25 February 2021
EMA/145012/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CABOMETYX

International non-proprietary name: cabozantinib

Procedure No. EMEA/H/C/004163/II/0017

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

1L	First line
2L	Second line
ADaM	Analysis data model
ADR	Adverse drug reaction
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BMS	Bristol-myers squibb company
BOR	Best overall response
cc	Clear cell
CI	Confidence interval
CL	Clearance
CL/F	Apparent oral clearance
CLS	Capillary leak syndrome
Cmax	Maximum observed concentration
CMH	Cochran-mantel-haenszel
CoC	Contribution of Components
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DoR	Duration of response
EAU	European Association of Urology
EBE	Empirical Bayes estimates
eGFR	Estimated glomerular filtration rate

EQ-5D-3L Euroqol Group's instrument to measure general health status

ERA Environmental risk assessment

ESCC Esophageal squamous cell carcinoma

ETM Event to monitor

FKSI-19 Functional Assessment of Cancer Therapy-Kidney Symptom Index

Fpen Penetration factor

GCP Good clinical practice

GI Gastrointestinal

HCC Hepatocellular carcinoma

HR Hazard ratio

HRQoL Health related quality of life

I/P Intermediate and poor

IA Interim analysis

ICI Immune checkpoint inhibitors

IMAEs Immune-mediated adverse events

IMDC International metastatic renal cell carcinoma database consortium

IND Investigational new drug

INR International normalized ratio

IRT Interactive response technology

ISE Integrated Summary of Effectiveness

ISS Integrated Safety Summary

ITT Intent-to-treat

IU International Unit

IV Intravenous(ly)

KM Kaplan-Meier

KPS Karnofsky Performance Status

LC-MS/MS Liquid chromatography tandem-mass spectrometry

LDH Lactate dehydrogenase

LPLV Last patient last visit

mAb Monoclonal antibody

MDSC Myeloid derived suppressor cell

MedDRA Medical Dictionary for Regulatory Activities

MID Minimally important difference

mRCC	Metastatic renal cell carcinoma
mTOR	Mammalian target of rapamycin
mUC	Metastatic urothelial cancer
MUGA	Multigated acquisition scan
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NIH	National Institute of Health
NR	Not reached
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death receptor 1
PD-L1	Programmed cell death receptor ligand 1
PD-L2	Programmed cell death receptor ligand 2
PEC	Predicted environmental concentration
PFS	Progression free survival
PK	Pharmacokinetic
PO	By mouth
popPK	Population pharmacokinetics
PR	Partial response
PT	Preferred term
P-Y	Person-years
QD	Once daily
QxW	Every x weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
ROW	Rest of world
RP2D	Recommended phase 2 dose
RTK	Receptor tyrosine kinase

RTOR	Real-Time Oncology Review
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
sBLA	Supplemental Biologics License Application
SCCHN	Squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCLC	Small cell lung cancer
SCS	Summary of Clinical Safety
SD	Stable disease; standard deviation
SDTM	Study Data Tabulation Model Implementation Guide
SI	International System of Units
sNDA	Supplemental New Drug Application
SOC	System organ class; standard of care
SVC	Superior vena cava
TAM	Tumor-assisted macrophages
TKI	Tyrosine kinase inhibitor
ToC	Table of contents
TTR	Time to response
ULN	Upper limit of normal
USPI	United States Prescribing Information
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel-Lindau
VPC	Visual predictive check
Vz	Terminal phase volume of distribution

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 25 August 2020 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 in combination with nivolumab first line treatment of advanced renal cell carcinoma 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 is updated in accordance. Version 5.0 of the RMP has also been submitted.

The variation requested 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 EMEA-001143-PIP01-11 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0331/2019 was not yet completed as some measures were deferred.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Submission date	25 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur Assessment Report	9 November 2020
PRAC Rapporteur Assessment Report	9 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 December 2020
Request for supplementary information (RSI)	10 December 2020
MAH's responses submitted to the CHMP on	21 December 2020
CHMP Rapporteur Assessment Report	26 January 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur Assessment Report	18 February 2021
Opinion	25 February 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application concerns an extension of indication to include the use of cabozantinib in combination with nivolumab for the first-line (1L) treatment of advanced renal cell carcinoma (RCC). The proposed posology for this new indication is 40 mg cabozantinib administered once daily in combination with either 240 mg nivolumab IV Q2W or 480 mg IV Q4W . This is a new posology for cabozantinib instead of the approved 60 mg daily (Cabometyx SmPC). The two dose regimens for nivolumab have already been approved for other indications (Opdivo SmPC).

Disease or condition

This application concerns an extension of indication to include the use of Opdivo in combination with cabozantinib the first-line (1L) treatment of advanced renal cell carcinoma.

The proposed posology for this new indication is either 240 mg nivolumab intravenous (IV) every 2 weeks (Q2W) or 480 mg IV every 4 weeks (Q4W) in combination with 40 mg cabozantinib administered orally once daily (QD) (see SmPC 4.2).

Epidemiology

Renal cell carcinoma (RCC) represents the sixth most common cancer in men and the eighth most common cancer in women, accounting for 3%-4% of all adult malignancies in the US (Siegel et al. CA A Cancer J Clin. 2019). The percentage of new cases across Europe in 2018 was 3.2%, with an estimated number of new cases over 136.000 and over 54.000 expected deaths (Globocan 2018). Well-known risk factors for RCC are cigarette smoking, obesity and hypertension (Chow et al. Nat Rev Urol. 2010).

Biologic features

Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer, comprising 80-90% of all kidney tumours (2020 European Association of Urology [EAU] RCC guidelines).

Approximately 2%-3% of all RCCs are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being von Hippel–Lindau (VHL) disease (Escudier et al. An Oncol. 2019).

Clinical presentation, diagnosis

Many renal masses remain asymptomatic until the late disease stages. Currently, >50% of RCCs are detected accidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases (2020 EAU RCC guidelines; Escudier et al. An Oncol. 2019). In addition, 25-40% of the patients that are radically treated (nephrectomy) will eventually relapse. '*Advanced*' RCC (hereafter simply referred to as advanced RCC) entails both locally advanced disease that is not amenable to local therapy, i.e. curative surgery or radiation therapy, as well as metastatic disease. Advanced RCC thus requires systemic treatment. All histological epithelial subtypes of RCC (clear cell, papillary, chromophobe) can present with sarcomatoid differentiation, which is the most aggressive form of RCC. A high proportion of RCC patients with sarcomatoid features presents with metastatic disease. These features are found in 5-8% of clear cell RCC.

RCC with sarcomatoid features is characterised by limited therapeutic options due to its relative resistance to established systemic targeted therapy. Most trials report on a poor median OS of 5 to 12 months. Studies have shown that sarcomatoid RCC express programmed death 1 (PD-1) and its ligand (PD-L1) at a much higher level than non-sarcomatoid RCC, suggesting that blockade of the PD-1/PD-L1 axis may be an attractive new therapeutic strategy (Pichler et al. Cancers (Basel). 2019).

Management

Current systemic treatment of advanced RCC

Recommendations mainly relate to clear cell histology, since most of the pivotal trials have been conducted in this common histological subtype (Escudier et al. An Oncol. 2019).

The clinical therapeutic scenario in advanced RCC changed radically in the last decade with the availability of targeted agents and, more recently, with the advent of immune checkpoint inhibitors (Moscetti et al. ESMO Open. 2020).

The choice of treatment is normally based on prognostic risk factors historically developed in the era of frontline vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) (UpToDate). The most commonly used prognostic model is the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model (Heng et al. Lancet Oncol. 2013), that includes the following six adverse factors:

- Karnofsky performance status (KPS) <80%;
- time from diagnosis to treatment <1 year;
- haemoglobin concentration less than the lower limit of normal;
- serum calcium greater than the upper limit of normal;
- neutrophil count greater than the upper limit of normal; and
- platelet count greater than the upper limit of normal.

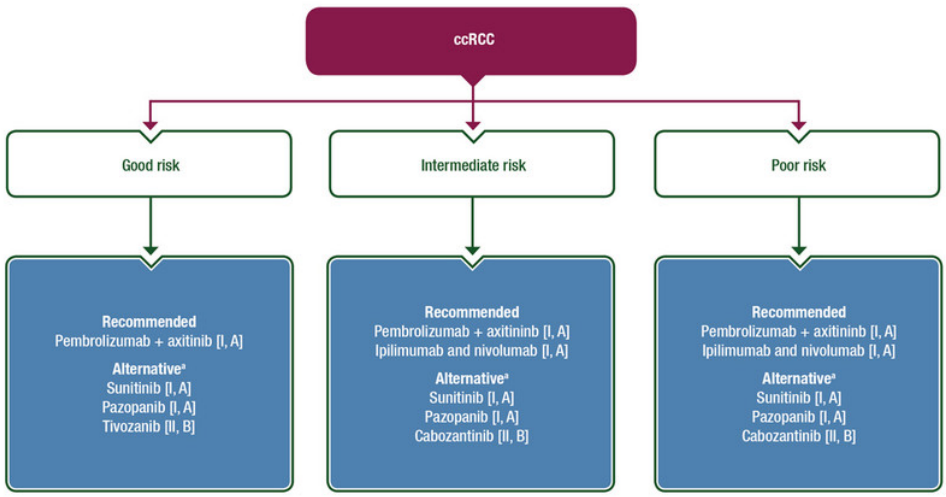
Patients with none (0) of these risk factors are considered good risk, those with one or two (1-2) are considered intermediate risk, and those with three or more (≥3) are considered poor risk. The estimated median overall survival (OS) for the patients in these risk groups is 43.2 months, 22.5 months, and 7.8 months, respectively.

The most appropriate time to start systemic therapy is not well defined. Because of the indolent course of some RCCs, a period of observation before starting treatment should be considered, especially in patients with limited tumour burden and few symptoms (Escudier et al. An Oncol. 2019).

First-line systemic treatment

The algorithm for first-line (1L) systemic treatment in ccRCC that is currently recommended by ESMO is presented in Figure 1 (eUpdate - ESMO RCC algorithm). Of note, all recommended medicinal products and combinations of medicinal products in this figure are approved by EMA, i.e. pembrolizumab + axitinib (Keytruda + Inlyta 1L RCC European public assessment report [EPAR]), sunitinib (Sutent 1L RCC EPAR), pazopanib (Votrient 1L RCC EPAR), tivozanib (Fotivda 1L RCC EPAR), nivolumab + ipilimumab (Opdivo + Yervoy 1L RCC EPAR), and cabozantinib (Cabometyx 1L RCC EPAR).

Figure 1 Systemic first-line treatment of clear cell renal cell carcinoma



[a] Where recommended treatment not available or contra-indicated.

Abbreviation: ccRCC= clear cell renal cell carcinoma

In addition, the combination of avelumab + axitinib has been approved by EMA for the 1L treatment of adult patients with advanced RCC (Bavencio + Inlyta 1L RCC EPAR).

Plus, the combination of atezolizumab + bevacizumab has been tested against sunitinib in a phase 3 study in the 1L RCC setting (Rini et al. Lancet. 2019).

Previously EMA-approved medicinal products that are no longer recommended by ESMO for the treatment of RCC are not discussed here.

2.1.2. About the product

Cabozantinib

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumour cell proliferation and/or tumour neovascularization including the VEGF receptor (VEGFR), MET, AXL, and RET. Inactivation of the von Hippel-Lindau (VHL) tumour suppressor protein in clear cell RCC (ccRCC) results in upregulation of VEGF, MET, and AXL. Increased expression of MET and AXL has been associated with poor prognosis in RCC. In addition, targets of cabozantinib, including TYRO3, MER, and AXL (TAM family kinases), are implicated in promoting suppression of an antitumor immune response.

Cabozantinib is currently approved as Cabometyx in the EU as monotherapy in RCC and hepatocellular carcinoma (HCC). In RCC, cabozantinib is approved both in the first line (intermediate and poor risk) population, and in the 2nd line (following prior VEGF-targeted therapy) across all risk groups.

Cabozantinib is also approved under the name Cometriq for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Nivolumab

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumors use PD-L1 expression as defense or escape mechanism against the host's anti-tumor T cell response; inhibiting PD-L1 restores the function of these anti-tumor T cells which have become ineffective or suppressed. Therefore, the efficacy of PD-L1 inhibition relies on a preexisting immune response.

Nivolumab is currently approved as OPDIVO in the EU. Initial and subsequent approvals have resulted in indications for advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, classical Hodgkin's lymphoma (cHL), and hepatocellular carcinoma (HCC). In RCC, nivolumab monotherapy is approved after previous therapy (2L+ setting). In combination with ipilimumab, nivolumab is approved in the 1st line intermediate and poor risk RCC population in the EU.

Cabozantinib + nivolumab

Multitargeted TKIs and immune checkpoint inhibitors (ICIs) represent two systemic modalities that have contributed in the recent advancements in treatment of advanced RCC the past years. Nivolumab (2nd line) and cabozantinib (1st and 2nd line) have individually demonstrated clinical activity and significant improvement in OS in the treatment of patients with advanced RCC. Based on their different mechanism of action and potentially complementary effect, the MAH hypothesized that combining nivolumab and cabozantinib could produce additive clinical activity. The aim of the pivotal study CA2099ER was to evaluate the benefits and risks versus (previous) standard of care in the first-line RCC population, sunitinib.

The combination of nivolumab (anti-PD-1) and cabozantinib (anti-RTKs) has currently no approved indication in the EU.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Nivolumab plus cabozantinib combination therapy

In an ongoing phase 1 study (CTEP-9681; Apolo et al. J Clin Oncol. 2020), the combinations nivo+cabo and nivolumab and ipilimumab with cabozantinib (nivo+ipi+cabo) are being evaluated in patients with previously treated advanced genitourinary cancers, including urothelial carcinoma (UC) and RCC. CTEP-9681 was the first clinical study evaluating the nivo+cabo combination and its results informed the nivo+cabo dose selection for CA2099ER the pivotal study for the current application. The primary objectives of CTEP-9681 were to determine the dose limiting toxicity (DLT) and recommended phase 2

dose (RP2D) of nivo+cabo and nivo+ipi+cabo in patients with genitourinary tumours. Patients were treated with a doublet regimen of nivo+cabo (1 mg/kg or 3 mg/kg Q2W nivolumab in combination with 40 mg or 60 mg cabozantinib) which was found to be tolerable with no DLTs reported. However, a trend toward fewer treatment-related adverse events (AEs) and dose reductions for the lower 40 mg/day cabozantinib dose + nivolumab (1 mg/kg or 3 mg/kg) compared to the 60 mg/day cabozantinib dose + nivolumab (1 mg/kg or 3 mg/kg) was observed. The recommended phase 2 dose from CTEP-9681 was nivolumab 3 mg/kg Q2W + cabozantinib 40 mg QD and expansion with this dose resulted in anti-tumour responses in genitourinary cancers, including RCC. This combination dose regimen was thus selected for study CA2099ER.

2.1.4. General comments on compliance with GCP

The MAH confirms that the clinical trials included in this submission were performed in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH) and were conducted to meet the ethical requirement of European Directive 2001/20/EC. Furthermore, it is stated that the clinical trials carried out outside the European Union also meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. For a free combination involving two marketed products and for which there is adequate clinical documentation on their co-administration, combination toxicity studies would generally not be recommended unless there is significant toxicological concern. Thus, considering different targets for nivolumab (anti-PD1) and cabozantinib (RTK-inhibitor), and existing clinical safety data, combination toxicity data are not required.

2.2.1. Ecotoxicity/environmental risk assessment

The applied Type II variation concerns an extension of indication to include the use of Cabometyx in combination with nivolumab for the first-line treatment of advanced Renal Cell Carcinoma (RCC) in adults. In previous ERAs, a refined Fpen was applied based on the occurrence of advanced RCC and advanced hepatocellular carcinoma (HCC). This led to a calculated $PEC_{surfacewater}$ of 0.0069 µg/L. As this value is below the action limit of 0.01 µg/L, a Phase II environmental fate and effects analysis was not triggered. The applied Type II variation does not lead to altered refined Fpen or PEC, since the extended indication falls under advanced RCC.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of cabozantinib.

Cabozantinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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 ID	Study Design	Dosing Regimen	Objectives
Pivotal Study			
CA2099ER N = 651[a] NCT03141177	A Phase 3 open label, randomized trial of nivolumab combined with cabozantinib (doublet regimen) versus sunitinib in participants with previously untreated (1L) advanced or metastatic RCC	Nivolumab 240 mg IV Q2W + cabozantinib 40 mg PO once daily [QD] (Arm A) or sunitinib 50 mg PO QD (Arm C) for 4 weeks, followed by a 2-week break.	**Primary:** Compare PFS per BICR of nivolumab combined with cabozantinib (Arm A: doublet) with sunitinib (Arm C) in all randomized participants **Secondary:** • Compare OS of Arm A with Arm C in all randomized participants • Compare ORR per BICR in all randomized participants • To assess overall safety and tolerability in all treated participants
Studies Referenced to Support Contribution of Components for Efficacy and/or Contextualize Safety of Pivotal Study			
CABOSUN N = 157 NCT01835158	A Phase 2, open label, randomized trial of cabozantinib vs sunitinib in subjects with previously untreated advanced or metastatic ccRCC who had intermediate or poor risk disease per IMDC criteria.[b] (Alliance for Clinical trials in Oncology A031203)	Cabozantinib 60 mg PO QD or sunitinib 50 mg PO QD for 4 weeks, followed by a 2-week break.	**Primary:** Compare BICR-assessed PFS[c,d] of cabozantinib with that of sunitinib. **Secondary**[e]**:** OS, ORR, and safety
METEOR N = 658 NCT01865747	A Phase 3, randomized, controlled study of cabozantinib vs everolimus in subjects with metastatic RCC that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Cabozantinib 60 mg PO QD or everolimus 10 mg PO QD	**Primary:** PFS per IRRC **Secondary:** OS, ORR
CA209669 N =123 NCT03117309	Phase 2, single-arm study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced RCC	Nivolumab 240 mg IV Q2W x 6 doses (2 cycles) then nivolumab 360 mg IV Q3W x 4 doses (2 cycles) followed by nivolumab 480 mg IV Q4W).	**Primary:** Determine the PFS[f] rate at 1 year of nivolumab in patients with previously untreated ccRCC based on tumor PD-L1 expression. **Secondary:** • Determine the PFS rate at 1 year- by both RECIST and irRECIST of nivolumab in patients with treatment naïve ccRCC based on the PD1- Blockade Durable Response Predictive (PRP) biomarker

Study ID	Study Design	Dosing Regimen	Objectives
			model developed in the DFHCC Kidney Cancer SPORE • Determine ORR (CR/PR=ORR), the ORR based on PD-L1 expression and the PRP model, and DoR for nivolumab in patients with treatment naïve ccRCC • Determine the response rate of combined nivo and ipi therapy at the time of nivolumab failure (or lack of response at 1 year) • Determine the clinical activity (CR, PR and SD) and PFS at 1 year of nivolumab in patients with treatment naive nccRCC • Assess the toxicity of nivolumab monotherapy in patients with previously untreated cc or nccRCC
CA209025 N = 821 NCT01668784	A Phase 3, randomized, open-label study of nivolumab vs everolimus in subjects with advanced RCC with a clear-cell component who had received 1 or 2 prior anti angiogenic therapy regimens in the advanced or metastatic setting.	Nivolumab 3 mg/kg IV Q2W or everolimus 10 mg PO QD	**Primary:** Compare duration of OS of nivolumab vs everolimus **Secondary:** • Compare ORR, duration of PFS of nivolumab vs everolimus • Assess duration of OR, overall safety and tolerability, and the disease-related symptom progression rate of nivolumab vs everolimus • Evaluate whether PD-L1 is a predictive biomarker for OS

[a] Overall, 701 patients were randomized in study CA2099ER; 651 to Arm A and C and 50 to Arm B.
[b] CABOSUN was the pivotal study for EMA registration of cabozantinib in 1L RCC.
[c] PFS was defined as the time from randomization to the earlier of radiographic progression per RECIST v1.1 or death due to any cause.
[d] Protocol defined primary endpoint was Investigator-assessed PFS.
[e] CABOSUN study did not have prespecified hypotheses for secondary endpoints; study was not powered for OS.
[f] PFS is defined as the time from Day 1 of treatment until the criteria for disease progression is met as defined by RECIST v1.1 or death as a result of any cause (primarily focusing on evaluation of PD-L1 expression levels to predict outcome).
Abbreviations: IMDC= International Metastatic Renal Cell Carcinoma Database Consortium; IRRC= independent radiology review committee; IV= intravenous; ORR= objective response rate; OS= overall survival; PFS= progression-free survival; PO= orally; QxW= every x weeks; QD= once daily; RCC= renal cell carcinoma; VEGFR= vascular endothelial growth factor receptor

2.3.2. Pharmacokinetics

The initial clinical pharmacology package for cabozantinib (Cabometyx) in the initial MAA (EMEA/H/C/4163) was based on the clinical pharmacology package for cabozantinib in medullary thyroid cancer (MTC; Cometriq) (EMEA/H/C/2640), with three additional studies. The clinical PK of cabozantinib have previously been investigated in 11 clinical studies. Table 1. shows the key PK characteristics of cabozantinib established based on previous submissions.

In this report the pharmacokinetics of cabozantinib will be discussed with nivolumab as covariate while in procedure **EMEA/H/C/003985/II/0092** the pharmacokinetics of nivolumab are discussed with cabozantinib as covariate.

Table 1. PK characteristics for cabozantinib. Source: Cabometyx EPAR

Absorption	• Absolute bioavailability is not determined, but higher than 27% • Tmax 2-5 hours • High fat meal increases Cmax and AUC by 41% and 57%, respectively
Distribution	• Terminal phase volume of distribution (Vz) is 319 L for a typical subject • Highly bound to plasma proteins (>99%)

Elimination	• Primarily through the hepatobiliary and renal routes
	• Radioactive drug recovery (total recovery 81%):
	  ○ Urine: 27% (primarily as metabolites)
	  ○ Faeces 54% (to some extent as unchanged drug)
	• Apparent clearance (CL/F): 2.48 L/h
	• Elimination half life ~ 120 hours

Metabolism	• Primary metabolic pathway: CYP3A4 to several metabolites • Secondary metabolic pathways: CYP2C9 and UDP-glucuronosyl transferase-mediated glucuronidation
Dose proportionality	• Demonstrated from 20 to 140 mg for the tablet formulation • Accumulation ratios after 15 days of dosing: 4.6 and 3.9 for AUC and Cmax, respectively
Pharmacokinetic variability	• Between subjects: Moderate to high (CV 46% in CL/F) • Within subjects: Not studied
Sources of variability	• Mild renal impairment (but not moderate) increases exposure (Cmax 19%, AUCss 30%) • A range of covariates have been identified to partly explain PK variability of cabozantinib. See below (popPK analysis) for details.

Overview of new pharmacokinetics data

No new dedicated clinical pharmacology studies have been submitted in support the current application.

PK data for cabozantinib were sparsely collected from patients in pivotal study CA2099ER in RCC patients receiving cabozantinib coadministered with nivolumab. These PK data were used to evaluate whether nivolumab may affect the PK of cabozantinib. Further, the PK data were added to an input data set of a previously developed population pharmacokinetic (popPK) model for cabozantinib. No exposure-response analyses were performed.

Methods

- **Analytical methods**

Plasma concentration analyses for cabozantinib were performed by a previously validated liquid chromatography tandem-mass spectrometry (LC-MS/MS). The method was validated for a range of 0.500 to 1000 ng/mL based on the analysis of 50.0 µL of plasma by LC-MS-MS.

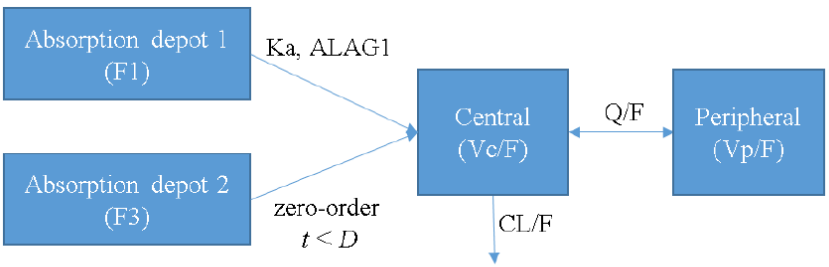
- **Pharmacokinetic data analysis**

The PK data from study CA2099ER was analysed with popPK methodology. No non-compartmental analyses were conducted.

- **Evaluation and Qualification of models**

Previous models

- Model #1 (EMEA/H/C/2640). A popPK model was previously developed for cabozantinib using data from 289 patients with solid tumours (including MTC) following QD oral administration of 140 mg cabozantinib capsules. A one-compartment model with first-order elimination, first-order absorption, and absorption lag time was used to describe the cabozantinib concentration-time profiles. Body mass index (BMI) and sex were identified as statistically significant predictors of cabozantinib CL/F, but they were not considered to be clinically relevant.
- Model #2 (EMEA/H/C/4163). A new popPK model was developed using data from 318 patients with RCC and 63 healthy volunteers. A two-compartment model with two parallel (fast and slow) lagged first-order absorption processes adequately described the pharmacokinetics of cabozantinib (Figure 1). The absorption rate constant for the faster absorption process was dose dependent. This feature was added to account for observed delay in the time to reach maximum concentration with increasing doses in Study XL184-020. The final covariate model included female gender (21% lower CL/F) and Asian race (27% lower CL/F than White subjects).
- Model #3 (EMEA/H/C/4163/II/5 and used in the current application). Model #2 was updated to include available PK data from 489 subjects with HCC, using the same structural model. Covariate effects evaluated in the development of Model #2 were reassessed in the updated dataset with a *full model* approach, thus including all potential covariates in the model regardless of statistical significance. The final model included capsule formulation on Ka and relative bioavailability, and age, sex, race, weight, cancer type and liver dysfunction on both CL/F and Vc/F. The MTC cancer type had the largest effect on cabozantinib PK parameters among the covariates examined (88% higher CL/F). The CL/F estimate was 24% lower in females. The most influential covariate effect on Vc/F included glioblastoma multiforme (~50% decrease in Vc/F). The parameter estimates for Model #3 are shown in Table 4. in this report.



Fraction in absorption depot 1: F1
Fraction in absorption depot 2: F3
F1 + F3 = 1

F1 = fraction of dose in the first depot; F3 = fraction of dose in the second depot; Ka = depot 1 absorption rate constant; ALAG1 = depot 1 absorption lag time; D = the duration of zero-order absorption; Vc/F = apparent volume of distribution (central compartment); Vp/F = apparent volume of distribution (peripheral compartment); Q/F = apparent flow between plasma (central) and peripheral compartments; CL/F = apparent plasma clearance

Figure 2. Structural popPK Model #2 and #3

Current application

For the current application, the MAH has submitted a popPK modelling and simulation report. The objectives of this analysis were:

1. Assess the predictive performance of a population PK model developed for cabozantinib in healthy subjects and patients with various cancer types (Model #3) when applied to cabozantinib administered in combination with nivolumab in patients with RCC from Study CA2099ER. The results are presented in the section Pharmacokinetics in target population.
2. Update the cabozantinib population PK model (Model #3) with pooled PK data from cabozantinib monotherapy studies and the combination therapy study with nivolumab, including appropriate covariates to account for differences between studies, if necessary. The results are presented in this section.
3. Generate individual predicted cabozantinib exposure measures for subsequent analyses (this was not performed).

Software and estimation method

PopPK predictions and updated modelling was performed using non-linear mixed effects modelling with NONMEM (v 7.3). Stochastic estimation methods including stochastic approximation expectation-maximization (SAEM) and importance sampling (IMP) were used for parameter estimation and objective function value, respectively.

Data

The popPK analysis included plasma cabozantinib concentration-time data from CA2099ER and 10 additional studies that supported the previous PopPK model . Plasma samples for cabozantinib concentration determination were collected in Study CA2099ER prior to the first dose in addition to a single sample at Weeks 5, 7, and 13 taken ~8 or more hours after prior evening dose.

A prospectively written modelling analysis plan was included in the submission.

The pooled analysis included 10,333 quantifiable PK samples obtained from 2331 subjects, including 823 PK samples from 308 subjects in Study CA2099ER. A small percentage (<1%) of post-dose samples had concentrations that were BLQ, and these samples were excluded from the analysis in accordance with the pre-specified analysis plan. No PK samples were excluded from Study CA2099ER (

Table 2).

The number of subjects, number of quantifiable PK samples and number of BLQ PK samples are listed by study in

Table 2.

Table 2. Number of subjects and PK samples included in the integrated analysis.

Study No.	Population	Number (%) of Subjects[a]	Number (%) of Quantifiable PK Samples Included	Number of Quantifiable PK Samples Excluded	Number (%) of post-dose BLQ Samples
XL184-001	Other[b]	40 (1.7)	417 (4)	190	0 (0)
XL184-010	Healthy	77 (3.3)	3055 (29.6)	0	0 (0)
XL184-020	Healthy	63 (2.7)	1176 (11.4)	1	15 (1.3)
XL184-201	GB	39 (1.7)	99 (1)	110	0 (0)
XL184-203	CRPC, HCC	321 (13.8)	1114 (10.8)	0	4 (0.4)
XL184-301	MTC	210 (9)	1107 (10.7)	267	0 (0)
XL184-306	CRPC	41 (1.8)	91 (0.9)	32	0 (0)
XL184-307	CRPC	498 (21.4)	764 (7.4)	380	12 (1.6)
XL184-308	RCC	282 (12.1)	474 (4.6)	129	4 (0.8)
XL184-309	HCC	452 (19.4)	1213 (11.7)	0	5 (0.4)
CA2099ER	RCC	308 (13.2)	823 (8)	0	20 (2.4)
Total		2331	10333	1109	60 (0.6)

PK = pharmacokinetic; BLQ = below the level of quantification; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma

[a] Includes subjects with at least one quantifiable concentration

[b] Unknown mixed cancer type in Study XL184-001

PK profiles of cabozantinib in Study CA2099ER are shown in Figure 2, with mean values stratified by the most recent dose prior to PK sample collection. All patients started at a dose regimen of 40 mg QD, except for 2 subjects who started at 20 mg QD, and 1 patient had a dose record of 60 mg. Doses were reduced from 40 mg QD to 20 mg QD for 134 of 320 (42%) subjects, and further from 20 mg QD to 20 mg every other day for 31 of 320 (10%) subjects.

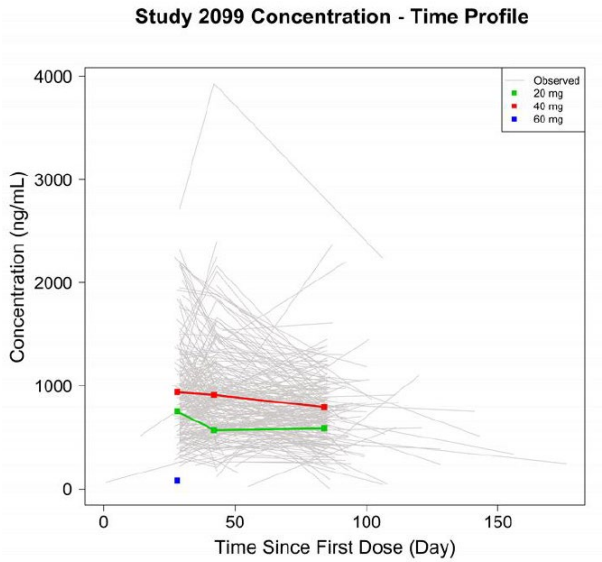


Figure 3. Individual and mean observed cabozantinib concentration-time profiles in study CA2099ER.

Note: Grey lines represent observed cabozantinib concentration-time profiles for individual subjects, and mean concentrations at nominal timepoints are shown by green, red and blue symbols

A total of 17 observations in the dataset were identified as potential outliers. To evaluate the influence of these outliers, the model was run with these data excluded and estimates of the key model parameters were compared to estimates from the base model with outliers included. Based on differences of <11% for all parameters, the outliers were not considered influential, in accordance with the pre-specified analysis plan.

Covariates

Covariate information for the 2331 subjects (2191 cancer patients and 140 healthy subjects) included in the integrated analysis was summarised by study (data not shown). The majority of subjects were male (83.3%) and 16.6% of subjects were female. The median age was 64 years (range, 18 to 90 years) and median body weight was 78.4 kg (range, 30.4 to 190.7 kg). Cancer patients were generally older (20 to 90 years) than healthy subjects (18 to 55 years). Distribution of subject race included 1809 (77.7%) White, 237 (10.1%) Asian, 54 (2.3%) Black and 72 (3%) other race, and 156 (6.7%) subjects had missing race information. Approximately 28% of the data were obtained with the capsule formulation and 72% with the tablet formulation. All subjects in CA2099ER received tablet formulation.

