required to not have received prior systemic treatment for RCC. No subjects in the cabozantinib arm received prior systemic treatment. One subject who received study treatment in the sunitinib arm received 'Prior Therapy Not Otherwise Specified (NOS)'. Another subject in the sunitinib arm received prior 'Drug and/or Immunotherapy' (drug name not specified); this subject did not receive study treatment.

No subjects in either treatment arm received the wrong study treatment or dosing levels not defined in the protocol.

Baseline data

Table 5: Key Demographic and Baseline Characteristics (ITT Population)

	Cabozantinib (N = 79)	Sunitinib (N = 78)
Median (range) age (years)	63.0 (40, 82)	64.0 (31, 87)
Male, n (%)	66 (84)	57 (73)
Female, n (%)	13 (16)	21 (27)
White	70 (89)	75 (96)
Black or African American	3 (4)	2 (3)
Asian	2 (3)	0
Other categories[a]	5 (6)	1 (1)
ECOG Performance Status, n (%)		
0 (normal activity)	36 (46)	36 (46)
1 (symptoms, but ambulatory)	33 (42)	32 (41)
2 (in bed < 50% of time, ambulatory and capable of self-care but not work activities)	10 (13)	10 (13)
Randomization Stratification Factors per IxRS, n (%)		
Bone metastases (yes)	29 (37)	28 (36)
Bone metastases (no)	50 (63)	50 (64)
IMDC criteria (intermediate risk)	64 (81)	63 (81)
IMDC criteria (poor risk)	15 (19)	15 (19)
Median (range) time to randomization since initial diagnosis of the primary tumor (years)	0.241 (0.02, 10.70)	0.268 (0.01, 14.77)
Nephrectomy, n (%)	57 (72)	60 (77)
Prior radiation therapy, n (%)	14 (18)	19 (24)
MET immunohistochemistry status, n (%)[b]		
Positive	32 (41)	30 (38)
Negative	39 (49)	30 (38)
Missing	8 (10)	18 (23)

ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic RCC Database Consortium; ITT, intent-to-treat; IxRS, interactive voice/web response system a "Other" comprises the American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Unknown categories. Subject 2000255 in the cabozantinib

arm recorded multiple race categories: Asian and Native Hawaiian or Other Pacific Islander b MET status information was determined from an optional substudy. Positive status is based on cutoff of ≥ 50% of tumour cells stained 2+ or 3+ (moderate or higher intensity) by immunohistochemistry, negative status is < 50% of tumour cells stained 2+ or 3+ (includes samples with no staining). Subjects who declined to participate in the substudy are summarized as missing.

Table 6: Cancer History and Baseline Disease Status (ITT Population)

Characteristic	Cabozantinib N = 79	Sunitinib N = 78
Time since initial diagnosis to randomization		
< 1 year, n (%)	61 (77)	57 (73)
≥ 1 year, n (%)	18 (23)	21 (27)
Median (range) (years)	0.241 (0.02, 10.70)	0.268 (0.01, 14.77)
Nephrectomy, n (%)	57 (72)	60 (77)
Status of primary tumor per Investigator, n (%)		
Resected, no residual tumor	50 (63)	50 (64)
Resected, residual tumor	9 (11)	12 (15)
Unresected	20 (25)	16 (21)
Metastectomy performed, n (%)	12 (15)	9 (12)
Metastatic sites/subject per Investigator per On-Study CRF, n (%)	79 (100)	78 (100)
Nodal	45 (57)	42 (54)
Visceral	61 (77)	56 (72)
Liver	15 (19)	20 (26)
Lung	55 (70)	54 (69)
Subcutaneous tissue	7 (9)	1 (1)
Abdominal wall	2 (3)	4 (5)
Bone[a]	31 (39)	30 (38)
CNS/Brain	3 (4)	2 (3)
Other[b]	19 (24)	29 (37)
Number of metastatic sites/subject per Investigator per On-Study CRF, n (%)		
0	0	0
1	17 (22)	26 (33)
2	37 (47)	20 (26)
≥ 3	25 (32)	32 (41)

Characteristic	Cabozantinib N = 79	Sunitinib N = 78
Number of bone metastases/subject per Investigator per On-Study CRF, n (%)		
0	48 (61)	48 (62)
1	13 (16)	8 (10)
2	7 (9)	6 (8)
3	1 (1)	5 (6)
4	1 (1)	5 (6)
> 4	9 (11)	6 (8)
Baseline SoD (cm) of target lesions per Investigator per RECIST CRF		
n	78	76
Mean (SD)	8.447 (5.5194)	11.130 (12.5968)
Median (range)	7.150 (1.00, 28.70)	8.100 (1.60, 104.00)
MET status, n (%)[c]		
Positive	32 (41)	30 (38)
Negative	39 (49)	30 (38)
Missing[d]	8 (10)	18 (23)

CNS, central nervous system; CRF, case report form; ITT, intent-to-treat; IxRS, interactive web/voice response system; RECIST, Response Evaluation Criteria for Solid Tumours; SD, standard deviation; SoD, sum of diameters.
[a] Baseline bone metastases data per CRF differ slightly from those reported by IxRS (Table 12).
[b] Baseline metastatic sites summarized under the category of 'other' for the cabozantinib arm included the adrenal glands, pancreas, pericardium, peritoneum and mesentery, omentum, vaginal wall, renal vein and interior vena cava, iliac node, soft tissue, and pleura. Metastatic sites of 'other' for the sunitinib arm included the adrenal glands, pancreas, paraspinal chest, subcutaneous fat left flank, psoas muscle, peritoneum, omentum, mediastinum, uterus and vagina, soft tissue, and pleura.
[c] Positive status is based on cutoff of ≥ 50% of tumour cells stained 2+ or 3+ (moderate or higher intensity) by immunohistochemistry, negative status is < 50% of tumour cells stained 2+ or 3+ (includes samples with no staining).
[d] MET status information was determined from an optional sub-study (A031203-ST1). Subjects who declined to participate in that optional sub-study are summarized as missing.

The baseline characteristics of the 30 subjects in the poor risk category are presented in Table 7.

Table 7: Baseline Characteristics of Subjects in the Poor Risk Category - Study A031203

	Cabozantinib (N=15)	Sunitinib (N=15)
Age (years)		
n	15	15
Mean (SD)	60.5 (6.76)	63.3 (11.31)
Median (range)	60.0 (51-73)	64.0 (43-82)
Age Category (years)		
< 65	10(67%)	9(60%)
65 to < 75	5(33%)	3(20%)
>=75	0	3(20%)
Gender		
Male	13(87%)	8(53%)
Female	2(13%)	7(47%)
Ethnicity		
Not Hispanic or Latino	13(87%)	14(93%)
Not Reported	2(13%)	1(7%)
Race [1]		
White	13(87%)	15(100%)
Asian	1(7%)	0
Other	2(13%)	0
Native Hawaiian or Other Pacific Islander	1(7%)	0
Not Reported	1(7%)	0
Weight (kg)		
< 60 kg	2(13%)	3(20%)
>= 60 to <= 80 kg	5(33%)	7(47%)
> 80 kg	8(53%)	5(33%)
Mean (SD)	80.05 (19.259)	75.45 (15.473)
Median (range)	83.90 (48.5-106.0)	76.40 (55.4-107.5)
ECOG Performance Status		
0	3(20%)	4(27%)
>= 1	12(80%)	11(73%)
1	9(60%)	10(67%)
2	3(20%)	1(7%)
Karnofsky Performance Status		
< 80%	3(20%)	1(7%)
>= 80%	12(80%)	14(93%)
Bone Metastases status per IxRS		
Yes	7(47%)	8(53%)
No	8(53%)	7(47%)
MET Status		
Positive	2(13%)	9(60%)
Negative	9(60%)	5(33%)
Missing	4(27%)	1(7%)

Table 8: Prior Radiation Therapies (ITT Population)

	Cabozantinib N = 79	Sunitinib N = 78
≥ 1 prior radiation therapy per subject, n (%)	14 (18)	19 (24)
Sites of prior radiation therapies per Medical History CRF		
Brain, thoracic cavity, abdomen, or pelvis	3 (4)	3 (4)
Bone	11 (14)	15 (19)
Other	1 (1)	2 (3)

Numbers analysed

Table 9: Study populations

	Cabozantinib n (%)	Sunitinib n (%)
Intent-to-Treat (ITT) population[a]	79 (100)	78 (100)
Safety population[b]	78 (99)	72 (92)

The Intent-To-Treat (ITT) Population, defined as all randomized subjects, was used for efficacy analyses with analyses according to the randomization assignment.

The Safety population comprised all randomized subjects who received at least one dose of study treatment (150 subjects); 78 subjects in the cabozantinib arm and 72 subjects in the sunitinib arm. Six subjects randomized to receive sunitinib and one subject randomized to receive cabozantinib did not receive any study treatment.

Outcomes and estimation

Primary endpoint: PFS

Alliance analysis of PFS

Table 10: Primary endpoint from the protocol – Progression Free Survival – Investigator – no censoring

Progression-Free Survival (Investigator-Determined Alliance Censoring Rules, ITT Population)		
Number (%) of subjects	Cabozantinib	Sunitinib
Death or progression	123	
Duration of progression free survival (months)		
Median (95% CI)	8.2 (6.2, 8.8)	5.6 (3.4, 8.1)
Two-sided log-rank p-value: stratified	0.024	
Hazard ratio (95% CI); stratified	0.66 (0.46, 0.95)	

The analysis was triggered when 123 events were observed, and there was no censoring due to subsequent anticancer therapy or missing assessments. In the Alliance analysis, PFS favoured cabozantinib with a stratified HR = 0.66 (95% CI 0.46, 0.95; 1-sided p-value = 0.012 (=2-sided

0.024)). At the time of that analysis (data cut-off 11 April 2016), 15 subjects (13 cabozantinib arm, 2 sunitinib arm) were still receiving study treatment and others were still in follow-up for PFS and OS; the study database remained open and active.

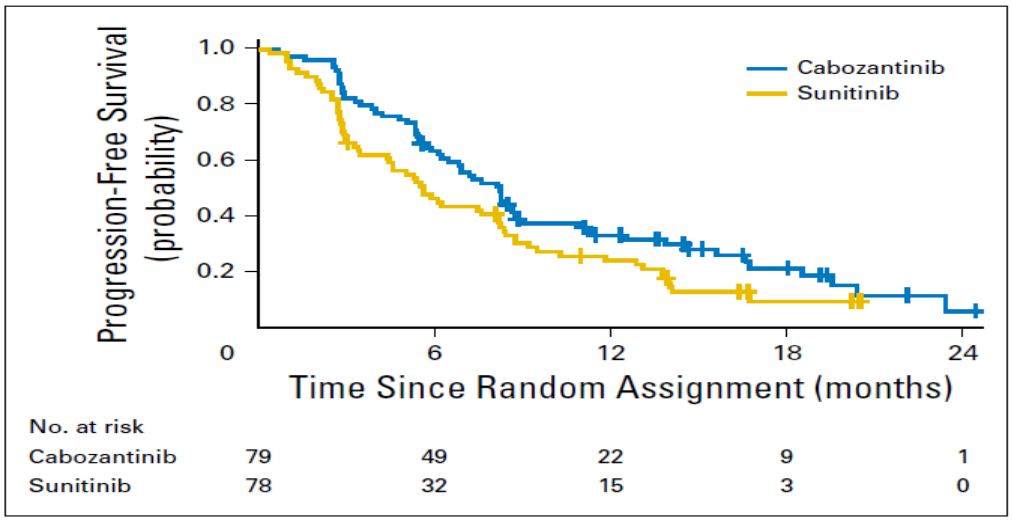


Figure 3: Kaplan-Meier plot of progression-free survival through April 11, 2016 (Choueiri et al 2017)

Primary analysis for the submission - PFS per IRC

PFS determined by the IRC using FDA-recommended censoring rules showed a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the sunitinib arm. The HR adjusted for stratification factors was 0.48 (95% CI 0.31, 0.74; p = 0.0008). The median duration of PFS was estimated to be 8.6 months in the cabozantinib arm vs 5.3 months in the sunitinib arm.

Table 11: Progression-Free Survival (IRC-Determined, FDA-Recommended Censoring Rules, ITT Population)

	Cabozantinib (N = 79)	Sunitinib (N = 78)
Number (%) of subjects		
Censored	36 (46)	29 (37)
2 or more missed ATAs prior to event	5 (6)	0
No baseline and postbaseline ATAs	0	2 (3)
No event by last ATA	10 (13)	3 (4)
No postbaseline ATA	1 (1)	6 (8)
Systemic anticancer therapy	20 (25)	18 (23)
Event	43 (54)	49 (63)
Death	3 (4)	6 (8)
Documented progression	40 (51)	43 (55)
Duration of progression free survival (months)[a]		
Median (95% CI)	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
25th percentile, 75th percentile	5.4, 22.1	2.7, 10.1
Range	0.0+, 27.3+	0.0+, 25.0+
Two-sided log-rank p-value: stratified[b]	0.0008	
Hazard ratio (95% CI); stratified[b,c]	0.48 (0.31, 0.74)	
Landmark Estimates (% of subjects event-free)	**Cabozantinib (N = 79)**	**Sunitinib (N = 78)**
3 months	79.7	64.2
6 months	63.1	41.5
12 months	43.1	21.1
18 months	31.4	8.0
21 months	28.7	5.4

+ indicates a censored observation; ATA, adequate tumour assessment; CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; IRC, independent radiology committee; ITT, intent-totreat; IxRS, interactive voice/web response system FDA-recommended censoring rules are described in the SCE.
a Median and percentiles are based on Kaplan-Meier survival estimates.
b Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk; Heng et al 2009) and bone metastasis (yes, no).
c Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. Hazard ratio < 1 indicates progression-free survival in favour of cabozantinib.

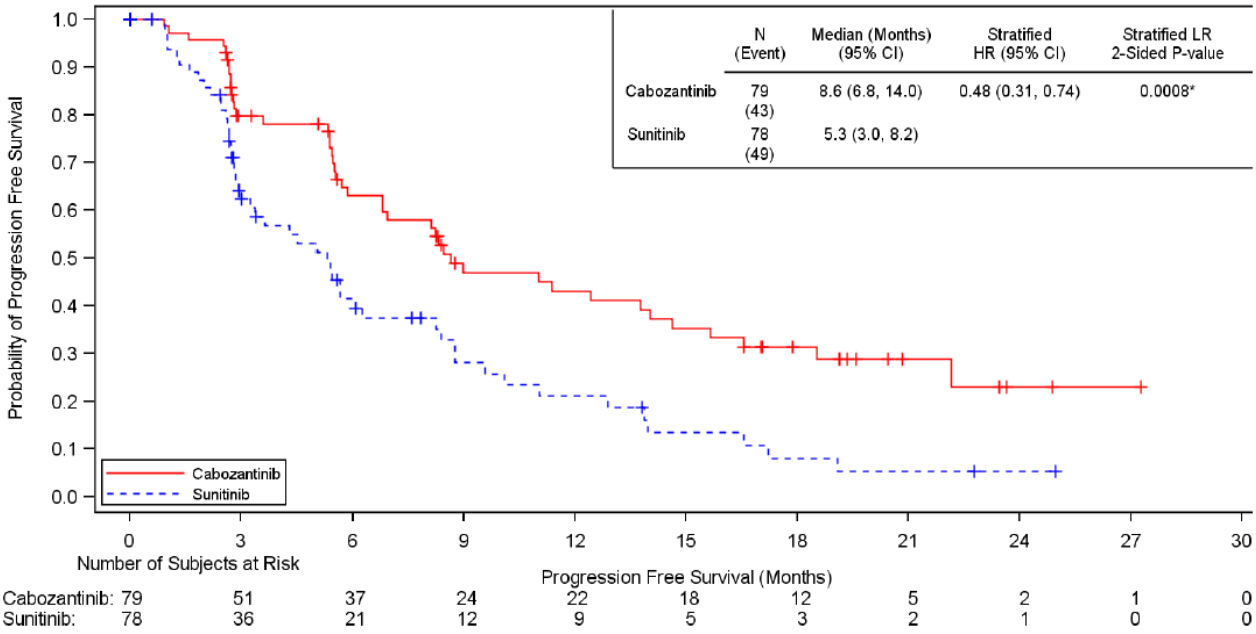


Figure 4: Kaplan-Meier Plot of Progression-Free Survival (IRC-Determined, FDA-Recommended Censoring Rules, ITT Population)

CI, confidence interval; HR, hazard ratio; IxRS, interactive voice/web response system; LR, logrank. Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk; Heng et al 2009) and bone metastasis (yes, no). * Indicates 2-sided p-value < 0.05. + indicates a censored observation

PFS per Investigator

Table 12: Progression-Free Survival (Investigator-Determined, FDA Censoring Rules, ITT Population)

	Cabozantinib (N = 79)	Sunitinib (N = 78)
Number (%) of subjects		
Censored	23 (29)	27 (35)
2 or more missed ATAs prior to event	2 (3)	1 (1)
No baseline and postbaseline ATAs	1 (1)	0
No event by last ATA	11 (14)	3 (4)
No postbaseline ATA	0	6 (8)
Systemic anticancer therapy	9 (11)	17 (22)
Event	56 (71)	51 (65)
Death	3 (4)	7 (9)
Documented progression	53 (67)	44 (56)
Duration of progression free survival (months) [a]		
Median (95% CI)	8.3 (6.5, 12.4)	5.4 (3.4, 8.2)
25th percentile, 75th percentile	5.1, 19.6	2.8, 10.3
Range	0.0+, 27.4+	0.0+, 25.2+
2-sided log-rank p-value; stratified[b]	0.0042	
Hazard ratio (95% CI); stratified[b,c]	0.56 (0.37, 0.83)	
Landmark Estimates (% of subjects event-free)	**Cabozantinib (N = 79)**	**Sunitinib (N = 78)**
3 months	81.9	66.3
6 months	62.8	44.0
12 months	38.9	22.7
18 months	28.0	5.1

+ indicates a censored observation; ATA, adequate tumour assessment; CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; ITT, intent-to-treat; IxRS, interactive voice/web response system.
FDA-recommended censoring rules are described in the Section 9.7.1.2.1.
[a] Median and percentiles are based on Kaplan-Meier survival estimates.
[b] Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk; 27) and bone metastasis (yes, no).
[c] Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. Hazard ratio < 1 indicates progression-free survival (PFS) in favor of cabozantinib.