No subjects from CA2099ER had missing categorical covariates, and 307 of 308 (99.7%) had ALT, AST, bilirubin and creatinine clearance measurements available. As prespecified, continuous covariates were to be imputed as the median value from the study population.

Results

Updated popPK model

Initially, the parameters of the previous model were re-estimated after inclusion of the CA2099ER population (not shown) and without any model modifications. Next, a covariate effect of nivolumab co-administration was added to cabozantinib CL/F (Run 3, results not shown), and the estimated covariate coefficient (95% confidence interval [CI]) was 0.947 (0.871, 1.03), indicating a lack of statistical significance for the effect of nivolumab after the effect of RCC on cabozantinib CL/F was accounted for (RCC on CL/F estimate [95% CI]: 0.908 [0.811, 1.02]). The objective function increased by ~ 43 units with the addition of the nivolumab coadministration covariate.

A preliminary visual predictive check (VPC) indicated overprediction of variability from day 40 (not shown). In order to improve the predictive performance, the model was refined by removing the effect of RCC on Vc/F for patients also receiving nivolumab, while retaining it for patients receiving cabozantinib monotherapy (Run 27). According to the MAH, this resulted in a slight improvement in the prediction of 95th percentile cabozantinib concentrations in Study CA2099ER. Run 27 was therefore considered the updated final model although some degree of bias still remained in the predicted 95th percentile at the 12 week timepoint according to the VPC (Figure 3). The change from Model 2 to Model 27 altered the estimated impact of nivolumab on CL/F to 0.99 (95% CI 0.93-1.06). The list of steps taken in the popPK model revision are shown in Table 3..

Table 3. List of steps in popPK model update. Source: Table 4, XL184-RCC-1popPK.AP.001

No.	Model Description	OFV	dOFV
2	Relative to previous final model, Included Study CA2099ER data	-4553.313	
3	Relative to model 2, + nivolumab on CL/F	-4510.136	43.177
27	Relative to model 2, + nivolumab on CL/F and exclude Study CA2099ER from assessment of RCC cancer type effect on Vc/F	-4560.081	-6.768

PK = pharmacokinetic; OFV = objective function value; dOFV = difference in OFV; CL/F = apparent plasma clearance; Vc/F = apparent volume of distribution (central compartment)

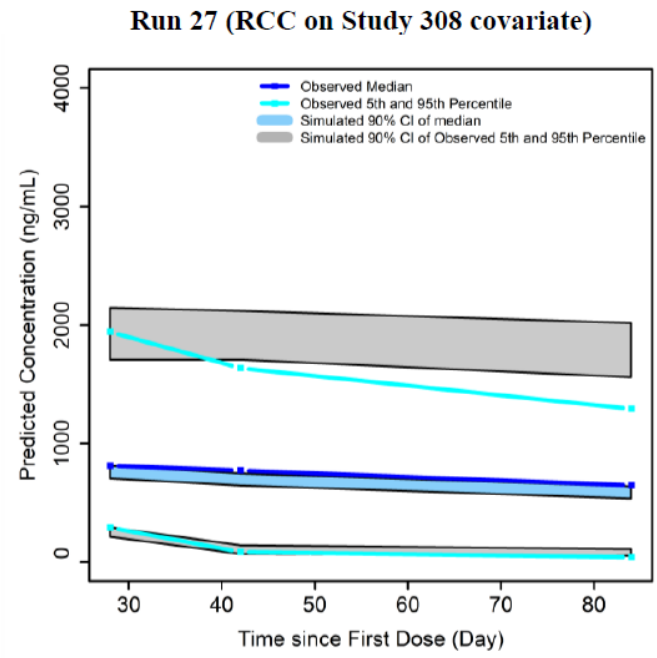


Figure 4. Model evaluation for study CA2099ER using VPC

Goodness-of-fit plots for the updated integrated PK model for cabozantinib (not shown here) suggested good agreement between observed data and model predictions.

Parameter estimates and corresponding 95% confidence intervals are shown in Table 4 for the previous model and the updated integrated model including RCC patients from Study CA2099ER. PK parameter estimates and covariate effects were similar to the previous integrated PK model; key parameter estimates (i.e., Ka, CL/F, and Vc/F) differed by ≤15%. For a White male subject, CL/F at steady state was estimated as 2.35 L/hr and Vc/F as 182 L.

Compared to healthy subjects, RCC patients (Studies XL184-308 and CA2099ER) showed no significant effect on CL/F based on the confidence interval of the fractional change estimate including the value of 1. The model estimated a non-significant effect of RCC (Study XL184-308) on Vc/F. The magnitude of the nivolumab coadministration effect on cabozantinib CL/F was <1% and the confidence interval of the estimate included the value of 1, indicating a lack of statistical significance.

Table 4. Comparison of parameter estimates for the previous popPK model (left) and the updated model including Study CA2099ER (right)

Parameter	Previous Integrated PopPK Model			Including Study CA2099ER		
	Estimate	SE	Transformed Estimate (90% CI)	Estimate	SE	Transformed Estimate (90% CI)
PK parameters						
Ka (hr-1)	0.213	0.229	1.24 (0.849, 1.8)	0.125	0.258	1.13 (0.741, 1.73)
Duration of zero-order absorption (hr)	0.908	0.0737	2.48 (2.2, 2.8)	0.884	0.0911	2.42 (2.08, 2.81)
CL/F (L/hr)	0.908	0.0539	2.48 (2.27, 2.71)	0.854	0.0488	2.35 (2.17, 2.55)
Vc/F (L)	5.36	0.1	212 (180, 250)	5.20	0.0863	182 (158, 210)
Q/F (L/hr)	3.4	0.0569	30.0 (27.3, 33)	3.41	0.0539	30.3 (27.8, 33.2)
Vp/F (L)	5.18	0.0413	177 (165, 189)	5.18	0.0372	177 (167, 188)
ALAG1 (hr)	-0.197	0.0196	0.821 (0.795, 0.848)	-0.205	0.0185	0.815 (0.790, 0.840)
Fraction of dose in first absorption depot F1[a]	1.62	0.146	0.83 (0.80, 0.87)	1.70	0.161	0.846 (0.808, 0.878)
Dose dependent Ka	0.734	0.245	0.734 (0.331, 1.14)	0.496	0.277	0.496 (0.0407, 0.951)
Covariates						
Capsule on Ka[b]	-0.911	0.358	0.402 (0.223, 0.725)	-0.465	0.489	0.628 (0.281, 1.40)
Capsule on overall relative oral availability[b]	-0.166	0.0127	0.847 (0.83, 0.865)	-0.182	0.0127	0.834 (0.816, 0.851)
Age on CL/F	-0.157	0.0647	-0.157 (-0.264, -0.0509)	-0.197	0.0584	-0.197 (-0.293, -0.101)
Female on CL/F[b]	-0.274	0.0382	0.76 (0.714, 0.81)	-0.268	0.0333	0.765 (0.724, 0.808)
Black on CL/F[b]	0.162	0.0743	1.18 (1.04, 1.33)	0.149	0.0723	1.16 (1.03, 1.31)
Asian on CL/F[b]	-0.0668	0.0446	0.935 (0.869, 1.01)	-0.106	0.0407	0.899 (0.841, 0.961)
Other Race on CL/F[b]	0.0279	0.0788	1.03 (0.903, 1.17)	-0.0271	0.0624	0.973 (0.878, 1.08)
Weight on CL/F	-0.0393	0.0652	-0.0393 (-0.147, 0.0679)	-0.0443	0.0586	-0.0443 (-0.141, 0.0521)
RCC[c] on CL/F[b]	-0.139	0.0625	0.87 (0.785, 0.965)	-0.0762	0.0579	0.927 (0.842, 1.02)
CRPC on CL/F[b]	-0.0115	0.0616	0.989 (0.893, 1.09)	0.0436	0.0563	1.04 (0.952, 1.15)
MTC on CL/F[b]	0.643	0.0626	1.9 (1.72, 2.11)	0.682	0.0597	1.98 (1.79, 2.18)
GB on CL/F[b]	0.178	0.11	1.2 (0.997, 1.43)	0.222	0.108	1.25 (1.05, 1.43)
Other malignancies on CL/F[b]	0.171	0.0995	1.19 (1.01, 1.4)	0.201	0.0970	1.22 (1.04, 1.43)
Age on Vc/F	0.0644	0.129	0.0644 (-0.148, 0.277)	-0.0692	0.118	-0.0692 (-0.263, 0.125)
Female on Vc/F[b]	0.0939	0.0737	1.1 (0.973, 1.24)	0.101	0.0730	1.11 (0.981, 1.25)
Black on Vc/F[b]	0.0441	0.183	1.05 (0.773, 1.41)	0.0723	0.189	1.07 (0.788, 1.47)
Asian on Vc/F[b]	-0.363	0.134	0.696 (0.558, 0.867)	-0.490	0.136	0.612 (0.490, 0.766)
Other Race on Vc/F[b]	-0.126	0.219	0.882 (0.615, 1.26)	-0.241	0.209	0.786 (0.558, 1.11)
Weight on Vc/F	1.19	0.158	1.19 (0.934, 1.46)	1.17	0.159	1.17 (0.911, 1.43)
RCC[d] on Vc/F[b]	-0.422	0.286	0.656 (0.41, 1.05)	-0.826	0.526	0.438 (0.184, 1.04)
CRPC on Vc/F[b]	-0.297	0.128	0.743 (0.602, 0.917)	-0.151	0.113	0.860 (0.715, 1.04)
MTC on Vc/F[b]	-0.0657	0.103	0.936 (0.79, 1.11)	0.0342	0.0956	1.03 (0.884, 1.21)
GB on Vc/F[b]	-0.735	0.221	0.479 (0.333, 0.689)	-0.784	0.253	0.457 (0.301, 0.692)
Other malignancies on Vc/F[b]	-0.272	0.152	0.762 (0.593, 0.979)	-0.123	0.143	0.884 (0.699, 1.12)
HCC on CL/F[b]	-0.13	0.0609	0.878 (0.794, 0.971)	-0.0641	0.0560	0.938 (0.855, 1.03)
HCC on Vc/F[b]	-0.166	0.121	0.847 (0.694, 1.03)	0.00518	0.105	1.01 (0.846, 1.19)
Nivolumab on CL/F[b]	-	-	-	-0.00807	0.0428	0.992 (0.925, 1.06)
Variance						
σ^2	0.127	0.00235	0.127 (0.123, 0.131)	0.131	0.00228	0.131 (0.127, 0.135)
ω^2 Ka	2.02	0.262	2.02 (1.59, 2.45)	2.52	0.667	2.52 (1.21, 3.83)
ω^2 CL/F	0.213	0.00903	0.213 (0.198, 0.227)	0.201	0.00802	0.201 (0.186, 0.217)
ω^2 CL/F:Vc/F	0.211	0.0205	0.211 (0.178, 0.245)	0.187	0.0188	0.187 (0.150, 0.224)
ω^2 Vc/F	0.443	0.0444	0.443 (0.370, 0.516)	0.432	0.0415	0.432 (0.350, 0.513)
ω^2 F1	2.55	0.335	2.55 (1.99, 3.1)	2.69	0.370	2.69 (1.97, 3.42)

Estimate = log of PK parameter; Transformed Estimate = PK parameter obtained by exponentiating the original estimate, if applicable; SE = standard error; CI = confidence interval; Ka = absorption rate constant from the 1st absorption depot; CL/F = apparent clearance; Vc/F = apparent distribution volume of the central compartment; Q/F = apparent flow parameter between compartments; Vp/F = apparent distribution volume of the peripheral compartment; ALAG1 = absorption lag time for the 1st absorption depot; RCC = renal cell carcinoma; CRPC = castration-resistant prostate cancer ; MTC = metastatic medullary thyroid cancer; GB = glioblastoma multiforme; HCC = hepatocellular carcinoma; σ^2 = variance of population predicted concentration; ω^2 = variance of population parameter

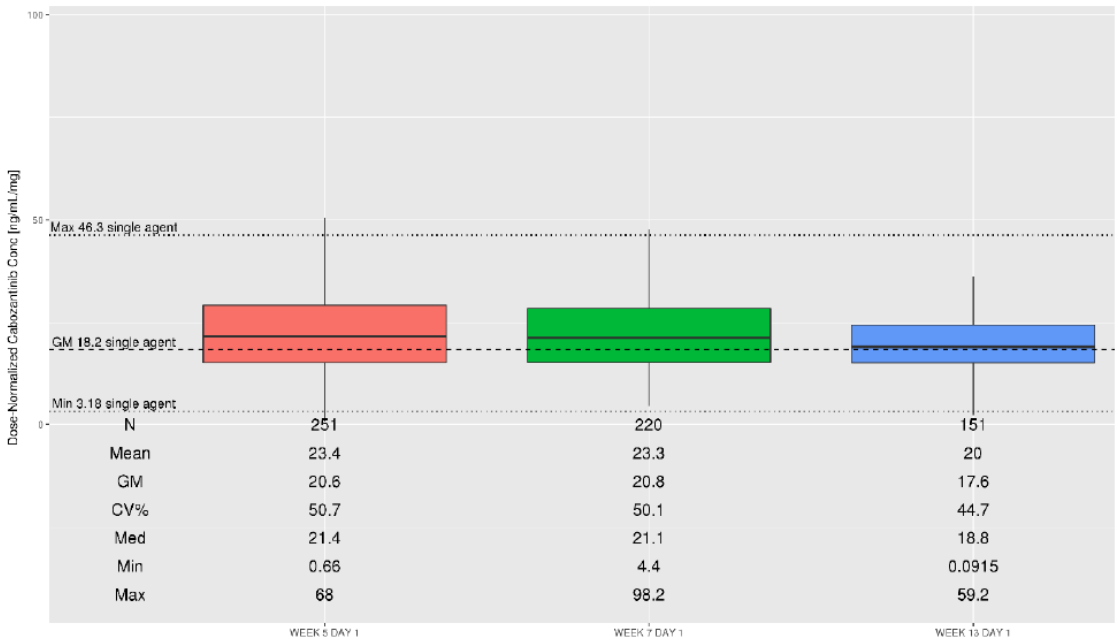
[a] Anti-logit transformation was used to obtain F1.
[b] For categorical covariates (e.g., capsule), transformed estimates correspond to fractional change from the reference level.
[c] For the model including Study CA2099ER, RCC for CL/F includes subjects in Studies XL184-308 and CA2099ER
[d] For the model including Study CA2099ER, RCC for Vc/F includes only subjects from Study XL184-308

Pharmacokinetics in target population

The target population in this application is patients receiving cabozantinib plus nivolumab as first line therapy for RCC. The PK of cabozantinib has previously been described in other populations (healthy volunteers, MTC, HCC, castration-resistant prostate cancer and glioblastoma multiforme), including subjects receiving cabozantinib monotherapy for RCC in second line following previous VEGFR-therapy. This section describes the comparison of cabozantinib PK with or without concomitant nivolumab therapy.

Exploratory analysis

Dose-normalised cabozantinib concentrations at Week 5, 7 and 13 from the subset of subjects receiving the cohort-assigned 40 mg/day dose combined with nivolumab (in 14 out of 15 prior doses; the "Steady-State Population") was compared with dose-normalised cabozantinib concentrations at Week 5 in the previous METEOR trial where PK from single agent cabozantinib at 60 mg QD was evaluated in RCC (see dashed and dotted lines indicating cabozantinib concentrations from METEOR (Figure 4)).



N	251	220	151
Mean	23.4	23.3	20
GM	20.6	20.8	17.6
CV%	50.7	50.1	44.7
Med	21.4	21.1	18.8
Min	0.66	4.4	0.0915
Max	68	98.2	59.2

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Notes: Dose-normalized geometric mean (GM), minimum (Min) and maximum (Max) cabozantinib concentrations from the METEOR clinical trial at Week 5 are indicated with dotted and dashed lines. Dose-normalized values were calculated from Table 4 in Exelixis Pharmacokinetics Study Report XL184-308.PK.001, Nov 2015 for Cabozantinib (XL184), NDA 208692.

Figure 5. Dose-normalised cabozantinib concentrations at week 5, week 7, and week 13 after overnight dosing in the steady state-population (40 mg/day) in CA2099ER compared to cabozantinib single agent (60 mg/day) from METEOR trial (2L RCC).

Model predictions

The ability of the previous PopPK model (Model #3, described above) to describe cabozantinib concentration-time data for CA2099ER RCC patients was assessed via an external prediction-corrected VPC. From the 500 simulated datasets conditioned upon the observed study designs, 90% confidence intervals were calculated for the median, 5th and 95th percentiles of the predicted plasma cabozantinib concentration-time profiles and overlaid with the same percentiles of the observed cabozantinib concentration data. Results are presented in Figure 5. Overall, the observed concentrations were generally contained within the confidence intervals, supporting that cabozantinib PK data in RCC patients receiving combination therapy with nivolumab are similar to previous cabozantinib monotherapy data.

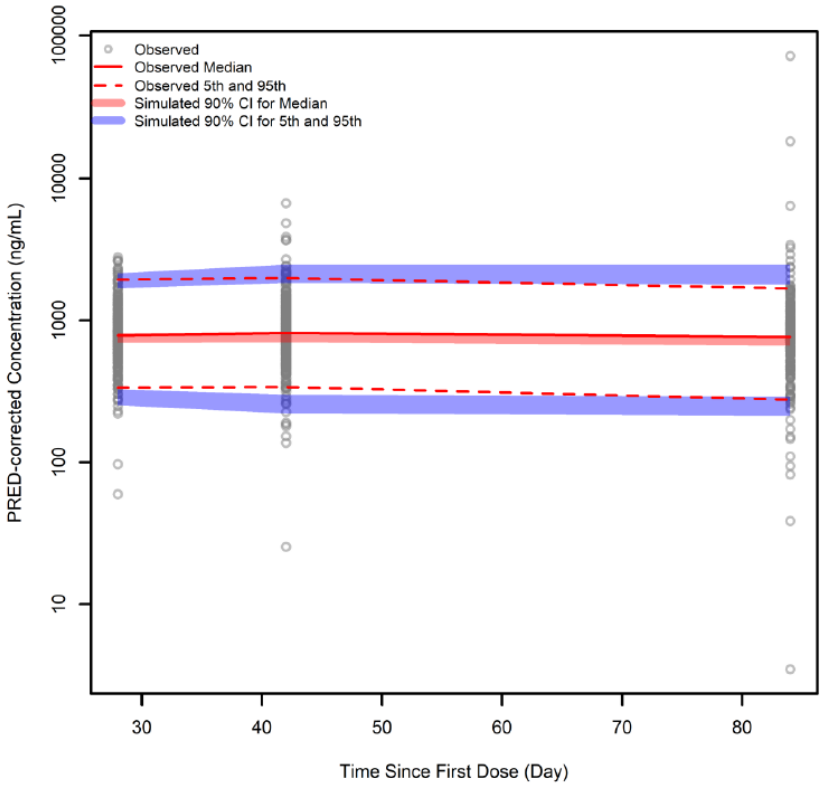


Figure 6. External prediction corrected VPC for patients in study CA2099ER

2.3.3. Pharmacodynamics

No new pharmacodynamic data has been submitted.

2.3.4. PK/PD modelling

No new PK/PD or exposure-response modelling for cabozantinib coadministered with nivolumab has been presented in this application. Results from the new dose finding study for the combination therapy (CTEP-9681) are presented in section 2.4.1.

2.3.5. Discussion on clinical pharmacology

Cabozantinib (Cabometyx), as monotherapy, is currently approved for the treatment of HCC after previous sorafenib treatment, and advanced RCC in (1) treatment-naïve adults with intermediate or poor risk and (2) adults following prior vascular endothelial growth factor (VEGF) targeted therapy. Characterisation of the clinical pharmacology of cabozantinib monotherapy has been provided in previous submissions.

The clinical pharmacology data supporting this new combination therapy of cabozantinib together with nivolumab for the indication first line treatment of advanced or metastatic renal cell carcinoma (RCC) consist of PK data from the pivotal CA2099ER study. In this study, plasma samples for cabozantinib concentration determination were sparsely collected (prior to the first dose, in addition to single samples at weeks 5, 7 and 13 at ~8 or more hours after prior evening dose). No clinical pharmacology data has

been presented from the dose finding trial, CTEP-9681. This was acceptable since the trial design, including only two cabozantinib dose-levels, in addition to the sparse number of subjects, of which only one patient had RCC, limits the information that could have been gathered from such data (see section 2.4.1 and 2.4.3).

The raw plasma concentration data for cabozantinib in study CA2099ER were also compared with dose-normalised raw plasma concentration data for XL184-308 (METEOR trial). At week 5, which is the only time-point with corresponding data from both trials, somewhat higher geometric mean exposure was observed in the CA2099ER trial (20.6 vs 18.2 ng/mL/mg). However, overall, the results do not indicate any relevant changes in cabozantinib PK when co-administered with nivolumab. Because nivolumab is a selective antibody, it is not expected to affect cabozantinib drug absorption or elimination pathways. The plasma concentration data for cabozantinib in the applied indication (1L RCC) in combination with nivolumab were compared with predictions using a previously developed popPK model based on cabozantinib monotherapy data. The observed concentrations of cabozantinib co-administered with nivolumab generally fell within the range of predicted concentrations from the cabozantinib monotherapy model. Together with the raw data comparison, this supports that nivolumab coadministration seemingly does not affect the PK of cabozantinib.

In addition to the analyses described above, the impact of nivolumab on cabozantinib CL/F was evaluated by including nivolumab treatment as a covariate in the popPK model after re-estimating the parameters based on the combined data set. The popPK model used as starting point for this analysis has been previously developed using a *full modelling approach* and includes 30 covariate parameters of which several have 90% CIs comprising the null value and/or with biologically implausible estimated values (e.g. negative effect of body weight on clearance). A concern regarding whether this model may be overparameterised has been raised in previous assessments. When the model was now updated by including nivolumab co-administration as an additional covariate, the OFV *increased* by 43 points. Such increases in OFV between nested models indicate that the model with the covariate added has not converged into its global minimum. This adds to the previous concern that the model may be overparameterised. Generally, the main limitation with the full modelling approach is sensitivity to correlating covariates and this was not addressed by the MAH. Thus, the results from these modelling exercises should be interpreted with caution and not used to derive conclusions. However, the model is not necessary to answer essential questions in this application. Nevertheless, for future applications in which the modelling results may have higher relevance, the MAH is encouraged to consider simplifying the model.

In the MAA for cabozantinib RCC monotherapy, relationships between increasing exposure and several adverse events have been demonstrated, while the optimal biologically active dose, i.e. the dose level where an increase in dose do not further improve clinical outcomes, is undetermined. Cabozantinib dose levels, safety and dose modifications are further discussed under section 2.4.1. Dose response study and 2.5 Clinical safety.

2.3.6. Conclusions on clinical pharmacology

The cabozantinib clinical pharmacology data are considered adequate for this application to extend the indication to include combination therapy with nivolumab.

The PK of cabozantinib do not seem to be affected by co-administration of nivolumab.

2.4. Clinical efficacy

The applied indication is based on results from CA2099ER, an open label, Phase 3, multicentre and 2-armed randomised comparative trial of nivolumab in combination with cabozantinib (nivo + cabo) versus sunitinib as first-line therapy for advanced or metastatic RCC.

Dose selection for nivolumab combined with cabozantinib is based on an investigator-sponsored Phase 1 trial (CTEP-9681), NCT02496208, supported by the National Cancer Institute NCI/NIH.

Selective data from the CABOSUN trial (Phase 2 study of cabozantinib monotherapy versus sunitinib in subjects with RCC, intermediate and poor IMDC risk groups) and the METEOR trial (Phase 3 comparative study of cabozantinib versus everolimus in 2L+ clear cell RCC, all IMDC risk groups) were included as supportive with the aim to justify the contribution of nivolumab to the efficacy of the cabozantinib + nivolumab regimen. In addition, the preliminary results from the ongoing CA209669 study (Phase 2 single-arm study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients with advanced RCC, all IMDC risk groups) were provided to justify the contribution of cabozantinib in the 1L treatment of RCC.

2.4.1. Dose response study

Dose selection for nivolumab combined with cabozantinib was based on an investigator-sponsored Phase 1 trial (CTEP-9681), NCT02496208, evaluating the combination of cabozantinib with nivolumab (doublet) or cabozantinib with nivolumab and ipilimumab (triplet) in subjects with previously treated advanced genitourinary (GU) cancers, including 1 subject with RCC. The data presented below are published in Apolo *et al* J Clin Oncol 2020, DOI: https://doi.org/10.1200/JCO.20.01652.

The primary objective of the trial was to determine dose-limiting toxicity (DLT) and the recommended phase 2 dose (RP2D) for the combination of cabozantinib and nivolumab and cabozantinib, nivolumab and ipilimumab. Data from subjects receiving triplet therapy are not presented.

Secondary objectives included objective response rate (ORR), progression-free survival (PFS), duration of response (DoR) and overall survival (OS).

Patients and methods

Eligible patients had a histologically confirmed diagnosis of metastatic GU tumours with new or progressive lesions on cross-sectional imaging, measurable by RECIST v1.1. Patients must have received one or more lines of standard therapy unless no standard treatment existed that had been shown to prolong survival.

The DLT period referred to the first 4 weeks during the dose-escalation phase for all dose levels. A DLT was defined as an adverse event (AE) potentially attributable to any of the study drugs or the combination that required permanent discontinuation of protocol therapy or was grade ≥ 3 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. If dose reduction or interruption of cabozantinib led to a patient taking ≤ 75% of the planned dose within the DLT observation period, the event was considered a DLT.

Part 1 had four escalating dose levels of continuous daily oral cabozantinib and intravenous (IV) nivolumab administrated every 2 weeks for a 28-day cycle (Table 5).

Dose reductions for cabozantinib (40 mg/day, 20 mg/day, then 20 mg every other day) and interruptions of study treatment were specified for management of AEs. After dose reduction, no dose escalation was permitted. No dose modification was allowed for nivolumab.

Table 5. Dose level cohorts in CTEP-9681.

Dose Level	Cabozantinib Dose	Nivolumab Dose[a]	Ipilimumab for 4 Doses	No. of Patients	Tumor Types
Part 1: cycle length, 28 days					
1	40 mg PO daily	1 mg/kg every 2 weeks	0	6	GCT (n = 3), urothelial carcinoma (n = 1), bladder squamous cell carcinoma (n = 1), urachal adenocarcinoma (n = 1)
2	40 mg PO daily	3 mg/kg every 2 weeks	0	6	Urothelial carcinoma (n = 2), bladder squamous cell carcinoma (n = 1), GCT (n = 1), urachal adenocarcinoma (n = 1), RCC (n = 1)
3	60 mg PO daily	1 mg/kg every 2 weeks	0	6	Prostate cancer (n = 4), urethral squamous cell carcinoma (n = 1), trophoblastic tumor (n = 1)
4	60 mg PO daily	3 mg/kg every 2 weeks	0	6	Urothelial carcinoma (n = 4), urachal adenocarcinoma (n = 2)

Source: Apolo et al, J Clin Oncol 2020

Results

For patients who received cabozantinib and nivolumab, the median duration of treatment was 6.36 months (IQR, 2.66-19.51 months), and the time to best response was 1.81 months (IQR, 1.71-3.68 months).

The most common treatment-related AEs (TRAEs) observed in patients who received cabozantinib 40 mg vs. 60 mg daily and the most common reasons for treatment discontinuation, dose hold, and dose reduction are reported in Table 6 and Table 7.

Table 6. Adverse events in CTEP-9681.

	Cabozantinib and Nivolumab (n = 24)			
	Cabozantinib 40 mg (n = 12)		Cabozantinib 60 mg (n = 12)	
Adverse Event	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Clinical events				
Fatigue	10 (83)	1 (8)	10 (83)	3 (25)
Diarrhea	8 (67)	0	10 (83)	1 (8)
Anorexia	7 (58)	0	9 (75)	0
Skin toxicity	9 (75)	0	5 (42)	0
Dysphonia	5 (42)	0	6 (50)	0
Nausea	4 (33)	0	7 (58)	1 (8)
Myalgia	5 (42)	0	5 (42)	0
Mucositis	2 (17)	0	8 (67)	0
Dry skin	3 (25)	0	3 (25)	0
Dry mouth	3 (25)	0	6 (50)	0
Dysgeusia	4 (33)	0	5 (42)	0
Weight loss	2 (17)	0	6 (50)	0
Vomiting	3 (25)	0	6 (50)	2 (17)
Palmar-plantar erythrodysesthesia	3 (25)	0	5 (42)	0
Abdominal pain	4 (33)	0	4 (33)	1 (8)
Sore throat	1 (8)	0	5 (42)	0
Hypertension	4 (33)	3 (25)	4 (33)	2 (17)
Headache	2 (17)	0	4 (33)	0
Cough	3 (25)	0	2 (17)	0
Blurred vision	2 (17)	0	2 (17)	0
Arthralgia	1 (8)	0	3 (25)	0
Edema limb	3 (25)	0	1 (8)	0
Constipation	2 (17)	0	2 (17)	0
Dehydration	1 (8)	0	2 (17)	2 (17)
Infection	1 (8)	0	1 (8)	1 (8)
Thromboembolic event	1 (8)	1 (8)	0	0
Fever	1 (8)	0	1 (8)	0
Immune-related events requiring high-dose corticosteroids[a]				
Any	2 (17)		1 (8)	
Aseptic meningitis	1 (8)	1 (8)	0	0
Hypogonadism	1 (8)	0	0	0
Pneumonitis	0	0	1 (8)	1 (8)
Hepatitis	0	0	0	0
Bullous pemphigoid	0	0	0	0
Colitis	0	0	0	0
Laboratory events				
Hematology				
Neutrophil count decrease	4 (33)	3 (25)	7 (58)	2 (17)
Lymphocyte count decrease	5 (42)	1 (8)	6 (50)	0
Anemia	1 (8)	0	7 (58)	2 (17)
Platelet count decrease	6 (50)	0	5 (42)	2 (17)
Electrolytes				
Hypocalcemia	6 (50)	0	6 (50)	0
Hyponatremia	6 (50)	1 (8)	5 (42)	2 (17)
Hypophosphatemia	5 (42)	2 (17)	6 (50)	3 (25)
Hypomagnesemia	4 (33)	0	5 (42)	1 (8)
Hypokalemia	4 (33)	0	1 (8)	0
Renal				
Proteinuria	5 (42)	1 (8)	3 (25)	1 (8)
Hepatic				
ALT elevation	8 (67)	0	8 (67)	0
AST elevation	8 (67)	1 (8)	8 (67)	1 (8)
Hypoalbuminemia	5 (42)	0	5 (42)	0
Pancreatic				
Amylase elevation	3 (25)	2 (17)	3 (25)	0
Lipase elevation	2 (17)	1 (8)	6 (50)	3 (25)
Endocrine				
Hyperthyroidism	1 (8)	0	3 (25)	1 (8)
Hypothyroidism	6 (50)	0	3 (25)	1 (8)

Source: Apolo et al, J Clin Oncol 2020

Table 7. Dose reductions in CTEP-9681.

Event	Cabozantinib and Nivolumab (n = 24)
All treatment-related adverse events, No. (%)	
All grade	24 (100)
Grade 3 or 4	18 (75)
Treatment-related adverse events leading to discontinuation (reason)	
No. (%)	4 (17)
Reason	Cabozantinib discontinued for grade 3 proteinuria and poor wound healing; nivolumab discontinued for grade 3 meningitis and grade 3 pneumonitis
Dose holding of nivolumab, No. (%)	14 (58)
Dose holding of cabozantinib	
Cabozantinib 40 mg, No./total No. (%)	10/12 (83)
Cabozantinib 60 mg, No./total No. (%)	10/12 (83)
Dose reduction of cabozantinib (at least once)	
Cabozantinib 40 mg, No./total No. (%)	4/12 (33)
One dose reduction, No.	4
Two dose reductions, No.	0
Cabozantinib 60 mg, No./total No. (%)	9/12 (75)
One dose reduction, No.	4
Two dose reductions, No.	5

Source: Apolo et al, J Clin Oncol 2020

In the dose escalation stage of the study, no dose limiting toxicities (DLTs) were reported during the defined observation period (28 days) for the doublet combination. However, a trend toward fewer treatment-related AEs and dose reductions for the lower 40 mg/day cabozantinib dose + nivolumab (33% cabozantinib dose reductions) compared with the 60 mg/day cabozantinib dose + nivolumab (75% cabozantinib dose reductions) were observed (Table 7). Based on the overall tolerability, RP2D for the doublet regimen was cabozantinib 40 mg QD administered orally with nivolumab 3 mg/kg Q2W administered IV.

2.4.2. Main study

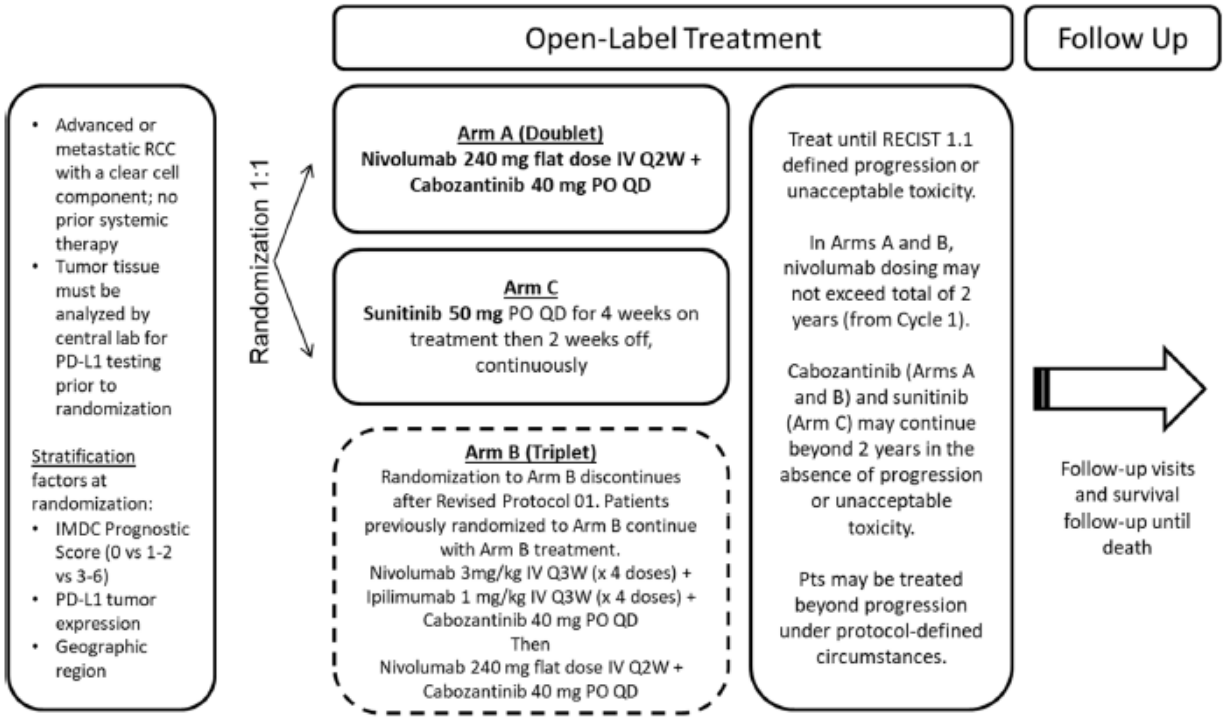
CA2099ER: A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma

Methods

A final clinical study report (CSR) was completed based on database lock date of 30-Mar-2020. These data form the basis of this application, and include efficacy and safety data with a median follow up of 18.1 months (minimum follow-up of 10.6 months).

CA2099ER consisted of 3 phases: screening, treatment and follow-up (see Figure 6 below). Subjects were assessed for response (Response Evaluation Criteria in Solid Tumours [RECIST] v1.1) by computed tomography or magnetic resonance imaging beginning 12 weeks (± 7 days) from randomisation and

continuing every 6 weeks (± 7 days) for the first 60 weeks, followed by every 12 weeks until progression or treatment discontinuation or death.



Abbreviations: DMC= data monitoring committee; IMDC= International Metastatic Renal Cell Carcinoma Database
Consortium; IV= intravenous; PD-L1= programmed death-ligand 1; PO= orally by mouth; Pts= patients/participants;
Q2W= every 2 weeks; Q3W= every 3 weeks; QD= once daily; RCC= renal cell carcinoma; RECIST= Response Evaluation Criteria in Solid Tumors.

Figure 7. Study CA2099ER Study design

Enrolment to Arm B (nivolumab + ipilimumab + cabozantinib) was stopped after the implementation of CA2099ER Revised Protocol Version 1, see below under **Conduct of the study** - Protocol amendments.

Study participants

Key inclusion criteria:

- Histological confirmation of RCC with a clear-cell component, including participants who may also have sarcomatoid features
- Advanced (not amendable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC
- No prior systemic therapy for RCC with the following exception:

One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

- Karnofsky Performance Status (KPS) ≥ 70%
- Measurable disease as per RECIST v1.1 per investigator
- Participants with favorable, intermediate and poor risk categories will be eligible for the study, following prognostic factors as per International Metastatic RCC Database Consortium (IMDC)

Key exclusion criteria:

- Any active CNS metastases. Participants with treated, stable CNS metastases for at least 1 month are eligible
- Any active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll
- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
- Any tumour invading the superior vena cava (SVC) or other major blood vessels
- History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, bowel obstruction, or gastric outlet obstruction within the past 6 months prior to randomisation
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of cabozantinib or sunitinib (e.g., malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection)
- Serious, non-healing wound or ulcer within 30 days prior to randomisation
- Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 3 months prior to randomisation
- Uncontrolled adrenal insufficiency
- History of cerebrovascular accident (CVA) including transient ischemic attack within the past 6 months prior to randomisation
- History of deep vein thrombosis (DVT) or pulmonary embolism (PE) within past 6 months prior to randomisation unless stable, asymptomatic, and treated with low molecular weight heparin (LMWH) for at least 6 weeks prior to randomisation
- Any unstable cardiac arrhythmia within 6 months prior to randomisation
- Prolongation of QTc > 450 msec for males and > 470 msec for females
- Poorly controlled hypertension (defined as systolic blood pressure [SBP] of > 150 mmHg or diastolic blood pressure [DBP] of > 90 mmHg), despite antihypertensive therapy
- History of any of cardiovascular condition within 6 months of randomisation
- Prior treatment with VEGF, MET, AXL, KIT, or RET targeted therapy

- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Concomitant strong CYP3A4 inducers or inhibitors within 14 days prior to randomisation
- Concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, thrombin or Factor Xa inhibitors. Aspirin (up to 325 mg/day) and prophylactic and therapeutic low molecular weight heparin (LMWH) are permitted
- Major surgery (e.g., nephrectomy) less than 6 weeks prior to randomisation
- Ejection fraction ≤ 50% on screening echocardiogram or MUGA (multigated acquisition scan)
- Abnormal laboratory test findings (hematology, liver included INR and kidney)

Treatments

The study treatments are outlined in Table 8.

Table 8. Treatments and timing of dose

Arm	Study Treatment	Dosage level(s) and Formulation	Frequency of Administration	Route of Administration
A (Doublet)	Nivolumab	240 mg IV	Q2W	IV
	Cabozantinib	40 mg (20 mg tablets)	QD	PO
B (Triplet) See Note	Nivolumab	3 mg/kg IV for 4 doses then 240 mg IV	Q3W for 4 doses then Q2W	IV
	Ipilimumab	1 mg/kg IV for 4 doses	Q3W for 4 doses	IV
	Cabozantinib	40 mg (20 mg tablets)	QD	PO
C	Sunitinib	50 mg (12.5 mg capsules)	A 6-week cycle, consisting of QD regimen for 4 weeks followed by no treatment for 2 weeks.	PO

Abbreviations: IV=intravenous; PO= by mouth; QD= once daily; QXW= every X weeks.
Note: Implementation of CA2099ER Global Revised Protocol 01 stopped further randomization into Arm B. Participants previously randomized to Arm B continued with Arm B treatment and continued with Arm B clinically planned events, per protocol.

Participants began study treatment within 3 days (72 hours) of randomisation. For Arm A, participants received nivolumab at a dose of 240 mg as an approximately 30-minute infusion on Day 1 of each 2-week treatment cycle. Cabozantinib was taken daily by mouth on an empty stomach, preferably at bed time. For Arm C, sunitinib was taken orally without regard to meals. The study used the label-recommended dose and schedule for RCC (50 mg QD 4 weeks on, 2 weeks off).

In both study arms treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. Nivolumab was administered for a maximum of two years. For cabozantinib and sunitinib dosing may continue beyond two years in absence of progression and unacceptable toxicity.

Per protocol, no crossover was allowed.

Dose delays and dose reductions

Dose delays for management of AEs during nivolumab, cabozantinib, or sunitinib treatment were allowed. Dosing of nivolumab could be delayed without delay of cabozantinib dosing if toxicity was felt to be

related to only nivolumab, and vice versa. For dose delay, criteria for nivolumab, sunitinib and cabozantinib were defined in the protocol. As a general approach, all AEs related to the study drugs were to be managed with supportive care when possible at the earliest signs of toxicity.

No dose reductions were allowed for nivolumab. Dose reductions for AE management were allowed for cabozantinib and sunitinib.

Two levels of dose reduction were permitted for cabozantinib: 20 mg daily, and then to 20 mg every other day. After toxicity requiring a dose delay had improved and met the criteria to resume dosing, cabozantinib dose could be resumed at a reduced dosing level. Participants who were receiving cabozantinib 20 mg daily prior to the delay and require another dose delay were to resume cabozantinib at 20 mg every other day. If more than 2 dose reductions were necessary (i.e., reduction to less than 20 mg every other day), cabozantinib was to be permanently discontinued. For sunitinib, dose reductions occurred in 12.5 mg decrements (e.g. 37.5 mg, 25 mg). No more than 2 dose reductions were allowed. If more than 2 levels of dose reductions were necessary (i.e., reduction to less than 25 mg daily), the participant was to be permanently discontinued.

Treatment discontinuation

Study treatments continue until progressive disease (PD) as assessed by the investigator and confirmed by BICR, unacceptable adverse events (AEs) or intercurrent illness prevents further administration of treatment, death or withdrawal of consent. For Arm A, although there is overlap among the discontinuation criteria, if discontinuation criteria were met for one study drug but not the other, it might be acceptable to continue treatment with the study drug that was not felt to be related to the toxicity as specified. If the investigator considered the toxicity to be related to both study drugs or was unable to determine which of the study drug was the cause of the toxicity, then both study drugs in the treatment regimen were to be discontinued, and the recommendations for management of toxicity related to both study drugs were to be promptly initiated.

After discontinuation of study therapy participants were followed for at least 100 days after last dose of study treatment (Follow-up Visit 2). After the Follow-up Visit 2, all participants will be followed for overall survival status every 3 months (+/- 14 days) until death, withdrawal of consent, loss to follow-up, or end of study. Adverse events (AEs) were followed until the toxicities resolved, returned to baseline, or were deemed irreversible.

Objectives

Primary objective

- To compare progression-free survival (PFS) per BICR of nivolumab combined with cabozantinib (Arm A: doublet) with sunitinib (Arm C) in all randomised participants

Secondary objectives

- To compare overall survival (OS) of Arm A with Arm C in all randomised participants
- To compare the objective response rate (ORR) per BICR of Arm A with Arm C in all randomised participants
- To assess overall safety and tolerability in all treated participants

In addition, nivolumab + cabozantinib was compared to sunitinib for the following *Exploratory objectives:*

- To explore potential predictive biomarkers, PD-L1 and myeloid-derived suppressor cells (MDSC), of clinical response to nivolumab and cabozantinib combination

- To evaluate health-related quality of life (HRQoL)
- To characterize the immunogenicity of nivolumab
- To characterize the PK of nivolumab and cabozantinib and explore exposure response relationships, if applicable
- To assess PFS after next line of treatment (PFS-2) in each arm

Outcomes/endpoints

Primary endpoint

- Progression-free survival (PFS) – RECIST v1.1 by BICR in nivolumab combined with cabozantinib (Arm A) compared to sunitinib (Arm C)
    - The primary definition of PFS was defined as the time from randomisation to the first documented disease progression per RECIST v.1.1 based on BICR or death due to any cause, whichever occurs first. Patients were censored in case of:
        - no baseline tumour assessment,
        - no on study tumour assessment and no death,
        - subsequent anti-cancer therapy started
        - no progression and no death and no new anti-cancer therapy started.
    - The secondary definition of PFS was defined as the time between the date of randomisation and the date of first documented tumour progression, based on BICR assessments (per RECIST v1.1 criteria) or death due to any cause, whichever occurs first (without censoring for subsequent therapy). Patients were censored in case of:
        - no baseline tumour assessment,
        - no on study tumour assessment and no death,
        - no progression and no death.

Secondary endpoints

- Overall survival (OS) comparison between Arm A and Arm C
    - OS is defined as the time between the date of randomisation and the date of death due to any cause. A participant who has not died will be censored at the last known alive date.
- Objective response rate (ORR) per RECIST v1.1 by BICR comparison between arm A and Arm C
    - ORR is defined as the proportion of randomised participants who achieve a best response of complete response (CR) or partial response (PR) using the RECIST 1.1 criteria.
    - Best overall response (BOR) is defined as the best response designation recorded between the date of randomisation and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first.

Exploratory endpoints:

- Progression free survival 2 (PFS2)- RECIST v1.1 by BICR comparison between arm A and Arm C

- PFS-2 was defined as the time from randomisation to the date of investigator-defined documented second objective disease progression after second-line therapy or death due to any cause, whichever comes first. Clinical deterioration was not to be considered as progression. A subject who neither progresses nor dies was to be censored on the date of his/her last adequate tumor assessment or last follow-up for progression/subsequent therapy. A subject who does not have any post-baseline tumor assessments and who has not died was to be censored on the date at which he/she was randomised.

- Biomarkers: PD-L1 and myeloid-derived suppressor cell (MDSC) expression in tumour specimens and in blood samples, and their potential relationship to efficacy and safety endpoints
- Immunogenicity: incidence of anti-nivolumab-antibodies and their potential relationship with safety and safety endpoints
- Health-related quality of life (HRQoL): assessed by the NCCN functional assessment of cancer therapy-kidney symptom index (FKSI-19) and the EuroQoL Group's EQ-5D (3L version)

Sample size

Sample size calculations were based on primary endpoint PFS by BICR in Arm A and Arm C, and the secondary OS endpoint. The total number of randomised subjects were higher due to Arm B that was stopped when implementing CA2099ER Global Revised Protocol 01. Assuming a 25% screen failure rate, it was expected that approximately 850 subjects would need to be enrolled in order to randomize 638 subjects (319 per arm) in a 1:1 ratio.

The analysis of PFS in Arm A vs Arm B was to be conducted on all randomised subjects after approximately 9-10 months minimum follow-up, when approximately 350 events had occurred in Arm A and Arm C combined. With a two-sided Type I error of 0.05 this was calculated to provide 95% power to detect a HR of 0.68, corresponding to a 47% increase in median PFS assuming median PFS of 18.2 and 12.4 months for Arm A and Arm C, respectively.

If the formal analysis of PFS among all randomised subjects was statistically significant, OS in the same population was to be tested in a hierarchical testing procedure. It was calculated that approximately 254 events (i.e., deaths) in Arm A and Arm C would provide at least 80% power to detect a HR of 0.70, assuming median OS of 47.1 and 33 months for Arm A and Arm C respectively, and an overall type 1 error of 0.05 (two-sided). There were two formal interim analyses planned for OS, the first at time of final PFS analysis, expecting to observe 165 OS events (65% of final targeted OS events), and the second when approximately 211 events (83% of targeted final OS events). The stopping boundaries for these analyses were derived based on actual number of observed events at the time of analysis using O'Brien and Flemming α-spending function.

Table 9. O'Brien Flemming boundaries

O'Brien Flemming boundaries			
No. OS Events	Two-sided α	Upper boundary of HR resulting in statistical significance	Median OS improvement
165	0.011	0.673	16 month (33 vs 49 month)

211	0.025	0.734	12 month (33 vs 45 month)
254	0.041	0.774	9.6 month (33 vs 42.6 month)

Randomisation

Participants were randomised between Arm A (nivolumab + cabozantinib) and Arm C (sunitinib monotherapy) in a 1:1 ratio. Prior to randomisation subjects were stratified according to the following factors:

1) International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score (0 [favorable risk] vs 1-2 [intermediate risk] vs 3-6 [poor risk]).
2) Programmed death-ligand 1 (PD-L1) tumour expression (≥ 1% vs < 1% or indeterminate).
3) Geographic region (US/Canada/Western Europe/Northern Europe vs rest of the world)

The randomisation to IMDC favorable risk participants was capped at approximately 25% to represent the typical frequency of favorable risk subjects among mRCC. Tumour PD-L1 expression levels were determined by immunohistochemistry (IHC) testing by the central lab (classified as PD-L1 expression ≥1%, <1%, or indeterminate) prior to randomization

Blinding (masking)

The study was open-label.

Statistical methods

Hypothesis

The hypothesis for the study was that treatment with nivolumab combined with cabozantinib (doublet regimen) would demonstrate an improvement in PFS per BICR compared to sunitinib monotherapy in subjects with previously untreated mRCC.

Interim analyses / Multiplicity

An independent statistician external to BMS was to perform the interim analyses. For details of the planned hierarchical testing / interim analyses for OS, see sample size section. In addition to the formal planned interim analyses for OS, the Data Monitoring Committee (DMC) had access to periodic un-blinded interim reports of efficacy and safety to allow a risk/benefit assessment, as per the DMC charter.

Analysis populations

All analyses were to be carried out using the treatment arm as randomised (intent to treat), with the exception of dosing and safety, for which the treatment arm as received were to be used. Analysis populations, for Arm A and Arm C, were as defined in Table 10 below.

Table 10. Analysis populations (Arm A and Arm C)

Population	Description
All Enrolled Subjects	All subjects who sign informed consent and were registered into the IRT.
All Randomized Subjects	All subjects who were randomized will be used for analyses of demography, protocol deviations, baseline characteristics, primary efficacy analysis, secondary efficacy analyses, and outcome research analysis which will be performed for this population.
All Treated Subjects	All subjects who received at least one dose of any study medication. This is the primary population for exposure and safety analyses.
Intermediate/Poor Risk Subjects	All subjects who were randomized with baseline IMDC prognostic score ≥1 at the time of randomization (per IRT). This population will be used for subset analyses of demography, protocol deviations, baseline characteristics, primary efficacy analysis, and secondary efficacy analyses on intermediate/poor risk subjects.
All Intermediate/Poor Risk Treated Subjects	All intermediate/poor risk subjects who received any dose of study therapy. This population will be used for subset analyses of exposure and safety analyses on intermediate/poor risk subjects.
Pharmacokinetic Subjects	All subjects with available serum time-concentration data from randomized subjects dose with nivolumab and cabozantinib.
Immunogenicity Subjects	All subjects with available data from randomized subjects dose with nivolumab and cabozantinib.
PD-L1 Treated Subjects	All subjects with a PD-L1 assessment at baseline who received any dose of study therapy.

Statistical method of analysis

In general, time-to-event variables were analysed using the Kaplan-Meier method, with medians reported, with 95% CI using Brookmeyer and Crowley method using log-log transformation for constructing the confidence intervals, and rates at fixed time points with their associated 95% CIs based on Greenwood formula for variance derivation and on log-log transformation applied survivor function. Confidence intervals for binomial proportions were derived using the Clopper-Pearson method. The unweighted difference in ORRs between the two treatment arms and corresponding asymptotic 95% CI were estimated using a Newcombe method.

PFS per BICR was compared between the treatment groups via stratified log-rank test among all randomised subjects at a two-sided α = 0.05 level. The stratification factors were; IMDC prognostic risk score (0 vs 1-2 vs 3-6), region (US/Canada/W Europe/N Europe vs ROW)' and PD-L1 status (≥ 1% vs < 1% or indeterminate). The hazard ratio was calculated using a stratified Cox proportional hazard model with treatment as the sole covariate. These analyses were performed for the primary and secondary definitions of PFS, i.e. adjusting for subsequent anticancer therapy or not.

A multivariate Cox regression model was used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors, including the same stratification factors as in the randomisation (IMDC score [0 vs 1-2 vs 3-6], Region [US/Canada/W.Europe/N.Europe vs. ROW], Baseline PD-L1+ status based on a 1% cut off) and including as covariates; Age categorisation (<65 vs. ≥ 65), Gender (Male vs. Female), Race, Karnofsky performance status (100-90, <90), Prior Nephrectomy (Yes, No), LDH level (≤ 1.5 x ULN , > 1.5 x ULN), Number of organ with metastasis (1 vs. ≥2).

Additional sensitivity analyses included: an un-stratified log rank test, a weighted log-rank test G(rho=0, gamma=1) to test for late separation KM-curves, PFS censoring for two missed assessments, PFS by

investigator assessment (and analysis of concordance with BICR assessment), an un-stratified Cox proportional hazards model with stratification factors of randomisation as covariates, or with a treatment by time interaction term, and a test for qualitative interaction of treatment and strata. Since no delayed effect in in PFS KM-curves was noted, a planned sensitivity analysis using a stratified time-dependent Cox model with effects for treatment and period-by-treatment interaction, where period was defined as before after 6mth, was not carried out.

Overall survival was compared between the treatment groups at the interim and final analyses, for all randomised subjects, using a log-rank test stratified by the same factors as for PFS. An O'Brien and Fleming α-spending function was employed to determine the nominal significance levels for the interim and final analyses, based on actual observed number of events at the time of analysis (see sample size section). The stratified hazard ratio between the treatment groups was presented along with 100*(1- α)% CI (adjusted for interim). These analyses were also applied to intermediate/poor-risk subjects in Arm A and Arm C.

Subgroup analyses – time to event endpoints

For the time to event endpoints, PFS and OS, medians based on KM estimates (with two-sided 95% CIs), and a forest plot of the unstratified hazard ratios (with two-sided 95% CIs) were to be presented for relevant subgroups.

Objective Response Rate

The number and percentage of subjects in each category of BOR per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) was presented, by treatment group, for all randomised subjects. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson were presented, by treatment group. In addition, a stratified Cochran-Mantel-Haenzel test of superiority, was carried out. These analyses were also performed for Intermediate/poor-risk subjects only. A forest plot presenting un-weighted differences in ORR between treatment groups, with 95% CI by Newcombe method, was presented for the same subsets as for PFS and OS subsets (where N > 10).

Time to Tumour Response, Duration of Response (DoR) and PFS-2

The DoR for each treatment group was estimated using the Kaplan-Meier (KM) product limit method, displayed graphically, and results tabulated presenting number of events, number of subjects involved, medians, and 95% CIs for the medians in each treatment group based on a log-log transformation method. DoR was censored for ongoing follow-up, off-study (lost to follow-up, withdraw consent, never treated) or Received subsequent anticancer therapy. TTR, which does not involve censoring, was summarised by treatment group in all responders using descriptive statistics. PFS-2 was analysed similarly to PFS.

Clinical Outcomes Assessments

FKSI-19 and EQ-5D-3L was summarised descriptively by treatment groups for randomised subjects in Arm A and C who had an assessment at baseline and at least one post-baseline assessment. Questionnaire completion rate, mean score and mean change from baseline at each assessment time point was summarised using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles, minimum, maximum), for total scores and subscales, and mean change from baseline plotted (including 95% CI).

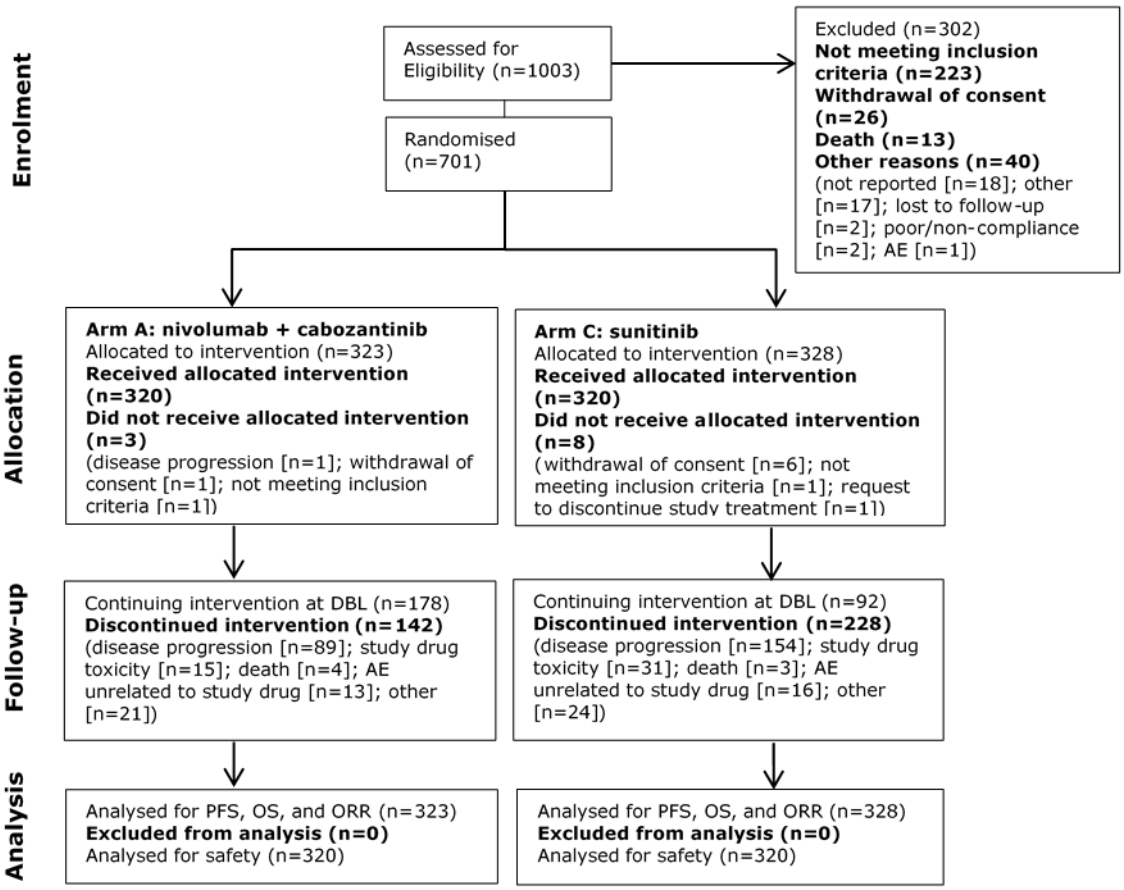
Results

Participant flow

The participant flow in study CA2099ER is shown in **Figure 7**.

Of the 640 treated patients, 270 patients (42.2%) were ongoing in the treatment period at the time of 30-Mar-2020 DBL: 178 (55.6%) with nivo+cabo and 92 (28.8%) with sunitinib. The percentage of patients who discontinued the treatment period were 44.4% and 71.3% in the nivo+cabo and sunitinib arms, respectively. The primary reason for not completing the treatment period was disease progression (243 patients, 38.0%): 89 (27.8%) with nivo+cabo and 154 (48.1%) with sunitinib. Of these, 15 (4.7%) and 31 (9.7%) patients in the nivo+cabo and sunitinib arms, respectively, discontinued treatment due to study drug toxicity.

Overall, 188 patients (29.4%) discontinued the study, and the most common reason for not continuing the study was death (146 patients [22.8%]: 62 patients [19.4%] with nivo+cabo and 84 patients [26.3%] with sunitinib). Study treatment was ongoing in 55.6% (N=178/320) of the subjects treated with cabo + nivo and in 28.8% (N=92/320) treated with sunitinib.



Note: 50 patients were randomized to Arm B, but enrolment to this arm was stopped after the implementation of CA2099ER Revised Protocol Version 1, see below at **Conduct of the study** - Protocol amendments.

Figure 8. Study CA2099ER Participant flow

Recruitment

This study was conducted at 125 sites in 18 countries (Argentina, Australia, Brazil, Chile, Czech Republic, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, Turkey, UK and US). The first patient first visit (FPFV) was on 22-Aug-2017. The first patient was randomized on 11-Sep-2017, and the last patient was randomized on 14-May-2019 and the clinical cut-off occurred on 12-Feb-2020 (LPLV).

Conduct of the study

Protocol amendments

The original study protocol for the pivotal study was dated 08-Mar-2017. As of 30-Mar-2020 DBL, two global revisions, three site-specific amendments and two global administrative letters were issued. The key changes are summarised as follow:

Protocol version 01 (18-Dec-2017):

1. stop enrolment into Arm B (nivolumab, ipilimumab and cabozantinib triplet)

2. include favourable risk participants (capped at 25%) in the study

3. add a Data Monitoring Committee review after 30 participants were treated for 6 weeks

Protocol version 02 (03-May-2019):

1. adjust the timing of the PFS and OS interim analyses with modified hypothesized OS hazard ratio (HR). The number of randomised participants increased from 290 to 319 per arm.

2. The interim analysis for ORR was removed, resulting in revised overall alpha for PFS and OS endpoints.

3. No change in eligibility or study procedure

4. Clinical data for nivolumab + ipilimumab in RCC have been updated

Protocol deviations

Significant protocol deviations were defined as related to inclusion and exclusion criteria, study conduct, and study management that differed significantly from the protocol, including GCP non-compliance. The total number of subjects with significant protocol deviations was 149/323 (46.2%) in Arm A and 126/328 (38.5%) in Arm C.

Deviations were reported across the following categories:

- Failure to obtain written consent prior to each subject's participation in the study (n=31 Arm A, n=30 Arm C)
- Failure to report all SAEs in accordance with the time period required by GCP, the protocol and applicable regulations (n=17 Arm A, n=20 Arm C)
- Implementation of protocol changes prior to review by IRB/IEC or failure to implement an IRB/IEC approved amendment (n=6 Arm A, n=5 Arm C)
- Inclusion/exclusion criteria (n=58 Arm A, n=50 Arm C)
- Incorrect dosing or study treatment assignment (n=14 Arm A, n=8 Arm C)
- Tumour assessment not per protocol (n=7 Arm A, n=4 Arm C)
- Lack of required lab tests prior to dosing (n=5 Arm A, n=2 Arm c)

- Discontinuation criteria (n=1 Arm A, n=1 Arm C)

The most common deviations in both arms were associated with inclusion/exclusion criteria (58 in Arm A vs. 50 in Arm C). The majority of cases in this category was due to "baseline labs collected not within 14 days of randomisation" (n=23 in Arm A vs. n=15 in Arm C) and "baseline tumour assessments not performed within 28 days prior to randomisation" (n=12 in Arm A vs. n=14 in Arm C).

Totally 61 protocol deviations (n=31 in Arm A vs. n=30 in Arm C) in the "failure to obtain written consent prior to each subject's participation in the study" category were registered. All randomised subjects signed an initial consent. However, 2 subjects had screening activities performed prior to signing the consent and 3 subjects had "incorrect written consent process". The remaining deviations were related to delays in re-consenting of updated written consent.

Baseline data

Baseline demographics and disease characteristics of all randomised subjects are presented in the table below.