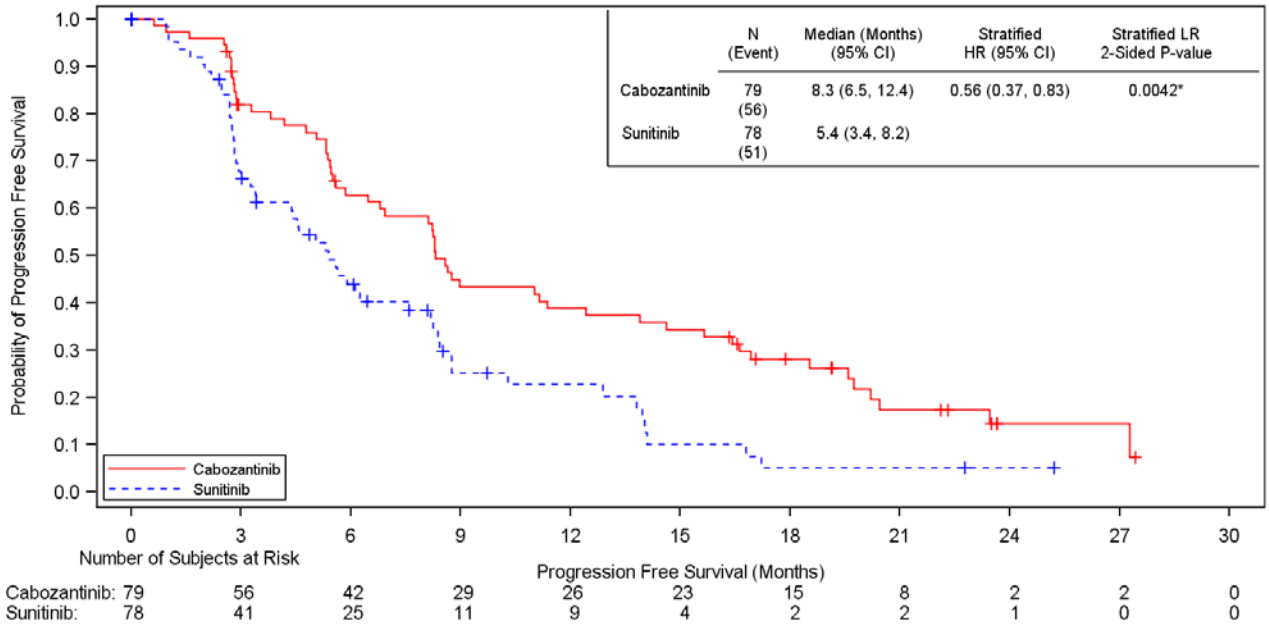


Figure 5: Kaplan-Meier Plot of Progression-Free Survival (Investigator-Determined, FDA-Recommended Censoring Rules, ITT Population)

PFS according to EU censoring rules

There were 5 patients in the cabozantinib arm who had events after having two or more missed visits, and none in the sunitinib arm. According to the FDA censoring rules these patients were censored. Table 13 below presents results according to EU censoring rules (these 5 patients were not censored) and FDA censoring rules (same 5 patients censored). PFS was determined by the IRC using analyses as per EMA censoring rules. In the EU analysis the HR was 0.48 (95%CI 0.32, 0.73; p=0.0005). In the analysis using the FDA-recommended censoring rules, the HR was 0.48 (95% CI 0.31, 0.74; p = 0.0008).

Table 13: Comparison of results of PFS Analyses when Subjects with 2 or more missed ATAs prior to event were censored (FDA censoring rules) or were not censored (EMA guideline EMA/CHMP/27994/2008/Rev.1) - Study A031203

	CABOMETYX (N=79)	Sunitinib (N=78)
Analysis per FDA censoring rules		
Progression-free survival (PFS) by IRC		
Median PFS in months (95% CI)	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
HR (95% CI); stratified [a,b]	0.48 (0.31, 0.74)	
Two-sided log-rank p-value: stratified [a]	p=0.0008	
Analysis per EMA Guideline (EMA/CHMP/27994/2008/Rev.1) for missed visits		
Progression-free survival (PFS) by IRC:		
Median PFS in months (95% CI)	8.6 (6.2, 14.0)	5.3 (3.0, 8.2)
HR (95% CI); stratified [a,b]	0.48 (0.32, 0.73)	
Two-sided log-rank p-value: stratified [a]	p=0.0005	

Investigator and IRC concordance on PD

The overall concordance for PD was 75%. The Investigator and IRC agreed on subjects' radiographic PD status (ie, radiographic PD yes vs no; subjects with ≥ 1 tumour assessment per Investigator and per IRC) 69% of the time for the cabozantinib arm and 84% of the time for the sunitinib arm (Table 15). When both the Investigator and IRC agreed that radiographic PD had occurred, the Investigator and IRC agreed on the dates of PD 63% of the time for the cabozantinib arm and 56% of the time for the sunitinib arm.

Table 14: Concordance between Investigator and IRC Read in Progressive Disease

Treatment	No. of Discordance (%)			No. of Concordance (%)		
	Investigator Progressed/ IRC Not Progressed	Investigator Not Progressed/ IRC Progressed	Total Discordance	Progressive Disease[a]	Not Progressive Disease	Total Concordance
Cabozantinib (N = 77)	18 (23)	6 (8)	24 (31)	41 (53)	12 (16)	53 (69)
Sunitinib (N = 61)	8 (13)	2 (3)	10 (16)	45 (74)	6 (10)	51 (84)
Total (N = 138)	26 (19)	8 (6)	34 (25)	86 (62)	18 (13)	104 (75)

Subgroup analyses of PFS

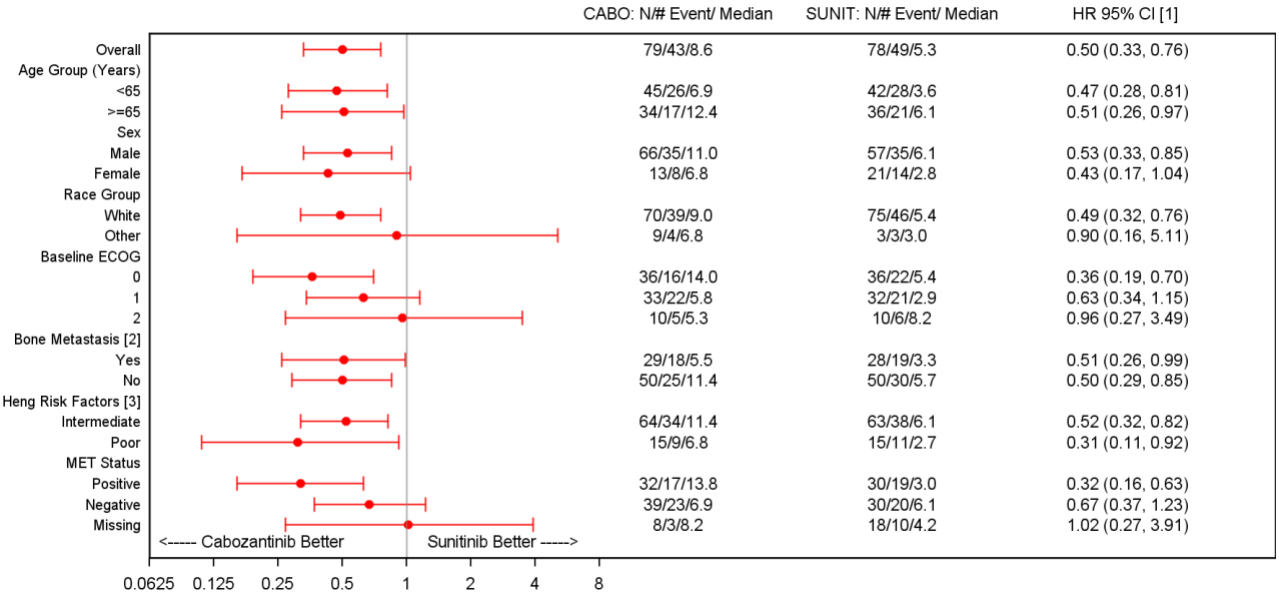


Figure 6: Forest Plot of Subgroup Analyses of IRC-Determined Progression-Free Survival (FDA-Recommended Censoring Rules, ITT Population)

MET status information was determined from an optional sub-study (A031203-ST1). Subjects who declined to participate in that optional sub-study are summarized as missing. Positive MET status is based on cutoff of ≥ 50% of tumor cells stained 2+ or 3+ (moderate or higher intensity) by immunohistochemistry, negative status is < 50% of tumor cells stained 2+ or 3+ (includes samples with no staining).
Results are presented based on censoring per FDA-recommended censoring rules (Section 9.7.1.2.1).
HRs were estimated using the Cox proportional hazard model. HR < 1 indicates PFS in favor of cabozantinib.

Secondary Endpoint: Overall Survival

The Exelixis analysis of OS included one more event in the cabozantinib arm and 4 additional events in the sunitinib arm, compared to the Alliance analysis. The median time of follow up for OS (through 13 January 2017) was 28.9 months.

Table 15: Analysis of Overall Survival (ITT Population)

	Cabozantinib (N = 79)	**Sunitinib (N = 78)**
Number (%) of subjects		
Censored (no event as of cutoff date)	41 (52)	33 (42)
Death	38 (48)	45 (58)
Duration of overall survival (months)[a]		
Median (95% CI)	30.3 (14.6, NE)	21.0 (16.3, 27.0)
25th percentile, 75th percentile	12.2, NE	8.3, NE
Range	0.4+, 38.4+	0.0+, 35.2+
Two-sided log-rank p-value; stratified[b]	0.1700	
Hazard ratio (95% CI); stratified[b,c]	0.74 (0.47, 1.14)	
Landmark Estimates (% of subjects event-free)	**Cabozantinib (N = 79)**	**Sunitinib (N = 78)**
3 months	97.4	93.3
6 months	91.0	82.5
12 months	75.6	68.9
18 months	58.6	59.0
24 months	55.8	43.3
30 months	50.7	30.3

+ indicates a censored observation; CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; ITT, intent-to-treat; IxRS, interactive voice/web response system; NE, not estimable

[a] Median and percentiles are based on Kaplan-Meier survival estimates.

[b] Stratification factors comprise IMDC risk categories (intermediate risk, poor risk; Heng et al 2009) and bone metastasis (yes, no).

[c] Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. A hazard ratio <1 indicates overall survival in favour of cabozantinib.

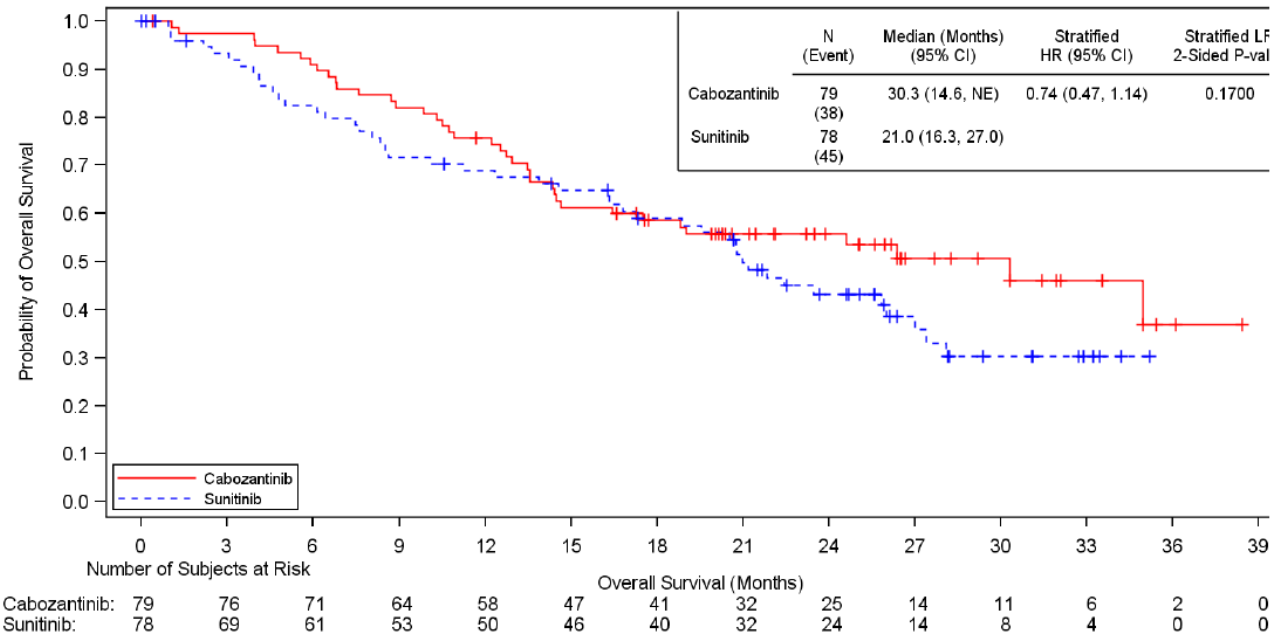


Figure 7: Kaplan-Meier Plot of Overall Survival (ITT Population) Cut-off 13 January 2017

CI, confidence interval; HR, hazard ratio; IxRS, interactive voice/web response system; LR, logrank; NE, not estimable Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk; Heng et al 2009) and bone metastasis (yes, no). * Indicates 2-sided p-value < 0.05. + indicates a censored observation

Alliance analysis of Overall survival (Choueiri et al 2017)

As of September 15, 2016, the median follow-up of surviving patients was 21.4 months. Overall, 37 deaths had occurred in the cabozantinib arm and 41 in the sunitinib arm. Median OS with cabozantinib was 30.3 months (95% CI, 14.6 to 35.0 months) versus 21.8 months (95% CI, 16.3 to 27.0 months) with sunitinib (adjusted HR, 0.80; 95% CI, 0.50 to 1.26).

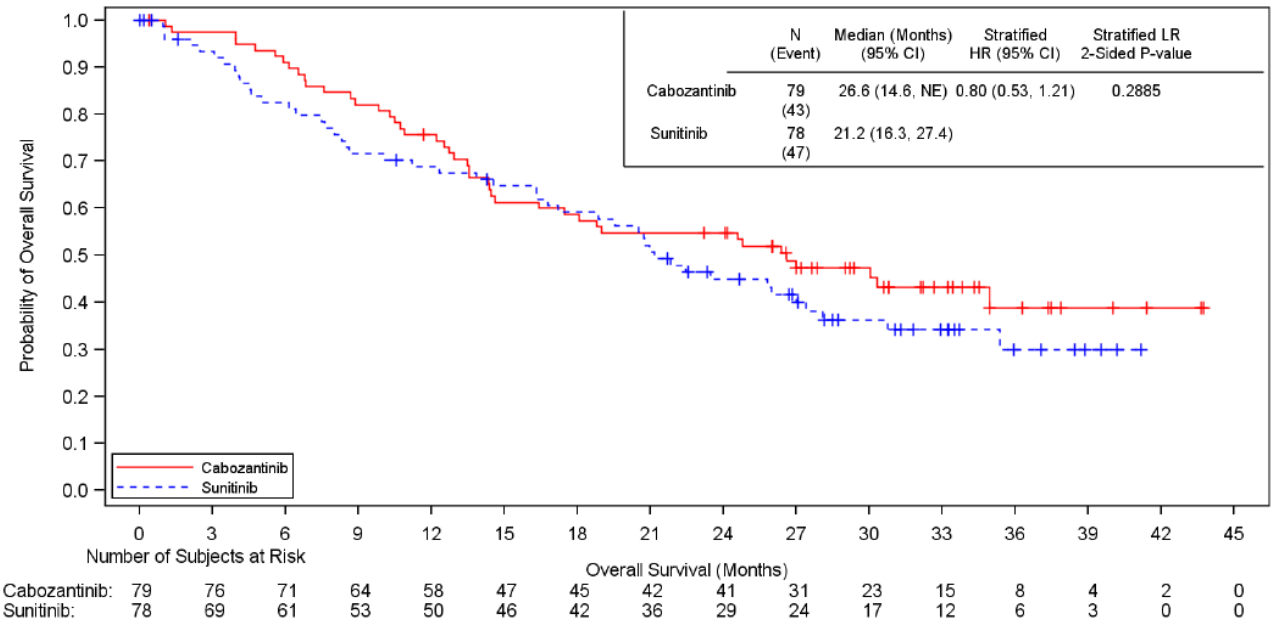
The Alliance presented OS results at the European Society for Medical Oncology (ESMO) annual meeting in September 2017, based on an analysis they conducted with a data cut-off of 01 July 2017 (Choueiri ESMO presentation 2017).