Table 11. Subjects characteristics (ITT population)

	Nivo+Cabo N = 323	Sunitinib N = 328	Total N = 651
Age (years)			
Median (range)	62.0 (29-90)	61.0 (28-86)	61.0 (28-90)
< 65, n (%)	191 (59.1)	210 (64.0)	401 (61.6)
≥ 65 and < 75, n, (%)	103 (31.9)	85 (25.9)	188 (28.9)
≥ 75, n (%)	29 (9.0)	33 (10.1)	62 (9.5)
≥ 65, n (%)	132 (40.9)	118 (36.0)	250 (38.4)
Male, n, (%)	249 (77.1)	232 (70.7)	481 (73.9)
Race, n (%)			
White	267 (82.7)	266 (81.1)	533 (81.9)
Black or African American	1 (0.3)	4 (1.2)	5 (0.8)
Asian	26 (8.0)	25 (7.6)	51 (7.8)
American Indian or Alaska Native	3 (0.9)	2 (0.6)	5 (0.8)
Other	26 (8.0)	30 (9.1)	56 (8.6)
Not reported	0	1 (0.3)	1 (0.2)

	Nivo+Cabo N = 323	Sunitinib N = 328	Total N = 651
Region (IRT), n (%)			
US/Canada/W.Europe/N.Europe	158 (48.9)	161 (49.1)	319 (49.0)
ROW	165 (51.1)	167 (50.9)	332 (51.0)
Karnofsky Performance Status, n (%)			
70	14 (4.3)	18 (5.5)	32 (4.9)
80	52 (16.1)	67 (20.4)	119 (18.3)
90	110 (34.1)	112 (34.1)	222 (34.1)
100	147 (45.5)	129 (39.3)	276 (42.4)
Not reported	0	2 (0.6)	2 (0.3)
Baseline IMDC Prognostic Score (CRF), n (%)			
Favorable risk (0)	74 (22.9)	73 (22.3)	147 (22.6)
Intermediate risk (1-2)	189 (58.5)	186 (56.7)	375 (57.6)
Poor risk (3-6)	60 (18.6)	68 (20.7)	128 (19.7)
Most Common Sites of Metastasis, n (%)			
Lung	238 (73.7)	249 (75.9)	487 (74.8)
Lymph node	130 (40.2)	131 (39.9)	261 (40.1)
Bone	78 (24.1)	72 (22.0)	150 (23.0)
Liver	73 (22.6)	53 (16.2)	126 (19.4)
Adrenal gland	36 (11.1)	36 (11.0)	72 (11.1)
PD-L1+ Status Based On A 1% Cut Off, n (%)			
≥ 1%	81 (25.1)	81 (24.7)	162 (24.9)
< 1% or indeterminate	232 (71.8)	240 (73.2)	472 (72.5)
Prior Nephrectomy, n (%)			
Yes	222 (68.7)	233 (71.0)	455 (69.9)
No	101 (31.3)	95 (29.0)	196 (30.1)
Number Of Sites With At Least One Lesion [a,b] (%)			
1	63 (19.5)	69 (21.0)	132 (20.3)
2	94 (29.1)	93 (28.4)	187 (28.7)
3	84 (26.0)	87 (26.5)	171 (26.3)
4	47 (14.6)	51 (15.5)	98 (15.1)
≥ 5	34 (10.5)	25 (7.6)	59 (9.1)
Sarcomatoid Features, n (%)			
Yes	34 (10.5)	41 (12.5)	75 (11.5)
No	279 (86.4)	278 (84.8)	557 (85.6)
Not reported	10 (3.1)	9 (2.7)	19 (2.9)

Baseline disease characteristics are based on the tumor measurements as entered in the CRF by sites.

[a] 17 subjects (8 in Nivo+Cabo arm and 9 in Sunitinib arm) had 2 different types of bone sites counted but all 17 subjects had at least 3 total sites of disease counted.

[b] Includes both target and non-target lesions

Abbreviations: cabo = cabozantinib; CRF = case report form; IMDC = International Metastatic Database Consortium; nivo = nivolumab; PD-L1 = programmed death–ligands 1; RCC = Renal Cell Carcinoma.

Three (3) subjects (0.9%) in the nivo + cabo arm and 2 subjects (0.6%) in the sunitinib arm received one prior systemic anticancer treatment, all of which were in the adjuvant setting. One subject in the nivo

+ cabo arm received prior treatment with pazopanib, and this was considered a relevant protocol deviation (see Section "Protocol deviations" above).

Concomitant medication

Most subjects (98.1%) received concomitant medication(s) during the treatment period. The frequency of immune modulating concomitant medications was all over high: 50.6% (324 subjects) of the ITT population; 60.6% (194 subjects) in the nivo + cabo arm and 40.6% (130 subjects) in the sunitinib arm. Included in these immune modulating medications are corticosteroids for systemic use: 55.9% and 33.4%, respectively in the two treatment arms.

Reasons for using systemic corticosteroids in the ITT population were categorised and listed as premedication, for adverse events (AE) or other use. The most frequent reason for concomitant use of systemic corticosteroids was treatment of AE (52.5% and 29.1%, in Arm A and C, respectively). No subject used systemic corticosteroids as premedication. The most frequently reported AEs of any grade that required immune modulating concomitant medication were palmar-plantar erythrodysaesthesia syndrome in both arms, followed by rash and diarrhoea in Arm A (nivo + cabo) and mucosal inflammation and stomatitis in Arm C (sunitinib).

High dose corticosteroids were administered to subjects in CA2099ER in approximately 20% of nivo+cabo treated subjects with immune-mediated adverse events (IMAEs) or Selected AEs; approximately 10% received high dose corticosteroids for a duration of at least 2 weeks and approximately 4% received high dose for a duration of at least 30 days.

Subsequent anticancer therapy

Subsequent cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 61 subjects (18.9%) in the nivo+cabo arm compared to 108 subjects (32.9%) in the sunitinib arm. Subsequent systemic therapy was received by 36 subjects (11.1%) in the nivo+cabo arm and 91 subjects (27.7%) in the sunitinib arm. Subsequent anti-PD1/anti-PD-L1 therapy was received by 2.8% of subjects in the nivo+cabo arm compared with 20.4% for the sunitinib arm. A similar percentage of subjects in the nivo+cabo arm and sunitinib arm received subsequent antiangiogenic drugs (9.6% vs 10.7%).

Numbers analysed

Populations for analyses refer to participants in Arm A and Arm C, with exception of "enrolled" which also included subjects screened and randomised to Arm B. The efficacy analyses were based on the ITT population, which included participants in the treatment group to which they were randomly assigned, regardless of whether or not they received study treatment. The patient populations analysed is provided in the Table below.

Table 12. Analysis populations presented in the final clinical study report

Population	Nivo+cabo	Sunitinib	Total
Enrolled: All participants who signed informed consent and were registered into the IRT.	--	--	1003[#]
Randomized: All participants randomized to any treatment arm (used for demography, protocol deviations, baseline characteristics, efficacy, and outcome research).	323	328	651
Treated: All participants who received at least one dose of any study medication (used for drug exposure and safety).	320	320	640
Immunogenicity: All participants with available data from randomized participants dosed with nivolumab	263	--	263
Biomarkers: All participants with available biomarker data from randomized participants.	323	328	651

Abbreviations: IRT - Interactive Response Technologies.

[#] 50 of the enrolled subjects were randomized to Arm B. One screen failure subject was entered in the database by mistake.

Outcomes and estimation

In study CA2099ER, the last participant was randomised on 14-may-2019 and clinical cut-off occurred on 12-Feb-2020 (Last patient last visit, LPLV). The median duration of follow-up (date of randomisation to the last known date alive or death date) was approximately 15.7 months for the nivo + cabo arm and 14.59 months for the sunitinib arm. By database lock (DBL) on 30-Mar-2020, the minimum and median follow-up for OS was approximately 10.6 and 18.1 months, respectively.

Efficacy

The overall efficacy results include the primary and secondary endpoints in all randomised subjects (ITT population), and are summarised in the table below.

Table 13. Summary of efficacy in study CA2099ER (ITT population)

	Nivo+Cabo N = 323	Sunitinib N = 328
PFS per BICR (1° Definition)		
Events, n (%)	144 (44.6)	191 (58.2)
Median PFS (95% CI), mo. [a]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)
HR (95% CI)[b]	0.51 (0.41, 0.64); p < 0.0001[c,d]	
6-month PFS Rates (95% CI), % [a]	80.3 (75.4, 84.3)	60.1 (54.1, 65.5)
9-month PFS Rates (95% CI), % [a]	68.3 (62.6, 73.2)	47.8 (41.7, 53.6)
OS		
Events, n (%)	67 (20.7)	99 (30.2)
Median OS (95% CI), mo.[a]	N.A.	N.A. (22.60, N.A)
HR (98.89% CI)[b]	0.60 (0.40, 0.89); p = 0.0010[c,d,e]	
6-month OS Rates (95% CI), % [a]	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)
9-month OS Rates (95% CI), % [a]	89.9 (86.0, 92.8)	80.5 (75.7, 84.4)
ORR per BICR (CR + PR)		
N responders (%)	180 (55.7)	89 (27.1)
95% CI[f]	(50.1, 61.2)	(22.4, 32.3)
Difference of ORR (95% CI), % [g]	28.6 (21.7, 35.6); p < 0.0001[h]	
Estimate of Odds Ratio [i]	3.52 (2.51, 4.95)	
Confirmed BOR per BICR, n (%)		
CR	26 (8.0)	15 (4.6)
PR	154 (47.7)	74 (22.6)
SD	104 (32.2)	138 (42.1)
PD	18 (5.6)	45 (13.7)
UTD	21 (6.5)	55 (16.8)
NR	0	1 (0.3)
TTR per BICR		
Median (min, max), mo.	2.83 (1.0, 19.4)	4.17 (1.7, 12.3)
DoR per BICR		
N events/N responders (%)	50/180 (27.8)	34/89 (38.2)

	Nivo+Cabo N = 323	Sunitinib N = 328
Median (95% CI), mo.[a]	20.17 (17.31, N.A)	11.47 (8.31, 18.43)
Min, Max, mo.	1.4+, 22.2+	1.3+, 18.4
Proportion of subjects with DoR (95% CI) of at least 6 months [a]	0.84 (0.78, 0.89)	0.73 (0.62, 0.82)

Symbol + indicates a censored value.

The median follow-up (date of randomization to the last known date alive or death date) was 15.70 months for the nivo+cabo arm and 14.59 months for the sunitinib arm. As of the 30-Mar-2020 DBL, the minimum and median follow-up was approximately 10.6 and 18.1 months, respectively.

Abbreviations: BICR - blinded independent central review; BOR - best overall response, cabo - cabozantinib; CI - confidence interval; CR - complete response; DoR - duration of response; HR - hazard ratio; nivo - nivolumab; NR - not reported, ORR - objective response rate; OS - overall survival; PFS - progression-free survival; PR - partial response; SD - stable disease, TTR - time to objective response, UTD - unable to determine due to various reasons including deaths prior to disease assessment

Footnotes from previous page:

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. Hazard Ratio is Nivo+Cabo over Sunitinib.

[c] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (>= 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.

[d] 2-sided p values from stratified regular log-rank test

[e] Boundary for statistical significance p-value < 0.0111

[f] CI based on the Clopper and Pearson method.

[g] Strata adjusted difference in objective response rate (Nivolumab+Cabozantinib - Sunitinib) based on DerSimonian and Laird.

[h] 2-sided p value from stratified CMH test.

[i] Strata adjusted odds ratio (Nivolumab+Cabozantinib over Sunitinib) using Mantel-Haenszel method.

The primary endpoint of PFS per BICR and both secondary endpoints (OS and ORR per BICR) were statistically significant for Arm A (nivo + cabo) vs Arm C (sunitinib). The OS data are still immature as the medians were not reached in either arm, and the rate of events was 20.7% in the study arm and 30.2% in the control arm.

The summary of efficacy in the table above refers to the primary definition of PFS, which does not account for tumour progression post sequent therapies. Analysis of PFS per BICR using the secondary definition is presented below. The Kaplan Meier Plot of PFS below represents the **secondary definition of PFS (Figure 8).**

Primary endpoint

Progression free survival (PFS)

PFS per BICR and censoring for subsequent therapy (primary definition) compared with sunitinib:

In all randomised subjects, nivo+cabo demonstrated a statistically significant improvement in PFS per BICR

- HR = 0.51 (95% CI: 0.41, 0.64); stratified log-rank test p-value <0.0001.
- Median PFS was longer with nivo+cabo compared with sunitinib: 16.59 (95% CI: 12.45, 24.94) vs 8.31 (95% CI: 6.97, 9.69) months, respectively.
- PFS rates were higher with nivo+cabo compared with sunitinib: 68.3% vs 47.8% at 9 months, respectively.

Analysis of PFS per BICR using the secondary PFS definition, which includes tumour scans post subsequent therapies:

These analyses were consistent with the analysis for the primary PFS definition.

- HR = 0.54 (95% CI: 0.44, 0.67), p <0.0001).
- Median PFS was longer with nivo+cabo compared to sunitinib: 14.29 (95% CI: 12.29, 19.84) vs 8.31 (95% CI: 7.00, 9.69) months, respectively.

At 30-Mar-2020 DBL, 55.4% and 41.8% of randomised subjects in the nivo + cabo and sunitinib arms, respectively, were censored for PFS, with "still on treatment" to be the most common reason for censoring.

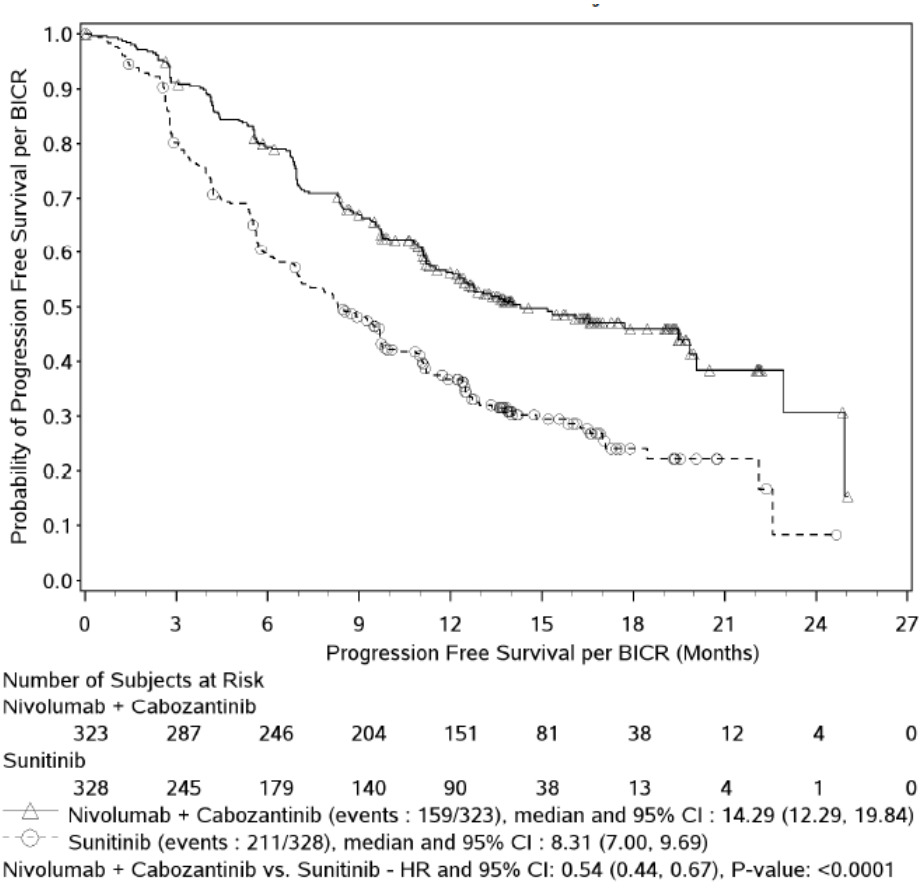


Figure 9. Kaplan-Meier Plot of PFS per BICR, secondary definition - all randomised subjects

Table 14. Reason for censoring, PFS per BICR, secondary definition - all randomised subjects

	Nivo+Cabo N = 323	Sun N = 328
NUMBER OF EVENTS (%)	159 (49.2)	211 (64.3)
TYPE OF EVENTS (%)		
PROGRESSION (1)	132 (40.9)	169 (51.5)
DEATH	27 (8.4)	42 (12.8)
NUMBER OF SUBJECTS CENSORED (%)	164 (50.8)	117 (35.7)
CENSORED ON RANDOMIZATION DATE	7 (2.2)	19 (5.8)
NO BASELINE TUMOR ASSESSMENT (2)	2 (0.6)	6 (1.8)
NEVER TREATED	0	1 (0.3)
OTHER	2 (0.6)	5 (1.5)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	5 (1.5)	13 (4.0)
NEVER TREATED	2 (0.6)	7 (2.1)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (3)	0	0
OTHER	3 (0.9)	6 (1.8)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	157 (48.6)	98 (29.9)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (3)	0	0
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	0
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0
STILL ON-TREATMENT	137 (42.4)	64 (19.5)
IN FOLLOW-UP	17 (5.3)	30 (9.1)
OFF STUDY	3 (0.9)	4 (1.2)
LOST TO FOLLOW-UP	0	0
SUBJECT WITHDREW CONSENT	3 (0.9)	4 (1.2)
OTHER	0	0

(1) RECIST 1.1 criteria.
(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.
(3) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy.
Program Source: /opt/zfs001/prd/lms237293/stats/interim/prog/tables/rt-ef-pfs-bicr-reasons.sas 14MAY2020:08:07:47

Concordance between BICR and investigator PFS assessments was high: 83.9% and 82.9% for nivo+cabo and sunitinib arms, respectively.

- Median investigator-assessed PFS by primary definition was 19.38 months (16.59, N.A.) and 9.20 months (7.06, 11.04) for nivo+cabo and sunitinib respectively, HR = 0.46 (95% CI: 0.36, 0.57) for nivo+cabo vs sunitinib, p < 0.0001.

Results for the sensitivity analysis of PFS (analysis using stratification factors as determined at baseline [CRF source]): HR= 0.47 (95% CI: 0.37, 0.59), p < 0.0001; for PFS secondary definition HR=0.51 (95% CI: 0.41, 0.63), p < 0.0001.

In a multivariate analysis, the treatment effect of nivo+cabo vs sunitinib when adjusted for the baseline factors of age (< 65, ≥ 65), gender (male, female), race, region, IMDC score 0, 1-2, 3-6), Karnofsky performance status (100-90, < 90), prior nephrectomy, LDH level (≤ 1.5* upper limit of normal (ULN) vs > 1.5*ULN), PD-L1 status (< 1%, ≥ 1%), and number of organ with metastasis (1, ≥ 2) was:

- HR = 0.51 (95% CI: 0.41, 0.64), p < 0.0001 (primary definition), for PFS secondary definition: HR=0.54 (95% CI: 0.43, 0.66), p < 0.0001.

Results for a sensitivity analysis of PFS using stratification factors as determined at baseline (CRF source) and a multivariate analysis (adjusting for several baseline factors) were consistent with the primary PFS analysis (both in regards to the primary and the secondary definition of PFS).

Overall, 301 progression events have been observed by DBL 30 March 2020.

For the assessment of PFS defined according to the primary definition, patients were censored due to receiving subsequent anticancer therapy: 7.1% of the patients were censored on date of last tumor assessment on-study due to start of new anti-cancer therapy in the cabo + nivo arm vs. 13.1% in the sunitinib arm (data not shown).

Updated PFS data according to DBL SEP-2020 are presented under *Ancillary analyses*.

Secondary endpoints

Overall Survival

As the formal analysis of PFS was statistically significant, the formal (first planned) IA of OS was tested, as per hierarchical testing procedure. As this IA of OS crossed the pre-specified boundary for statistical significance (nominal significance level $p < 0.0111$), it is considered the final analysis and no additional analysis will be performed.

At 30-Mar-2020 database lock, the event rates for OS were 20.7% and 30.2% of randomised subjects in the nivo+cabo and sunitinib arms, respectively. A total of 79.3% and 69.8%, respectively, were censored for OS (Table 15).

- The HR showed a statistically significant improvement in OS for nivo+cabo compared with sunitinib; HR = 0.60 (98.89% CI: 0.40, 0.89), p = 0.0010.
- Median OS was not reached in either treatment groups (Table 13).
- OS rates were slightly higher in the nivo+cabo arm compared with the sunitinib arm: 89.9% vs 80.5% at 9 months.
- Results for the sensitivity analyses, i.e., tests for qualitative interaction, tests for assumptions gave a p-value of 0.9181 and 0.2615, respectively.
- In a multivariate analysis, the treatment effect of nivo+cabo vs sunitinib when adjusted for the baseline factors of age (< 65, ≥ 65), gender (male, female), race, region, IMDC score (0, 1-2, 3-6), Karnofsky performance status (100-90, < 90), prior nephrectomy, LDH level (≤1.5*ULN vs > 1.5*ULN), PD-L1 status (< 1%, ≥ 1%), and number of organ with metastasis (1, ≥ 2), was: HR 0.60 (95% CI: 0.43, 0.82), p = 0.0015.

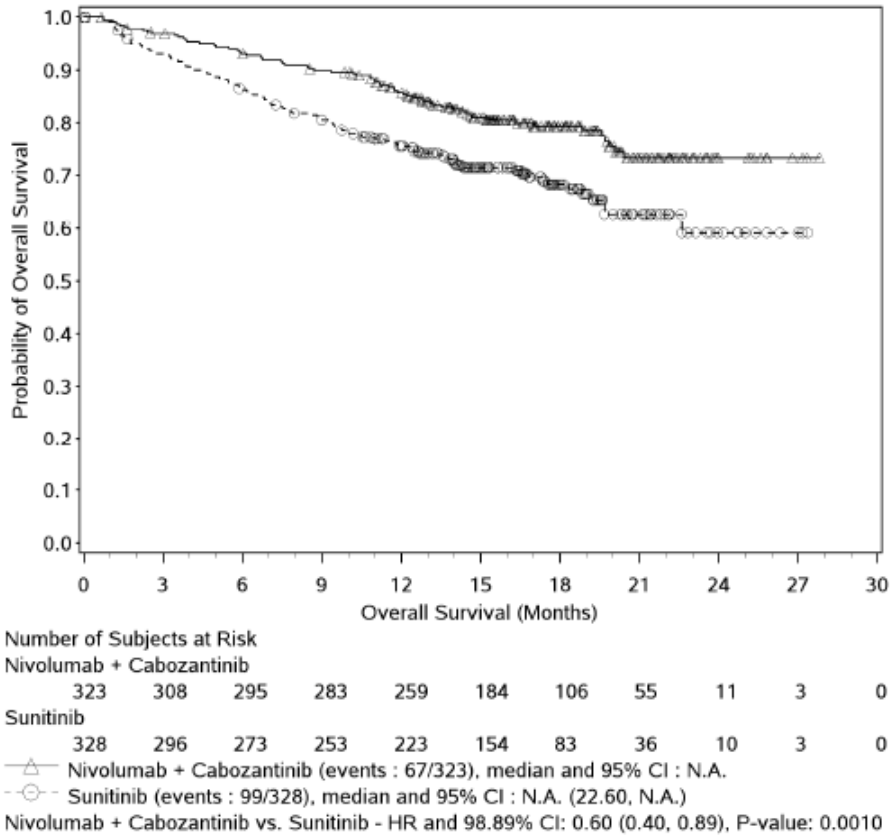


Figure 10. Kaplan-Meier plot of Overall Survival - all randomised subjects

Updated OS data (DBL SEP-2020) are presented in the section *Ancillary analyses.*

Table 15. Status of censored subjects, Overall Survival, all randomised subjects

	Number of Subjects (%)	
	Nivo+Cabo N = 323	Sunitinib N = 328
NUMBER OF DEATHS (%)	67 (20.7)	99 (30.2)
NUMBER OF SUBJECTS CENSORED (%)	256 (79.3)	229 (69.8)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON TREATMENT	178 (55.1)	92 (28.0)
NOT PROGRESSED	148 (45.8)	76 (23.2)
PROGRESSED (1)	30 (9.3)	16 (4.9)
IN FOLLOW-UP	64 (19.8)	118 (36.0)
OFF STUDY	14 (4.3)	19 (5.8)
SUBJECT WITHDREW CONSENT	9 (2.8)	14 (4.3)
LOST TO FOLLOW-UP	2 (0.6)	1 (0.3)
OTHER	3 (0.9)	4 (1.2)

Objective Response Rate

At 30-Mar-2020 database lock, as the formal interim analysis of OS was statistically significant, the formal analysis of ORR was tested, as per hierarchical testing procedure.

Table 16. Best Overall Response per BICR and per investigator - all randomised subjects

	Number of Subjects (%)	
	Nivo + Cabo N = 323	Sun N = 328
Per BICR		
CONFIRMED BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	26 (8.0)	15 (4.6)
PARTIAL RESPONSE (PR)	154 (47.7)	74 (22.6)
STABLE DISEASE (SD)	104 (32.2)	138 (42.1)
PROGRESSIVE DISEASE (PD)	18 (5.6)	45 (13.7)
UNABLE TO DETERMINE (UTD)	21 (6.5)	55 (16.8)
NOT REPORTED	0	1 (0.3)
OBJECTIVE RESPONSE RATE (1)	180/323 (55.7%)	89/328 (27.1%)
(95% CI)	(50.1, 61.2)	(22.4, 32.3)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	28.6%	
(95% CI)	(21.7, 35.6)	
ESTIMATE OF ODDS RATIO (3, 4)	3.52	
(95% CI)	(2.51, 4.95)	
P-VALUE (5)	<0.0001	
Per Investigator		
CONFIRMED BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	11 (3.4)	6 (1.8)
PARTIAL RESPONSE (PR)	181 (56.0)	99 (30.2)
STABLE DISEASE (SD)	97 (30.0)	116 (35.4)
PROGRESSIVE DISEASE (PD)	17 (5.3)	69 (21.0)
UNABLE TO DETERMINE (UTD)	17 (5.3)	38 (11.6)
NEVER TREATED	3 (0.9)	7 (2.1)
WRONG CANCER DIAGNOSIS	0	0
DEATH PRIOR TO DISEASE ASSESSMENT	10 (3.1)	20 (6.1)
EARLY DISCONTINUATION DUE TO TOXICITY	1 (0.3)	5 (1.5)
OTHER	2 (0.6)	4 (1.2)
NOT REPORTED	1 (0.3)	2 (0.6)
OBJECTIVE RESPONSE RATE (1)	192/323 (59.4%)	105/328 (32.0%)
(95% CI)	(53.9, 64.8)	(27.0, 37.4)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	28.2%	
(95% CI)	(21.1, 35.3)	
ESTIMATE OF ODDS RATIO (3, 4)	3.21	
(95% CI)	(2.31, 4.46)	
P-VALUE (5)	<0.0001	

Per RECIST 1.1, confirmation of response required.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivo+Cabo - Sunitinib) based on DerSimonian and Laird
(3) Stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (>= 1% versus < 1% or indeterminate), and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
(4) Strata adjusted odds ratio (Nivo+Cabo over Sunitinib) using Mantel-Haenszel method.
(5) Two-sided p-value from stratified CMH Test.

Time to response and duration of response

Median TTR per BICR was 2.83 months (min,max: 1.0, 19.4) for all confirmed responders treated with nivo+cabo and 4.17 months (min,max: 1.7, 12.3) for all confirmed responders treated with sunitinib at 30-Mar-2020 database lock. The median DoR was longer for all confirmed responders treated with nivo+cabo than with sunitinib: 20.17 (95% CI: 17.31, N.A.) vs 11.47 (95% CI: 8.31, 18.43) months (Table 13). 84% and 73% of responders in the nivo+cabo and sunitinib arms, respectively, had a DoR of at least 6 months.

The first post baseline tumor assessment was at 12 week per protocol.

Exploratory endpoints

Progression free survival-2 (PFS-2)

Median PFS-2 per investigator was not reached in either treatment arms. HR favoured the nivo+ cabo arm over the sunitinib arm: 0.52 (95% CI: 0.39, 0.70). PFS-2 results in the two treatment arms are presented in the figure below.

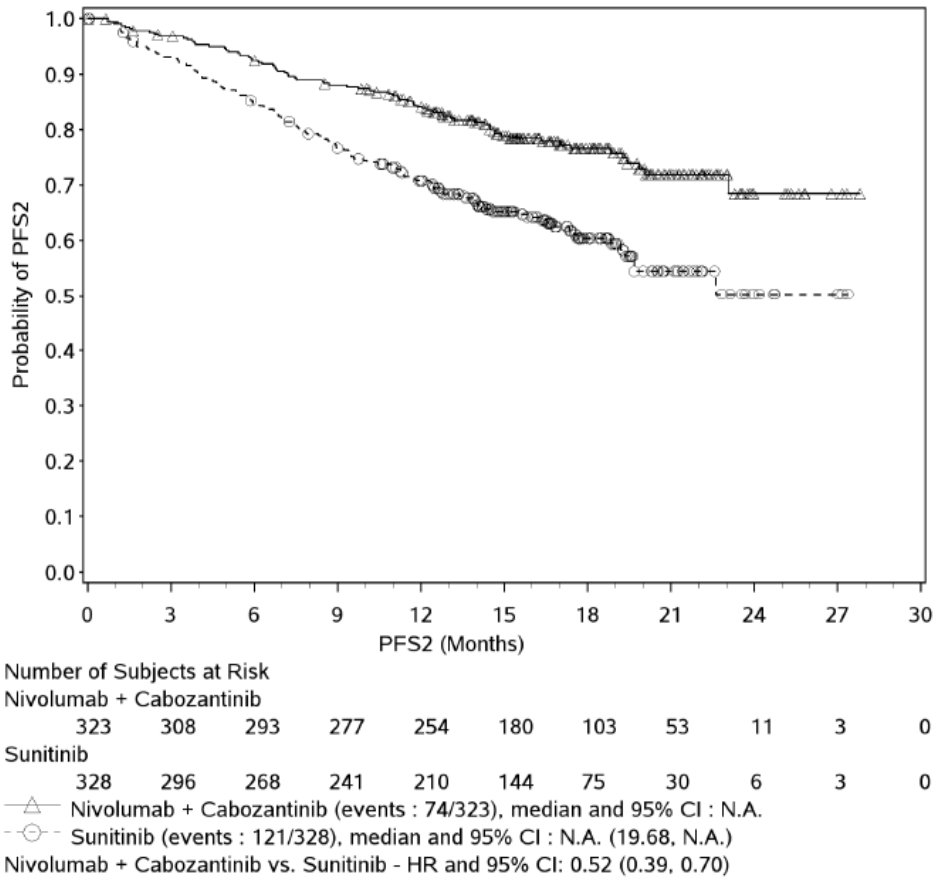


Figure 11. Kaplan-Meier Plot of PFS-2- all randomised subjects

Biomarker analysis

Efficacy by PD-L1

The efficacy benefit of nivo+cabo vs sunitinib was observed regardless of PD-L1 tumor cell expression status (< 1%, ≥ 1%) and across all efficacy endpoints (PFS, OS, ORR).

Efficacy by Myeloid-derived Suppressor Cells (MDSC)

The efficacy benefit of nivo+cabo vs sunitinib was observed regardless of MDSC status at baseline (tertiles with 33.33% and 66.67% cut off) and across all efficacy endpoints (PFS, OS, and ORR) for both monocytic and granulocytic MDSCs.

Patient-reported outcome (PRO) assessment

PROs were assessed over the time of the study using valid and reliable scales: the NCCN Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19) and a 3-level version of the EQ-5D. The FKSI-19 is a 19-item scale that measures tumour specific health-related quality of life (HRQoL) in kidney cancer patients. The EQ-5D-3L is a generic measure used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations.

Analysis of the FKSI-19 and EQ-5D-3L was restricted to randomised subjects in Arm A and Arm C who had an assessment at baseline and at least one post-baseline assessment. Both measures were completed on Day 1 of each treatment cycle (Q2W for nivo+cabo, Q6W for sunitinib) prior to any study related procedures.

Questionnaire completion rate (number of subjects who filled the questionnaire/number of available subjects), mean score and mean change from baseline (for both total and subscale scores) at each assessment time point were analysed.

For both the *FKSI-19* and *EQ-5D* higher scores are indicative of better quality of life. Positive changes in score reflect improvement in HRQoL, while negative changes reflect a decrease in HRQoL.

93.4% of subjects completed the FKSI-19 at baseline in the nivo+cabo arm while 97.2% of the sunitinib subjects had a baseline assessment. Completion rates were ≥ 80% in both treatment arms at all subsequent on-treatment assessments, through Week 105 for the nivo+cabo arm and Week 97 for the sunitinib arm.

94.1% of subjects completed the EQ-5D-3L at baseline in the nivo+cabo arm while 97.5% of the sunitinib subjects had a baseline assessment. Completion rates were ≥ 80% in both treatment arms at all subsequent on-treatment assessments, through Week 105 for nivo+cabo and Week 97 for sunitinib, with the exception of the nivo+cabo arm at Week 93 (76.6%).

Mean *FKSI-19 total scores* were 58.74 (SD: 10.57) in the nivo+cabo arm and 58.39 (SD: 9.92) in the sunitinib arm at baseline. Mean changes from baseline were generally stable for the nivo+cabo arm, whereas subjects in the sunitinib arm had a trend toward decreased scores. These changes are illustrated in the figure below.

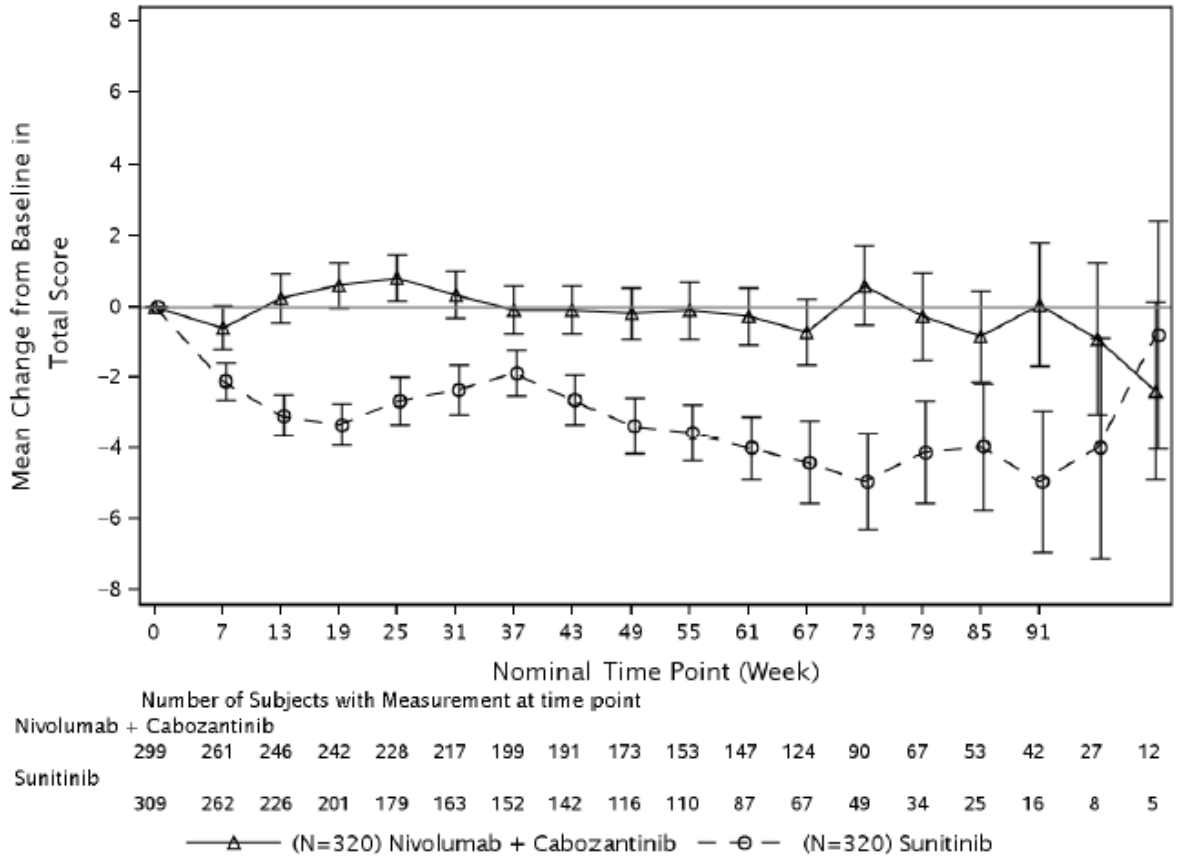


Figure 12. Mean changes in overall self-related health status FKSI-19 from baseline - all treated subjects

Mean baseline scores for the *EQ-5D VAS* were 74.23 (SD: 22.23) in the nivo+cabo arm and 75.68 (SD: 20.92) in the sunitinib arm. The mean EQ-5D VAS scores increased over time in the nivo+cabo arm, indicating better overall health status for subjects remaining on treatment. In the sunitinib arm, mean *EQ-5D VAS* scores varied with a decreased trend from Weeks 37-91. Results are summarised in the figure below.

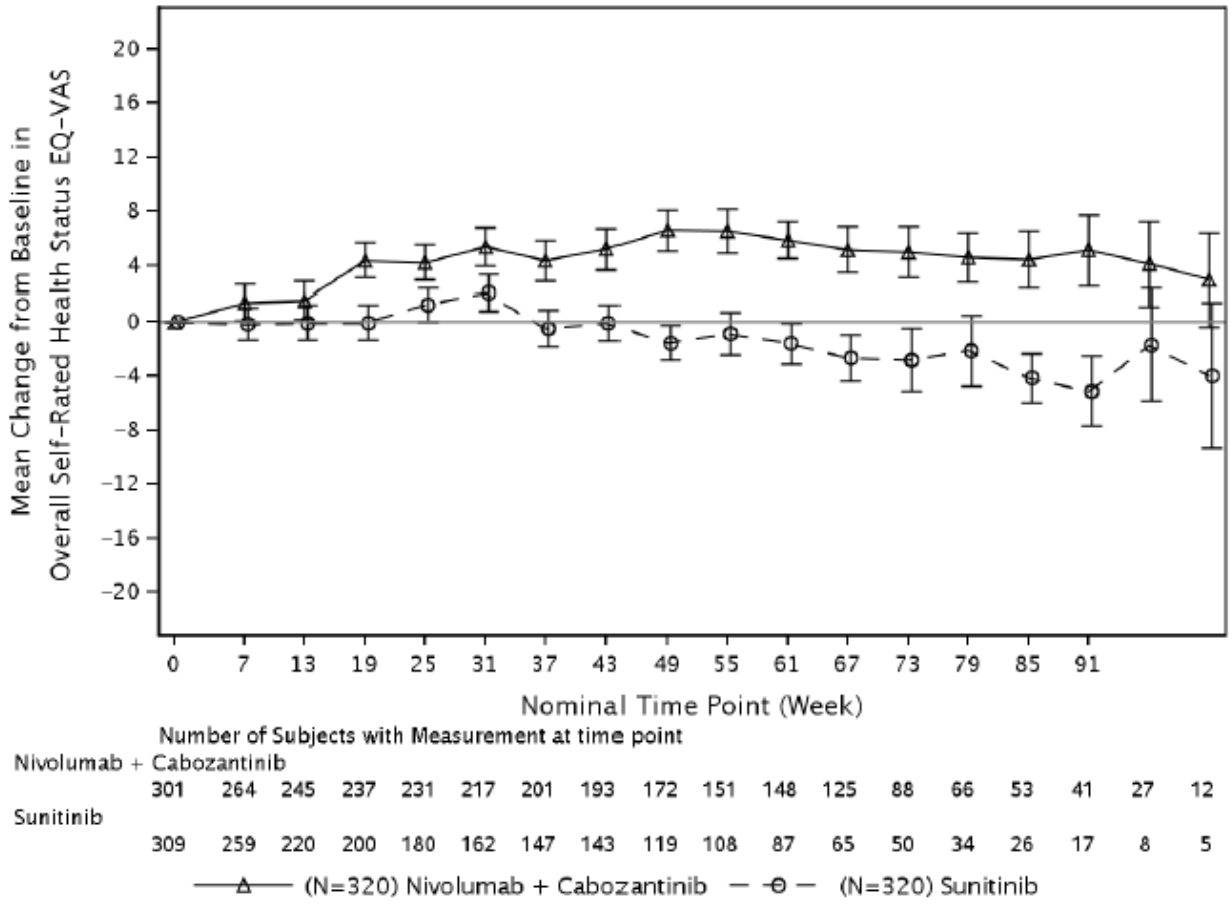


Figure 13. Mean changes in overall self-related health status EQ-VAS from baseline - all treated subjects

The mean *EQ-5D-3L utility index score* remained generally stable in the nivo+cabo arm. Subjects in the sunitinib arm were generally stable through Week 55, with subsequent decline by Week 85. For on-treatment time points, the mean scores for both arms did not attain the UK general population norm (0.86) at any time point. The changes are illustrated in the figure below.

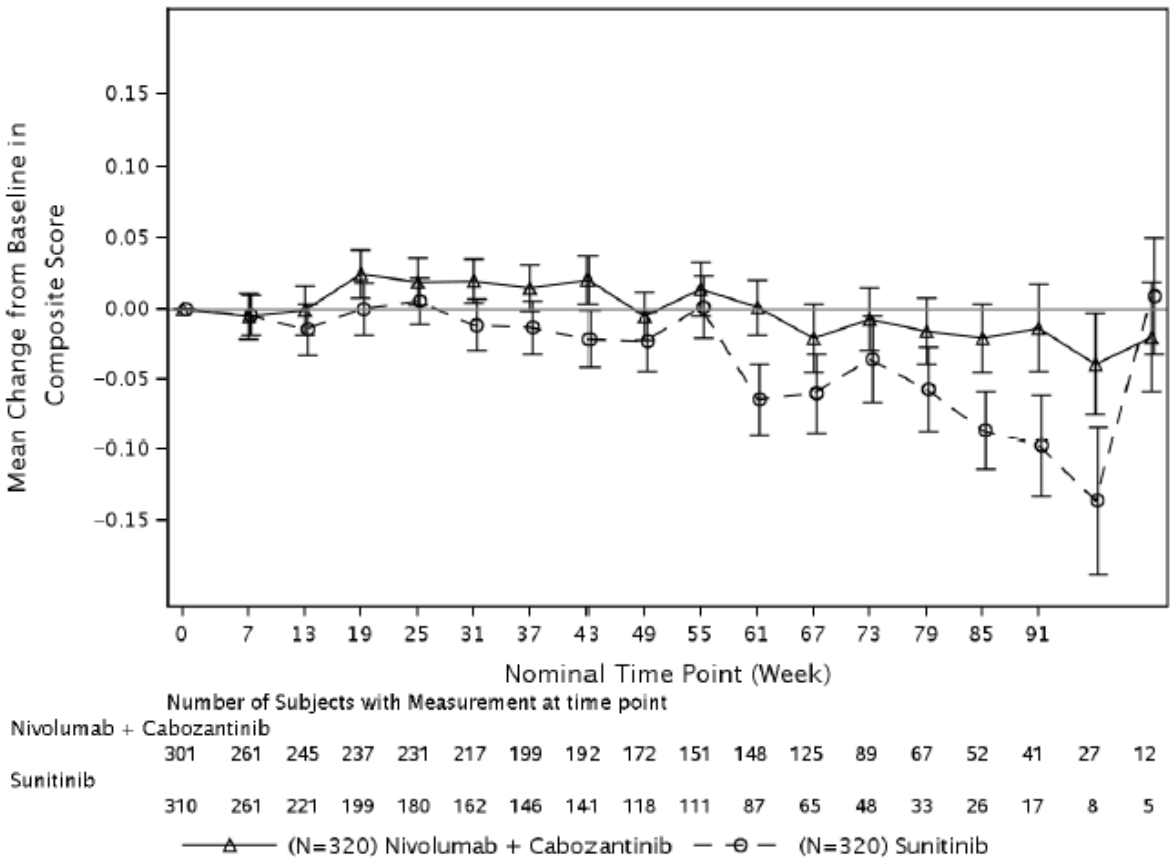


Figure 14. Mean changes in EuroQoL EQ-5D-3L utility index score from baseline - all treated subjects

Ancillary analyses

PFS by subgroups

PFS results (primary definition) for the three stratification factors:

- Baseline IMDC prognostic score (CRF):
    - 0 (favorable risk): median PFS was not reached for nivo + cabo, and was 12.81 months for sunitinib; HR = 0.60 (95% CI: 0.37, 0.98)
    - 1-2 (intermediate risk): median PFS was 17.71 vs 8.38 months, respectively; HR = 0.54 (95% CI: 0.41, 0.73)
    - 3-6 (poor risk): median PFS was 12.29 vs 4.21 months, respectively; HR = 0.36 (95% CI: 0.23, 0.58)
- PD-L1 expression status (≥ 1%, < 1%):
    - PD-L1 ≥ 1%: median PFS was 13.08 vs 4.67 months, respectively; HR = 0.45 (95% CI: 0.29, 0.68)
    - PD-L1 < 1%: median PFS was 19.84 vs 9.26 months, respectively; HR = 0.50 (95% CI: 0.38, 0.65)
- Region:

- US/Canada/W. and N. Europe: median PFS was 20.07 vs 9.56 months, respectively; HR = 0.46 (95% CI: 0.33, 0.64)
- Rest of the world (ROW): median PFS was 12.29 vs 7.03 months, respectively; HR = 0.57 (95% CI: 0.42, 0.76)

PFS per BICR in all subgroups is summarised in the Forest Plot below.

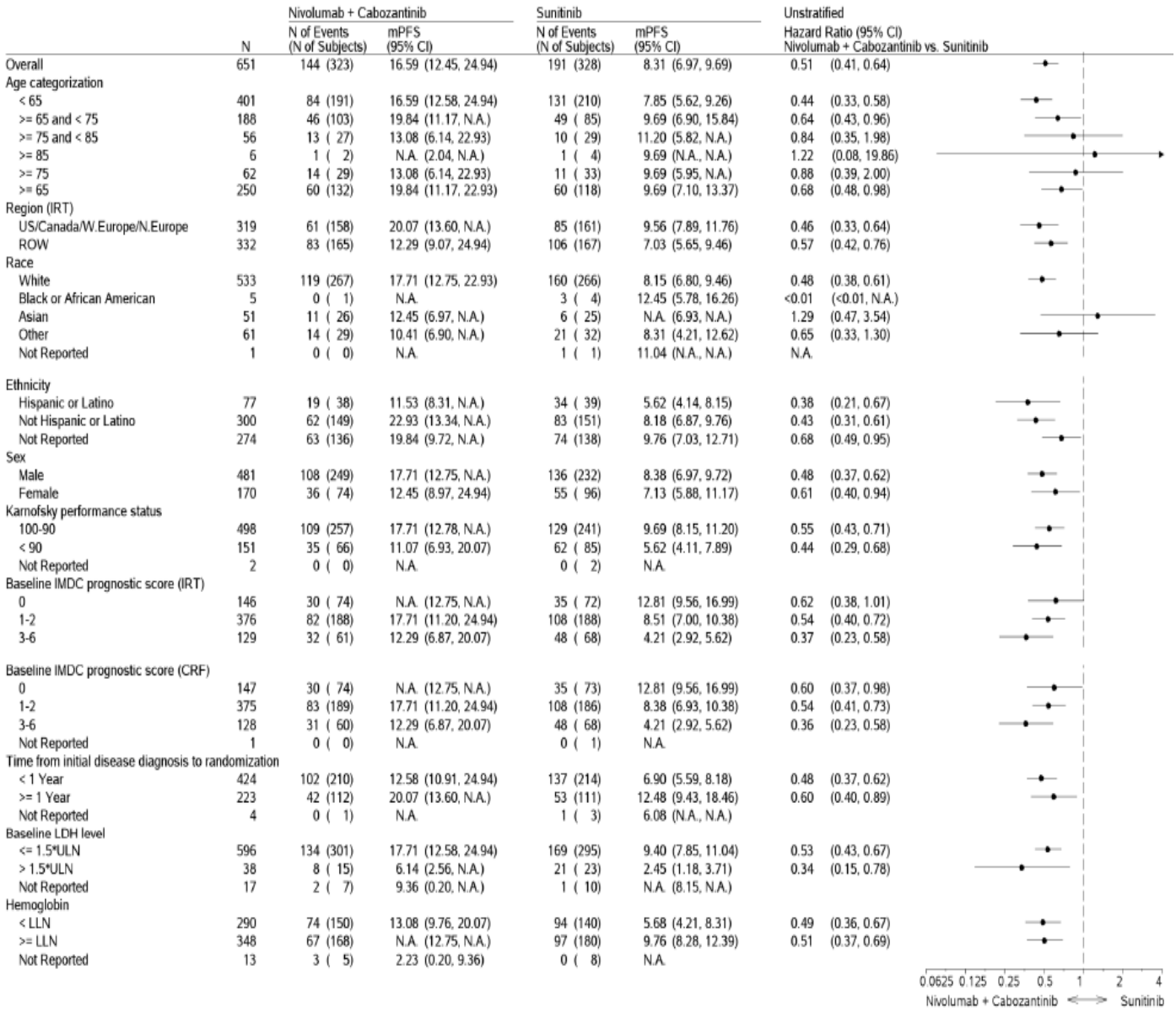
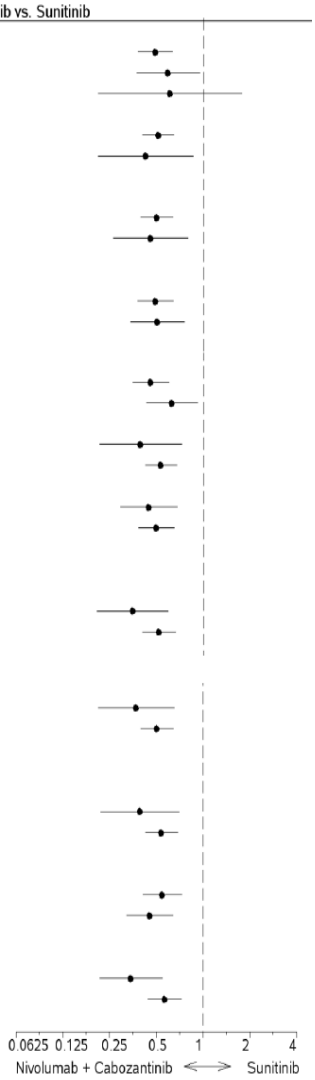


Figure 15. Forest Plot for treatment effect on PFS per BICR (primary definition) in predefined subgroups - all randomised subjects

	N	Nivolumab + Cabozantinib N of Events (N of Subjects)	Nivolumab + Cabozantinib mPFS (95% CI)	Sunitinib N of Events (N of Subjects)	Sunitinib mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab + Cabozantinib vs. Sunitinib
Corrected Calcium						
<= 10 mg/dl	488	103 (247)	19.84 (13.34, N.A.)	143 (241)	9.43 (7.39, 11.04)	0.49 (0.38, 0.63)
> 10 mg/dl	126	33 (58)	9.76 (5.55, 20.07)	42 (68)	5.62 (4.21, 8.15)	0.59 (0.37, 0.95)
Not Reported	37	8 (18)	12.78 (6.74, N.A.)	6 (19)	8.38 (2.10, N.A.)	0.61 (0.21, 1.77)
Absolute Neutrophil Count						
<= ULN	593	128 (298)	19.84 (13.08, 24.94)	170 (295)	9.23 (7.85, 10.38)	0.51 (0.41, 0.64)
> ULN	45	13 (20)	5.52 (2.79, N.A.)	21 (25)	2.53 (1.31, 3.25)	0.42 (0.21, 0.86)
Not Reported	13	3 (5)	2.23 (0.20, 9.36)	0 (8)	N.A.	
Platelet Count						
<= ULN	555	117 (275)	19.84 (12.78, 24.94)	162 (280)	9.26 (7.89, 10.38)	0.50 (0.39, 0.64)
> ULN	82	24 (43)	10.91 (6.87, 20.07)	29 (39)	3.15 (2.60, 5.62)	0.46 (0.26, 0.79)
Not Reported	14	3 (5)	2.23 (0.20, 9.36)	0 (9)	N.A.	
Baseline Alkaline phosphatase						
< ULN	479	94 (233)	19.84 (13.08, 24.94)	140 (246)	9.26 (7.89, 10.38)	0.49 (0.38, 0.64)
>= ULN	159	48 (86)	11.07 (8.80, 16.59)	50 (73)	5.62 (3.45, 9.69)	0.51 (0.34, 0.75)
Not Reported	13	2 (4)	4.78 (0.20, 9.36)	1 (9)	2.76 (N.A., N.A.)	
Prior nephrectomy						
Yes	455	90 (222)	20.07 (15.18, N.A.)	136 (233)	9.23 (7.00, 10.38)	0.46 (0.35, 0.60)
No	196	54 (101)	11.20 (8.80, 15.34)	55 (95)	7.06 (5.32, 9.40)	0.63 (0.43, 0.92)
Prior radiotherapy						
Yes	91	19 (46)	16.59 (9.95, N.A.)	26 (45)	7.89 (3.98, 9.76)	0.39 (0.21, 0.73)
No	560	125 (277)	17.71 (11.86, 22.93)	165 (283)	8.51 (6.97, 9.69)	0.53 (0.42, 0.67)
Baseline PD-L1+ status based on a 1% cut off						
>= 1%	162	39 (81)	13.08 (8.97, N.A.)	53 (81)	4.67 (3.15, 9.69)	0.45 (0.29, 0.68)
< 1%	472	96 (232)	19.84 (13.34, N.A.)	135 (240)	9.26 (7.85, 10.87)	0.50 (0.38, 0.65)
Indeterminate/NE	0	0 (0)	N.A.	0 (0)	N.A.	
Not Reported	17	9 (10)	7.10 (1.64, 9.53)	3 (7)	N.A. (2.56, N.A.)	
Baseline PD-L1+ status based on a 5% cut off						
>= 5%	109	23 (53)	22.93 (6.97, 22.93)	39 (56)	3.98 (2.83, 5.95)	0.35 (0.21, 0.59)
< 5%	525	112 (260)	17.71 (12.78, N.A.)	149 (265)	9.40 (8.11, 10.38)	0.52 (0.40, 0.66)
Indeterminate/NE	0	0 (0)	N.A.	0 (0)	N.A.	
Not Reported	17	9 (10)	7.10 (1.64, 9.53)	3 (7)	N.A. (2.56, N.A.)	
Baseline PD-L1+ status based on a 10% cut off						
>= 10%	88	20 (42)	9.95 (6.93, 22.93)	34 (46)	3.98 (2.83, 5.95)	0.37 (0.21, 0.66)
< 10%	546	115 (271)	19.84 (13.08, N.A.)	154 (275)	9.26 (7.85, 9.76)	0.51 (0.40, 0.65)
Indeterminate/NE	0	0 (0)	N.A.	0 (0)	N.A.	
Not Reported	17	9 (10)	7.10 (1.64, 9.53)	3 (7)	N.A. (2.56, N.A.)	
Sarcomatoid features						
Yes	75	20 (34)	10.91 (5.62, 24.94)	30 (41)	4.21 (2.63, 8.31)	0.39 (0.22, 0.70)
No	557	121 (279)	17.71 (12.78, N.A.)	157 (278)	9.40 (7.39, 10.87)	0.54 (0.43, 0.69)
Not Reported	19	3 (10)	N.A. (2.69, N.A.)	4 (9)	5.42 (2.86, 15.84)	
Stage at the initial diagnosis						
Stage IV	340	85 (167)	11.30 (9.07, 22.93)	108 (173)	5.82 (4.67, 8.15)	0.55 (0.41, 0.73)
Non-Stage IV	298	56 (150)	20.07 (16.59, N.A.)	80 (148)	9.76 (8.51, 12.48)	0.46 (0.32, 0.64)
Not Reported	13	3 (6)	10.53 (5.55, N.A.)	3 (7)	4.21 (1.77, N.A.)	
Bone metastasis						
Yes	150	33 (78)	20.07 (8.71, 24.94)	45 (72)	4.44 (3.71, 7.00)	0.34 (0.22, 0.55)
No	501	111 (245)	16.59 (12.29, N.A.)	146 (256)	9.56 (8.11, 11.10)	0.57 (0.44, 0.73)



Forest Plot for treatment effect on PFS per BICR (primary definition) in predefined subgroups - all randomised subjects, cont.

Overall Survival by subgroups

In a subgroup analysis for all randomised subjects, OS HRs for most subgroups favored (HR < 1) nivo+cabo vs sunitinib. OS by all subgroups are summarised in the Forest Plot of treatment effect below.

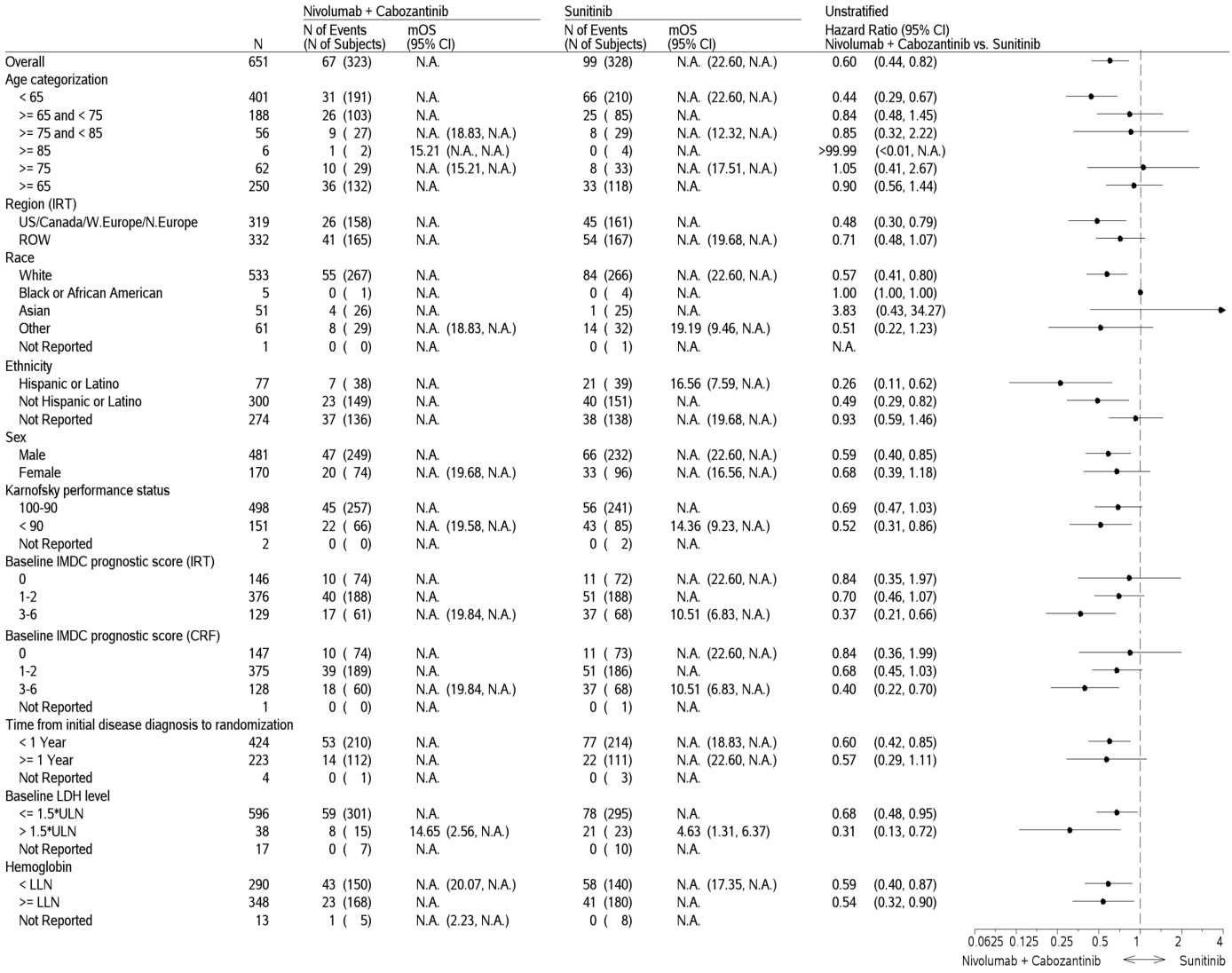
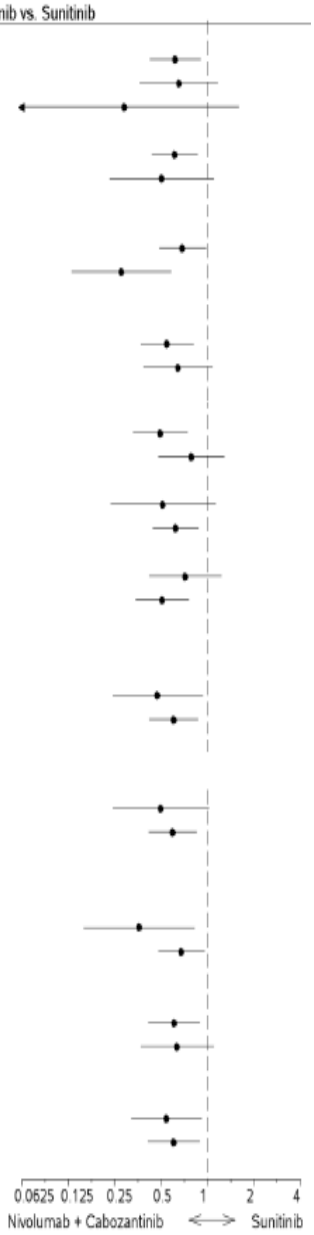


Figure 16. Forest Plot of treatment effect on OS in predefined subgroups- all randomised subjects

	N	Nivolumab + Cabozantinib N of Events (N of Subjects)	Nivolumab + Cabozantinib mOS (95% CI)	Sunitinib N of Events (N of Subjects)	Sunitinib mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab + Cabozantinib vs. Sunitinib
Corrected Calcium						
<= 10 mg/dl	488	46 (247)	N.A.	66 (241)	N.A. (22.60, N.A.)	0.62 (0.42, 0.90)
> 10 mg/dl	126	19 (58)	N.A. (20.07, N.A.)	29 (68)	N.A. (9.89, N.A.)	0.65 (0.37, 1.16)
Not Reported	37	2 (18)	N.A.	4 (19)	N.A. (3.71, N.A.)	0.29 (0.05, 1.59)
Absolute Neutrophil Count						
<= ULN	593	56 (298)	N.A.	81 (295)	N.A.	0.61 (0.44, 0.86)
> ULN	45	10 (20)	N.A. (3.45, N.A.)	18 (25)	3.55 (1.35, 12.48)	0.50 (0.23, 1.10)
Not Reported	13	1 (5)	N.A. (2.23, N.A.)	0 (8)	N.A.	
Platelet Count						
<= ULN	555	56 (275)	N.A.	75 (280)	N.A. (22.60, N.A.)	0.69 (0.49, 0.98)
> ULN	82	10 (43)	N.A. (20.07, N.A.)	24 (39)	8.94 (5.45, N.A.)	0.28 (0.13, 0.58)
Not Reported	14	1 (5)	N.A. (2.23, N.A.)	0 (9)	N.A.	
Baseline Alkaline phosphatase						
< ULN	479	39 (233)	N.A.	68 (246)	N.A.	0.55 (0.37, 0.81)
>= ULN	159	28 (86)	N.A. (20.07, N.A.)	31 (73)	22.60 (12.48, N.A.)	0.65 (0.39, 1.08)
Not Reported	13	0 (4)	N.A.	0 (9)	N.A.	
Prior nephrectomy						
Yes	455	36 (222)	N.A.	66 (233)	N.A.	0.49 (0.33, 0.74)
No	196	31 (101)	N.A. (19.84, N.A.)	33 (95)	22.60 (16.82, N.A.)	0.79 (0.48, 1.29)
Prior radiotherapy						
Yes	91	10 (46)	N.A.	17 (45)	18.83 (14.09, N.A.)	0.51 (0.24, 1.12)
No	560	57 (277)	N.A.	82 (283)	N.A. (22.60, N.A.)	0.62 (0.44, 0.87)
Baseline PD-L1+ status based on a 1% cut off						
>= 1%	162	25 (81)	N.A. (20.07, N.A.)	29 (81)	N.A. (18.33, N.A.)	0.72 (0.42, 1.23)
< 1%	472	38 (232)	N.A.	68 (240)	N.A. (22.60, N.A.)	0.51 (0.34, 0.76)
Indeterminate/NE	0	0 (0)	N.A.	0 (0)	N.A.	
Not Reported	17	4 (10)	N.A. (1.64, N.A.)	2 (7)	N.A. (5.72, N.A.)	
Baseline PD-L1+ status based on a 5% cut off						
>= 5%	109	14 (53)	N.A. (19.68, N.A.)	23 (56)	19.68 (9.92, N.A.)	0.48 (0.24, 0.93)
< 5%	525	49 (260)	N.A.	74 (265)	N.A.	0.60 (0.42, 0.87)
Indeterminate/NE	0	0 (0)	N.A.	0 (0)	N.A.	
Not Reported	17	4 (10)	N.A. (1.64, N.A.)	2 (7)	N.A. (5.72, N.A.)	
Baseline PD-L1+ status based on a 10% cut off						
>= 10%	88	12 (42)	N.A. (14.65, N.A.)	20 (46)	19.68 (6.60, N.A.)	0.50 (0.24, 1.02)
< 10%	546	51 (271)	N.A.	77 (275)	N.A.	0.59 (0.42, 0.85)
Indeterminate/NE	0	0 (0)	N.A.	0 (0)	N.A.	
Not Reported	17	4 (10)	N.A. (1.64, N.A.)	2 (7)	N.A. (5.72, N.A.)	
Sarcomatoid features						
Yes	75	8 (34)	N.A. (19.68, N.A.)	20 (41)	19.68 (8.94, N.A.)	0.36 (0.16, 0.82)
No	557	57 (279)	N.A.	76 (278)	N.A.	0.68 (0.48, 0.95)
Not Reported	19	2 (10)	N.A. (10.81, N.A.)	3 (9)	11.60 (3.15, N.A.)	
Stage at the initial diagnosis						
Stage IV	340	45 (167)	N.A.	65 (173)	19.68 (17.51, N.A.)	0.61 (0.42, 0.89)
Non-Stage IV	298	22 (150)	N.A.	31 (148)	N.A.	0.64 (0.37, 1.10)
Not Reported	13	0 (6)	N.A.	3 (7)	N.A. (1.77, N.A.)	
Bone metastasis						
Yes	150	24 (78)	N.A. (20.07, N.A.)	33 (72)	18.33 (12.32, N.A.)	0.54 (0.32, 0.92)
No	501	43 (245)	N.A.	66 (256)	N.A.	0.61 (0.41, 0.89)



Forest Plot of treatment effect on OS in predefined subgroups- all randomised subjects, cont.