Table 16: Results from Three Analyses - Study A031203

	15 September 2016	13 January 2017	01 July 2017
Number of events	78	83	90
Median OS (95% CI), months (cabozantinib vs. sunitinib)	30.3 (14.6, 35.0) vs 21.8 (16.3, 27.0)	30.3 (14.6, NE) vs 21.0 (16.3, 27.0)	26.6 (14.6, NE) vs 21.1 (16.3, 27.4)
HR (95% CI)	0.80 (0.50, 1.26)	0.74 (0.47, 1.14)	0.80 (0.53, 1.21)
Number of patients active on study drug	12	10	Not reported

Table 17: Overall Survival - Study A031203 (Cut-off Date 01 July 2017)

	Cabozantinib (N=79)	Sunitinib (N=78)
Number (%) of subjects		
Censored	36 (46%)	31 (40%)
ALIVE	36 (46%)	31 (40%)
Event	43 (54%)	47 (60%)
DEATH	43 (54%)	47 (60%)
K-M estimate (months)		
n	79	78
25th percentile	12.2	8.3
Median (95% CI)	26.6 (14.6, NE)	21.2 (16.3, 27.4)
75th percentile	NE	NE
Min, Max	0.4+, 43.8+	0.0+, 41.2+



Data source: Choueiri 2017 ESMO Presentation Figure 5 and Updated Study A031230 Response to Questions Appendix Table 14.2.2.1 (01July 2017)

Figure 8: Kaplan-Meier Plot of Overall Survival - Study A031203 (Cut-off Date 01 July 2017)

Subsequent systemic non-radiation anticancer therapies

The arithmetic median (range) time to first systemic non-radiation anticancer therapy was longer in the cabozantinib arm: 196 (56, 877) days in the cabozantinib arm and 147 (4, 725) days in the sunitinib arm.

After progression, systemic non-protocol anticancer therapy (NPACT) was used by a similar proportion of subjects in each arm: 57% of subjects in the cabozantinib arm and 58% in the sunitinib arm. Similar proportions of patients used VEGFR-TKI therapy; 46% and 45%, and Anti-PD-1/PD-L1 targeting agents, 13% and 15%, in the cabozantinib arm and sunitinib arm, respectively. There was a higher usage of everolimus in the sunitinib arm (cabozantinib arm 8% vs sunitinib arm 19%), while

there was a higher use of temsirolimus in the cabozantinib arm (cabozantinib arm 9% vs sunitinib arm 4%). Crossover between study arms was not prescribed in this study. However, 5 patients (6%) in the sunitinib arm received cabozantinib after progression.

Secondary Efficacy Endpoint: Objective Response Rate (ORR)

Exelixis analysis of ORR

Table 18: Tumour Response per RECIST (IRC- and Investigator-Determined, ITT Population)

Subjects in ITT Population	IRC-Determined		Investigator-Determined	
	Cabozantinib (N = 79)	Sunitinib (N = 78)	Cabozantinib (N = 79)	Sunitinib (N = 78)
Subjects with any tumor reduction compared with baseline, n (%)	63 (80)	39 (50)	67 (85)	30 (38)
Subjects with ≥ 1 baseline and ≥ 1 post-baseline SoD[a]	69 (87)	58 (74)	72 (91)	54 (69)
Best overall response, n (%)[b]				
Confirmed complete response (CR)	0	0	1 (1)	0
Confirmed partial response (PR)	16 (20)	7 (9)	25 (32)	9 (12)
Stable disease (SD)	43 (54)	30 (38)	34 (43)	29 (37)
Unconfirmed CR	0	0	0	0
Unconfirmed PR	10 (13)	5 (6)	10 (13)	3 (4)
Non-CR/non-PD[c]	2 (3)	1 (1)	NA	NA
Progressive disease (PD)	14 (18)	23 (29)	14 (18)	19 (24)
Unable to evaluate (UE)	4 (5)	6 (8)	3 (4)	6 (8)
Missing[d]	2 (3)	12 (15)	2 (3)	15 (19)
No baseline assessments	0	2 (3)	1 (1)	2 (3)
No postbaseline assessments (irrespective of baseline status)	2 (3)	12 (15)	2 (3)	15 (19)
Objective response rate (ORR)[e]				
n (%)	16 (20)	7 (9)	26 (33)	9 (12)
95% CI	12.0, 30.8	3.7, 17.6	22.7, 44.4	5.4, 20.8
ORR treatment difference (95% CI)	11.3 (0.4, 22.2)		21.4 (8.8, 33.9)	
Stratified CMH test 2-sided p-value[f]	0.0406		0.0010	

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IMDC, International Metastatic RCC Database Consortium; IRC, independent radiology committee; ITT, intent-to-treat; IxRS, interactive voice/web response system; NA, not applicable; RECIST, Response Evaluation Criteria In Solid Tumours; SoD sum of diameters.

[a] Subjects with ≥ 1 baseline and ≥ 1post-baseline SoD prior to or on the date of first progression and prior to or on date of first systemic non-radiation therapy

[b] Best overall response is assessed based on RECIST criteria 1.1. Only responses prior to progression are considered. Qualifying assessments are those that result in an overall response of either CR, PR, SD, or PD.

[c] This category does not apply to subjects with measurable disease. All subjects were required per protocol to have measurable disease per RECIST per Investigator. Measurable disease was not documented by the IRC for some subjects.

[d] Subjects are counted once in the Missing row but may be counted in multiple missing subcategories. Subjects with UE/Missing radiographic assessments had the following study treatment discontinuation reasons: IRC Cabozantinib: AEs (5), withdrew consent prior to treatment (1) Sunitinib: AEs (6), death on study (2), disease progression during treatment (1), withdrew consent prior to treatment (5), withdrew consent after starting treatment (4) Investigator Cabozantinib: AEs (4), withdrew consent prior to treatment (1) Sunitinib: AEs (7), death on study (2), disease progression during treatment (2), withdrew consent prior to treatment (6), withdrew consent after starting treatment (3), other (1 [referred for hospice treatment])
[e] ORR is defined as the proportion of subjects achieving (IRC- or Investigator-determined) best overall response of CR or PR per RECIST v1.1 confirmed by a subsequent scan at least 28 days later.
[f] Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk; Heng et al 2009) and bone metastasis (yes, no).

Alliance analysis of ORR

Table 19: ORR - Study A031203[18]

Table 2. Tumor Response

Response	Cabozantinib (n = 79), No. (%)	Sunitinib (n = 78), No. (%)
ORR, % (95% CI)*	46 (34 to 57)	18 (10 to 28)
Best overall response, No. (%)		
Confirmed CR	1 (1.3)	1 (1.3)
Confirmed PR	35 (44.3)	13 (16.7)
Stable disease	26 (32.9)	28 (35.9)
Progressive disease	14 (17.7)	20 (25.6)
Not evaluable or missing†	3 (3.8)	16 (20.5)

NOTE. All randomly assigned patients were included in the analysis. Data are as of April 11, 2016.
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response.
*Proportion of patients achieving an overall response of confirmed CR or PR per RECIST (version 1.1).
†No postbaseline imaging performed for the following reasons: cabozantinib: clinical progression (n = 1), withdrawal of consent (n = 1), or initiation of alternative therapy (n = 1); sunitinib: clinical progression (n = 2), withdrawal of consent (n = 7), adverse event (n = 4), death (n = 2), or initiation of alternative therapy (n = 1).

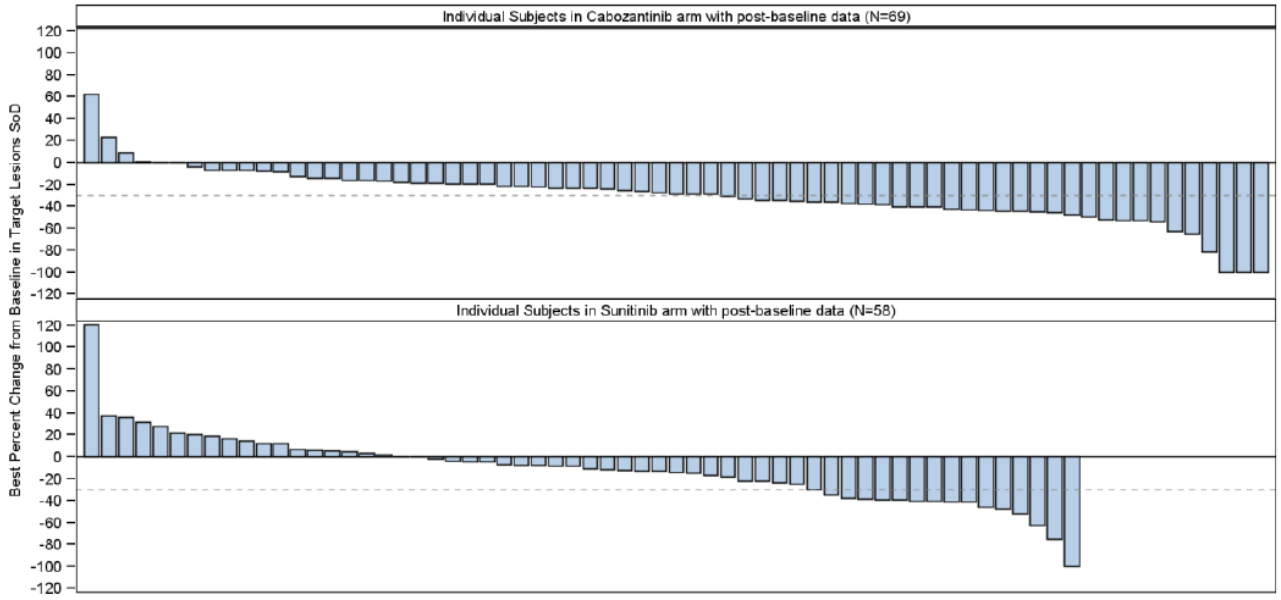


Figure 9: Plot of Best Percentage Change in Tumour Size from Baseline (IRC-Determined, ITT Population [Subjects with At Least One Baseline and Post-baseline Assessment])

Note: Date for the following subjects are not included in this figure: 14 subjects (cabozantinib 2, sunitinib 12) did not have post-baseline data. In addition, three subjects (cabozantinib 2, sunitinib 1) had only nontarget lesions (response of non-CR/non-PD); 7 subjects (cabozantinib 3, sunitinib 4) were unevaluable due to NPACT; disease progression was assessed for 5 subjects (cabozantinib 2, sunitinib 3) on the basis of new lesions or progression in non-target lesions, target lesions did not contribute to the assessment. Additionally, 1 cabozantinib subject with an overall response of UE did not have any post-baseline target lesions measured.

Duration of Response

Median duration of response per IRC using FDA-recommended censoring rules was not reached (95% CI 8.5 months, NE) in the cabozantinib arm and was 8.1 (95% CI 6.0, NE) months in the sunitinib arm. The stratified HR was 0.21 (0.05, 0.90) in favour of cabozantinib.

Median duration of response per Investigator using FDA-recommended censoring rules was 17.4 (95% CI 11.7, NE) months in the cabozantinib arm and 11.0 (95% CI 7.6, NE) months in the sunitinib arm. The stratified HR was 0.39 (0.12, 1.26) in favour of cabozantinib.

Time to Response

The arithmetic median (range) time from randomization to the first assessment which showed IRC-determined response that was subsequently confirmed was 4.91 (2.6, 10.9) months in the cabozantinib arm and 5.78 (2.6, 22.3) months in the sunitinib arm.

The corresponding median (range) time from randomization to the first assessment which showed Investigator-determined response that was subsequently confirmed was 2.91 (1.3, 13.0) months in the cabozantinib arm and 3.09 (2.6, 16.7) months in the sunitinib arm.

Expression of MET

All subjects were asked for their consent to participate in the sub-study of MET expression by the tumor tissue, though participation was optional. Required tissue included paraffin-embedded tissue obtained from earlier biopsies or nephrectomies.

Table 21 shows the results of the MET status analysis in patients that entered the substudy.

Table 20: MET Status of Subjects - Study A031203

Characteristic	Cabozantinib N=79	Sunitinib N=78
MET status, n (%)[a]		
Positive	32 (41)	30 (38)
Negative	39 (49)	30 (38)
Missing[b]	8 (10)	18 (23)

a Positive status is based on cutoff of ≥50% of tumor cells stained 2+ or 3+ (moderate or higher intensity) by immunohistochemistry, negative status is <50% of tumor cells stained 2+ or 3+ (includes samples with no staining).

b MET status information was determined from an optional sub-study (A031203-ST1). Subjects who declined to participate in that optional sub-study are summarized as missing.

Table 21: Subgroup Analyses for Progression-Free Survival and Objective Response Rate per IRC

Subgroup Level	PFS per IRC							ORR per IRC				
	Cabozantinib N=79			Sunitinib N=78				Cabozantinib N=79		Sunitinib N=78		
	N	Events (%)	Median	N	Events (%)	Median	HR[a] (95% CI)	N	Response (%)	N	Response (%)	OR[b] (95% CI)
MET Status												
Positive	32	17 (53)	13.8	30	19 (63)	3.0	0.32 (0.16, 0.63)	32	11 (34)	30	3 (10)	4.71 (1.16, 19.08)
Negative	39	23 (59)	6.9	30	20 (67)	6.1	0.67 (0.37, 1.23)	39	5 (13)	30	3 (10)	1.32 (0.29, 6.04)
Missing[c]	8	3 (38)	8.2	18	10 (56)	4.2	1.02 (0.27, 3.91)	8	0	18	1 (6)	0.69 (0.03, 18.68)

ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; IMDC=International Metastatic RCC Database Consortium; IRC=Independent Radiology Committee; ITT=intent-to-treat; NE=not estimable; OR=odds ratio; ORR=objective response rate; PFS=progression-free survival.

IMDC risk factors = 0 (favorable), 1-2 (intermediate), 3-6 (poor) (27).

a HR and 95% CI are estimates from the Cox Proportional-Hazards model. HR < 1 indicates survival in favor of cabozantinib. Results are

unstratified except for the Overall HR which is stratified.

b OR > 1 indicates survival in favor of cabozantinib. Results, including the Overall OR, are unstratified.

c MET status information was determined from an optional sub-study (A031203-ST1). Subjects who declined to participate in that optional sub-study are summarized as missing. Positive MET status is based on cutoff of ≥ 50% of tumor cells stained 2+ or 3+ (moderate or higher intensity) by immunohistochemistry, negative status is < 50% of tumor cells stained 2+ or 3+ (includes samples with no staining.

Ancillary analyses

Additional analyses of PFS

A set of alternative analyses (censoring per FDA-recommended rules) based on IRC-determined and Investigator-determined data and supportive analyses using alternative definitions of progression (Uniform dates or Clinical claims), and sensitivity analyses using alternative definitions of informative censoring were performed (see *Statistical methods* for description of analyses).

Table 22: Summary of Progression-Free Survival Analyses

Reader	Censoring rules	Description	Data cutoff	# Events		Median (95% CI), months		Stratified logrank, 2-sided p-value	Stratified HR (95% CI)
				Cabo	Sun	Cabo	Sun		
INV	Alliance	Alliance publication[a]	11 Apr 2016	123		8.2 (6.2, 8.8)	5.6 (3.4, 8.1)	0.024 (1-sided = 0.012)	0.66 (0.46, 0.95)
IRC	FDA	Standard	15 Sep 2016	43	49	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)	0.0008	0.48 (0.31, 0.74)
		Uniform dates[b]	15 Sep 2016	42	41	11.4 (8.1, 16.6)	5.7 (3.9, 8.4)	0.0085	0.54 (0.35, 0.85)
		Informative censoring 1[d]	15 Sep 2016	44	49	8.4 (6.2, 14.0)	5.3 (3.0, 8.2)	0.0010	0.49 (0.32, 0.75)
		Informative censoring 2[d]	15 Sep 2016	48	55	8.3 (5.7, 12.4)	4.3 (2.9, 5.7)	0.0004	0.48 (0.32, 0.73)
		Informative censoring 3[d]	15 Sep 2016	44	49	8.4 (6.2, 14.0)	5.3 (3.0, 8.2)	0.0010	0.49 (0.32, 0.75)
		Informative censoring 4[d]	15 Sep 2016	48	49	8.3 (5.7, 12.4)	5.3 (3.0, 8.2)	0.0028	0.53 (0.35, 0.81)
INV	FDA	Standard	15 Sep 2016	56	51	8.3 (6.5, 12.4)	5.4 (3.4, 8.2)	0.0042	0.56 (0.37, 0.83)
		Clinical claims[c]	15 Sep 2016	65	68	8.2 (5.4, 9.0)	4.4 (2.9, 5.6)	0.0002	0.51 (0.35, 0.73)
		Uniform dates[b]	15 Sep 2016	49	43	11.0 (8.2, 16.6)	5.6 (5.0, 8.4)	0.0153	0.59 (0.38, 0.91)
		Informative censoring 1[d]	15 Sep 2016	57	51	8.3 (6.2, 11.4)	5.4 (3.4, 8.2)	0.0050	0.56 (0.38, 0.84)
		Informative censoring 2[d]	15 Sep 2016	62	60	8.2 (5.5, 11.0)	4.6 (3.0, 6.1)	0.0009	0.53 (0.37, 0.78)
		Informative censoring 3[d]	15 Sep 2016	57	51	8.3 (6.2, 11.4)	5.4 (3.4, 8.2)	0.0050	0.56 (0.38, 0.84)
		Informative censoring 4[d]	15 Sep 2016	62	51	8.2 (5.5, 11.0)	5.4 (3.4, 8.2)	0.0166	0.62 (0.42, 0.92)

Cabo, cabozantinib; CI, confidence interval; HR, hazard ratio; INV, Investigator; IRC, independent radiology committee; NPACT, nonprotocol anticancer therapy; Sun, sunitinib

[a] Choueiri et al (J Clin Oncol) 2017

[b] Uniform dates: aligns radiographic progression dates with the planned assessment schedule to address the potential for inconsistent imaging frequency

[c] Clinical claims: inclusion of clinical outcomes as events per FDA-recommended censoring rules

[d] To explore the effect of potentially informative censoring resulting from **(a)** discontinuation of study treatment for reasons other than radiographic progression with no NPACT or **(b)** receipt of NPACT prior to progression, four IRC-determined sensitivity analyses, designated Scheme 1-4, were conducted based on censoring of subjects per FDA-recommended rules:

- Scheme 1: censored subjects meeting criterion (a) were classified as events in both treatment arms.
- Scheme 2: censored subjects meeting criteria (a) or (b) were classified as events in both treatment arms.
- Scheme 3: censored subjects in the cabozantinib arm meeting criterion (a) were classified as events in the cabozantinib arm and remained censored in the sunitinib arm.
- Scheme 4 (the most conservative analysis): censored subjects in the cabozantinib arm meeting criteria (a) or (b) were classified as events in the cabozantinib arm and remained censored in the sunitinib arm.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23: Summary of Efficacy for trial A031203

Title: Randomized Phase II Study Comparing Cabozantinib (NSC #761968 and IND #116059) with Commercially Supplied Sunitinib in Subjects with Previously Untreated Locally Advanced or Metastatic Renal Cell Carcinoma			
Study identifier	**A031203**		
Design	2-arm, randomized, open-label phase 2 trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		FPFV: 15 July 2013 LPLV: 13 January 2017 (data cutoff for survival not applicable not applicable
Hypothesis	To demonstrate superiority of cabozantinib compared to sunitinib in terms of PFS in previously untreated locally advance or metastatic RCC patients with poor to intermediate IMDC risk		
Treatments groups	Cabozantinib		cabozantinib 60 mg administered orally daily until disease progression, intolerance to therapy, or withdrawal of consent, 79 patients randomized
	Sunitinib		50 mg administered orally daily for 4 weeks, followed by 2 weeks without treatment, repeated every 6 weeks until disease progression, intolerance to therapy, or withdrawal of consent 78 patients randomized
Endpoints and definitions	Primary endpoint	PFS	time from randomization to the earlier of disease progression per RECIST v1.1 or death due to any cause.
	Secondary endpoint	OS	time from randomisation to death from any cause.
	Secondary endpoint	ORR	proportion of subjects at the time of data cut-off with a best overall response of complete response (CR or partial response (PR) per RECIST v1.1 which was confirmed at a subsequent visit ⩾28 days later
Database lock	13 January 2017		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Cabozantinib 60 mg	Sunitinib 50 mg
	Number of subject	79	78

	Median PFS (months)	8.6	5.3
	95% CI	6.2, 14.0	3.0, 8.2
	Median OS (months)	30.3	21.0
	95% CI	14.6, NE	16.3, 27.0
	ORR by IRC N (%)	16 (20)	7 (9)
	95% CI	12.0, 30.8	3.7, 17.6
	Confirmed complete response (CR)	0	0
	Confirmed partial response (PR)	16 (20)	7 (9)
	Stable Disease (SD)	43 (54)	30 (38)
	Progressive disease	14 (18)	23 (29)
Effect estimate per comparison	PFS	Comparison groups	Cabozantinib vs Sunitinib
		HR	0.48
		95%CI	0.32, 0.73
		two sided log-rank P-value stratified	0.0005
	OS	Comparison groups	Cabozantinib vs Sunitinib
		HR	0.74
		95%CI	0.47, 1.14
		two sided log-rank P-value stratified	0.1700
	ORR	Comparison groups	Cabozantinib vs Sunitinib
		treatment difference	11.3
		95%CI	0.4, 22.2
		Stratified CMH test 2-sided p-value	0.0406

2.4.2. Discussion on clinical efficacy

The MAH proposes to extend the indication for Cabometyx to treatment naïve RCC patients:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk per IMDC criteria.

Exelixis collaborated with Alliance personnel to gain access to the study data and undertook activities to prepare this study report for regulatory submission.

Design and conduct of clinical studies

Conduct of the study

The application is based on one Phase 2, randomized, open-label study of cabozantinib vs sunitinib, Study A031203. The study was sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and conducted by the Alliance for Clinical Trials in Oncology (the Alliance). The study was performed according to the Alliance Policies and Procedures 2013 and sites were audited and monitored for the central review of key data to ensure data integrity for analyses of primary and secondary endpoints. The primary and secondary endpoints of Study A031203 were originally analysed by the Alliance and reported in the literature[18], [19]..

A statistical analysis plan (SAP) was developed retrospectively and activities to bring the study to fit current registrational requirements included: forming an IRC to conduct retrospective independent image review, facilitating radiographic image retrieval for the IRC, facilitating source-data verification on a sample of study data (63 subjects across 35 sites).

Patient population

The study population was considered relevant for the proposed indication where patients should not have received any prior anticancer therapy. Study A031203 included patients with histologically confirmed locally advanced or metastatic RCC complying with intermediate or poor-risk factors according to the IMDC criteria. MSKCC (Memorial Sloane Kettering Cancer Centre model) has been the gold standard for the risk assessment during cytokine treatment in metastatic RCC. Further refinement was introduced with the IMDC model, which has been validated against the MSKCC model. The IMDC model was shown to give the best model fit[7]. Patients with ECOG 0-2 were allowed in the study, which is acceptable.

Comparator

Patients in the control arm were treated with sunitinib. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of renal cell carcinoma (2016) presents an algorithm for systemic treatment in mRCC with a clear cell component. According to the algorithm, sunitinib is the recommended first-line treatment of clear cell RCC for patients with good or intermediate risk, while temsirolimus is the first choice in patients with poor risk, however, with sunitinib as a “reasonable alternative”. Thus, the comparator is considered adequate.

Treatments

Based on treatment assignment, subjects were randomized (1:1) to one of the following regimens:

- Cabozantinib treatment arm: oral cabozantinib (60 mg) once-daily (qd) (as tablets)
- Sunitinib treatment arm: oral sunitinib (50 mg) qd for 4 weeks (as capsules) followed by a 2-week rest per cycle (approved dosing regimen from the registrational Phase 3 sunitinib study; Motzer et al [N Engl J Med] 2007)

Both treatments are in accordance with the approved SmPC for Cabometyx and Sutent.

Blinding

Study A031203 is an open-label study, and thus, there is a clear risk of bias. Originally, there was no independent review of radiographic scans. However, Exelixis retrospectively introduced central independent review of all scans. Ideally, independent review should be performed consecutively. However, many oncology trials deviate from the recommendations in the cancer guideline (Guideline

[19] Choueiri TK, Halabi S, Sanford B, Hahn O, Michaelson MD, Walsh M, et al. CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups: Results from ALLIANCE A031203 trial. Presented at the 41st European Society for Medical Oncology conference; 2016 Oct 7-11; Copenhagen, Denmark. Abstract LBA30_PR.

the guideline on the evaluation of anticancer medicinal products in man http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/11/WC500238764.pdf) of conducting real-time independent review before taking patients off treatment. The IRC reviewed all available radiographic images and was blinded to treatment identity and to clinical data that could have led to inadvertent unblinding. Thus, the retrospective introduction of IRC could be considered adequate.

The non-blinded fashion of the study could be problematic in terms of patient compliance and adherence to the study plan. However, the patients in the control arm were treated with the current standard of care and there were no clear indications in advance of the study that cabozantinib would be a more favourable treatment than sunitinib.

Sample size

The study was originally designed by the Alliance to provide 85% power for an event-driven analysis of PFS, and 123 events were required. The sample size was based on an assumption of a median PFS in the sunitinib arm of 8 months, with background in the COMPARZ study of pazopanib vs sunitinib. The sample size calculation gave an estimated sample size of 150 subject. The study enrolled 79 patients in the cabozantinib arm and 78 patients in the sunitinib arm.

Endpoints

The primary endpoint of this study was originally PFS by Investigator using RECIST 1.1., with ORR and OS as secondary endpoints. With the SAP, IRC determined PFS was introduced, and is considered the most robust endpoint, although not explicitly stated to be the primary endpoint. The results of both analyses are presented in the SmPC in section 5.1. PFS is considered acceptable as primary endpoint for cabozantinib in this setting. Results from the METEOR study indicates that there is a correlation between PFS and OS for cabozantinib. Tumour assessments were performed every 12 weeks (± 10 days) while on study treatment. In the METEOR study, which formed the basis for the MA for Cabometyx, tumour assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter. A shorter interval between assessments in the current study would have been preferred to give a more accurate estimate of the time of progression. In addition, 12 weeks is concurrent with the end of the 2-weeks rest in the sunitinib arm, which may have been unfortunate for this study arm but does not raised any serious concerns.

Randomisation

Subjects were randomized 1:1 to treatment with either cabozantinib or sunitinib. Randomization was stratified by the presence or not of bone metastasis at baseline and IMDC risk categories, Intermediate or Poor. Additional, stratification by ECOG and age would have been preferred as they are important risk factors. Fortunately, the study arms turned out quite well balanced also according to these factors.

Statistics

Standard methods were used to estimate PFS, OS and ORR.

The Exelixis SAP v1 was approved on 31 May 2017, prior to the receipt of IRC results. At this time point, the outcome of the Alliance analyses was known. The SAP implemented event and censoring definitions recommended by FDA guidance, a.o. this included right censoring of subjects who received non-protocol systemic anticancer treatment (NPACT) before experiencing an event. Exelixis also implemented sensitivity analyses to address the potential for bias arising from inconsistent imaging schedules or informative censoring. The application of FDA-recommended censoring rules for PFS reduced the number of events available for analysis compared to the Alliance analysis. To increase the number of events, the data cut-off for radiographic endpoints was extended to September 15, 2016

(database extract January 13, 2017; the latest date for which OS data were available). The median time of follow-up at that data cut-off was 25.0 months.

As the initial protocol specified analysis was positive it does not create multiplicity concerns that the MAH then conducted a new analysis for the purposes of the submission. The analysis was fully specified in the SAP before results from the IRC scan readings, on which the analysis was based, were available.

According to the Applicant, the Alliance did not document protocol deviations in the database because the statistical data analysis was based on the ITT population and no separate analyses related to protocol deviations were included. Still, for monitoring of the study conduct it seems inappropriate not to register protocol deviations. On request, the Applicant has provided a PP analysis which excluded 10 patients. The results of these analyses are in line with the results of the primary ITT analyses (data not shown).

Efficacy data and additional analyses

PFS

PFS determined by the IRC using FDA-recommended censoring rules showed a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the sunitinib arm. The HR adjusted for stratification factors was 0.48 (95% CI 0.31, 0.74; p = 0.0008). The median duration of PFS was estimated to be 8.6 months in the cabozantinib arm vs 5.3 months in the sunitinib arm. Taking into account that the patients are intermediate and poor risk, a 3 months prolongation in PFS is considered clinically relevant.

If PFS is analysed according to EU censoring rules, there were 5 patients in the cabozantinib arm who had events after being censored for having two or more missed visits, and none in the sunitinib arm. Consequently, including these patients was the same 0.48 (95%CI 0.32, 0.73; p=0.0005), compared to 0.48 (0.31, 0.74) p=0.0008.

The IRC-determined PFS result was supported by the Investigator PFS analysis and sensitivity analyses of PFS.

For the sample size assumptions, PFS was estimated to 8 months in the sunitinib arm based on the COMPARZ study of pazopanib vs sunitinib which included also favourable risk patients (25%). In the registrational study for sunitinib in RCC (Phase 3 trial vs IFN-alfa) the median PFS was estimated to 10.7 months in the intermediate risk patients and 2.5 months in the poor risk patients[13]. According to subgroup analyses of PFS, sunitinib seems to be underperforming in intermediate risk patients in the current study with a median PFS of 6.1 months. It is possible that the shorter median PFS in Study A031203 could be due to differences in baseline risk factors between the studies, e.g. the current study allowed patients with ECOG 2 (10 patients in each arm [13%]). The confidence interval for the poor risk group, although wide (only 15 patients in each arm), was below 1, i.e. in favour of cabozantinib. Median PFS was 6.8 months and 2.7 months in the cabozantinib arm and sunitinib arm, respectively. Sunitinib performed in accordance with the analyses by Rini mentioned above. Considering the small patient group, no definite conclusion can be drawn, but it seems reasonable to conclude that cabozantinib is not inferior to sunitinib for patients in the poor risk category.

Both MET positive and MET negative patients seem to benefit from treatment with cabozantinib compared to sunitinib, with the most favourable PFS HR in the MET positive patients, HR 0.32 (95% CI: 0.16, 0.63). PFS analysis in the MET negative patients resulted in a HR of 0.67 (95% CI: 0.37, 1.23) (SmPC section 5.1).

For patients with ECOG 2, there was no difference between the treatment arms; HR 0.96 (95% CI 0.27, 3.49). There were only 10 patients in each arm with ECOG 2 and only 5 and 6 patients with an event in the cabozantinib arm and the sunitinib arm, respectively. Thus, no conclusion can be drawn regarding these patients.

Efficacy analyses were conducted on the ITT population, i.e. patients who never received any treatment were included in these analyses, i.e. 7 patients (7/157; 4.4%) never received treatment, 6 of them in the sunitinib arm. Excluding these patients from the analysis, gives a similar result as the primary analysis. Also when excluding 10 patients that in retrospect were found to be protocol violators, the result is similar to the primary ITT analysis. The overall concordance for Investigator and IRC determined PD was 75%. The largest discordance between Investigator and IRC Read pertained to PD in the cabozantinib arm, i.e. the Investigator read PD while the IRC did not for 18 patients (23%). Thus, it seems the Investigator was not biased in favour of the cabozantinib arm.

OS

The median time of follow up for OS (through 13 January 2017) was 28.9 months. The Kaplan-Meier estimates for median duration of OS were 30.3 months (95% CI 14.6, NE) in the cabozantinib arm vs 21.0 months (95% CI 16.3, 27.0) in the sunitinib arm in the Exelixis analysis, an estimated 9.3 months difference in the medians. The difference between treatment arms did not reach statistical significance; HR adjusted for stratification factors 0.74 (95% CI 0.47, 1.14; p = 0.1700). Although more than 50% of the patients have had an OS event overall, less than half of the patients in the cabozantinib arm have died, and there is a notable degree of censoring around the medians. Considering that PFS analyses showed an approximately 3 months improvement with cabozantinib compared with sunitinib, the median OS gain of 9 months is clearly overestimated. Taking into account the long time between progression and death, it is likely that non-protocol anticancer therapy (NPACT) has influenced the result. After progression, systemic NPACT was used by a similar proportion of subjects in each arm (57-58%). Five patients (6%) in the sunitinib arm received cabozantinib after progression.

Based on this analysis, it may be concluded that cabozantinib does not have a detrimental effect on survival compared to sunitinib. More recently, the Alliance presented OS results at the European Society for Medical Oncology (ESMO) annual meeting in September 2017, based on an analysis they conducted with a data cut-off of 01 July 2017 (Choueiri ESMO presentation 2017). This analysis includes 7 more deaths. The result of this analysis is similar to the two previous analyses, with a HR of 0.80, 95% CI (0.53, 1.21), p=0.2885. According to the Applicant, the study is planned to be closed, and no further survival analyses are planned. None of the OS analyses shows statistically significant improvement in OS. Despite some crossing of the curves, cabozantinib does not seem to have a detrimental effect on OS.

ORR

The IRC-determined ORR was 20% (95% CI 12.0, 30.8) in the cabozantinib arm, compared with 9% (95% CI 3.7, 17.6) in the sunitinib arm (p=0.0406). All the subjects who had a confirmed response in either treatment arm had PRs. The Investigator analysis, considered more patients to have response. This is largely due to more patients being categorized as having stable disease in the IRC-analysis. Thus, the disease control rate (SD+PR+CR) seems similar across analyses, i.e. 74% - 75% in the cabozantinib arm and 47% - 49% in the sunitinib arm.

Correlative sub-study (A031203-ST1)

A correlative sub-study (A031203-ST1) has also been conducted. All subjects were asked for their consent to participate in the optional sub-study. This study was also performed to assess target

inhibition, tumour response, bone response and resistance to targeted therapies. However, the data analysis is now not planned.

2.4.3. Conclusions on the clinical efficacy

Cabozantinib was approved in the EU for treatment of adults following prior vascular endothelial growth factor (VEGF)-targeted therapy, based on the results of the phase III study XL184-308. The new clinical data in this submission are derived from the phase II study A031203, in treatment-naïve advanced RCC adults with intermediate or poor risk per IMDC criteria. In this study, cabozantinib demonstrated a clinically relevant and statistically significant improvement in PFS, with a favourable trend in overall survival. The ORR was also higher in the cabozantinib arm relative to sunitinib. The superiority of cabozantinib over sunitinib may reflect cabozantinib's mechanistic profile, that includes inhibition not only of VEGFR but also of MET and AXL. In support of this, increased PFS benefit is seen in those patients that were shown to be high MET expressers.

2.5. Clinical safety

Introduction

Summary of existing safety profile

The safety profile of Cabometyx in the existing indication was established based on a phase 3, randomized, controlled study of cabozantinib (so called "METEOR study") vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.

The safety profile of cabozantinib was found similar to other VEGFR-TKIs used to treat RCC. Overall, the safety profile of cabozantinib in RCC appears manageable and no major safety concerns were raised.

Clinical safety for new indication

The safety data for this extension of indication in advanced RCC treatment naïve patients is based on Study A031203, a randomized phase II study comparing cabozantinib with commercially supplied sunitinib in subjects with previously untreated locally advanced or metastatic renal cell carcinoma.

Patient exposure

Table 24 : Study Treatment Exposure (Safety Population)

	Cabozantinib N = 78	Sunitinib N = 72
Duration of exposure (months)[a]		
Mean (SD)	9.4 (7.97)	5.7 (5.44)
Median (range)	6.5 (0.2, 28.7)	3.1 (0.2, 25.5)
Average daily dose (mg/day)[b]		
Mean (SD)	49.4 (11.17)	43.7 (26.78)
Median (range)	50.3 (19.6, 61.5)	44.7 (1.7, 245.5[c])
Dose intensity (%)[c]		
Mean (SD)	82.4 (18.62)	87.4 (53.56)
Median (range)	83.8 (32.6, 102.6)	89.4 (3.4, 490.9[c])

qd, once daily; SD, standard deviation
a Duration of exposure = (date of decision to discontinue study treatment – date of first dose + 1)/30.4375. For subjects still on study, duration of exposure = (data cut-off date – date of first dose +1)/30.4375.
b Average daily dose = total doses received (mg) / sum of duration of exposure (days) for each cycle.
c Outliers likely arise from idiosyncrasies in data collection in the sunitinib arm, as dose data were collected by cycle; sunitinib was administered qd for 4 weeks followed by a 2-week rest per cycle.
d Percent dose intensity of cabozantinib = 100*(average daily dose mg/day) / (60 mg/day) and for sunitinib calculated as 100*(average daily dose mg/day) / (50 mg/day).