Subgroup analysis of OS results for the three stratification factors:

- Baseline IMDC prognostic score:
  - 0 (favorable risk) : HR = 0.84 (95% CI: 0.36, 1.99)
  - 1-2 (intermediate risk): HR = 0.68 (95% CI: 0.45, 1.03)
  - 3-6 (poor risk): HR = 0.40 (95% CI: 0.22, 0.70)

- PD-L1 status (≥ 1%, < 1%):
  - PD-L1 ≥ 1%: HR = 0.72 (95% CI: 0.42, 1.23)

- PD-L1 < 1%: HR = 0.51 (95% CI: 0.34, 0.76)

- Region:
  - US/Canada/Western and Northern Europe: HR = 0.48 (95% CI: 0.30, 0.79)
  - ROW: HR = 0.71 (95% CI: 0.48, 1.07)

Median OS is not reached for any subgroup in both arms. KM curves for OS by each IMDC prognostic group were provided (see *Updated results according to DBL SEP-2020*)

Objective Response Rate by subgroups

In a subgroup analysis for all randomised subjects, ORR for all subgroups favoured nivo + cabo vs sunitinib, including all age subgroups and Asian subjects. The ORR for the stratified subgroups are listed below:

- Baseline IMDC prognostic score:
  - 0 (favorable risk): 67.6% (95%CI: 55.7, 78.0) vs 41.7% (95%CI: 30.2, 53.9)
  - 1-2 (intermediate risk): 56.4% (95%CI: 49.0, 63.8) vs 28.0% (95%CI: 21.6, 35.0)
  - 3-6 (poor risk): 39.3% (95%CI: 27.1, 52.7) vs 8.8% (95%CI: 3.3, 18.2)
- PD-L1 status (≥ 1%, < 1%):
  - PD-L1 ≥ 1%: 56.8% (95%CI: 45.3, 67.8) vs 23.5% (95%CI: 14.8, 34.2)
  - PD-L1 < 1%: 55.6% (95%CI: 49.0, 62.1) vs 28.3% (95%CCI: 22.7, 34.5)
- Region
  - US/Canada/Western and Northern Europe: 61.4% (95%CI: 53.3, 69.0) vs 28.6% (95%CI: 21.7, 36.2)
  - ROW: 50.3% (95%CI: 42.4, 58.2) vs 25.7% (95%CI: 19.3, 33.1)

Updated results according to DBL SEP-2020

Upon request, the MAH provided updated data from a 10-Sep-2020 DBL, including updated PFS and OS (ITT plus IMDC subgroups for both), PFS2, and subsequent anti-cancer treatment. In addition, updated ORR and DoR analysis results were described.

A summary of the provided updated efficacy data is presented in Table 17, side by side with the results from the 30-Mar-2020 DBL, for reference. In a similar fashion (i.e. Sep-2020 DBL results side by side with Mar-2020 DBL results), Kaplan-Meier plots for PFS per BICR (primary definition), PFS per BICR (secondary definition), and OS are shown in

Figure 16, Figure 17 and Figure 18.

Also in the updated efficacy data, PFS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status. For the IMDC subgroups the original and updated PFS per BICR (primary definition) Kaplan-Meier plots are shown in Figure 19. For tumour PD-L1 expression status (≥1%, <1%) the updated results were (refer to or Figure 14 for the Mar-2020 DBL results):

- PD-L1 ≥1%: median PFS was 13.08 vs 4.67 months, respectively, HR = 0.41 (95% CI: 0.27, 0.61)

- PD-L1 <1%: median PFS was 18.23 vs 9.23 months, respectively, HR = 0.55 (95% CI: 0.43, 0.71)

Similarly, in the updated efficacy data OS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status as well. For the IMDC subgroups the original and updated OS Kaplan-Meier plots are shown in Figure 20. For tumour PD-L1 expression status (≥1%, <1%) the updated results were (refer to Figure 15 for the Mar-2020 DBL results):

- PD-L1 ≥1%: HR = 0.86 (95% CI: 0.52, 1.41), median OS was not reached in both arms
- PD-L1 <1%: HR = 0.53 (95% CI: 0.37, 0.76), median OS was not reached for nivo+cabo, and was 29.47 months for sunitinib

Table 17. CA2099ER summary of efficacy – All randomised patients - Mar-2020 DBL vs Sep-2020 DBL

	Mar-2020 DBL		**Sep-2020 DBL**	
	Nivo+Cabo N = 323	**Sunitinib N = 328**	**Nivo+Cabo N = 323**	**Sunitinib N = 328**
Minimum Follow-up for OS, mos	10.6		16.0	
Median Follow up for OS, mos	18.1		23.5	
PFS per BICR (1° Definition)				
Events, n (%)	144 (44.6)	191 (58.2)	175 (54.2)	206 (62.8)
Median PFS (95% CI), mo.[a]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)	16.95 (12.58, 19.38)	8.31 (6.93, 9.69)
HR (95% CI)[b]	0.51 (0.41, 0.64); p < 0.0001[c,d]		0.52 (0.43, 0.64)	
PFS per BICR (2° Definition)				
Events, n (%)	159 (49.2)	211 (64.3)	190 (58.8)	230 (70.1)
Median PFS (95% CI), mo.[a]	14.29 (12.29, 19.84)	8.31 (7.00, 9.69)	16.10 (12.29, 19.32)	8.31 (6.97, 9.69)
HR (95% CI)[b]	0.54 (0.44, 0.67); p < 0.0001[c,d]		0.57 (0.47, 0.69)	
OS				
Events, n (%)	67 (20.7)	99 (30.2)	86 (26.6)	116 (35.4)
Median OS (95% CI), mo.[a]	N.A.	N.A. (22.60, N.A.)	N.A.	29.47 (28.35, N.A.)
HR[b]	0.60 (98.89% CI: 0.40, 0.89); p = 0.0010[c,d,e]		0.66 (95% CI: 0.50, 0.87)	
ORR per BICR (CR+PR)				
N responders (%)	180 (55.7)	89 (27.1)	177 (54.8)	93 (28.4)

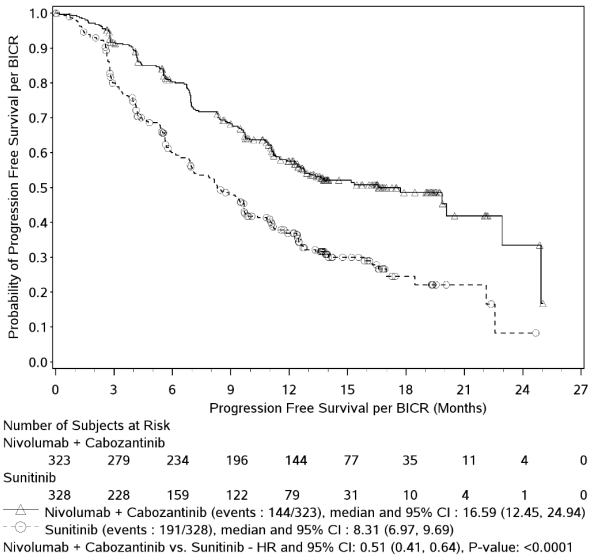
	Mar-2020 DBL		Sep-2020 DBL	
	Nivo+Cabo N = 323	**Sunitinib N = 328**	**Nivo+Cabo N = 323**	**Sunitinib N = 328**
95% CI[f]	50.1, 61.2	22.4, 32.3	49.2, 60.3	23.5, 33.6
ORR Difference, %[g,h]	28.6 (95% CI: 21.7, 35.6); p < 0.0001[i]		26.6 (95% CI: 19.5, 33.6)	
Estimate of Odds Ratio[h,j]	3.52 (2.51, 4.95)		3.17 (2.27, 4.44)	
Confirmed BOR per BICR, n (%)				
CR	26 (8.0)	15 (4.6)	30 (9.3)	14 (4.3)
PR	154 (47.7)	74 (22.6)	147 (45.5)	79 (24.1)
SD	104 (32.2)	138 (42.1)	108 (33.4)	136 (41.5)
PD	18 (5.6)	45 (13.7)	20 (6.2)	45 (13.7)
UTD	21 (6.5)	55 (16.8)	18 (5.6)	53 (16.2)
NR	0	1 (0.3)	0	1 (0.3)
DoR per BICR				
N events/N responders (%)	50/180 (27.8)	34/89 (38.2)	67/177 (37.9)	41/93 (44.1)
Median (95% CI), mo.[a]	20.17 (17.31, N.A.)	11.47 (8.31, 18.43)	21.65 (17.31, N.A.)	12.68 (9.56, 20.73)

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model. Hazard Ratio is nivo+cabo over sunitinib.
[c] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (>= 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[d] 2-sided p value from stratified log-rank test.
[e] Boundary for statistical significance p-value < 0.0111
[f] CI based on the Clopper and Pearson method
[g] Strata adjusted difference in objective response rate (nivo+cabo - sunitinib) based on DerSimonian and Laird
[h] Stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (>= 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[i] 2-sided p value from stratified Cochran-Mantel-Haenszel test.
[j] Strata adjusted odds ratio (nivo+cabo over sunitinib) using Mantel-Haenszel method.
Abbreviations: BICR=blinded independent central review; BOR=best overall response; cabo=cabozantinib; CI=confidence interval; CR=complete response; CSR=clinical study report; DoR=duration of response; HR=hazard ratio; NA=not available; nivo=nivolumab; NR=not reported; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease; TTR=time to objective response; UTD=unable to determine due to various reasons including death prior to disease assessment.

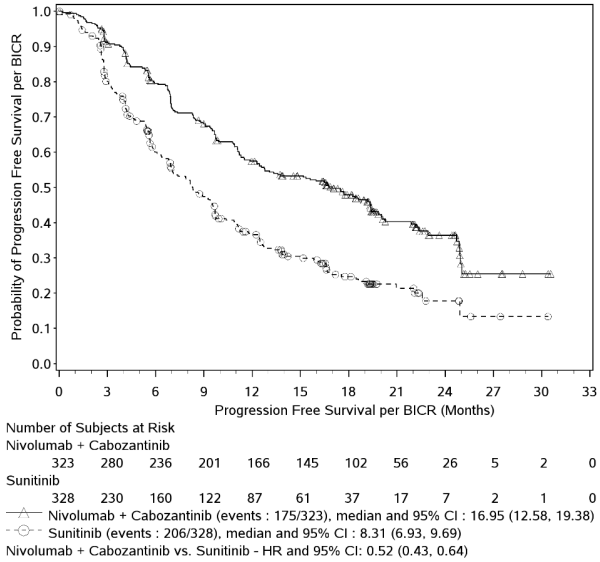
Kaplan-Meier curves

PFS – primary definition

Mar-2020 DBL



Sep-2020 DBL

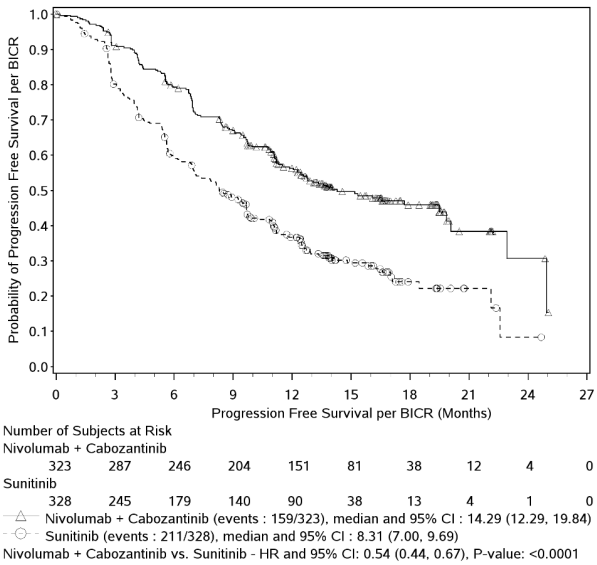


Symbols represent censored observations.

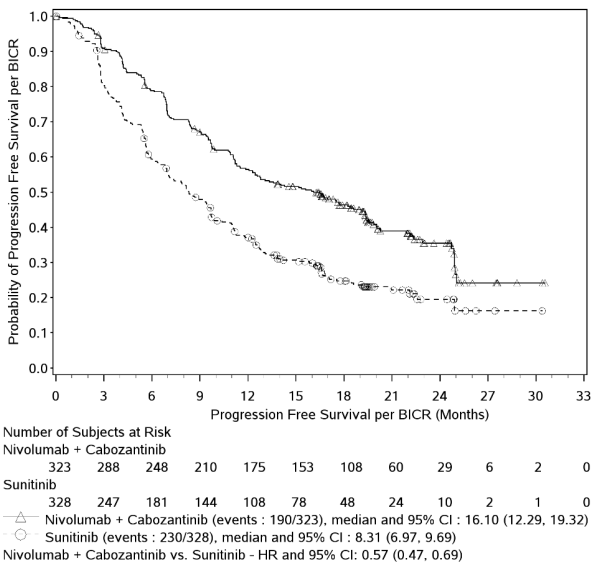
Figure 17. Kaplan-Meier plot of progression-free survival per BICR (primary definition) - All randomised patients - Mar-2020 DBL vs Sep-2020 DBL

PFS – secondary definition

Mar-2020 DBL



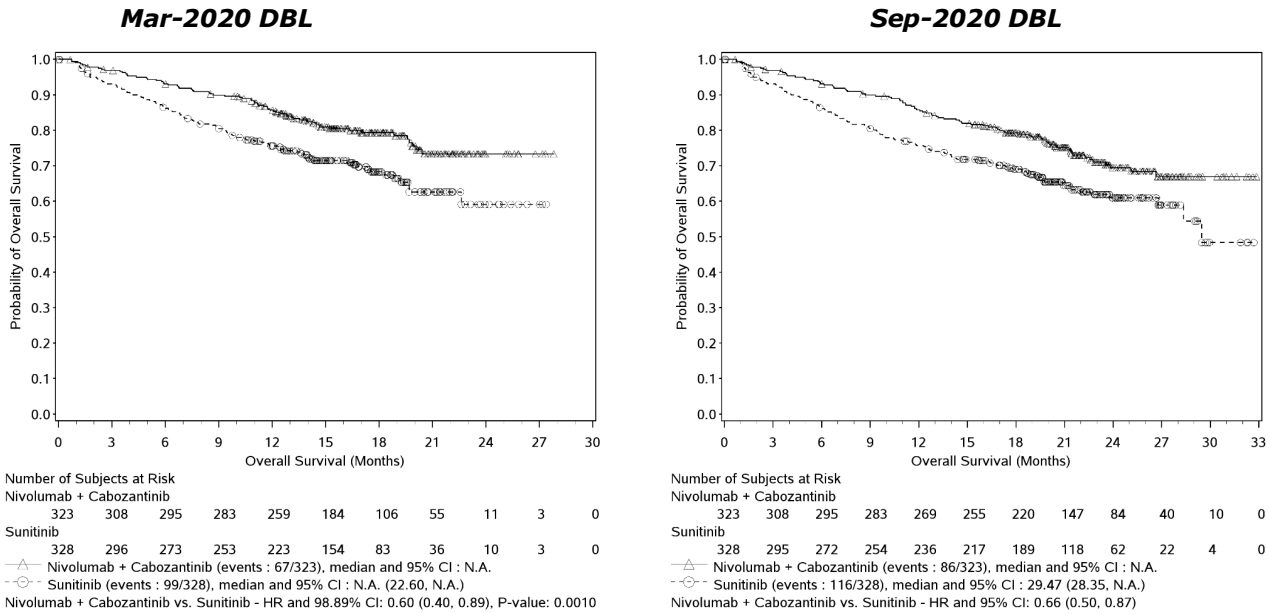
Sep-2020 DBL



Symbols represent censored observations.

Figure 18. Kaplan-Meier plot of progression-free survival per BICR (secondary definition) - All randomised patients - Mar-2020 DBL vs Sep-2020 DBL

OS

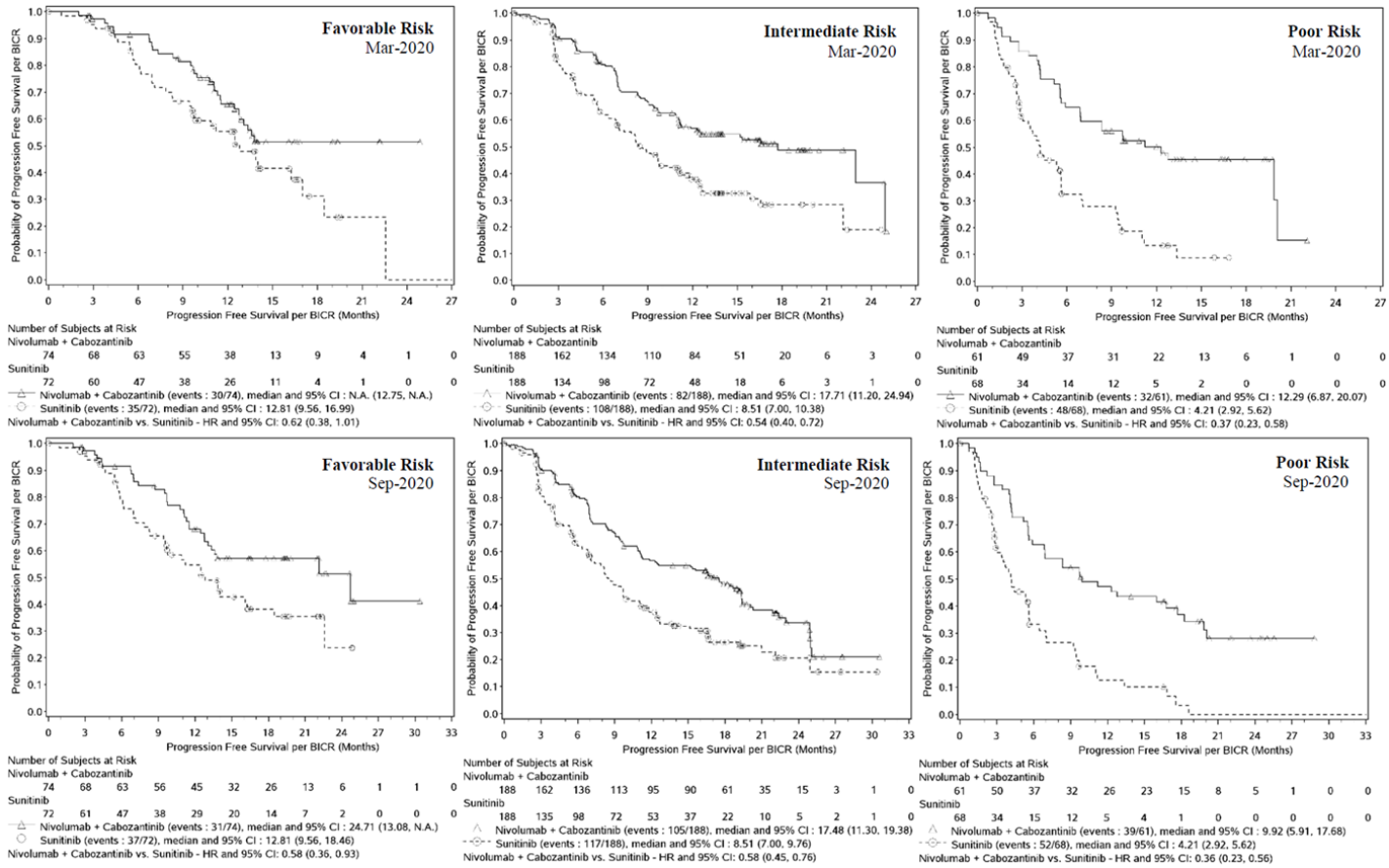


Symbols represent censored observations.

Figure 19. Kaplan-Meier plot of overall survival - All randomised patients - Mar-2020 DBL vs Sep-2020 DBL

Updated PFS and OS Kaplan-Meier curves for the IMDC subgroups are shown in Figure 19 and Figure 20, respectively, below.

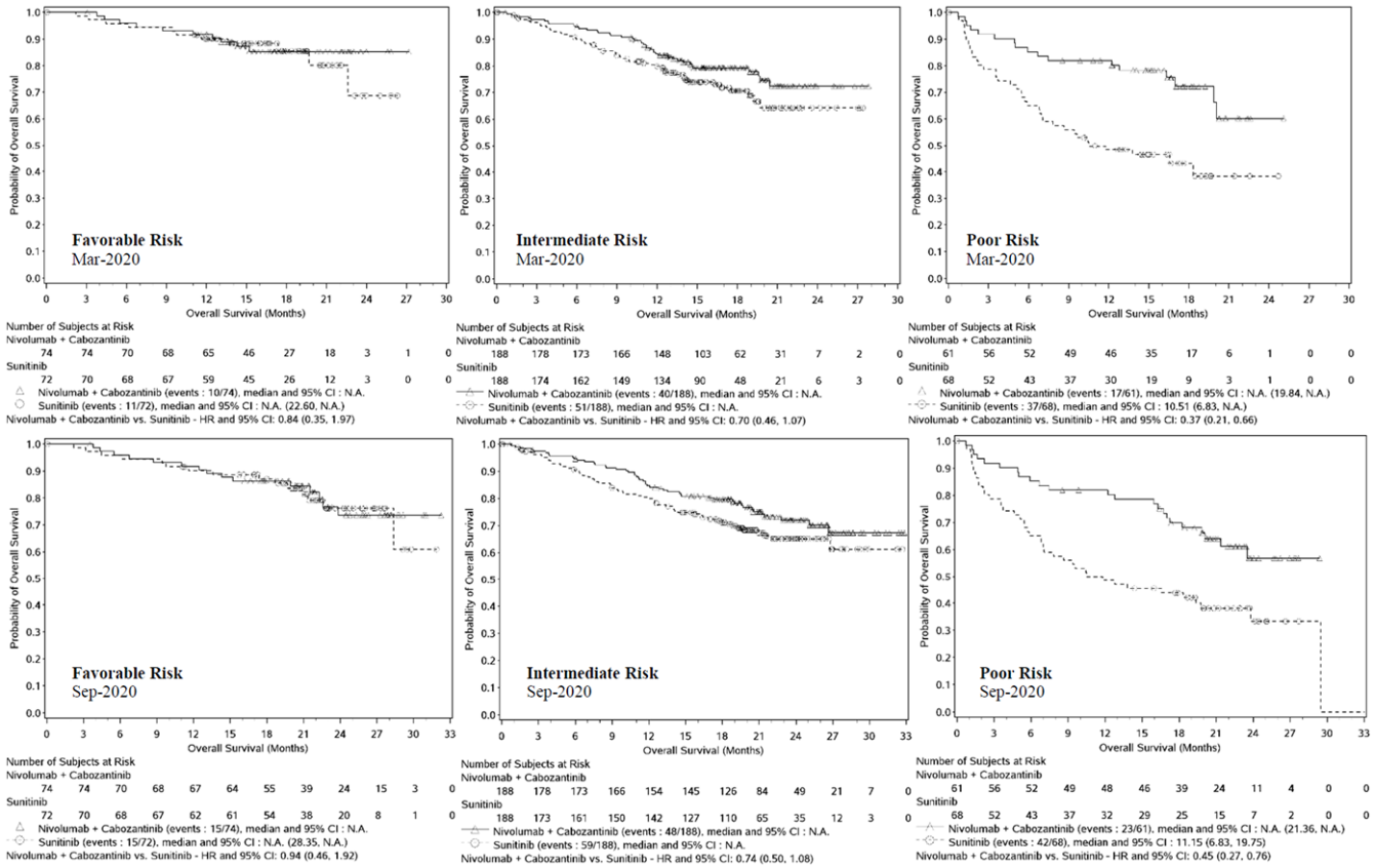
PFS – IMDC subgroups



Symbols represent censored observations.

Figure 20. Kaplan Meier plot of PFS per BICR, primary definition - All randomised patients by IMDC risk category (Favorable/Intermediate/Poor) - Mar-2020 and Sep-2020

OS – IMDC subgroups



Symbols represent censored observations.

Figure 21. Kaplan Meier plot of OS - All randomised patients by IMDC risk category (Favorable/Intermediate/Poor) - Mar-2020 and Sep-2020

Subsequent anti-cancer treatment

At the 10 Sep 2020 DBL, subsequent anti-cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 84 patients (26.0%) in the nivo+cabo arm compared to 128 patients (39.0%) in the sunitinib arm.

Subsequent systemic anti-cancer therapy was received by 56 patients (17.3%) in the nivo+cabo arm and 112 patients (34.1%) in the sunitinib arm. Subsequent immunotherapy (anti-PD1/anti-PD-L1 therapy, anti-CTLA4 therapy or the combination of anti-PD1 and anti-CTLA4) was received by 20 patients (6.2%) in the nivo+cabo arm compared with 95 (29.0%) for the sunitinib arm. This included subsequent anti-PD1/anti-PD-L1 therapy in 13 patients (4.0%) in the nivo+cabo arm compared with 78 (23.8%) for the sunitinib arm. Subsequent antiangiogenic drugs were received by 44 patients (13.6%) in the nivo+cabo arm and 48 patients (14.6%) sunitinib arm.

Summary of main study(ies)

The following table summarises the efficacy results from the main study 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 18. Summary of efficacy for trial CA2099ER

Title: A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma			
Study identifier	CA2099ER (NCT03141177)		
Design	Phase 3, multicentre, randomised, open-label, active-controlled		
	Duration of main phase:		Approximately 29 months (first patient randomized 11-Sep-2017, last patient randomized 14-May-2019, and clinical data cut-off [last patient last visit] 12-Feb-2020)
Hypothesis	Superiority		
Treatments groups	**Nivolumab + cabozantinib**		**N = 323** Nivolumab 240 mg IV Q2W + cabozantinib 40 mg PO QD -> Nivolumab was to be continued until disease progression or unacceptable toxicity with maximum treatment of 2 years from the first dose in Cycle 1. -> Cabozantinib was to be continued until disease progression or unacceptable toxicity.
	Sunitinib		**N = 328** Sunitinib 50 mg PO QD for 4 weeks, followed by 2 weeks off, per cycle -> Sunitinib was to be continued until progression or unacceptable toxicity.
Endpoints and definitions	Primary endpoint	Progression-free survival (**PFS**)	Time between date of randomization and date of first documented tumour progression, based on BICR assessments (per RECIST v1.1), or death due to any cause, whichever occurs first
	Secondary endpoint	Overall survival (**OS**)	Time between date of randomization and date of death due to any cause
	Secondary endpoint	Objective response rate (**ORR**)	Proportion of randomized patients who achieve best response of complete response (CR) or partial response (PR) using RECIST v1.1
Database lock	30-Mar-2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat (ITT) Minimum and median follow-up for OS was approximately 10.6 and 18.1 months, respectively			
Descriptive statistics and estimate variability	Treatment group	**Nivolumab + cabozantinib**	**Sunitinib**	
	Number of patients	323	328	
	Median **PFS** (months)	16.59	8.31	
	95% confidence interval (CI)	12.45, 24.94	6.97, 9.69	
	Median **OS** (months)	Not reached	Not reached	
	95% CI	NA, NA	22.60, NA	
	ORR (%)	55.7	27.1	
	95% CI	50.1, 61.2	22.4, 32.3	
Effect estimate per comparison	Primary endpoint **PFS**	Comparison groups	Nivolumab + cabozantinib vs sunitinib	
		Hazard ratio (HR)	0.51	
		95% CI	0.41, 0.64	
		P-value	<0.0001	
	Secondary endpoint **OS**	Comparison groups	Nivolumab + cabozantinib vs sunitinib	
		Hazard ratio (HR)	0.60	
		98.89% CI	0.40, 0.89	
		P-value	0.0010	
	Secondary endpoint **ORR**	Comparison groups	Nivolumab + cabozantinib vs sunitinib	
		Odds ratio	3.52	
		95% CI	2.51, 4.95	
		P-value	<0.0001	
Notes	The results of an analysis of PFS (per BICR) using the secondary PFS definition were as follows (for nivo+cabo vs sunitinib): median PFS 14.29 (95% CI: 12.29, 19.84) vs 8.31 (95% CI: 7.00, 9.69) months; HR = 0.54 (95% CI: 0.44, 0.67).			
Database lock	10-Sep-2020			
Updated Results and Analysis				
Analysis description	**Primary Analysis**			

Analysis population and time point description	Intent to treat (ITT) Minimum and median follow-up for OS was approximately 16.0 and 23.5 months, respectively			
Descriptive statistics and estimate variability	Treatment group	**Nivolumab + cabozantinib**	**Sunitinib**	
	Number of patients	323	328	
	Median **PFS** (months)	16.95	8.31	
	95% confidence interval (CI)	12.58, 19.38	6.93, 9.69	
	Median **OS** (months)	Not reached	29.47	
	95% CI	NA, NA	28.35, NA	
	ORR (%)	54.8	28.4	
	95% CI	49.2, 60.3	23.5, 33.6	
Effect estimate per comparison	Primary endpoint **PFS**	Comparison groups	Nivolumab + cabozantinib vs sunitinib	
		Hazard ratio (HR)	0.52	
		95% CI	0.43, 0.64	
		P-value	NA	
	Secondary endpoint **OS**	Comparison groups	Nivolumab + cabozantinib vs sunitinib	
		Hazard ratio (HR)	0.66	
		98.89% CI	0.50, 0.87	
		P-value	NA	
	Secondary endpoint **ORR**	Comparison groups	Nivolumab + cabozantinib vs sunitinib	
		Odds ratio	3.17	
		95% CI	2.27, 4.44	
		P-value	NA	
Notes	The results of an analysis of PFS (per BICR) using the secondary PFS definition were as follows (for nivo+cabo vs sunitinib): median PFS 16.10 (95% CI: 12.29, 19.32) vs 8.31 (95% CI: 6.97, 9.69) months; HR = 0.57 (95% CI: 0.47, 0.69).			

Clinical studies in special populations

The below table shows the number of elderly patients in the studies included in this application, further specified per age category (i.e. age 65-74, age 75-84, and age 85+). Notably, the pivotal study CA2099ER is the only study in this application. Refer also to the forest plot of PFS subgroup analyses (Figure 14).

	Age 65-74 (older patients number/total number)	**Age 75-84 (older patients number/total number)**	**Age 85+ (older patients number/total number)**
Controlled trials	188 / 651 (28.9%)	56 / 651 (8.6%)	6 / 651 (0.9%)
Non-controlled trials	Not applicable	Not applicable	Not applicable

Supportive studies

Supportive studies to establish contribution of individual components

To establish the contribution of the individual components nivolumab and cabozantinib to the nivo+cabo regimen, the MAH has compared the CA2099ER results to cabozantinib monotherapy data from the CABOSUN trial (Alliance for Clinical Trials in Oncology study A031203) and the METEOR trial. Nivolumab monotherapy data were gathered from Study CA209669.

Contribution of nivolumab

CABOSUN trial

To justify the contribution of nivolumab monotherapy into the combination, the MAH is referring to the CABOSUN trial. It is a randomised Phase 2 study of cabozantinib vs sunitinib (total N=157) in participants with previously untreated intermediate (81%) or poor risk (19%) advanced RCC. This trial was the basis for approving the 1L indication of advanced RCC in patients with intermediate or poor risk for cabozantinib.