The median average daily doses of cabozantinib and sunitinib were above the protocol defined first dose reduction level: 50.3 mg and 44.7 mg, respectively. In both treatment arms, the median dose intensity was > 80% the protocol-defined maximum dose. Re-escalation after dose reductions were not allowed.

Adverse events

Table 25: Summary of Adverse Event Incidence (Safety Population)

	Cabozantinib N = 78 n (%)	Sunitinib N = 72 n (%)
AE	75 (96)	71 (99)
Related AE	74 (95)	70 (97)
Worst AE, Grade 3/4	53 (68)	47 (65)
Worst related AE, Grade 3/4	47 (60)	45 (63)
Worst AE, Grade 4	8 (10)[a]	5 (6.9)
Worst related AE, Grade 4	4 (5.1)[a]	3 (4.2)
Grade 5 AE at any time	4 (5.1)	9 (13)
Grade 5 AE through 30 days after last dose of study treatment[b]	3 (3.8)	6 (8.3)
Grade 5 AE > 30 days after last dose of study treatment	1 (1.3)	3 (4.2)
Related Grade 5 AE at any time	2 (2.6)	4 (5.6)
Related Grade 5 AE through 30 days after last dose of study treatment	2 (2.6)	4 (5.6)
Related Grade 5 AE > 30 days after last dose of study treatment	0	0
SAE[c]	38 (49)	37 (51)
Related SAE[c]	28 (36)	26 (36)
Deaths	38 (49)	43 (60)
Death through 30 days after last dose of study treatment[b]	4 (5.1)	8 (11)
Death > 30 days after last dose of study treatment	34 (44)	35 (49)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event A small fraction of the total AEs reported could not be coded in MedDRA at the time of the data cutoff, and limited information is available on the nature of these events. Only ten of the events were Grade 3, and none had a severity of Grade 4 or 5. Since the majority events were low grade, it is unlikely that these events would significantly impact the overall safety evaluation from the study.
Subjects are counted only once in each category but may be counted in multiple categories. Incidence of solicited and unsolicited AEs or SAEs. Unsolicited Grade 1 and 2 events not related to study treatment were not collected. For incidence of specific solicited or unsolicited preferred terms see Table 40 (AEs) or Table 46 (SAEs).
a Cabozantinib subject 9101012 experienced a related Grade 4 AE of jejunal perforation and subsequently died < 30 days after receiving the last dose of study treatment; the initially reported cause of death for this subject was tumor (ie, progressive disease). However, follow-up reporting included in the safety narrative but not the clinical database indicates that the Investigator later re-assessed the cause of death as jejunal perforation (Grade 5 AE related to study treatment).
b Grade 5 AEs were not reported for 3 subjects (1 cabozantinib, 2 sunitinib) who died < 30 days after the last dose of study treatment.
c Grade 1 or 2 SAEs that did not entail hospitalization ≥ 24 h were not recorded in the clinical database.

Table 26: Frequent Adverse Events Regardless of Causality Presented by Grade

Preferred Term	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
	Grade		Grade	
	Any	3/4	Any	3/4
Number of subjects with at least one AE	75 (96)	53 (68)	71 (99)	47 (65)
Solicited AEs				
Number of subjects with at least one solicited AE	75 (96)	38 (49)	68 (94)	41 (57)
Diarrhoea	57 (73)	8 (10)	39 (54)	8 (11)
Hypertension	52 (67)	22 (28)	32 (44)	15 (21)
Fatigue	50 (64)	5 (6.4)	49 (68)	12 (17)
Aspartate aminotransferase increased	47 (60)	2 (2.6)	22 (31)	2 (2.8)
Alanine aminotransferase increased	43 (55)	4 (5.1)	20 (28)	0
Palmar-plantar erythrodysaesthesia syndrome	33 (42)	6 (7.7)	24 (33)	3 (4.2)
Platelet count decreased	30 (38)	1 (1.3)	44 (61)	8 (11)
Neutrophil count decreased	12 (15)	0	25 (35)	3 (4.2)
Blood bilirubin increased	11 (14)	0	5 (6.9)	1 (1.4)
Electrocardiogram QT prolonged	3 (3.8)	0	5 (6.9)	2 (2.8)
Pancreatitis	1 (1.3)	0	1 (1.4)	1 (1.4)
Unsolicited AEs Reported in ≥ 10% of Subjects in Either Treatment Arm				
Number of subjects with at least one unsolicited AE	70 (90)	42 (54)	65 (90)	38 (53)
Decreased appetite	37 (47)	4 (5.1)	23 (32)	1 (1.4)
Dysgeusia	32 (41)	0	21 (29)	0
Stomatitis	29 (37)	4 (5.1)	21 (29)	4 (5.6)
Anaemia	26 (33)	1 (1.3)	33 (46)	2 (2.8)
Nausea	25 (32)	2 (2.6)	28 (39)	3 (4.2)
Weight decreased	25 (32)	3 (3.8)	12 (17)	0
Dyspepsia	21 (27)	0	12 (17)	0
Blood creatinine increased	19 (24)	2 (2.6)	15 (21)	2 (2.8)
Hypophosphataemia	18 (23)	7 (9.0)	12 (17)	5 (6.9)
Hypothyroidism	18 (23)	0	4 (5.6)	0
Vomiting	18 (23)	1 (1.3)	16 (22)	2 (2.8)
Dizziness	17 (22)	1 (1.3)	16 (22)	0

Preferred Term	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
	Grade		Grade	
	Any	3/4	Any	3/4
Dysphonia	17 (22)	1 (1.3)	1 (1.4)	0
Hypomagnesaemia	17 (22)	2 (2.6)	8 (11)	0
Hyperglycaemia	16 (21)	0	11 (15)	4 (5.6)
Dry mouth	15 (19)	0	9 (13)	0
Dry skin	15 (19)	0	6 (8.3)	0
Hypoalbuminaemia	15 (19)	0	12 (17)	0
Alopecia	14 (18)	0	2 (2.8)	0
Constipation	14 (18)	1 (1.3)	11 (15)	0
Hypocalcaemia	14 (18)	2 (2.6)	11 (15)	0
Dyspnoea	13 (17)	1 (1.3)	14 (19)	4 (5.6)
Dermatitis acneiform	12 (15)	0	2 (2.8)	0
Hypokalaemia	12 (15)	1 (1.3)	5 (6.9)	0
Rash maculo-papular	12 (15)	0	9 (13)	2 (2.8)
Hyponatraemia	11 (14)	7 (9.0)	16 (22)	6 (8.3)
Abdominal pain	10 (13)	0	8 (11)	3 (4.2)
Blood alkaline phosphatase increased	10 (13)	0	9 (13)	1 (1.4)
Lymphocyte count decreased	10 (13)	1 (1.3)	13 (18)	4 (5.6)
Pain	10 (13)	4 (5.1)	4 (5.6)	0
Cough	9 (12)	0	5 (6.9)	0
Dehydration	9 (12)	3 (3.8)	7 (9.7)	1 (1.4)
Embolism[a]	9 (12)	6 (7.7)	1 (1.4)	0
Headache	9 (12)	1 (1.3)	12 (17)	1 (1.4)
White blood cell count decreased	9 (12)	0	25 (35)	2 (2.8)
Arthralgia	8 (10)	1 (1.3)	5 (6.9)	0
Back pain	8 (10)	3 (3.8)	4 (5.6)	0
Epistaxis	8 (10)	0	3 (4.2)	0
Hypotension	8 (10)	4 (5.1)	3 (4.2)	1 (1.4)
Insomnia	8 (10)	0	6 (8.3)	0
Oral pain	8 (10)	0	6 (8.3)	0
Pain in extremity	8 (10)	2 (2.6)	7 (9.7)	0
Peripheral sensory neuropathy	8 (10)	1 (1.3)	4 (5.6)	0

Preferred Term	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
	Grade		Grade	
	Any	3/4	Any	3/4
Hyperkalaemia	7 (9.0)	1 (1.3)	8 (11)	2 (2.8)
Oedema peripheral	6 (7.7)	0	10 (14)	0
Proteinuria	5 (6.4)	2 (2.6)	10 (14)	1 (1.4)
Muscular weakness	3 (3.8)	0	12 (17)	1 (1.4)

Denominators for percentages are N, the total number of subjects in each treatment arm. At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events. A total of 25 subjects (32%) in the cabozantinib arm and 18 subjects (25%) subjects in the sunitinib arm had reported verbatim terms that were uncoded. Four uncoded Grade 3 events were reported for 4 subjects (5.1%) in the cabozantinib arm, and 6 were reported for 5 subjects (6.9%) in the sunitinib arm. There were no Grade 4 or 5 uncoded events. The Grade 3 events had the following verbatim-text descriptions:

☐ cabozantinib arm: pulmonary embolism, acute renal failure, burn, and hypophosphatemia.

☐ sunitinib arm: difficulty swallowing, stomatitis, polycythemia, planned craniotomy surgery, scrotum rash, and herpes zoster.

Note that Grade 1 or 2 unsolicited AEs were only required to be collected if the Investigator considered them to be treatment related. Note that there is no CTCAE Grade 1 category for pancreatitis or Grade 4 category for fatigue or PPES.

a Events of embolism from the Exelixis cabozantinib global safety database included pulmonary embolism, deep vein thrombosis, stroke, thrombosis of the axillary artery, or thrombosis of the left internal carotid artery. In addition, there was one uncoded Grade 3 AE described as a 'pulmonary embolism' reported in the cabozantinib arm.

For the following AEs, there were ≥ 10% higher incidence in the cabozantinib arm relative to the sunitinib arm: AST increased, ALT increased, hypertension, dysphonia, diarrhoea, hypothyroidism, decreased appetite, weight decreased, alopecia, dermatitis acneiform, dysgeusia, dry skin, hypomagnesemia, dyspepsia, and embolism.

For the following AEs, there were ≥ 10% higher incidence in the sunitinib arm relative to the cabozantinib arm: platelet count decreased, white blood cell count decreased, neutrophil count decreased, anaemia, and muscular weakness.

Comparison of Study A031203 and METEOR

A comparison of AEs in the cabozantinib arm of Study A031203 and the cabozantinib arm of the METEOR study in patients previously treated with a VEGF-targeted therapy was also performed (Table 29). Dose and exposure were similar in the two studies. The study populations are, however, not identical. The METEOR study allowed all three RCC risk categories (20% were favourable), while Study A031203 was limited to patients with intermediate and poor risk. In the METEOR study, ECOG status was limited to 0 and 1, while in Study A031203 patients also with ECOG 2 were allowed.

There are also differences between the studies regarding collection of AEs.

- In study A031203, dose and AE data were collected by cycle and non-AE data (laboratory values, vital signs) were not collected. In the METEOR study a complete set of dose, AE, and non-AE data were provided.
- In Study A031203, the Investigator entered into the CRF an AE term from the limited CTCAE v4 list. This list provides fewer specific terms than those available using MedDRA terms in the METEOR study.

- All AEs were unsolicited in the METEOR study whereas in study A031203 AEs were collected as either solicited AEs or unsolicited AEs. Grade 1 or 2 unsolicited AEs not related to study treatment were not required to be reported in Study A031203 whereas all grades of AEs were reported in METEOR.
- SAEs were collected in study A031203 if they met requirements for being expedited in the Investigator's opinion, regardless of medical importance (or were Grade 5 AEs). This was done for completeness. However, these events identified as expedited included non-serious events thereby leading to a potential over-reporting of the incidence of SAEs. In METEOR, all SAEs were collected on a specific CRF page.

Table 27: Frequent Adverse Events (≥ 20% Any Grade or ≥ 5% Grade 3 or 4) for Cabozantinib Arm of Study A031203 (CABOSUN) or of Study XL184-308 (METEOR)

	Study A031203 Cabozantinib (n = 78)		Study A031203 Sunitinib (n = 72)		Study XL184-308 Cabozantinib (n = 331)	
	Grade		Grade		Grade	
Adverse Event Laboratory Abnormality	**Any n (%)**	**3 or 4 n (%)**	**Any n (%)**	**3 or 4 n (%)**	**Any n (%)**	**3 or 4 n (%)**
Any adverse event	75 (96)	53 (68)	71 (99)	47 (65)	331 (100)	226 (68)
Diarrhea[a]	57 (73)	8 (10)	39 (54)	8 (11)	245 (74)	38 (11)
Hypertension[a]	52 (67)	22 (28)	32 (44)	15 (21)	122 (37)	49 (15)
Fatigue[a]	50 (64)	5 (6.4)	49 (68)	12 (17)	186 (56)	30 (9.1)
Aspartate aminotransferase increased[a]	47 (60)	2 (2.6)	22 (31)	2 (2.8)	58 (18)	6 (1.8)
Corresponding laboratory abnormality	NA	NA	NA	NA	245 (74)	11 (3.3)
Alanine aminotransferase increased[a]	43 (55)	4 (5.1)	20 (28)	0	53 (16)	8 (2.4)
Corresponding laboratory abnormality	NA	NA	NA	NA	224 (68)	10 (3.0)
Anorexia[b]	37 (47)	4 (5.1)	23 (32)	1 (1.4)	152 (46)	9 (2.7)
Palmar-plantar erythrodysaesthesia syndrome[a]	33 (42)	6 (7.7)	24 (33)	3 (4.2)	139 (42)	27 (8.2)
Dysgeusia	32 (41)	0	21 (29)	0	78 (24)	0
Platelet count decreased[a]	30 (38)	1 (1.3)	44 (61)	8 (11)	9 (2.7)	1 (0.3)
Corresponding laboratory abnormality	NA	NA	NA	NA	84 (25)	2 (0.6)
Stomatitis	29 (37)	4 (5.1)	21 (29)	4 (5.6)	74 (22)	8 (2.4)
Anemia	26 (33)	1 (1.3)	33 (46)	2 (2.8)	56 (17)	18 (5.4)
Corresponding laboratory abnormality	NA	NA	NA	NA	102 (31)	14 (4.2)
Nausea	25 (32)	2 (2.6)	28 (39)	3 (4.2)	166 (50)	13 (3.9)
Weight loss[c]	25 (32)	3 (3.8)	12 (17)	0	104 (31)	6 (1.8)
Dyspepsia	21 (27)	0	12 (17)	0	40 (12)	1 (0.3)
Blood creatinine increased	19 (24)	2 (2.6)	15 (21)	2 (2.8)	15 (4.5)	1 (0.3)
Corresponding laboratory abnormality	NA	NA	NA	NA	192 (58)	1 (0.3)
Hypophosphataemia	18 (23)	7 (9.0)	12 (17)	5 (6.9)	33 (10)	12 (3.6)
Corresponding laboratory abnormality	NA	NA	NA	NA	160 (48)	27 (8.2)
Hypothyroidism	18 (23)	0	4 (5.6)	0	68 (21)	0
Vomiting	18 (23)	1 (1.3)	16 (22)	2 (2.8)	106 (32)	7 (2.1)
Dizziness	17 (22)	1 (1.3)	16 (22)	0	36 (11)	0
Dysphonia	17 (22)	1 (1.3)	1 (1.4)	0	66 (20)	3 (0.9)
Hypomagnesaemia	17 (22)	2 (2.6)	8 (11)	0	52 (16)	16 (4.8)
Corresponding laboratory abnormality	NA	NA	NA	NA	102 (31)	24 (7.3)

Adverse Event Laboratory Abnormality	Study A031203 Cabozantinib (n = 78)		Study A031203 Sunitinib (n = 72)		Study XL184-308 Cabozantinib (n = 331)	
	Grade		Grade		Grade	
	Any n (%)	3 or 4 n (%)	Any n (%)	3 or 4 n (%)	Any n (%)	3 or 4 n (%)
Hyperglycaemia	16 (21)	0	11 (15)	4 (5.6)	15 (4.5)	2 (0.6)
Corresponding laboratory abnormality	NA	NA	NA	NA	123 (37)	7 (2.1)
Hyponatraemia	11 (14)	7 (9.0)	16 (22)	6 (8.3)	20 (6.0)	13 (3.9)
Corresponding laboratory abnormality	NA	NA	NA	NA	100 (30)	28 (8.5)
Pain	10 (13)	4 (5.1)	4 (5.6)	0	18 (5.4)	4 (1.2)
Embolism[d]	9 (12)	6 (7.7)	1 (1.4)	0	1 (0.3)	0
Hypotension	8 (10)	4 (5.1)	3 (4.2)	1 (1.4)	15 (4.5)	3 (0.9)
Syncope	4 (5.1)	4 (5.1)	0	0	7 (2.1)	5 (1.5)

AE, adverse event; NA, not applicable; SAE, serious adverse event.
a. Solicited events in Study A031203.
b. Anorexia was not reported as a PT on Study XL184-308. Data are presented for decreased appetite.
c. Weight loss was not reported as a PT on Study XL184-308. Data are presented for weight decreased.
d. Events of embolism included pulmonary embolism, deep vein thrombosis, stroke, thrombosis of the axillary artery, or thrombosis of the left internal carotid artery;, there was one uncoded Grade 3 AE described as a 'pulmonary embolism' reported in the cabozantinib arm (Subject 9100447), and one subject that did not have an AE with the PT of embolism had an event of pulmonary embolism (Subject 2000193) in an SAE report.

Treatment-Related Adverse Events

Frequently reported treatment-related AEs are summarized in Table 30. Overall, the number of subjects with treatment-related AEs was similar between treatment arms (cabozantinib arm 95%, sunitinib arm 97%). Grade 3/4 treatment related AEs were reported in respectively 60% and 63% of the subjects in the cabozantinib and sunitinib arm.