Key efficacy results for CA2099ER and CABOSUN are presented in the table below:

Table 18. Summary of efficacy in CA2099ER and CABOSUN- intermediate and poor risk population

Study	CA2099ER[a]		CABOSUN[b]	
	Enrollment: Aug-2017 to May-2019		Enrollment: Jul-2013 to Apr-2015	
	Nivo+Cabo (n=249)	Sunitinib (n=256)	Cabozantinib (n=79)	Sunitinib (n=78)
Follow-up (months)				
Median	18.1		25 (PFS); 34.5 (OS)	
ORR per BICR %, (95% CI)	52.2 (45.8, 58.6)	23.0 (18.0, 28.7)	20 (12.0, 30.8)	9 (3.7, 17.6)
CR n (%)	21 (8.4)	9 (3.5)	0	0
PR n (%)	109 (43.8)	50 (19.5)	16 (20)	7 (9)
PD n (%)	16 (6.4)	43 (16.8)	14 (18)	23 (29)
PFS per BICR (months) Median (95% CI)	16.59 (11.17, 22.93)	7.06 (5.68, 8.90)	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
HR (95% CI)	0.48 (0.37, 0.61)		0.48 (0.31, 0.74)	
OS (months) Median (95% CI)	NR	NR (19.68, NA)	26.6 (14.6, NR)	21.2 (16.3, 27.4)
HR (95% CI)	0.56 (0.40, 0.79)		0.80 (0.53, 1.21)	

[a] Refer to Figure 5.30IP.3 (PFS), Figure 5.30IP.1 (OS), and Table 5.5IP.2 (ORR) of the CA2099ER Final CSR
[b] Data presented as reported in Choueiri et al., Eur J Cancer. 2018; 94: 115.

There was a cross-study difference in ORR between nivo+cabo (52.2%) and cabozantinib monotherapy (20%). The absolute ORR increase in CA2099ER was 29% (52.2% in the nivo+cabo arm minus 23.0% in the sunitinib arm) vs 11% (20% in the cabozantinib arm minus 9% in the sunitinib arm) in CABOSUN. There was an increase in median PFS in CA2099ER, compared to the 3.3 month increase in CABOSUN, however a similar HR of 0.48 was achieved in both trials.

Baseline characteristics in the CABOSUN trial were similar to study CA2099ER, except for the lack of favorable risk patients (data not shown). As the CABOSUN-population had poorer prognosis, the effect size is expected to be lower than in the CA2099ER. The comparator, sunitinib, was identical in the two trials.

METEOR trial

To establish that the contribution of components demonstrated also accounts for 1L favorable risk participants, additional supportive data from the METEOR study were provided to compare the effect of cabozantinib monotherapy in the favorable population to the intermediate or poor risk populations. METEOR was a randomised, open-label, Phase 3 study that evaluated the efficacy of cabozantinib, as compared with everolimus, in patients with RCC who had progressed after VEGFR-targeted therapy. This study formed the basis for the approval of this 2L indication in RCC for cabozantinib. The primary endpoint was PFS as assessed by BICR and secondary endpoints were OS and ORR. Cabozantinib treatment resulted in improved PFS, OS, and ORR compared with everolimus across all IMDC risk groups. ORR from cabozantinib monotherapy in METEOR was similar between the favorable risk subgroup and the intermediate and poor risk subgroups: 16.7%, 19.0% and 11.1%, respectively, see table below.

Table 19. Summary of efficacy in METEOR across IMDC risk categories

	IMDC Risk Categories						Overall	
	Favorable		Intermediate		Poor			
	Cabozantinib (n=66)	Everolimus (n=62)	Cabozantinib (n=210)	Everolimus (n=214)	Cabozantinib (n=54)	Everolimus (n=52)	Cabozantinib (N=330)	Everolimus (N=328)
PFS per BICR								
Events, n (%)	34 (51.5)	37 (59.7)	107 (51.0)	137 (64.0)	39 (72.2)	40 (76.9)	180 (54.5)	214 (65.2)
HR (95% CI)	0.47 (0.30, 0.76)		0.48 (0.37, 0.62)		0.67 (0.48, 1.04)		0.51 (0.41, 0.62)	
OS								
Events, n (%)	14 (21.2)	17 (27.4)	89 (42.4)	121 (56.5)	37 (68.5)	42 (80.8)	140 (42.4)	180 (54.9)
HR (95% CI)	0.70 (0.34, 1.41)		0.65 (0.49, 0.85)		0.74 (0.48, 1.15)		0.66 (0.53, 0.83)	
ORR per BICR % [a]	16.7	3.2	19.0	2.8	11.1	5.8	17.3	3.4

Data presented as reported in Choueiri et al., Lancet Oncol. 2016: 917- 27.[51]

The baseline population in the METEOR trial and the CA2099ER trial differs significantly in the sense of treatment line (METEOR 2L+, CA2099ER 1L). Of note, 64% of the cabozantinib patients in the METEOR trial had used sunitinib previously and the comparator was everolimus.

Contribution of cabozantinib

Nivolumab is not approved for the use in the 1L RCC population as monotherapy (MA only granted for nivolumab monotherapy after prior therapy in RCC, 2L+).

To justify the contribution of cabozantinib, the MAH provided a comparison of the data from the nivo + cabo combination in CA2099ER with nivolumab monotherapy data from Study CA209669. The CA209669 study is an ongoing Investigator-sponsored, single-arm study designed to evaluate the efficacy and safety of nivolumab monotherapy in previously untreated advanced RCC (n=123), as well as the efficacy of nivolumab + ipilimumab salvage therapy in participants with tumours resistant to initial nivolumab monotherapy. Study CA209669 included all IMDC risk groups. Only results from the nivolumab monotherapy arm were presented. There was a cross-study difference in ORR between nivo+cabo (55.7%, 95% CI [50.1, 61.2]) and nivolumab monotherapy (31.7%, 95% CI [23.6, 40.7]), with non-overlapping 95% CIs.

The CA209669 is still ongoing. Baseline characteristics were similar among studies, except for the higher proportion of poor risk subjects enrolled in CA2099ER compared with CA209669 (18.6% vs 9.8%).

2.4.3. Discussion on clinical efficacy

Study CA2099ER was the main study submitted for the extension of indication to include the use of cabozantinib in combination with nivolumab in adult patients with advanced renal cell carcinoma (RCC). Selected data from CABOSUN trial (cabozantinib vs sunitinib in 1L RCC), study CA209669 (single-arm nivolumab [salvage nivolumab + ipilimumab] 1L RCC) and the METEOR trial (cabozantinib vs everolimus in 2L+ RCC) have been included as supportive with the aim to provide justification on the contribution of each of the components to the efficacy of the nivolumab + cabozantinib combination. To support the choice of the proposed reduced cabozantinib dose in the combination (40 mg) a dose finding phase 1b/2 trial (CTEP-9861) is submitted.

Design and conduct of clinical studies

Study design and patient population

Study CA2099ER is an open label, randomised, Phase 3 trial comparing nivolumab 240 mg Q2W combined with cabozantinib 40 mg orally once daily [nivo + cabo; Arm A] versus sunitinib 50 mg orally QD (4 weeks, 2 weeks off) [Arm C] in participants with previously untreated (first line) advanced or metastatic renal cell carcinoma (RCC).

Subjects ≥18 years of age and who had previously untreated advanced RCC (not amenable for surgery or radiotherapy) or metastatic RRC, with histology confirmed RCC with clear cell component with or without sarcomatoid features, were eligible provided they had not received prior systemic therapy for advanced RCC. Prior neoadjuvant or adjuvant therapy for RCC was acceptable if completed ≥ 6 months prior to randomisation. No crossover was allowed.

It is also noted that some medicinal-product-specific exclusion criteria did apply. The most important ones have been reflected in the respective SmPCs: patients with an autoimmune disease or any condition requiring systemic treatment with corticosteroids or other immunosuppressive medications (nivolumab specific); and patients receiving concomitant treatment with anticoagulants (cabozantinib specific). Additionally, patients with any active brain metastases were excluded.

Only patients with RCC with a clear-cell component were eligible for CA2099ER. Only a few (three) patients were documented to also have non-clear cell component. Even if patients with only non-clear cell RCC were not included in the trial, they were not excluded from the sought indication, which is acceptable because cabozantinib has shown efficacy in non-clear cell RCC in a retrospective study (Martinez Chanzá et al. Lancet Oncol. 2019).

Patients were enrolled regardless of PD-L1 tumour expression, however, it was used as a stratification factor (≥ 1% vs < 1%). Subgroup analyses according to PD-L1 expression have been included in the protocol.

In addition to PD-L1 tumour expression, participants were also stratified according to International Metastatic RCC Database Consortium (IMDC) risk group (favourable, intermediate and poor) and geographic region (North America and Western Europe and Northern Europe vs rest of the world [ROW]). Stratification factors are considered appropriate.

Inclusion across all three IMDC risk categories results in heterogeneity of the patient population in terms of prognosis. It is a fact that two other similar combination regimens (PD-L1-inhibitor + TKI; pembrolizumab +axitinib and avelumab +axitinib) are already approved across all three IMDC risk categories. Stratified subgroup analyses by IMDC risk categories have been included in the protocol.

Sunitinib is considered to be an acceptable comparator in the target population as the study started inclusion in 2017. The shift to new standard of care in first line RCC across IMDC risk categories to combination regimens (pembrolizumab + axitinib [all risk categories] or nivolumab + ipilimumab [intermediate and poor risk categories]) occurred in European guidelines (ESMO, EAU) during 2018 and 2019.

The patient population was adequate and inclusion/exclusion criteria are acceptable. The open-label design is acceptable on the basis of the different administration route and schedule of administration. The assessment of response has been performed based on blinded independent central review (BICR). BICR reviewed tumour assessments scans for all randomised participants to determine RECIST v1.1 response for the analysis of PFS and ORR.

Overall, the study design is considered acceptable.

Study endpoints and statistics

The primary objectives of the study were to compare PFS per BICR in participants treated with nivolumab + cabozantinib (Arm A) vs sunitinib (Arm C). OS, ORR, DoR, and safety were secondary outcomes.

PFS as primary objective is considered appropriate considering OS was defined as a secondary objective. The MAH has evaluated PFS based on two definitions. The primary definition entailed censoring for subsequent therapy while the secondary definition was irrespective of subsequent therapy and did not account for it. According to the EMA Guideline on the evaluation of anticancer treatment medicinal products in man*, Appendix 1 (EMA/CHMP/27994/2008/Rev1)* it is the secondary definition of PFS used in the pivotal trial that is recommended. Starting new anti-cancer treatment cannot be assumed to be non-informative and therefore censored.

All analyses (apart from dosing and safety) were to be carried out using the treatment arm as randomised (intent to treat). Overall, the statistical analyses are considered appropriate and the sample size calculations are acceptable.

Cabozantinib dose

A formal Phase II dose-finding study in order to support the proposed lower dose of 40 mg daily has not been conducted. The dose selection of cabo+nivo is rather based on an investigator-initiated Phase I trial (CTEP-9681) evaluating the combination of cabo+nivo or cabo+nivo+ipi in patients with genitourinary cancers (including RCC). The primary objective was to determine dose-limiting toxicity (DLT) and recommended phase 2 dose (RP2D) for the combination of cabo+nivo (and cabo+nivo+ipi). There was only one RCC patient included in the cabo+nivo dose cohort, thus efficacy was not assessed. As expected, no DLTs were reported during the first 4 weeks of therapy. For molecularly targeted agents, such as cabozantinib, it is common that patients present grade 3-4 toxicity after cycle 1. The RP2D (40 mg cabozantinib QD co-administered with 3 mg/kg nivo Q2W) was therefore selected based on cabozantinib dose reductions past the first 4 weeks of therapy. Four (4) of 12 (33%) patients starting with 40 mg cabozantinib had dose reductions, compared to 9 of 12 (75%) patients starting with 60 mg cabozantinib. Albeit a limited number of subjects, there were somewhat more subjects with treatment related adverse events (TRAEs) of any grade in the 60 mg groups compared to 40 mg groups. This supports that the 40 mg dose may be more tolerable than 60 mg dose in combination with nivolumab.

In the pivotal CA2099ER trial, dose modifications were abundant. The majority of subjects had cabozantinib dose interruptions (68%) and dose reductions (51%) due to adverse events (see section 2.5 for further discussion on safety profile and dose-reductions). The limited data from CTEP-9681 indicate that an even lower cabozantinib starting dose could have reduced the risk of adverse events. This is also supported by previous exposure-response analyses in cabozantinib RCC monotherapy where higher exposure has been linked with increased risks of adverse events and dose reductions. It is unknown whether a lower cabozantinib dose could have resulted in similar efficacy, but it is likely that the risk of AEs would be reduced. Thus, a lower cabozantinib starting dose may provide a better benefit-risk profile in RCC patients co-treated with nivolumab. The MAH is recommended to investigate lower dose levels for cabozantinib in future studies both in monotherapy and when co-administered with nivolumab or other agents [**REC**].

For nivolumab, the MAH proposes two doses: 240 mg Q2W or 480 mg Q4W iv. At the time of the CA2099ER protocol initiation, nivolumab 240 mg Q2W flat dose had been shown to be comparable to 3 mg/kg Q2W in multiple tumour types, including RCC (2L). As the 480 mg Q4W dose was not approved at the time of the initiation of study CA2099ER, this dose was not explored in the pivotal study. The doses of nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W have been accepted to have a similar benefit-risk balance for treatment of melanoma and RCC (EMEA/H/C/003985/II/0036/G).

Study conduct

Originally, an Arm B was included in study CA2099ER, intended for studying the triplet cabo+nivo+ipi. However, this arm was later removed from the study protocol due to incoming data from the CA209314 trial demonstrating superior OS with nivo + ipi compared to sunitinib in the 1L RCC population. At the time of the revised protocol version 01, 15 participants had been randomised to CA2099ER (5, 4 and 6 participants to Arm A, B and C respectively). Revised protocol v.01 was implemented at the sites when approved locally. Thus, a delay occurred from the date of the new protocol version (18-Dec-2017) to the implementation at the last site (Sep-2018). Fifty (50) participants had been randomised to Arm B before the revised protocol was implemented on all study sites due to a delay of revised protocol implementation. According to the MAH, the delay was mainly due to dependence on the national approval process before implementation. The national approval process in one particular site in Mexico was particularly slow. At the same time, the protocol was also amended to include participants with favourable risk (according to IMDC criteria) into the study. The statistical analysis plan was updated with respect to the two protocol amendments well before database lock (30-Mar-2020) and subsequent availability of unblinded data, which is reassuring. Patients allocated to Arm B continued with the triplet-treatment per protocol version 00, and planned clinical evaluation per protocol. Data collected for subjects in Arm B are included in the dataset, however, not included in the "Analysed population"- see section Numbers Analysed.

The total number of subjects with significant protocol deviations was 149 (46.2%) in Arm A and 126 (38.5%) in Arm C. In total, 61 protocol deviations (31 in Arm A vs. 30 in Arm C) in the "failure to obtain written consent prior to each subject's participation in the study" category were registered. All randomised subjects signed an initial consent, thus most of these deviations were related to delays in re-consenting of updated written consent. Two sites, in Mexico and Chile respectively, reported a higher number of protocol deviations due to delayed implementation of protocol changes and failure to obtain written consent prior to participation in the study. According to the MAH, these PDs occurred due to lack of experience and unsatisfactory GCP routines on site. Still, it appears that the training of the PIs and the staff has been acceptable. Of note is that one (0.3%) subject in the experimental arm (nivo + cabo) received prohibited prior anti-cancer therapy with pazopanib in adjuvant therapy setting. No subjects were excluded from the intent to treat (ITT) analyses. Furthermore, there were also violations on basic rules of GCP such as failure to report all SAEs in accordance with the time period required and implementation of protocol changes prior to review by IRB/IEC. However, the number of these cases was low. The MAH has also satisfactorily justified that these significant PDs had no impact on trial results or interpretation. Overall, it is considered there is no impact on the overall data quality and integrity of the study.

Efficacy data and additional analyses

The data cut-off date for the primary data analysis in the CA2099ER study occurred on 12-Feb-2020. The median duration of follow-up (date of randomisation to the last known date alive or death date) was approximately 15.7 months for the nivo + cabo arm and 14.59 months for the sunitinib arm. By database lock (DBL) on 30-Mar-2020, the minimum and median follow-up for OS was approximately 10.6 and 18.1 months, respectively.

Baseline and disease characteristics

In general, the ITT population's baseline characteristics were well balanced between treatment arms, and the enrolled population is overall representative for the intended patients population. The percentage of participants in the IMDC risk categories of favourable, intermediate and poor risk was 22.6%, 57.6% and 19.7%, respectively, which reflects, in general, what is observed in clinical practice. A total of 24.9% of participants had tumor tissue PD-L1 expression score ≥ 1%. 11.5% of the participants had sarcomatoid features in the confirmed histology, and were well balanced between Arm A and C.

There was more extensive use of corticosteroids in the cabo + nivo arm, this is as expected due to more immune related toxicity in this arm. High dose corticosteroids were administered to approximately 20% of nivo+cabo treated subjects with immune-mediated adverse events (IMAEs) or Select AEs. Approximately 10% received high dose corticosteroids for a duration of at least 2 weeks and approximately 4% received high dose for a duration of at least 30 days.

Administration of systemic corticosteroids might decrease the AUC of cabozantinib by 20-50% via CYP3A4 induction. The potential clinical impact of lower exposure cannot be ascertained since cabozantinib exposure-response relationships are undetermined.

The impact of the use of systemic corticosteroids on cabozantinib exposure and efficacy cannot be concluded based on a post-hoc analysis in a small subgroup in the pivotal trial (data not shown). Exploratory data from nivolumab trials, support the assumption that concomitant use of corticosteroids has no detrimental effect on nivolumab efficacy. No such data is available for cabozantinib. The SmPC sections 4.2, 4.4 and 4.5 reflect that use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided.

Primary endpoint: PFS

At the original DBL 30-Mar-2020, a statistically significant benefit in PFS (secondary definition) was observed for nivolumab + cabozantinib over sunitinib (HR 0.54, 95% CI: 0.44, 0.67; $p < 0.0001$) with 159 (49.2%) and 211 (64.3%) events in the experimental and the control arm, respectively. The main reason for censoring was ongoing without event (48.6% in the nivo + cabo arm vs 29.9% in the sunitinib arm), no tumour assessment on-study (1.5% and 4%, respectively) and no baseline tumour assessment (0.6% and 1.8%, respectively). Of the patients censored due to no event, the majority was still on treatment (42.4% in the experimental arm vs 19.5% in the control arm).

The median PFS (nivo + cabo vs sunitinib) was 14.29 (95%CI: 12.29, 19.84) vs 8.31 (95%CI: 7.00, 9.69) months. Separation of the Kaplan-Meier (K-M) curves favoring nivo+cabo occurred early, and with no crossing of the curves. A lot of censoring is observed from approximately month 10-11.

Results from a sensitivity analysis of PFS using stratification factors as determined at baseline (CRF source) and a multivariate analysis (adjusting for several baseline factors) were consistent with the primary PFS analysis (both in regards to the primary and the secondary definition of PFS).

The MAH provided updated data with a 10-Sep-2020 DBL, corresponding to a minimum follow-up of 16.0 months (instead of 10.6) and a median follow-up of 23.5 months (instead of 18.1 months).

The updated PFS data were consistent with the primary data and thus confirmed the PFS benefit of nivo+cabo over sunitinib (

Figure 16 and Figure 17). Updated PFS results using the secondary definition were also consistent. At the 10-Sep-2020 DBL the difference between median PFS using the secondary vs the primary definition has decreased, aligning PFS results across definitions.

At the original DBL 30-Mar-2020, a benefit in PFS favouring the cabo + nivo arm was seen across the three pre-specified stratification categories: baseline IMDC prognostic score, PD-L1 tumor expression and region. However, median PFS was not reached in the favourable IMDC risk group in the nivo + cabo arm (event-rate 40.5%). For both the intermediate and poor risk groups median PFS was reached and the event-rates were slightly higher for the cabo+nivo arm (43.9% and 51.7%, respectively). Although a benefit in favour of the experimental arm was observed in the favourable risk group (HR = 0.60 [95% CI: 0.37, 0.98], per CRF), the immaturity of the data contributed to an uncertainty in the interpretation of the primary endpoint results for this subgroup.

The updated data showed a benefit of nivo+cabo vs sunitinib regardless of baseline IMDC prognostic score for PFS. Also for the favourable risk group, the PFS result remained clearly favourable (HR = 0.58 [95% CI: 0.36, 0.93] and median PFS was reached with 24.71 months in the nivo+cabo group vs 12.81 months in the sunitinib group.

A benefit in PFS in favour of the cabo + nivo arm was also seen across most other subgroups, except in Asian participants (7.8% of ITT, n = 51). It was concluded that the subgroup of Asian patients is too small and the number of PFS events is too limited to draw any firm conclusions that would question the clinical benefit of nivo+cabo in this subgroup (see below also). Of note, in the pivotal avelumab + axitinib study there was no discordance of efficacy results for the subgroup of Asian patients (n=133; 15.0% of full analysis set; Bavencio + Inlyta 1L RCC EPAR).

Of note, the PFS benefit was also observed in the subgroup of patients with sarcomatoid features in the tumor (11.5% of ITT).

Secondary endpoints:

OS

At the original DBL 30-Mar-2020, a statistically significant benefit was observed in the ITT population for nivolumab + cabozantinib over sunitinib (HR 0.60; 95%CI: 0.40, 0.89, p = 0.0010). There were 67 (20.7%) events in the experimental arm and 99 (30.2%) events in the control arm. The median OS was not reached in either study arm. The estimated percentage of patients who was alive at 9 months was 89.9% (95%CI: 86.0, 92.8) in the nivo + cabo arm and 80.5% (95%CI: 75.7, 84.4) in the sunitinib arm. The K-M curves for the two treatment arms seem to separate early with no crossing of the curves, and no detrimental effect is expected. Updated OS data were provided with DBL 10-Sep-2020 with an event rate of 26.6% in the nivo+cabo vs 35.4% in the sunitinib arm. Median OS was still not reached in nivo+cabo arm. Overall, these data were consistent with the primary data (Figure 18).

A benefit in OS in favour of the cabo + nivo arm was observed across the three pre-specified stratification categories: baseline IMDC prognostic score, PD-L1 tumour expression and region. However, median OS was not reached in the majority of the subgroups, and based on the DBL 30-Mar-2020, the data were considered too immature to draw any definitive conclusions.

The updated data showed a benefit of nivo+cabo vs sunitinib regardless of baseline IMDC prognostic score although, the OS HR for IMDC favourable-risk patients increased slightly, i.e. from 0.84 (30-Mar-2020 DBL) to 0.94 (10-Sep-2020 DBL) raising uncertainty on the OS benefit in this subgroup. However, updated OS data for this subgroup remain immature with only 15/74 vs 15/72 deaths/patients, respectively. Furthermore, there is no apparent detrimental effect on OS in this subgroup, the PFS result remained clearly favourable for this subgroup (HR = 0.58 [95% CI: 0.36, 0.93]; median PFS 24.71 vs 12.81 months) and ORR provided support (66.2% vs 44.4%, respectively).

Only in the small subgroup of Asian patients (n=51) and the small subgroup of patients ≥75 years of age (n=62) did the point estimate of the OS HR (numerically) favour sunitinib (i.e. 3.83 and 1.05, respectively). The 95% CI for OS HR was, however, wide for both these subgroups and, importantly, did encompass unity ('1'). It is also considered that the subgroup of Asian patients is too small and the number of deaths (4 vs 1, respectively) too few to question the clinical benefit of nivo+cabo in this subgroup. Of note, ORR results did favour nivo+cabo in this subgroup.

ORR

The objective responses rate based on BICR assessment favoured the nivo + cabo arm, 55.7% (95%CI: 50.1, 61.2) vs 27.1% (95%CI: 22.4, 32.3) in the sunitinib arm, and was irrespective of PD-L1 expression, IMDC risk group and region (original DBL 30-Mar-2020).

The updated ORR and DoR results were consistent with the original data (Table 17).

The updated data for ORR also showed a benefit of nivo+cabo vs sunitinib regardless of baseline IMDC prognostic score.

The median time to response (TTR) per BICR was 2.83 months (min, max: 1.0, 19.4) for all confirmed responders in the nivo + cabo arm and 4.17 months (min, max: 1.7, 12.3) for all confirmed responders in the sunitinib arm.

The median duration of response (DoR) favoured the participants treated in the nivo + cabo arm over the sunitinib arm: 20.17 months (95% CI: 17.31, N.A.) vs 11.47 months (95% CI: 8.31, 18.43).

Exploratory endpoints

PFS-2: At the original DBL 30-Mar-2020, median PFS-2 per investigator was not reached in either treatment arm. HR favoured the nivo+ cabo arm over the sunitinib arm: 0.52 (95% CI: 0.39, 0.70). Thus, there seems to be no detrimental impact of first-line treatment with the combination of nivolumab and cabozantinib on subsequent benefit from second-line treatments. Updated data were provided (event rate nivo+cabo: 30.3%; sunitinib: 42.4%; median PFS2 not reached in nivo+cabo arm) and these were consistent with the primary PFS2 data (data not shown). The interpretation of PFS-2 is hampered as the second-line treatment was not predefined per protocol.

HRQoL:

Even though PROs were captured through the use of two validated questionnaires (FKSI-19 and EQ-5D-3L), the HRQoL results are considered of a descriptive, hypothesis-generating nature only. It is, nevertheless, noted that patients in the sunitinib arm had a trend toward decreased scores/decline, whereas the patients in the nivo+cabo arm did not.

Biomarkers

Across all above efficacy endpoints (PFS, OS, and ORR), an efficacy benefit of nivo+cabo vs sunitinib was observed regardless of tumour cell PD-L1 expression status (<1%, ≥1%). This is in line with the results of the three recently approved ICI combinations in the 1L RCC setting (Moscetti et al. ESMO Open. 2020).

The updated efficacy data (PFS and OS) for the PD-L1 expression status subgroups confirmed the original results.

Special populations

Elderly patients: study CA2099ER included 250 patients (38.4%) ≥65 years of age and 62 patients (9.5%) ≥75 years of age. This is acceptable.

Contribution of each component in the combination regimen

The clinical trial design of the study CA2099ER is lacking a monotherapy arm, testing the combination (cabozantinib + nivolumab) against either of the two components of the combination. This leads to uncertainties when it comes to reaching a conclusion on the contribution of each agent to the combination. The MAH has presented several cross-trial comparisons to address this issue.

To justify the efficacy of nivolumab monotherapy in the 1st line RCC population, the MAH presented an investigator sponsored single arm phase 2 trial (CA209669) in RCC across all IMDC groups, which is still ongoing. The results from this study also serve the purpose of justifying the contribution of cabozantinib into the combination. The study is designed to evaluate the efficacy and safety of nivolumab monotherapy in the previously untreated RCC population, as well as the efficacy and safety of nivolumab + ipilimumab as salvage therapy in participants with tumors resistant to initial nivolumab monotherapy.

Of note, nivolumab is currently not approved as monotherapy for 1st line treatment in advanced RCC but only as monotherapy for the treatment of advanced RCC after prior therapy.

Based on the cross-trial difference observed in pooled ORR in favor of the nivo + cabo combination, the add-on activity of cabozantinib to nivolumab monotherapy can be supported. The provided data are indicative of an increase in ORR when cabozantinib is combined with nivolumab. As the nivolumab single-arm study in totality is small, the number of patients in each IMDC risk group becomes limited and it is not possible to conclude on the efficacy of nivolumab for each of these subgroups with certainty.

The benefit of cabozantinib monotherapy (thus, contribution of nivolumab into the combination) as 1st line treatment of RCC is justified by the CABOSUN trial. This was a Phase 2 trial comparing cabozantinib and sunitinib as 1st line treatment of patients with RCC leading to the approval of cabozantinib in the intermediate and poor risk population. Based on the cross trial increased ORR, the add-on tumor activity of nivolumab to cabozantinib monotherapy in patients with intermediate and poor risk can be supported.

To establish that the demonstrated contribution of components can be extrapolated to the 1st line favourable risk population, additional supportive data from the METEOR study were provided to compare the efficacy in the favourable risk population to the intermediate and poor risk populations. The METEOR trial was an open label trial in 2nd line plus patients that evaluated the efficacy of cabozantinib monotherapy compared with everolimus after progression on VEGF-targeted therapy. The differences in the patient populations greatly hamper the cross-study comparison between METEOR and CA2099ER. Even though the ORR was demonstrated to be similar across risk groups in METEOR, given all the limitations in this comparison, the justification of the extrapolation from data obtained in a 2L setting to a first line setting is deficient.

The lack of data on 1st line efficacy for Cabometyx in the favourable risk group is a fact. However, despite this uncertainty, the totality of the submitted data provide sufficient support of the efficacy for Cabometyx in the favourable risk group.

2.4.4. Conclusions on the clinical efficacy

In the single pivotal study CA2099ER, **the nivo+cabo combination demonstrated a clinically relevant and statistically significant improvement in PFS** per BICR (primary definition) compared with sunitinib treatment. This result was robust as results of all sensitivity analyses and of the analysis of PFS according to the secondary definition in line with the EMA/CHMP guideline were consistent with the primary analysis. Nivo+cabo also demonstrated a statistically significant improvement in the secondary endpoints **OS and ORR** (per BICR) **compared with sunitinib**.

An efficacy benefit of nivo+cabo vs sunitinib was observed regardless of baseline IMDC prognostic score and tumour cell PD-L1 expression status (<1%, ≥1%).

Updated results (10-Sep-20 DBL) were confirmative but remain somewhat immature regarding OS. Thus, there remains some uncertainty regarding an OS benefit, particularly in the subgroup of IMDC favourable-risk patients. This is, however, acceptable as there is no apparent detrimental effect on OS in any subgroup, including the subgroup of IMDC favourable-risk patients that has clearly favourable PFS results with support from ORR.

Regarding the contribution of the individual components, the additive efficacy of both individual components has been shown in a qualitative sense based primarily on an increase in ORR over the individual agents. This is considered acceptable despite the limitations of cross-study comparisons.

2.5. Clinical safety

Introduction

The previously EU-approved indications for cabozantinib (monotherapy) in advanced renal cell carcinoma (RCC) include treatment-naïve adults with intermediate or poor risk, and adults following prior VEGF-targeted therapy. The recommended dose is 60 mg cabozantinib PO QD (by mouth, once daily).

The safety profile of cabozantinib in the approved RCC indications is largely similar to other approved VEGFR-TKIs (e.g. sunitinib, sorafenib, regorafenib). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) include diarrhoea, fatigue, nausea, decreased appetite, PPES, hypertension, weight decreased, vomiting, dysgeusia, constipation, and AST increased. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%). The most common serious adverse reactions (SAEs) associated with cabozantinib in the RCC population (frequency ≥1%) are abdominal pain, diarrhoea, nausea, hypertension, embolism, hyponatraemia, pulmonary embolism, vomiting, dehydration, fatigue, asthenia, decreased appetite, deep vein thrombosis, dizziness, hypomagnesaemia and PPES.

The known safety profile of nivolumab includes fatigue, gastrointestinal complaints (including diarrhoea and nausea), and multiple immune-related AEs, including immune-related pneumonitis, colitis, hepatitis, nephritis, rash, and endocrinopathies (including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis).

The safety data presented here, in support of the new indication, are derived from 320 subjects treated with nivolumab +cabozantinib (nivo+cabo) in the ongoing **CA2099ER** study. The data are based on a 30 March 2020 database lock (DBL) with minimum 10.6 months of follow-up for overall survival. Updated safety data were submitted (DBL 10 September 2020), and are presented separately, as indicated.