Of the treatment related AEs, there were clearly more (>10% difference) of the following AEs with cabozantinib compared to sunitinib: diarrhoea (72% vs 49%), hypertension (56% vs 38%), PPES (42% vs 32%), decreased appetite (45% vs 31%), dysgeusia (41% vs 29%), weight decreased (31% vs 17%), hypothyroidism (22% vs 5.6%), dysphonia (21% vs 1.4%), hypomagnesaemia (21% vs 11%), dry skin (19% vs 8.3%), alopecia (17% vs 2.8%), dermatitis acneiform (15% vs 2.8%), in addition to liver enzyme elevations.

The treatment-related AEs that were more frequent (>10% difference) in the sunitinib arm than in the cabozantinib arm, were related to blood counts, i.e. decreased platelets (58% vs 37%), neutrophils (35% vs 15%), WBC (35% vs 12%) and anaemia (44% vs 29%). There were also more hyponatraemia (18% vs 7.7%) and muscular weakness (14% vs 3.8%).

It is known from the METEOR study that diarrhoea, PPES, fatigue, and hypertension were the most frequent AEs leading to dose modification. The reason for dose modification was not collected in study A031203.

Table 28: Frequent Treatment Related Adverse Events Presented by Grade (Safety Population)

	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
	Grade		Grade	
Preferred Term	**Any**	**3/4**	**Any**	**3/4**
Number of subjects with at least one related AE	74 (95)	47 (60)	70 (97)	45 (63)
Solicited Related AEs				
Number of subjects with at least one solicited related AE	73 (94)	32 (41)	68 (94)	38 (53)
Diarrhoea	56 (72)	7 (9.0)	35 (49)	6 (8.3)
Fatigue	48 (62)	4 (5.1)	48 (67)	12 (17)
Aspartate aminotransferase increased	47 (60)	1 (1.3)	18 (25)	2 (2.8)
Hypertension	44 (56)	17 (22)	27 (38)	13 (18)
Alanine aminotransferase increased	42 (54)	3 (3.8)	18 (25)	0
Palmar-plantar erythrodysaesthesia syndrome	33 (42)	6 (7.7)	23 (32)	3 (4.2)
Platelet count decreased	29 (37)	1 (1.3)	42 (58)	8 (11)
Neutrophil count decreased	12 (15)	0	25 (35)	3 (4.2)
Blood bilirubin increased	11 (14)	0	4 (5.6)	0
Electrocardiogram QT prolonged	2 (2.6)	0	5 (6.9)	2 (2.8)
Pancreatitis	1 (1.3)	0	0	0
Unsolicited Related AEs (Reported in ≥ 10% of Subjects in Either Treatment Arm)				
Number of subjects with at least one unsolicited related AE	69 (88)	33 (42)	62 (86)	30 (42)
Decreased appetite	35 (45)	4 (5.1)	22 (31)	1 (1.4)
Dysgeusia	32 (41)	0	21 (29)	0
Stomatitis	29 (37)	4 (5.1)	21 (29)	4 (5.6)
Nausea	24 (31)	2 (2.6)	26 (36)	2 (2.8)
Weight decreased	24 (31)	3 (3.8)	12 (17)	0
Anaemia	23 (29)	0	32 (44)	1 (1.4)
Dyspepsia	18 (23)	0	12 (17)	0
Hypophosphataemia	18 (23)	7 (9.0)	12 (17)	5 (6.9)
Hypothyroidism	17 (22)	0	4 (5.6)	0
Blood creatinine increased	16 (21)	1 (1.3)	14 (19)	2 (2.8)
Dysphonia	16 (21)	1 (1.3)	1 (1.4)	0
Hypomagnesaemia	16 (21)	1 (1.3)	8 (11)	0
Dry mouth	15 (19)	0	8 (11)	0
Dry skin	15 (19)	0	6 (8.3)	0
Vomiting	15 (19)	1 (1.3)	15 (21)	1 (1.4)
Constipation	14 (18)	1 (1.3)	9 (13)	0
Dizziness	14 (18)	0	12 (17)	0
Alopecia	13 (17)	0	2 (2.8)	0

Preferred Term	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
	Grade		Grade	
	Any	3/4	Any	3/4
Hypoalbuminaemia	13 (17)	0	12 (17)	0
Hypocalcaemia	13 (17)	2 (2.6)	10 (14)	0
Dermatitis acneiform	12 (15)	0	2 (2.8)	0
Dyspnoea	12 (15)	1 (1.3)	8 (11)	1 (1.4)
Hypokalaemia	12 (15)	1 (1.3)	4 (5.6)	0
Rash maculo-papular	11 (14)	0	9 (13)	2 (2.8)
Blood alkaline phosphatase increased	10 (13)	0	8 (11)	0
Lymphocyte count decreased	10 (13)	0	13 (18)	3 (4.2)
Headache	9 (12)	0	11 (15)	1 (1.4)
White blood cell count decreased	9 (12)	0	25 (35)	2 (2.8)
Abdominal pain	8 (10)	0	5 (6.9)	2 (2.8)
Dehydration	8 (10)	3 (3.8)	7 (9.7)	1 (1.4)
Hyperglycaemia	8 (10)	0	8 (11)	2 (2.8)
Insomnia	8 (10)	0	6 (8.3)	0
Peripheral sensory neuropathy	8 (10)	1 (1.3)	3 (4.2)	0
Hyponatraemia	6 (7.7)	2 (2.6)	13 (18)	4 (5.6)
Oedema peripheral	5 (6.4)	0	9 (13)	0
Proteinuria	5 (6.4)	2 (2.6)	9 (13)	1 (1.4)
Muscular weakness	3 (3.8)	0	10 (14)	0

Denominators for percentages are N, the total number of subjects in each treatment arm. At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events. Note that there is no CTCAE Grade 1 category for pancreatitis or Grade 4 category for fatigue or PPES.

Concomitant Medications

Concomitant medications were used by 88% of subjects in each arm. Antipropulsives (eg, loperamide) were taken as concomitant medications by more than 3 times as many cabozantinib subjects as sunitinib subjects (28% vs 8%). In addition, more than twice as many cabozantinib subjects received thyroid hormones compared with sunitinib subjects (28% vs 11%). This complies with the observed safety profile of cabozantinib.

Study Treatment Modifications (Reductions or Interruptions)

Table 29: Study Treatment Modifications (Safety Population)

	Cabozantinib N = 78	Sunitinib N = 72
Subjects with any dose modification, n (%)[a]	63 (81)	55 (76)
Subjects with any dose reduction, n (%)	36 (46)	25 (35)
Subjects with any dose interruption, n (%)	57 (73)	51 (71)

a Dose modifications include reductions and interruptions

Grade 3 / 4 Adverse Events

Table 30: Summary of Frequent Grade 3 / 4 Adverse Events Regardless of Causality

	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
Preferred Term	**Grade 3/4**	**Grade 4**	**Grade 3/4**	**Grade 4**
Number of subjects with at least one Grade 3/4 AE	53 (68)	8 (10)[a]	47 (65)	5 (6.9)
Solicited AEs				
Number of subjects with at least one solicited Grade 3/4 AE	38 (49)	1 (1.3)	41 (57)	3 (4.2)
Hypertension	22 (28)	0	15 (21)	1 (1.4)
Diarrhoea	8 (10)	0	8 (11)	0
Palmar-plantar erythrodysaesthesia syndrome	6 (7.7)	0	3 (4.2)	0
Fatigue	5 (6.4)	0	12 (17)	0
Alanine aminotransferase increased	4 (5.1)	1 (1.3)	0	0
Aspartate aminotransferase increased	2 (2.6)	1 (1.3)	2 (2.8)	0
Platelet count decreased	1 (1.3)	0	8 (11)	2 (2.8)
Blood bilirubin increased	0	0	1 (1.4)	0
Electrocardiogram QT prolonged	0	0	2 (2.8)	0
Neutrophil count decreased	0	0	3 (4.2)	0
Pancreatitis	0	0	1 (1.4)	0
Unsolicited AEs (≥ 2% in Either Treatment Arm)				
Number of subjects with at least one unsolicited Grade 3/4 AE	42 (54)	8 (10)	38 (53)	5 (6.9)
Hyponatraemia	7 (9.0)	0	6 (8.3)	1 (1.4)
Hypophosphataemia	7 (9.0)	0	5 (6.9)	0
Embolism[b]	6 (7.7)	2 (2.6)	0	0
Decreased appetite	4 (5.1)	0	1 (1.4)	0
Hypotension	4 (5.1)	0	1 (1.4)	1 (1.4)
Pain	4 (5.1)	0	0	0
Stomatitis	4 (5.1)	0	4 (5.6)	0
Syncope	4 (5.1)	0	0	0
Back pain	3 (3.8)	0	0	0
Dehydration	3 (3.8)	0	1 (1.4)	0

Preferred Term	Cabozantinib| N = 78 n (%)		Sunitinib N = 72 n (%)	
	Grade 3/4	Grade 4	Grade 3/4	Grade 4
Depression	3 (3.8)	0	0	0
Lung infection	3 (3.8)	0	0	0
Nervous system disorder	3 (3.8)	0	2 (2.8)	1 (1.4)
Renal failure acute[c]	3 (3.8)	1 (1.3)	1 (1.4)	0
Weight decreased	3 (3.8)	0	0	0
Blood creatinine increased	2 (2.6)	0	2 (2.8)	0
Bone pain	2 (2.6)	0	1 (1.4)	0
Hypocalcaemia	2 (2.6)	0	0	0
Hypomagnesaemia	2 (2.6)	2 (2.6)	0	0
Nausea	2 (2.6)	0	3 (4.2)	0
Pain in extremity	2 (2.6)	0	0	0
Proteinuria	2 (2.6)	0	1 (1.4)	0
Skin ulcer	2 (2.6)	0	0	0
Anaemia	1 (1.3)	0	2 (2.8)	0
Dyspnoea	1 (1.3)	0	4 (5.6)	0
Hyperkalaemia	1 (1.3)	0	2 (2.8)	0
Lymphocyte count decreased	1 (1.3)	0	4 (5.6)	0
Vomiting	1 (1.3)	0	2 (2.8)	0
Abdominal pain	0	0	3 (4.2)	0
Hyperglycaemia	0	0	4 (5.6)	0
Lipase increased	0	0	3 (4.2)	2 (2.8)
Pleural effusion	0	0	2 (2.8)	0
Rash maculo-papular	0	0	2 (2.8)	0
White blood cell count decreased	0	0	2 (2.8)	0

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PPES, palmar-plantar erythrodysaesthesia syndrome. Denominators for percentages are N, the total number of subjects in each treatment arm. At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events. Note that there is no CTCAE Grade 4 category for fatigue or PPES.
a Cabozantinib subject 9101012 experienced a Grade 4 AE of jejunal perforation and subsequently died < 30 days after receiving the last dose of study treatment; the initially reported cause of death for this subject was tumor (ie, progressive disease). However, follow-up reporting included in the safety narrative but not the clinical database indicates that the Investigator later re-assessed the cause of death as jejunal perforation (Grade 5 AE related to study treatment). This subject is discussed in greater detail in Section 12.3.4.2.7.
b Events of embolism from the Exelixis cabozantinib global safety database included pulmonary embolism, stroke, thrombosis of the axillary artery, or thrombosis of the left internal carotid artery; further information on these AEs is provided in Sections 12.3.4.2.4 and 12.3.4.2.5. In addition, there was one uncoded Grade 3 AE described as a 'pulmonary embolism' reported in the cabozantinib arm.
c There was also an uncoded Grade 3 AE of 'acute renal failure' reported in the cabozantinib arm.

Serious adverse event / deaths / other significant events

Serious adverse events

Per protocol, adverse events that met the definition of serious, based on the Investigator's assessment, were to be flagged as "expedited" on the CRF and were to be submitted directly to NCI-CTEP by the investigators. All events flagged as "expedited" on the CRFs were assumed by Exelixis to be SAEs as were all Grade 5 AEs. However, per Alliance procedures, events flagged as "expedited" in the clinical data base and those reported to NCI-CTEP were not reconciled. Safety review by NCI-CTEP and Exelixis determined that not all "expedited" events met seriousness criteria. As a result, events identified as "expedited" included non-serious events leading to a potential over-reporting of the incidence of SAEs.

Table 31: Serious Adverse Events Regardless of Causality (Safety Population)

Preferred Term	Cabozantinib N = 78 n (%)	Sunitinib N = 72 n (%)
Number of subjects with at least one SAE	38 (49)	37 (51)
Solicited SAEs		
Number of subjects with at least one solicited SAE	15 (19)	15 (21)
Hypertension	7 (9.0)	3 (4.2)
Diarrhoea	4 (5.1)	5 (6.9)
Palmar-plantar erythrodysaesthesia syndrome	4 (5.1)	1 (1.4)
Alanine aminotransferase increased	2 (2.6)	2 (2.8)
Aspartate aminotransferase increased	1 (1.3)	1 (1.4)
Blood bilirubin increased	0	1 (1.4)
Electrocardiogram QT prolonged	0	1 (1.4)
Fatigue	0	4 (5.6)
Neutrophil count decreased	0	3 (4.2)
Pancreatitis	0	1 (1.4)
Platelet count decreased	0	3 (4.2)
Unsolicited SAEs (Reported in ≥ 2% of Subjects in Either Treatment Arm)		
Number of subjects with at least one unsolicited SAE	34 (44)	33 (46)
Embolism[a]	7 (9.0)	0
Renal failure acute[b]	4 (5.1)	2 (2.8)
Dehydration	3 (3.8)	2 (2.8)
Hypotension	3 (3.8)	2 (2.8)
Syncope	3 (3.8)	0
Weight decreased	3 (3.8)	0
Anaemia	2 (2.6)	1 (1.4)
Back pain	2 (2.6)	0

Preferred Term	Cabozantinib N = 78 n (%)	Sunitinib N = 72 n (%)
Blood creatinine increased	2 (2.6)	0
Decreased appetite	2 (2.6)	0
Depression	2 (2.6)	0
Hypophosphataemia	2 (2.6)	3 (4.2)
Lung infection	2 (2.6)	0
Nausea	2 (2.6)	4 (5.6)
Sepsis	2 (2.6)	1 (1.4)
Skin ulcer	2 (2.6)	0
Stomatitis	2 (2.6)	1 (1.4)
Hyponatraemia	1 (1.3)	2 (2.8)
Nervous system disorder	1 (1.3)	2 (2.8)
Vomiting	1 (1.3)	4 (5.6)
Atrial fibrillation	0	2 (2.8)
Headache	0	3 (4.2)
Investigation	0	2 (2.8)
Lipase increased	0	2 (2.8)
Pyrexia	0	2 (2.8)
Respiratory failure	0	3 (4.2)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event, Denominators for percentages are N, the total number of subjects in each treatment arm. At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events. Note: CTCAE Grade 1 or 2 events that did not entail hospitalization ≥ 24 h are not recorded in the clinical database.
A total of 3 subjects (3.8%) in the cabozantinib arm and 1 subject (1.4%) in the sunitinib arm had serious events with reported verbatim terms that were uncoded. All these events had a severity of Grade 3; there were no Grade 4 or 5 uncoded serious events. The uncoded events had the following verbatim-text descriptions: acute renal failure, burn, and hypophosphatemia in the cabozantinib arm; planned craniotomy surgery in the sunitinib arm.
a Events of embolism from the safety database included pulmonary embolism, deep vein thrombosis, stroke, thrombosis of the axillary artery, or thrombosis of the left internal carotid artery; further information on these AEs is provided in Sections 12.3.4.2.4 and 12.3.4.2.5. In addition, there was one uncoded Grade 3 SAE described as a 'pulmonary embolism' reported in the cabozantinib arm.
b There was also an uncoded Grade 3 SAE of 'acute renal failure' reported in the cabozantinib arm

Treatment-Related Serious Adverse Events

Table 32: Treatment-Related Serious Adverse Events (Safety Population)

Preferred Term	Cabozantinib N = 78 n (%)	Sunitinib N = 72 n (%)
Number of subjects with at least one related SAE	28 (36)	26 (36)
Solicited SAEs		
Number of subjects with at least one solicited related SAE	14 (18)	13 (18)
Hypertension	7 (9.0)	3 (4.2)
Diarrhoea	4 (5.1)	4 (5.6)
Palmar-plantar erythrodysaesthesia syndrome	4 (5.1)	1 (1.4)
Alanine aminotransferase increased	1 (1.3)	2 (2.8)
Aspartate aminotransferase increased	0	1 (1.4)
Blood bilirubin increased	0	1 (1.4)
Electrocardiogram QT prolonged	0	1 (1.4)
Fatigue	0	4 (5.6)
Neutrophil count decreased	0	3 (4.2)
Platelet count decreased	0	3 (4.2)
Unsolicited SAEs (Reported in ≥ 2% of Subjects in Either Treatment Arm)		
Number of subjects with at least one unsolicited related SAE	23 (29)	22 (31)
Embolism[a]	4 (5.1)	0
Dehydration	3 (3.8)	2 (2.8)
Weight decreased	3 (3.8)	0
Decreased appetite	2 (2.6)	0
Hypophosphataemia	2 (2.6)	3 (4.2)
Hypotension	2 (2.6)	0
Lung infection	2 (2.6)	0
Nausea	2 (2.6)	3 (4.2)
Renal failure acute[b]	2 (2.6)	2 (2.8)
Skin ulcer	2 (2.6)	0
Stomatitis	2 (2.6)	1 (1.4)
Syncope	2 (2.6)	0
Hyponatraemia	1 (1.3)	2 (2.8)

Preferred Term	Cabozantinib N = 78 n (%)	Sunitinib N = 72 n (%)
Vomiting	1 (1.3)	3 (4.2)
Headache	0	3 (4.2)
Investigation	0	2 (2.8)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.
Denominators for percentages are N, the total number of subjects in each treatment arm. At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.
Note: CTCAE Grade 1 or 2 events that did not entail hospitalization ≥ 24 h are not recorded in the clinical database.
a Events of embolism from the safety database included pulmonary embolism, deep vein thrombosis, stroke, thrombosis of the axillary artery, or thrombosis of the left internal carotid artery.
b There was also an uncoded Grade 3 SAE of 'acute renal failure' not related to study treatment reported in the cabozantinib arm;

Deaths

Survival information was collected on subjects during the study through disease progression and at 6-month intervals thereafter until death or until 5 years after registration. A total of 81 deaths were reported in the Safety population as of the safety data cut-off date of 15 September 2016; the deaths comprised 38 subjects (49%) in the cabozantinib arm and 43 subjects (60%) in the sunitinib arm Table 35).

Table 33: Summary of Deaths (Safety Population)

	Cabozantinib N = 78	Sunitinib N = 72
	n (%)	n (%)
All deaths	38 (49)	43 (60)
Deaths through 30 days after last dose	4 (5)	8 (11)
Deaths > 30 days after last dose	34 (44)	35 (49)

Grade 5 AEs at any time occurred in 4 subjects (5.1%) in the cabozantinib arm and 9 subjects (13%) in the sunitinib arm (Table 36).

Table 34: Grade 5 Adverse Events with Death Dates Through 30 Days after the Last dose of study treatment

Preferred Term	Cabozantinib N = 78 n (%)		Sunitinib N = 72 n (%)	
	All Causality	Related	All Causality	Related
Number of subjects with at least 1 event[a]	3 (3.8)	2 (2.6)	6 (8.3)	4 (5.6)
Death	1 (1.3)	0	0	0
Renal failure acute	1 (1.3)	1 (1.3)	0	0
Sepsis	1 (1.3)	1 (1.3)	1 (1.4)	1 (1.4)
Angiopathy	0	0	1 (1.4)	1 (1.4)
Hypotension	0	0	1 (1.4)	0
Respiratory failure	0	0	2 (2.8)[b]	1 (1.4)
Sudden death	0	0	1 (1.4)	1 (1.4)

Among subjects with Grade 5 AEs that started through 30 days after last dose of study treatment, six experienced events assessed as treatment related; these subjects comprised two in the cabozantinib arm (acute renal failure and sepsis) and four in the sunitinib arm (sepsis, angiopathy, respiratory failure, and sudden death).

Three subjects who died before 30 days after last dose did not have corresponding Grade 5 AEs reported in the clinical database: one cabozantinib subject (cause of death: tumour [ie, disease progression]) and two sunitinib subjects (causes of death: complete atelectasis, respiratory insufficiency and accident). The cabozantinib subject had a jejunal mass eroding adjacent bowel and experienced an AE of jejunal perforation initially reported as Grade 4 severity in the clinical database; however, follow-up reporting included in the safety narrative but not the clinical database indicates that the Investigator later re-assessed the cause of death as jejunal perforation (Grade 5 AE related to study treatment).

Grade 5 AEs that started more than 30 days after the last dose of study treatment included one Grade 5 AE of respiratory failure in each treatment arm. The other Grade 5 AEs that started more than 30 days after the last dose of study treatment were reported in one subject each, both in the sunitinib arm. None of these Grade 5 AEs were assessed as related to study treatment

Events To Monitor (ETMs)

Exelixis has defined a set of Events to Monitor (ETMs) for cabozantinib to track events known to be associated with TKIs or VEGF pathway inhibition (Ravaud 2011, Eisen et al 2012), may have potentially serious consequences, or were determined to warrant ongoing routine surveillance. These comprise gastrointestinal (GI) perforation, fistula, abscess – all, intra-abdominal and pelvic abscess, ≥ Grade 3 haemorrhage, venous and mixed thrombotic events (VTEs), arterial thrombotic events (ATEs), wound complications, hypertension, osteonecrosis, PPES, proteinuria, reversible posterior leukoencephalopathy syndrome (RPLS, also known as PRES), diarrhoea, and QT prolongation.

As shown in Table 37, there was a higher incidence of all grades diarrhoea, hypertension, PPES and embolism in the cabozantinib arm than in the sunitinib arm. The incidence of Grade 3 diarrhoea was similar in each arm (cabozantinib 10%, sunitinib 11%) and there were no Grade 4 diarrhoea in either

treatment arm. There was a higher incidence of Grade 3 or 4 hypertension in the cabozantinib arm (28% vs 21%); however, there was no Grade 4 hypertension in the cabozantinib arm whereas one subject in the sunitinib arm had a Grade 4 AE. There was also a higher incidence of Grade 3 or 4 pulmonary embolism in the cabozantinib arm (9.0% vs 0%; see below), including two subjects with a Grade 4 AE. Two subjects had GI perforations in the cabozantinib arm while there were none in the sunitinib arm.

Table 35: Events to Monitor in Study A031203 (Safety Population)

	Cabozantinib (N=78)			Sunitinib (N=72)		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GI Perforation[a]	2 (2.6)	2 (2.6)	0	0	0	0
Fistula	0	0	0	0	0	0
Abscess – all	0	0	0	0	0	0
Intra-abdominal and pelvic abscess	0	0	0	0	0	0
Haemorrhage (≥ Grade 3)	4 (5.1)[b]	4 (5.1)	0	1 (1.4)	1 (1.4)	0
Venous and mixed thrombotic events	1 (1.3)	1 (1.3)	0	1 (1.4)	1 (1.4)	0
Embolism	9 (12)	6 (7.7)[c]	0	1 (1.4)	0	0
Arterial thrombotic events	0	0[d]	0	4 (5.6)	1 (1.4)	0
Wound complications[e]	0	0	0	1 (1.4)	0	0
Hypertension[f]	52 (67)	22 (28)	0	32 (44)	15 (21)	0
Osteonecrosis	0	0	0	0	0	0
PPES[f]	33 (42)	6 (7.7)	0	24 (33)	3 (4.2)	0
Proteinuria	5 (6.4)	2 (2.6)	0	10 (14)	1 (1.4)	0
RPLS	0	0	0	0	0	0
Diarrhoea[f]	57 (73)	8 (10)	0	39 (54)	8 (11)	0
QT prolongation[f,g]	3 (3.8)	0	0	5 (6.9)	2 (2.8)	0

Laboratory findings

Clinical laboratory assessments were evaluated at intervals throughout the study, but these data were not collected in the clinical database; clinically significant findings and solicited events were to be reported as AEs.

Safety in special populations

The incidence of AEs and ETMs in Study A031203 was summarized by age group, gender, race, baseline weight and ECOG performance status.

Table 36: Related Adverse Events by Age Group (Safety Population) in Study

MedDRA Terms	Cabozantinib (N = 78)		
	< 65 (N = 44)	65-74 (N = 27)	75-84 (N = 7)
Number of events, n			
Total Related AEs[a]	1738	1197	283
Total Related SAEs	28	31	10
Fatal	1	2	0
Hospitalization	9	18	6
Life-threatening	0	0	0
Disability	0	0	0
Medically significant	19	16	4
Subject Incidence, n (%)[b]			
Drug Withdrawal (SMQ)	0	0	0
Psychiatric Disorders (SOC)	5 (11.4)	5 (18.5)	3 (42.9)
Nervous System Disorders (SOC)	24 (54.5)	17 (63.0)	5 (71.4)
Accidents and Injuries (SMQ)	1 (2.3)	3 (11.1)	2 (28.6)
Cardiac Disorders (SOC)	2 (4.5)	2 (7.4)	0
Vascular Disorders (SOC)	34 (77.3)	17 (63.0)	4 (57.1)
Cerebrovascular Disorders (SMQ)	2 (4.5)	1 (3.7)	0
Infections and Infestations (SOC)	7 (15.9)	5 (18.5)	1 (14.3)
Quality of Life Decreased (PT)	0	0	0
Anticholinergic Syndrome (SMQ)	7 (15.9)	8 (29.6)	3 (42.9)
Sum of Postural Hypotension, Falls, Blackouts, Syncope, Dizziness, Ataxia, Fractures (PTs)	9 (20.5)	10 (37.0)	4 (57.1)
Aspartate aminotransferase increased (PT)	22 (50)	19 (70)	6 (86)
Alanine aminotransferase increased (PT)	20 (45)	17 (63)	5 (71)
Hypocalcaemia (PT)	3 (6.8)	7 (26)	3 (43)

Safety related to drug-drug interactions and other interactions

All relevant drug interaction studies were included in the original Cabometyx filing. No further drug interaction studies have been conducted.

Discontinuation due to adverse events

Adverse events were reported by cycle. Action taken with study treatment in response to each AE was not collected, nor was outcome, start date, or stop date. Based on subject disposition, 21% of subjects in the cabozantinib arm and 22% in the sunitinib arm discontinued study treatment due to an AE (not excluding events of disease progression) in the Safety population.

Post marketing experience

Cabozantinib capsules (Cometriq) were first approved by the FDA on 29 November 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) at a dose of 140 mg qd. Cometriq was made commercially available in the United States on 24 January 2013. On 21 March 2014, cabozantinib capsules (Cometriq) at the 140 mg dose received approval through the centralized procedure by the European Commission for the treatment of adults with progressive, unresectable locally advanced or metastatic MTC. Cabozantinib tablets (Cabometyx) were approved by the FDA on 25 April 2016 for patients with advanced RCC who have received prior anti-angiogenic therapy and by the European Commission on 09 September 2016 for the treatment of advanced RCC in adults following prior VEGF-targeted therapy.

The post-marketing patient population for cabozantinib (Cabometyx and Cometriq combined) through 28 November 2016 comprised 4325 total patients exposed including 3693 in the US, 586 in the EU (221 marketed, 365 named patient use [NPU] and managed access program), and 46 from other countries (NPU). Through 28 November 2016, patients in the US marketed setting have received cabozantinib for treatment of RCC (n=1255) and thyroid cancer (n=1952) as well as malignancies other than the approved indication, including prostate, lung, and hepatocellular cancer. In the EU, information on treated indication is not available.

Cumulatively, 1126 serious adverse reactions (SARs) have been reported in the postmarketing setting for Cabometyx (165 SARs in 115 patients) and Cometriq (961 SARs in 507 patients) through 28 November 2016. Postmarketing SARs reported in patients who received Cabometyx through 28 November 2016:

- In 105 patients who received Cabometyx on-label for the indication of renal cancer (including RCC, metastatic RCC, and renal cancer), 151 postmarketing SARs were received. The most frequent non-fatal SARs (excluding events of hospitalization) included thrombosis (n=7), pneumonia (n=4), diarrhoea, nausea, and vomiting (each n=3). These most frequently reported SARs are generally consistent with the known Cabometyx safety profile. Similarly, in 10 patients who received Cabometyx for off-label indications, the SARs reported are also generally consistent with the known Cabometyx safety profile.

Postmarketing SARs reported in patients who received Cometriq through 28 November 2016:

- In 224 patients who received Cometriq on-label for the indication of thyroid cancer (including thyroid cancer, MTC, thyroid neoplasm, thyroid cancer metastatic, and thyroid disorder), 474 postmarketing SARs were received. The most frequent non-fatal SAR reported in more than 5 patients included dehydration (n=27), diarrhoea (n=16), pneumonia (n=13), asthenia, vomiting (each n=11), weight decreased, hypertension (each n=8), dyspnoea (n=7), pancreatitis, loss of consciousness, hypotension, pulmonary embolism, and confusional state (each n=6). These most frequently reported SARs are generally consistent with the known Cometriq safety profile.
- A total of 283 patients received Cometriq off-label, of which 128 patients received Cometriq for the indication of renal cancer (including RCC and malignant neoplasm of the renal pelvis or urinary tract). The 128 patients who received Cometriq for the indication of renal cancer experienced 192 post-marketing SARs. The most frequent nonfatal SARs included dehydration, pneumonia (each n=8), diarrhoea (n=4), hypertension, vomiting, urinary tract infection, rectal haemorrhage, pulmonary embolism, pain, thrombosis, cerebrovascular accident, diarrhoea, and infection (each n=3); the observed frequency of these SARs is generally consistent with the known Cometriq safety profile.

2.5.1. Discussion on clinical safety

Exposure

The median duration of exposure was longer in the cabozantinib arm, with 10 cabozantinib subjects still on treatment at cut-off versus 2 in the sunitinib arm. Some differences between the study arms might be the result of the longer duration of exposure in the cabozantinib arm compared with the sunitinib arm.

Adverse events

Overall, the incidence of AEs was similar between treatment arms (cabozantinib arm 96%, sunitinib arm 99%).

The AEs observed with cabozantinib treatment in Study A031203 are in line with the known safety profile of cabozantinib and there were no new safety signals. However, there was a higher incidence in Study A031203 than METEOR of the following cabozantinib AEs of any grade (≥ 10% difference): hypertension (67%, 37%), dysgeusia (41%, 24%), stomatitis (37%, 22%), dyspepsia (27%, 12%) and dizziness (22%, 11%), and embolism (12%, 0.3%)/

The incidences of laboratory-associated AEs were generally similar to the corresponding METEOR laboratory abnormalities, reflecting the difference in collection of safety parameters between the two studies.

Comparing Grade 3 /4 AEs between the studies, there are smaller differences in the incidences of the individual AEs. However, there is clearly a higher reporting of Grade 3 /4 hypertension (28%,15%) and embolism (7.7%, 0%) in Study A031203 than in METEOR.

A plausible explanation for the lower rate of hypertension in the METEOR study is that patients in the METEOR study had previously received more treatment for hypertension than patients in study A031203 because they had received a prior VEGFR-TKI. Hypertension was a solicited AE in study A031203, which may also have contributed to a higher reporting of this AE compared to the METEOR study.

The higher incidence of embolism in Study A031203 relative to METEOR may be an artefact of differences in reporting of thromboembolic events in the two studies. In METEOR, thromboembolic events were generally assigned more specific PTs that could be categorized as arterial (eg, myocardial infarction or stroke) or venous thrombotic events (eg, pulmonary embolism or DVT). In contrast, no further specification was used on Study A031203, and thromboembolic events were generally reported as the PT embolism. In METEOR, the incidence of venous and mixed/unspecified thrombotic ETMs (Events to Monitor) was 7.3% (24 subjects), of which 12/24 had event of grade 3 or 4.

For both hypertension and thromboembolic events, sufficient warnings are already included in the SmPC, section 4.4.

For the remainder of the AEs, the applicant has pointed to the differences in the patient populations as a possible explanation, i.e. subjects in Study A031203 were treatment-naive and may have been more prone to reporting non-serious AEs than the pre-treated subjects in METEOR. Furthermore, differences in reporting AEs can also explain the higher frequency of adverse events in study A031203 compare to METEOR study.

Most of the observed AEs are considered treatment related. There are some differences between the two treatments with regards to type of treatment related adverse events most frequently reported,

e.g. there are more liver enzyme elevations in the cabozantinib arm, while blood counts are more often affected in the sunitinib arm.

The overall perception is that the number of treatment related AEs is higher in the cabozantinib arm compared to the sunitinib arm. This could be explained by the longer exposure in the cabozantinib arm compared to the sunitinib arm.

doses modifications (reduction and interruption)

Dose data were collected on the CRF by treatment cycle and not by date; thus information on study treatment modifications is limited. There were less dose reductions with cabozantinib in the current study compared to the METEOR study. In the METEOR study, dose reductions and dose interruptions occurred in 60% and 70% patients, respectively (versus 46% and 73% in the cabozantinib arm for this study), with diarrhoea, PPES and fatigue as the most common causes.

The applicant has updated the SmPC section 4.4 with the additional frequencies of dose reductions and interruptions from Study A031203.

Grade 3/4 AEs

A similar incidence of Grade 3/4 AEs was observed across treatment arms (68% and 65%), while there were more subjects with Grade 4 AEs in the cabozantinib arm than the sunitinib arm (10% vs 6.9%)

The most common solicited Grade 3/4 AEs were hypertension, diarrhoea, PPES and fatigue in both treatment arms. The Grade 3/4 AE with the largest difference in incidence between the treatment arms, is fatigue (all Grade 3), with 17% in the sunitinib arm and 6.4% in the cabozantinib arm. Grade 3/4 embolism was reported in 6 patients (7.7%) in the cabozantinib arm. Two of them were Grade 4. There were none in the sunitinib arm.

Serious adverse events and deaths

The overall incidence of SAEs regardless of causality was similar in both treatment arms (49% cabozantinib, 51% sunitinib). The overall incidence of treatment-related SAEs was similar in both treatment arms (36% each).

The overall incidence of SAEs of any grade was 49% in the cabozantinib arm of Study A031203 and 40% in the cabozantinib arm of the METEOR study. The fact that SAEs may have been over-reported in Study A031203 compare to the METEOR study could explained the difference in overall incidence. In addition, there is some uncertainty in the detected frequencies in study A031203 due to the rather small sample size.

Deaths

There were more deaths reported as Grade 5 AEs in the sunitinib arm, both before and after 30 days after last dose of study treatment. There were more deaths in the sunitinib arm through 30 days after last dose compared to the cabozantinib arm, 8.3% and 3.8%, respectively.

There were 3 deaths in the cabozantinib arm which were considered related to the treatment; one case of jejunal perforation, one sepsis and one acute renal failure. For the sepsis case, it was considered secondary to the large intestinal perforation which is a known adverse reaction for cabozantinib. Therefore sepsis has not been shown to be causally related to cabozantinib at this time.

In the sunitinib arm, deaths considered related to the treatment consisted of one patient who died from angiopathy, one sepsis, one sudden death, and one respiratory failure.

The overall incidence of Grade 5 AEs through 30 days after last dose was similar in the cabozantinib arm of Study A031203 and the METEOR study, 3.8% and 4.5%, respectively.

Events to monitor

There were in general more all grades and Grade 3/4 AEs in the cabozantinib arm compared to the sunitinib arm among the ETMs.

Safety in special population

No conclusions could be drawn regarding the effects of sex, race or weight as few subjects were female, non-White or weighed < 60 kg. There were higher incidences in the cabozantinib arm with increasing age of aspartate aminotransferase (AST), alanine aminotransferase (AST), and hypocalcemia (Table 38). However, there were no Grade 4 AEs of hypocalcemia in any cabozantinib-treated subject.

In the METEOR study, there were no marked clinically important differences in safety noted for age, gender, baseline weight and ECOG performance status although as few subjects were non-White no meaningful conclusions could be drawn regarding the effect of race.

Discontinuation due to adverse events

Similar proportions of patients in the two study arms discontinued due to AEs (not excluding events of disease progression). The reason for discontinuation has not routinely been captured and very little information is available. In the METEOR study, the incidence of treatment discontinuations due to AEs (excluding AEs related to disease progression) in the cabozantinib arm was 9.7%. The most frequent AEs that led to treatment discontinuation were decreased appetite (1.8%) and fatigue (1.2%). It is of concern that so little is known about the cause of discontinuation.

Finally no new safety findings have been identified in the post marketing experience.

No changes were proposed to the list of safety concerns of the Risk management plan as a result of data coming from the study supporting the new indication or data coming from post maketing experience.

The section 4.8 of the SmPC was revised to include data in treatment-naïve renal cell carcinoma. Since most of the adverse reactions are the same for both indications, a single table listing all adverse actions observed for both indications was included with the with the principle of using the higher frequency when the same adverse reactions have been reported with different frequencies between the 2 indications.

The main differences were also highlighted in the section “description of selected adverse reactions” below the table.

2.5.2. Conclusions on clinical safety

Overall, there seems to be more AEs with cabozantinib compared to sunitinib. This could be explained by the longer exposure in the cabozantinib arm compared to the sunitinib arm. Similar proportions of patients in the two study arms discontinued due to AEs which could indicate that the safety profile of the products are equally acceptable. There were no new safety signals compared to experience with cabozantinib in the METEOR study. However, there were clearly more of some AEs compared to the METEOR study. This might be due to differences in study populations and treatment duration. Overall, the safety profile for cabozantinib seems acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal perforation • Gastrointestinal and non-gastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Reversible posterior leukoencephalopathy syndrome (RPLS) • Osteonecrosis
Important potential risks	• Renal Failure • Hepatotoxicity • Embryotoxicity
Missing information	• Use in paediatric population • Use in pregnant or lactating women • Use in patients with cardiac impairment • Use in patients with severe hepatic impairment • Use in patients with severe renal impairment • Carcinogenicity

In line with the RMP guidance introduced by GVP V rev 2, the following important identified risks were removed from the RMP: hypertension, diarrhoea, palmar-plantar erythrodysaesthesia syndrome, hypothyroidism, and proteinuria. Removal of these important identified risks is accepted as no additional pharmacovigilance or risk minimisation activities are in place and these risks are sufficiently characterized and addressed in the current Product information. Furthermore, the assessment of the information regarding those important identified risks in the previous PSURs did not show any significant changes in the safety profile.

In addition, the MAH proposed to remove the following important potential risks: QT prolongation, fertility impairment and medication error.

-QT prolongation was removed since no medically meaningful QT prolongation was observed in renal cell carcinoma patients. Also, no cases of Torsade de Pointes and grade 3,4, or 5 events were identified. In the latest PSUR (DLP 28 November 2016) it is described that in the post-marketing phase, no cases of QT prolongation and Torsade de Pointes were observed. Currently, in SmPC section 4.4 it is described that cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Based on the information provided, it is accepted to remove QT prolongation.

-Fertility impairment was removed as it has limited influence on the benefit-risk balance and it is sufficiently covered in the SmPC.

- Risk of medication errors was removed as no cases were identified in the post marketing phase.

Pharmacovigilance plan

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Prospective noninterventional study of cabozantinib tablets in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy/planned (cat 3)	**Primary:** • 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:** • 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 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).	To assess the risk-benefit profile of Cabometyx with respect to identified and potential risks	1. Protocol submission to PRAC 2. PRAC approval 3. Study start 4. Study finish 5. Progress report 6. Interim report 7. Final report	1. Submitted 24 April 2017 2. 12 October 2017 3. Planned March 2018 (FPI) 4. Planned December 2020 (LPO) 5. Planned December 2018 6. Planned December 2019 7. Planned December 2021

AE=adverse event; FPI=first patient in; LPO=last patient out; PRAC=Pharmacovigilance Risk Assessment Committee; RCC=renal cell carcinoma.

Risk minimisation measures

Safety concern	Risk minimisation measures
Gastrointestinal perforation	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Gastrointestinal and non-gastrointestinal fistulas	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Thromboembolic events	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8[a] PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Haemorrhage	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Wound complications	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Reversible posterior leukoencephalopathy syndrome (RPLS)	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

Safety concern	Risk minimisation measures
Osteonecrosis	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Renal failure	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None
Embryotoxicity	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.5 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None
Use in paediatric population	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None
Use in pregnant or lactating women	**Routine risk minimisation measures:** SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None
Use in patients with cardiac impairment	**Routine risk minimisation measures:** SmPC Section 4.2 Restricted medical prescription **Additional risk minimisation measures:** None
Use in patients with severe hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None

Safety concern	Risk minimisation measures
Use in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC Section 4.2 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None
Carcinogenicity	**Routine risk minimisation measures:** SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None

The table of risk minimisations measures was adjusted to reflect the change in the list of safety concerns (deletion/reclassification of safety concerns due to revision of GVP module V and RMP template).

Having considered the data submitted, the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indications.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the product information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the changes introduced in the PL as part of this variation application do not have a relevant impact on the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for the following extension of the indication for CABOMETYX:

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk per IMDC criteria.

The aim of the therapy is to prolong progression free survival and overall survival.

3.1.2. Available therapies and unmet medical need

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of renal cell carcinoma (2016) presents an algorithm for systemic treatment in mRCC with a clear cell component. According to the algorithm, sunitinib is the recommended first-line treatment of clear cell RCC for patients with good or

intermediate risk, while temsirolimus is the first choice in patients with poor risk, however, with sunitinib as a “reasonable alternative”. In addition to immunotherapy, several TKIs and temsirolimus/everolimus are recommended as second and further lines of therapy.

The vast majority of patients with advanced RCC will experience disease progression due to acquired or a priori resistance to VEGFR- or mTOR-targeted therapy. The median overall survival for patients with advanced RCC ranges from about 8 months (poor risk score) to 4 years (favourable risk score). Therefore, an unmet need remains for treatments that will prolong time to progression and improve survival.

3.1.3. Main clinical studies

The safety and efficacy of CABOMETYX for the treatment of treatment-naïve renal cell carcinoma were evaluated in a randomized, open-label, multicenter study (CABOSUN). Patients (N=157) with previously untreated, locally advanced or metastatic RCC with a clear cell component were randomized (1:1) to receive CABOMETYX (N=79) or sunitinib (N=78). Patients had to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no). Approximately 75% of patients had a nephrectomy prior to onset of treatment. The primary endpoint was PFS. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumor assessments were conducted every 12 weeks.

The study was sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and conducted by the Alliance for Clinical Trials in Oncology (the Alliance). The primary and secondary endpoints of Study A031203 were originally analysed by the Alliance and reported in the literature[18,19].

3.2. Favourable effects

PFS determined by the IRC using FDA-recommended censoring rules showed a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the sunitinib arm. The HR adjusted for stratification factors was 0.48 (95% CI 0.31, 0.74; p = 0.0008). The median duration of PFS was estimated to be 8.6 months in the cabozantinib arm vs 5.3 months in the sunitinib arm. PFS was determined by the IRC using analyses as per EMA censoring rules. The median PFS was the same with a HR=0.48 (95%CI 0.32, 0.73; p=0.0005).

Subgroup analyses of PFS in patients according to IMDC risk intermediate (N=127) and poor (N=30), resulted in HRs of 0.52 (95% CI: 0.32, 0.82) and 0.31 (95% CI: 0.11, 0.92) in the two groups, respectively.

The results of the Investigator analysis demonstrated a statistically significant improvement in PFS for subjects in the cabozantinib arm compared with the sunitinib arm, much in line with the IRC analysis.

CABOMETYX treatment was associated with a trend for longer survival compared to sunitinib. The study was not powered for the OS analysis and the data are immature. The Kaplan-Meier estimates for median duration of OS were 30.3 months (95% CI: 14.6, NE) in the cabozantinib arm vs 21.0 months (95% CI: 16.3, 27.0) in the sunitinib arm. HR adjusted for stratification factors was 0.74 (95% CI 0.47, 1.14) with a p-value = 0.1700; i.e. not statistically significant. More recently, the Alliance presented OS results at the European Society for Medical Oncology (ESMO) annual meeting in September 2017, based on an analysis they conducted with a data cut-off of 01 July 2017[19]. This

analysis includes 7 more deaths. The result of this analysis is similar to the two previous analyses, with a HR of 0.80, 95% CI (0.53, 1.21), p=0.2885.

The IRC-determined ORR was 20% (95% CI 12.0, 30.8) in the cabozantinib arm, compared with 9% (95% CI 3.7, 17.6) in the sunitinib arm (p=0.0406).

Patients with both positive and negative MET status showed a favourable effect with CABOMETYX compared to sunitinib, with greater activity in patients with a positive MET status compared to patients with a negative MET status (HR=0.32 (0.16, 0.63) vs 0.67 (0.37, 1.23)) respectively (see SmPC section 5.1).

3.3. Uncertainties and limitations about favourable effects

Although more than 50% of the patients have had an OS event overall, less than half of the patients in the cabozantinib arm have died. Thus, there is a notable degree of censoring around the median estimates in the OS analysis. Considering that PFS analyses showed an approximately 3 months improvement with cabozantinib compared with sunitinib, the median OS gain of 9 months seems overestimated. In addition, none of the OS analyses shows statistically significant improvement in OS. Therefore, no definitive conclusion can be drawn from the OS data. However, despite some crossing of the curves, it can be concluded that cabozantinib does not appear to have a detrimental effect on OS.

3.4. Unfavourable effects

Overall, the incidence of AEs was similar between treatment arms (cabozantinib arm 96%, sunitinib arm 99%). A similar incidence of Grade 3/4 AEs was observed across treatment arms (68% and 65%), while there were more subjects with Grade 4 AEs in the cabozantinib arm than the sunitinib arm (10% vs 6.9%). There were more deaths reported as Grade 5 AEs in the sunitinib arm, both before and after 30 days after last dose of study treatment.

Common AEs regardless of study drug relationship:

The most frequent AEs (≥ 20% of subjects) in the cabozantinib arm in descending order of frequency were diarrhoea (73%), hypertension (67%), fatigue (64%), AST increased (60%), ALT increased (55%), decreased appetite (47%), PPES (42%), dysgeusia (41%), platelet count decreased (38%), stomatitis (37%), anaemia (33%), nausea (32%), weight decreased (32%), dyspepsia (27%), blood creatinine increased (24%), hypophosphatemia (23%), hypothyroidism (23%), vomiting (23%), dizziness (22%), dysphonia (22%), hypomagnesemia (22%), and hyperglycaemia (21%). The summary of the safety profile in the SmPC section 4.8 has been updated.

The most common Grade 3/4 AEs (≥ 5% of subjects) in the cabozantinib arm were hypertension, diarrhoea, PPES, fatigue, ALT increased, hyponatraemia, hypophosphataemia, embolism, decreased appetite, hypotension, pain, stomatitis, and syncope. The Grade 3/4 AE with the largest difference in incidence between the treatment arms and the only one with more than 10% difference, is fatigue (all Grade 3), with 17% in the sunitinib arm and 6.4% in the cabozantinib arm.

SAEs:

The number of subjects with at least one SAE was similar in both treatment arms (49% cabozantinib, 51% sunitinib). The most frequent SAE PTs (≥ 5% of subjects) in the cabozantinib arm in descending order of frequency were hypertension (9.0%), embolism (9.0%), diarrhoea (5.1%), PPES (5.1%) and acute renal failure (5.1%). The most frequent SAE PTs (≥ 5% of subjects) in the sunitinib arm in

descending order of frequency were diarrhoea (6.9%), fatigue (5.6%), nausea (5.6%) and vomiting (5.6%). The majority of these SAEs were considered treatment related.

On-treatment deaths:

There were more deaths in the sunitinib arm through 30 days after last dose compared to the cabozantinib arm, 8.3% (6/72) and 3.8% (3/78), respectively. The 3 deaths in the cabozantinib arm were considered related to the treatment; one case of jejunal perforation, one sepsis and one acute renal failure. In the sunitinib arm, deaths considered related to the treatment consisted of one patient who died from angiopathy, one sepsis, one sudden death, and one respiratory failure.

Discontinuations:

Not excluding events of disease progression, 21% of subjects in the cabozantinib arm and 22% in the sunitinib arm discontinued study treatment due to an AE.

3.5. Uncertainties and limitations about unfavourable effects

There were no new safety concerns that have been raised in this application. However, there were only 15 patients in each arm that were in the poor risk category and hence, the safety database is small for this patient population. In general, there was a higher incidence in Study A031203 than the METEOR study of the following cabozantinib AEs of any grade (≥ 10% difference): hypertension (67%, 37%), dysgeusia (41%, 24%), stomatitis (37%, 22%), dyspepsia (27%, 12%) dizziness (22%, 11%), and embolism (12%, 0.3%). There is clearly a higher reporting of Grade 3/4 hypertension (28%, 15%) and embolism (7.7%, 0%) in Study A031203 than in METEOR. In addition, more patients discontinued due to AEs of cabozantinib than in the METEOR study, 21% (not excluding events of disease progression) and 9.7% (excluding events of disease progression), respectively. The reason for discontinuation in Study A031203 was not routinely captured and very little information is available if discontinuation is due to the tolerability of cabozantinib. However, a similar number of patients in the two treatment arms of Study A31202 discontinued due to AEs, reassuring that the tolerability is not worse than sunitinib. Further safety data will be gathered during post-authorisation and as part of routine pharmacovigilance, guided questionnaires have been developed for identified risks of gastrointestinal (GI) perforation, GI and non-GI fistula, arterial thromboembolic events, haemorrhage, RPLS and osteonecrosis. The next PSUR for cabozantinib will include a cumulative review of literature and post-marketing data for the risks for which follow-up questionnaires are in place.

3.6. Effects Table

Table 39. Effects Table for cabozantinib treatment-naïve adults with renal cell carcinoma with intermediate or poor risk disease (data cut-off: 15-09-16).

Effect	Short description	Unit	Cabozantinib	Sunitinib	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death (IRC; EU censoring)	Months (95% C.I)	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)	HR=0.48 (95% CI 0.32, 0.73; p = 0.0005)	
Unfavourable Effects						
G 3-4 ADRs	Incidence of worst related Grade 3-4 adverse event	%	60	65		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for CABOMETYX compared to sunitinib. Study A031203 provided a 3 months improvement in PFS which is of clinical relevance as it is expected to delay next-line therapy and may potentially also result in an improvement in overall survival since in previously treated RCC (METEOR study), there seems to be a correlation between improved PFS and OS. The ORR was also higher in the cabozantinib arm relative to sunitinib. The results from the Investigator determined analysis and IRC-determined analysis of PFS were consistent.

The safety profile of cabozantinib observed in Study A031203 is similar to the safety profile that is already known, although hypertension, dysgeusia, stomatitis, dyspepsia and dizziness were reported much more frequently compared to the METEOR study. While a similar number of patients in the two treatment arms of Study A31202 discontinued due to AEs, there were more AEs in the cabozantinib arm compared with the sunitinib arm. This may be due to patients in the cabozantinib arm being treated for a longer time. Thus, the safety and tolerability of cabozantinib is acceptable and manageable.

3.7.2. Balance of benefits and risks

The CHMP considers that the benefits in terms of PFS outweigh the risks in the agreed indication in treatment-naïve adults with intermediate or poor risk disease (see SmPC section 5.1).

3.7.3. Additional considerations on the benefit-risk balance

Treatment-naïve patients with advanced RCC of IMDC Intermediate and Poor risk have a poor prognosis. An unmet need remains for treatments that will prolong time to progression and improve survival. The study A031203 has shown that cabozantinib can improve PFS compared to sunitinib, which is the current standard of care for treatment-naïve patients. It is expected that a prolonged PFS could result in an improvement in OS, although no firm conclusion can be drawn from the currently submitted data. As no information has been provided for patients with favourable risks, the CHMP has restricted the indication for the patient population that has been well described in the study. Hence, the indication is restricted to treatment-naïve patients with IMDC intermediate risk disease, where one or two of the following risk factors were met, and poor risk, where three or more factors were met: time from diagnosis of RCC to systemic treatment < 1 year, Hgb < LLN, Corrected calcium > ULN, KPS < 80%, Neutrophil count > ULN and Platelet count > ULN (see Section 5.1 of the SmPC).

Approximately 40% of subjects in each arm had MET-positive disease. MET upregulation is associated with poor pathologic features and unfavourable prognosis in RCC patients. The superiority of cabozantinib over sunitinib for this patient subgroup may reflect cabozantinib's mechanism of action, that includes inhibition not only of VEGFR but also of MET and AXL. This is reflected in section 5.1 of the SmPC.

3.8. Conclusions

The overall B/R of CABOMETYX is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include for the treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk' for CABOMETYX; as a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package Leaflet and risk management plan (version 3.2) are also updated accordingly.
In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the product information.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cabometyx is not similar to Torisel (temsirolimus) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include for the treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk' for CABOMETYX; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package Leaflet and risk management plan (version 3.2) are also updated accordingly.
In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the product information.

Summary

Please refer to Scientific Discussion CABOMETYX - EMEA/H/C/004163/II/0003