In order to characterise the contribution of each drug to the safety profile of the nivo+cabo combination, the most common adverse events reported for the combination are presented in the context of available monotherapy data for nivolumab and cabozantinib in RCC indications as listed in *Table 20.*

Table 20. Monotherapy Studies Referenced for Nivolumab and Cabozantinib in Advanced RCC

Study ID / No. of Treated Subjects	Study Design	Dosing Regimen	Objectives
Nivolumab monotherapy studies			
CA209025 / N = 803 (406 nivolumab- treated subjects	A Phase 3 study of nivolumab vs everolimus in subjects with advanced or metastatic clear cell RCC who have received prior angiogenic therapy	Nivolumab at 3 mg/kg Q2W by IV infusion or everolimus 10 mg as a daily oral dose.	**Primary**: compare the clinical benefit, as measured by the duration of OS **Secondary**: ORR, PFS, DOR, safety and tolerability
CA209669 / N = 123 nivolumab-treated subjects	Phase 2, single-arm study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients with advanced RCC	Nivolumab 240 mg IV Q2W x 6 doses (2 cycles) then nivolumab 360 mg IV Q3W for 4 doses (2 cycles) followed by nivolumab 480 mg IV Q4W	**Primary:** Determine the PFS rate[a] at 1 year of nivolumab in patients with previously untreated ccRCC based on tumor PD-L1 expression. **Secondary**: • Determine the PFS rate at 1 year- by both RECIST and irRECIST of nivolumab in patients with treatment naïve ccRCC based on the PRP biomarker model developed in the DFHCC Kidney Cancer SPORE • Determine ORR, the ORR based on PDL-1 expression and the PRP model, and DoR • Determine the response rate of combined nivo and ipi therapy at the time of nivolumab failure (or lack of response at 1 year) • Determine the clinical activity (CR, PR and SD) and PFS at 1 year of nivolumab in patients with treatment naive nccRCC • Assess the toxicity of nivolumab monotherapy in patients with treatment naïve cc or nccRCC
Cabozantinib monotherapy studies			
METEOR / N = 653 (331 cabozantinib-treated subjects	A Phase 3, randomized, controlled study of cabozantinib vs everolimus in subjects with metastatic RCC that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Cabozantinib 60 mg PO QD or everolimus 10 mg PO QD	**Primary**: Compare PFS per IRRC of cabozantinib with that of everolimus **Secondary**: OS, ORR
CABOSUN / N = 150 (78 cabozantinib-treated subjects	CABOSUN (Alliance for Clinical Trials in Oncology A031203) is a randomized, phase 2 trial in advanced or metastatic ccRCC subjects who had intermediate or poor risk disease per IMDC criteria.[b]	Cabozantinib 60 mg PO QD or sunitinib 50 mg PO QD for 4 weeks, followed by a 2-week break.	**Primary:** Compare BIRC-assessed PFS [c,d] of cabozantinib with that of sunitinib. **Secondary:**[e] OS, ORR, and safety

[a] PFS is defined as the time from Day 1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause (primarily focusing on evaluation of PD-L1 expression levels to predict outcome)

[b] CABOSUN was a pivotal study for the FDA and EMA registration in first-line RCC

[c] PFS was defined as the time from randomization to the earlier of radiographic progression per RECIST version 1.1 or death due to any cause

[d] Retrospective blinded IRC radiographic data were also included

[e] Study did not have prespecified hypotheses for secondary endpoints

Abbreviations: ccRCC: clear cell RCC; CR: complete response; DFHCC: Dana-Farber/Harvard Cancer Center (DFHCC); DoR: duration of response; ir: immune-related; IRRC: Independent Radiology Review Committee; IV: intravenous; ncc RCC: non-clear cell RCC; ORR: objective response rate; OS: overall survival; PO: per os (orally); PD-L1: programmed death-ligand 1; PFS: progression-free survival; PR: partial response; PRP: PD1- Blockade Durable Response Predictive (biomarker model); QD: once daily; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; SPORE: Specialized Program in Research Excellence

Patient exposure

Overall, 1003 subjects were enrolled and 701 were randomized, including 323 to the nivo+cabo arm (Arm A), 328 to the sunitinib arm (Arm C), and 50 to the nivo+ipi+cabo arm (Arm B). Of the 651 randomized subjects in the nivo+cabo (N = 323) and sunitinib (N = 328) arms, 640 subjects were treated: 320 with nivo+cabo and 320 with sunitinib. At the time of the first DBL, study treatment was ongoing in 55.6% of the subjects treated with nivo+cabo and 28.8% with sunitinib. The data for study arm B have not been provided.

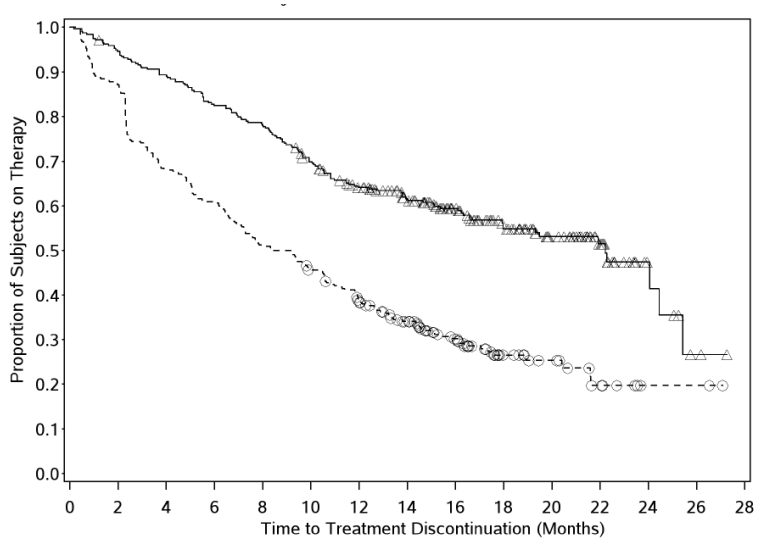
Table 21. Duration of Study Therapy

	Nivo + Cabo N = 320			Sun N = 320
	Nivo Only N = 320	Cabo Only N = 320	Overall N = 320	Sun N = 320
DURATION OF THERAPY (MONTHS)				
MEAN (MIN, MAX)	12.30 (0.0, 24.0)	12.65 (0.2, 27.3)	13.33 (0.2, 27.3)	9.68 (0.8, 27.6)
MEDIAN	13.31	13.78	14.26	9.23
Q1-Q3	6.93 - 17.31	7.11 - 17.49	8.66 - 18.20	2.94 - 14.93
> 3 MONTHS (%)	282 (88.1)	284 (88.8)	290 (90.6)	239 (74.7)
> 6 MONTHS (%)	248 (77.5)	252 (78.8)	263 (82.2)	196 (61.3)
> 9 MONTHS (%)	216 (67.5)	222 (69.4)	235 (73.4)	160 (50.0)
> 12 MONTHS (%)	172 (53.8)	182 (56.9)	193 (60.3)	129 (40.3)
DURATION OF THERAPY (MONTHS) (EXCLUDING DOSE HOLDS) [1]				
N		320		318
MEAN (MIN, MAX)		11.63 (0.2, 26.9)		6.52 (0.8, 17.3)
MEDIAN		12.62		6.05
Q1-Q3		6.78 - 15.97		2.33 - 9.82
> 3 MONTHS (%)		278 (86.9)		217 (68.2)
> 6 MONTHS (%)		247 (77.2)		160 (50.3)
> 9 MONTHS (%)		207 (64.7)		100 (31.4)
> 12 MONTHS (%)		167 (52.2)		41 (12.9)

[1] Subjects with negative duration are excluded.
Duration of therapy was defined as: last dose date - start dose date + 1 day

Source: Refer to Table 6.1-2 of the CA2099ER Final CSR[2]

Figure 22. Kaplan-Meier Plot of Time to Treatment Discontinuation



Number of Subjects at Risk

Nivolumab + Cabozantinib

320 302 285 263 249 220 193 163 118 82 56 31 8 2 0

Sunitinib

320 279 218 195 164 144 118 89 62 30 19 8 2 2 0

Nivolumab + Cabozantinib (events : 142/320), median and 95% CI : 22.21 (17.97, 25.43)

Sunitinib (events : 228/320), median and 95% CI : 8.77 (7.13, 10.55)

Symbols represent censored observations.
Subjects in Nivolumab + Cabozantinib arm considered as off treatment if both Nivolumab and Cabozantinib treatments are discontinued.

Table 22. End of Treatment Period Subject Status Summary

	Nivo + Cabo N = 320	Sun N = 320	Total N = 640
CONTINUING IN THE TREATMENT PERIOD	178 (55.6)	92 (28.8)	270 (42.2)
NOT CONTINUING IN THE TREATMENT PERIOD	142 (44.4)	228 (71.3)	370 (57.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD			
DISEASE PROGRESSION	89 (27.8)	154 (48.1)	243 (38.0)
STUDY DRUG TOXICITY	15 (4.7)	31 (9.7)	46 (7.2)
DEATH	4 (1.3)	3 (0.9)	7 (1.1)
ADVERSE EVENT UNRELATED TO STUDY DRUG	13 (4.1)	16 (5.0)	29 (4.5)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	2 (0.6)	6 (1.9)	8 (1.3)
SUBJECT WITHDREW CONSENT	4 (1.3)	8 (2.5)	12 (1.9)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.3)	1 (0.3)	2 (0.3)
COMPLETED TREATMENT AS PER PROTOCOL	1 (0.3)	0	1 (0.2)
OTHER	11 (3.4)	8 (2.5)	19 (3.0)
NOT REPORTED	2 (0.6)	1 (0.3)	3 (0.5)
CONTINUING IN THE STUDY	242 (75.6)	210 (65.6)	452 (70.6)
NOT CONTINUING IN THE STUDY	78 (24.4)	110 (34.4)	188 (29.4)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	62 (19.4)	84 (26.3)	146 (22.8)
SUBJECT WITHDREW CONSENT	9 (2.8)	13 (4.1)	22 (3.4)
LOST TO FOLLOW-UP	2 (0.6)	1 (0.3)	3 (0.5)
OTHER	4 (1.3)	11 (3.4)	15 (2.3)
NOT REPORTED	1 (0.3)	1 (0.3)	2 (0.3)

Table 23. Cumulative Dose and Relative Dose Intensity

	Nivo + Cabo N = 320		Sun N = 320
	Nivo N = 320	Cabo N = 320	Sun N = 320
NUMBER OF DOSES RECEIVED			
MEAN	25.9	341.1	188.2
(SD)	(14.1)	(188.6)	(133.5)
MEDIAN	27.5	352.5	173.0
(MIN - MAX)	(1 - 53)	(5 - 820)	(11 - 704)
CUMULATIVE DOSE (1)			
MEAN	6201.76	10841.80	8037.97
(SD)	(3368.69)	(6485.84)	(5641.58)
MEDIAN	6600.00	10120.00	7100.00
(MIN - MAX)	(240.0 - 12720.0)	(200.0 - 29080.0)	(550.0 - 22600.0)
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	1 (0.3)	12 (3.8)
90% TO < 110%	238 (74.4)	114 (35.6)	128 (40.0)
70% TO < 90%	69 (21.6)	52 (16.3)	99 (30.9)
50% TO < 70%	13 (4.1)	100 (31.3)	70 (21.9)
< 50%	0	53 (16.6)	11 (3.4)
AVERAGE DAILY DOSE (MG/DAY) (2)			
MEAN		29.55	27.84
(SD)		(10.29)	(6.06)
MEDIAN		29.37	28.42
(MIN - MAX)		(10.0 - 112.1)	(14.3 - 47.3)

(1) Dose units are mg.
(2) Only for Sunitinib and Cabozantinib.

Source: Refer to Table 6.1-1 of the Final CSR[2]

Table 24. Dose Reduction Summary for Cabozantinib

	Nivo + Cabo N = 320	Cabo N = 320
SUBJECTS TREATED	320	
SUBJECTS WITH ANY DOSE REDUCTION DUE TO AE	162 (50.6)	
EVER RECEIVED [40 MG DAILY] (ASSIGNED DOSE LEVEL)	320 (100.0)	
EVER RECEIVED [20 MG DAILY], RESULTING FROM AE (a)	161 (50.3)	
EVER RECEIVED [20 MG EVERY OTHER DAY], RESULTING FROM AE (a)	26 (8.1)	
LOWEST DOSE LEVEL RECEIVED (EXCLUDING DOSE HOLDS)		
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	155 (48.4)	
[20 MG DAILY], RESULTING FROM AE	134 (41.9)	
[20 MG EVERY OTHER DAY], RESULTING FROM AE	31 (9.7)	
LAST DOSE LEVEL RECEIVED (EXCLUDING DOSE HOLDS)		
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	167 (52.2)	
[20 MG DAILY], RESULTING FROM AE	122 (38.1)	
[20 MG EVERY OTHER DAY], RESULTING FROM AE	31 (9.7)	
LAST DOSE LEVEL RECEIVED (INCLUDING DOSE HOLDS)		
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	123 (38.4)	
[20 MG DAILY], RESULTING FROM AE	58 (18.1)	
[20 MG EVERY OTHER DAY], RESULTING FROM AE	22 (6.9)	
0 MG, RESULTING FROM AE	117 (36.6)	
TIME ON TREATMENT [MEDIAN (RANGE)] (DAYS) [1] AT:		
MORE THAN 0 MG	378.0 (5 - 820)	
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	129.0 (3 - 727)	
[20 MG DAILY], RESULTING FROM AE	224.0 (8 - 795)	
[20 MG EVERY OTHER DAY], RESULTING FROM AE	135.0 (7 - 489)	
0 MG, RESULTING FROM AE	26.5 (1 - 212)	
TIME TO FIRST DOSE LEVEL (20 MG) REDUCTION DUE TO AE (DAYS) [2]		
N	161	
MEAN (SD)	135.5 (101.7)	
MEDIAN (RANGE)	98.0 (9 - 506)	
25TH, 75TH PERCENTILES	63.0, 182.0	
TIME TO SECOND DOSE LEVEL (20 MG EVERY OTHER DAY) REDUCTION DUE TO AE (DAYS) [3]		
N	26	
MEAN (SD)	219.0 (160.6)	
MEDIAN (RANGE)	173.0 (65 - 613)	
25TH, 75TH PERCENTILES	102.0, 252.0	

[1] Time on treatment = sum of total days subject actually received the specified dose level; in each row, include all and only subjects who received treatment at that level, regardless of reason (exclude subjects who never received treatment at that level)
[2] Only subjects who had dose reduction due to AE were considered.
[3] Only subjects who had second dose reduction due to AE were considered.

(a) Reason associated to the first time ever receiving 20 mg daily or 20 mg every other day dosing resulting from AE is reported.

Source: Refer to Table 6.3-5 of the CA2099ER Final CSR[2]

Table 25. Dose Delay Summary

	Nivo + Cabo N = 320			Sun N = 320
	Nivo Only N = 320	Cabo Only N = 320	Both N = 320	Sun N = 320
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	230 (71.9)	218 (68.1)	267 (83.4)	166 (51.9)
NUMBER OF DOSE DELAYED PER SUBJECT (%)				
0	90 (28.1)	102 (31.9)	53 (16.6)	154 (48.1)
1	97 (30.3)	62 (19.4)	46 (14.4)	66 (20.6)
2	52 (16.3)	44 (13.8)	46 (14.4)	39 (12.2)
3	30 (9.4)	39 (12.2)	31 (9.7)	28 (8.8)
>= 4	51 (15.9)	73 (22.8)	144 (45.0)	33 (10.3)
TOTAL NUMBER OF DOSE DELAYED / TOTAL NUMBER OF DOSES RECEIVED (%) (A)	561/7955 (7.1)	823/108833 (0.8)	1384/116788 (1.2)	427/59888 (0.7)
REASON FOR DOSE DELAY (%) (B)				
ADVERSE EVENT	283 (50.4)	823 (100.0)	1106 (79.9)	427 (100.0)
DOSING ERROR	1 (0.2)	0	1 (<0.1)	0
NO CHANGE	1 (0.2)	0	1 (<0.1)	0
OTHER	199 (35.5)	0	199 (14.4)	0
NOT REPORTED	77 (13.7)	0	77 (5.6)	0
LENGTH OF DOSE DELAY (%) (B)				
1 - 3 DAYS	0	242 (29.4)	242 (17.5)	88 (20.6)
4 - 7 DAYS	257 (45.8)	182 (22.1)	439 (31.7)	162 (37.9)
8 - 14 DAYS	172 (30.7)	262 (31.8)	434 (31.4)	75 (17.6)
15 - 42 DAYS	107 (19.1)	118 (14.3)	225 (16.3)	97 (22.7)
> 42 DAYS	25 (4.5)	19 (2.3)	44 (3.2)	5 (1.2)

A dose was considered as actually delayed if the delay is exceeding 3 days for Nivolumab.
For Cabozantinib, daily dose of 0 mg entered with CRF reason "Adverse Event" will be considered as delay if cabozantinib is given daily. If cabozantinib is given every other day, then more than one 0 mg daily dose entered with CRF reason "Adverse Event" consecutively is considered as delay. For Sunitinib, a dose was considered delayed if subjects had 0 mg with a CRF reason "Adverse Event".
If reason for dose delay is not reported as "Adverse Event", "Dosing Error", or "No Change", then sites enter reason = "Other".
(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.
(B) Percentages are computed out of the total number of doses delayed.

Source: Refer to Table 6.3-3 of the CA2099ER Final CSR[2]

Demographics and Baseline Characteristics

For an overview of baseline characteristics of the patients included in the CA2099ER study, refer to clinical efficacy (Table 11).

Adverse events

Safety data (AEs, SAEs, AEs leading to treatment discontinuation, laboratory abnormalities, Select AEs for nivolumab, Events to Monitor for cabozantinib) from the **all treated population** (subjects who received at least one dose of any study medication) in the pivotal **CA2099ER** study is presented, including a safety window of 30 days after the last dose, with the intention of safety characterisation without influence of AEs associated with subsequent therapies. In addition, reported immune-mediated AEs (IMAEs) and other events of special interest (OESI) associated with the use of nivolumab are analysed within 100 days of the last dose (see section on other significant events below).

Table 26. Summary of Safety – All Treated Patients

	No. of Patients (%)			
Safety Parameters	**Nivo+Cabo (N =320)**		**Sunitinib (N =320)**	
Deaths at any time during the study	67 (20.9)		99 (30.9)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	148 (46.3)	109 (34.1)	127 (39.7)	94 (29.4)
Drug-related SAEs	78 (24.4)	66 (20.6)	41 (12.8)	31 (9.7)
All-causality AEs leading to DC (of any study drugs)	63 (19.7)	34 (10.6)	54 (16.9)	32 (10.0)
Drug-related AEs leading to DC (of any study drugs)	49 (15.3)	28 (8.8)	28 (8.8)	21 (6.6)
All-causality AEs	319 (99.7)	225 (70.3)	317 (99.1)	209 (65.3)
Drug-related AEs	309 (96.6)	194 (60.6)	298 (93.1)	162 (50.6)

For contextualisation, the most common AEs reported for the combination in the pivotal trial are presented along with available monotherapy safety data (see Table 28 below).

Table 27. Adverse Events by Worst CTC Grade, PTs reported in ≥10% of Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	319 (99.7)	225 (70.3)	16 (5.0)	317 (99.1)	209 (65.3)	17 (5.3)
Gastrointestinal disorders	267 (83.4)	47 (14.7)	2 (0.6)	252 (78.8)	34 (10.6)	1 (0.3)
Diarrhoea	204 (63.8)	22 (6.9)	0	151 (47.2)	14 (4.4)	0
Nausea	85 (26.6)	2 (0.6)	0	98 (30.6)	1 (0.3)	0
Vomiting	55 (17.2)	6 (1.9)	0	66 (20.6)	1 (0.3)	0
Stomatitis	54 (16.9)	8 (2.5)	0	79 (24.7)	7 (2.2)	0
Abdominal pain	50 (15.6)	5 (1.6)	0	27 (8.4)	1 (0.3)	0
Constipation	39 (12.2)	3 (0.9)	0	40 (12.5)	1 (0.3)	0
Dyspepsia	26 (8.1)	0	0	39 (12.2)	1 (0.3)	0
Gastrooesophageal reflux disease	25 (7.8)	0	0	36 (11.3)	0	0
Skin and subcutaneous tissue disorders	234 (73.1)	39 (12.2)	0	187 (58.4)	26 (8.1)	0
Palmar-plantar erythrodysaesthesia syndrome	128 (40.0)	24 (7.5)	0	130 (40.6)	24 (7.5)	0
Rash	69 (21.6)	6 (1.9)	0	26 (8.1)	0	0
Pruritus	60 (18.8)	1 (0.3)	0	14 (4.4)	0	0
General disorders and administration site conditions	221 (69.1)	31 (9.7)	2 (0.6)	229 (71.6)	38 (11.9)	3 (0.9)
Fatigue	103 (32.2)	11 (3.4)	0	111 (34.7)	15 (4.7)	0
Asthenia	71 (22.2)	14 (4.4)	0	59 (18.4)	10 (3.1)	0
Mucosal inflammation	66 (20.6)	3 (0.9)	0	81 (25.3)	8 (2.5)	0
Pyrexia	39 (12.2)	2 (0.6)	0	27 (8.4)	1 (0.3)	0
Oedema peripheral	34 (10.6)	1 (0.3)	0	28 (8.8)	0	0
Investigations	215 (67.2)	61 (19.1)	0	177 (55.3)	68 (21.3)	0
Alanine aminotransferase increased	90 (28.1)	17 (5.3)	0	27 (8.4)	7 (2.2)	0
Aspartate aminotransferase increased	81 (25.3)	11 (3.4)	0	35 (10.9)	4 (1.3)	0
Lipase increased	53 (16.6)	20 (6.3)	0	38 (11.9)	15 (4.7)	0
Amylase increased	47 (14.7)	10 (3.1)	0	29 (9.1)	8 (2.5)	0
Blood creatinine increased	42 (13.1)	4 (1.3)	0	43 (13.4)	1 (0.3)	0
Blood alkaline phosphatase increased	37 (11.6)	3 (0.9)	0	26 (8.1)	2 (0.6)	0
Weight decreased	35 (10.9)	2 (0.6)	0	10 (3.1)	0	0
Platelet count decreased	18 (5.6)	0	0	61 (19.1)	15 (4.7)	0
Metabolism and nutrition disorders	194 (60.6)	72 (22.5)	0	137 (42.8)	41 (12.8)	0
Decreased appetite	90 (28.1)	6 (1.9)	0	65 (20.3)	4 (1.3)	0
Hyponatraemia	51 (15.9)	30 (9.4)	0	28 (8.8)	19 (5.9)	0
Hypophosphataemia	46 (14.4)	19 (5.9)	0	18 (5.6)	4 (1.3)	0
Hypomagnesaemia	44 (13.8)	2 (0.6)	0	15 (4.7)	2 (0.6)	0
Musculoskeletal and connective tissue disorders	172 (53.8)	22 (6.9)	0	124 (38.8)	20 (6.3)	0
Arthralgia	59 (18.4)	1 (0.3)	0	29 (9.1)	1 (0.3)	0
Back pain	58 (18.1)	5 (1.6)	0	40 (12.5)	6 (1.9)	0
Muscle spasms	38 (11.9)	0	0	5 (1.6)	0	0
Infections and infestations	168 (52.5)	32 (10.0)	1 (0.3)	109 (34.1)	19 (5.9)	1 (0.3)
Upper respiratory tract infection	36 (11.3)	1 (0.3)	0	12 (3.8)	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	165 (51.6)	27 (8.4)	0	123 (38.4)	21 (6.6)	4 (1.3)
Cough	55 (17.2)	0	0	51 (15.9)	0	0
Dysphonia	55 (17.2)	1 (0.3)	0	11 (3.4)	0	0
Epistaxis	22 (6.9)	0	0	32 (10.0)	0	0
Nervous system disorders	163 (50.9)	11 (3.4)	1 (0.3)	146 (45.6)	12 (3.8)	0
Dysgeusia	76 (23.8)	0	0	69 (21.6)	0	0
Headache	50 (15.6)	0	0	37 (11.6)	2 (0.6)	0
Dizziness	33 (10.3)	1 (0.3)	0	19 (5.9)	0	0
Vascular disorders	130 (40.6)	48 (15.0)	0	133 (41.6)	47 (14.7)	0
Hypertension	111 (34.7)	40 (12.5)	0	119 (37.2)	42 (13.1)	0
Endocrine disorders	128 (40.0)	11 (3.4)	0	100 (31.3)	1 (0.3)	0
Hypothyroidism	109 (34.1)	1 (0.3)	0	94 (29.4)	1 (0.3)	0
Hyperthyroidism	32 (10.0)	2 (0.6)	0	9 (2.8)	0	0
Blood and lymphatic system disorders	85 (26.6)	10 (3.1)	0	146 (45.6)	40 (12.5)	0
Anaemia	48 (15.0)	6 (1.9)	0	81 (25.3)	12 (3.8)	0
Thrombocytopenia	25 (7.8)	2 (0.6)	0	62 (19.4)	15 (4.7)	0
Neutropenia	15 (4.7)	2 (0.6)	0	50 (15.6)	12 (3.8)	0
Renal and urinary disorders	73 (22.8)	17 (5.3)	0	65 (20.3)	17 (5.3)	0
Proteinuria	33 (10.3)	9 (2.8)	0	25 (7.8)	7 (2.2)	0

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Refer to Table 8.5-1 of the CA2099ER Final CSR[2]

Table 28. Assessment of Most Common All Causality AEs (>20%) in CA2099ER and Occurrence with Monotherapies

Adverse Event (PT)	CA2099ER[a] Nivo+Cabo N = 320		CA209025[a] Nivolumab N = 406		CA209669[b] Nivolumab N = 123		METEOR[a] Cabozantinib N = 331		CABOSUN Cabozantinib N = 78	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Diarrhea	204 (63.8)	22 (6.9)	96 (23.6)	5 (1.2)	38 (30.9)	4 (3.3)	245 (74)	38 (11)	57 (73)[f]	8 (10)[f]
Palmar-plantar erythrodys-aesthesia syndrome	128 (40.0)	24 (7.5)	10 (2.5)	0	1 (<0.1)[c]	0[c]	139 (42)	27 (8.2)	33 (42)[f]	6 (7.7)[f]
Hypertension	111 (34.7)	40 (12.5)	35 (8.6)	9 (2.2)	35 (28.4)	21 (17.1)	122 (37)	49 (15)	52 (67)[f]	22 (28)[f]
Hypothyroidism	109 (34.1)	1 (0.3)	28 (6.9)	1 (0.2)	21 (17.1)	0	68 (21)	0	18 (23)	0
Fatigue	103 (32.2)	11 (3.4)	195 (48.0)	18 (4.4)	52 (42.3)	4 (3.3)	186 (56)	30 (9.1)	50 (64)[f]	5 (6)[f]
ALT increased	90 (28.1)	17 (5.3)	26 (6.4)	12 (3.0)	21 (17.1)	3 (2.4)	53 (16)	8 (2.4)	43 (55)[f]	4 (5.1)[f]
Decreased appetite	90 (28.1)	6 (1.9)	93 (22.9)	5 (1.2)	NR[c]	NR[c]	152 (46)	9 (2.7)	37 (47)	4 (5.1)
Nausea	85 (26.6)	2 (0.6)	115 (28.3)	2 (0.5)	28 (22.8)	0	166 (50)	13 (3.9)	25 (32)	2 (2.6)
AST increased	81 (25.3)	11 (3.4)	31 (7.6)	11 (2.7)	19 (15.4)	3 (2.4)	58 (18)	6 (1.8)	47 (60)[f]	2 (2.6)[f]
Dysgeusia	76 (23.8)	0	14 (3.4)	0	3 (<0.1)[c]	0[c]	78 (24)	0	32 (41)	0
Asthenia	71 (22.2)	14 (4.4)	36 (8.9)	6 (1.5)	NR[c]	NR[c]	62 (19)	14 (4.2)	NR	NR
Rash	69 (21.6)	6 (1.9)	64 (15.8)	3 (0.7)	40 (32.5)[d]	4 (3.3)[d]	50 (15)	2 (0.6)	12 (15)[d,g]	0[d,g]
Mucosal inflammation	66 (20.6)	3 (0.9)	15 (3.7)	0	6 (<0.1)[c,e]	0[c,e]	64 (19)	3 (0.9)	NR	NR

NR = not reported in available sources. All listings in this table are AEs as reported by the Investigator.

[a] all events presented are within 30 days of last dose

[b] In CA209669, all events presented are within 100 days of last dose

[c] Source: Table 4d in CA209669 Report[14]

[d] Reported as rash (maculopapular)

[e] Reported as mucositis (oral)

[f] Solicited Adverse event

[g] Source: Table 26 in CABOMETYX - EMA assessment Report 2018[16]

Source: Table 2-1 (CA2099ER), Table 7.1.1-1 (CA209025), Table 7.1.2-1 (CA209669), Table 7.2.1-1 (METEOR), Table 7.2.2-1 (CABOSUN)

Exposure-adjusted AE summary

When incidence rates were exposure-adjusted, all-causality AE incidence rates (events per 100 person-years) were 1705.2 in the nivo+cabo treatment arm and 1852.6 in the sunitinib arm. The following was noted when comparing exposure-adjusted event data with non-exposure adjusted event data:

• AEs of diarrhoea, AST/ALT increased and hepatotoxicity, and rash remain more frequent in the nivo+cabo arm compared to the sunitinib arm in the exposure-adjusted event data also.

• In the exposure-adjusted data, relatively more events in Investigations, General disorders and administration site conditions (mainly due to fatigue), Skin and subcutaneous tissue disorders (mainly due to a relative increase in PPE and rash), Nervous system disorders and Vascular disorders were counted in the sunitinib arm compared to the nivo+cabo arm, while the rate of events was comparable across the two study arms or higher in the nivo+cabo arm in the non-exposure adjusted event data.

Drug-related AEs

Causal relationship to study drug was determined by the investigator and assessed as related (there is a reasonable causal relationship between study drug administration and AE) or not related (there is not a reasonable causal relationship between study drug administration and AE).

Table 29. Drug-Related Adverse Events by Worst CTC Grade Reported in ≥5% of Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	309 (96.6)	194 (60.6)	0	298 (93.1)	162 (50.6)	1 (0.3)
Gastrointestinal disorders	235 (73.4)	34 (10.6)	0	234 (73.1)	28 (8.8)	0
Diarrhoea	182 (56.9)	18 (5.6)	0	136 (42.5)	14 (4.4)	0
Nausea	68 (21.3)	2 (0.6)	0	81 (25.3)	0	0
Stomatitis	50 (15.6)	7 (2.2)	0	74 (23.1)	7 (2.2)	0
Vomiting	36 (11.3)	4 (1.3)	0	52 (16.3)	1 (0.3)	0
Abdominal pain	27 (8.4)	3 (0.9)	0	14 (4.4)	0	0
Dyspepsia	18 (5.6)	0	0	32 (10.0)	1 (0.3)	0
Gastrooesophageal reflux disease	15 (4.7)	0	0	29 (9.1)	0	0
Skin and subcutaneous tissue disorders	210 (65.6)	37 (11.6)	0	171 (53.4)	26 (8.1)	0
Palmar-plantar erythrodysaesthesia syndrome	122 (38.1)	24 (7.5)	0	129 (40.3)	24 (7.5)	0
Rash	62 (19.4)	5 (1.6)	0	22 (6.9)	0	0
Pruritus	52 (16.3)	1 (0.3)	0	13 (4.1)	0	0
Rash maculo-papular	24 (7.5)	1 (0.3)	0	4 (1.3)	0	0
Dry skin	16 (5.0)	0	0	11 (3.4)	0	0
Yellow skin	0	0	0	21 (6.6)	0	0
Investigations	180 (56.3)	49 (15.3)	0	158 (49.4)	58 (18.1)	0
Alanine aminotransferase increased	80 (25.0)	15 (4.7)	0	20 (6.3)	2 (0.6)	0
Aspartate aminotransferase increased	75 (23.4)	10 (3.1)	0	28 (8.8)	2 (0.6)	0
Lipase increased	48 (15.0)	17 (5.3)	0	35 (10.9)	15 (4.7)	0
Amylase increased	39 (12.2)	8 (2.5)	0	25 (7.8)	7 (2.2)	0
Blood alkaline phosphatase increased	29 (9.1)	2 (0.6)	0	21 (6.6)	2 (0.6)	0
Blood thyroid stimulating hormone increased	23 (7.2)	0	0	19 (5.9)	0	0
Weight decreased	23 (7.2)	2 (0.6)	0	8 (2.5)	0	0
Blood creatinine increased	20 (6.3)	2 (0.6)	0	20 (6.3)	0	0
Platelet count decreased	17 (5.3)	0	0	59 (18.4)	14 (4.4)	0
Blood bilirubin increased	16 (5.0)	1 (0.3)	0	11 (3.4)	1 (0.3)	0
Neutrophil count decreased	12 (3.8)	1 (0.3)	0	27 (8.4)	16 (5.0)	0
White blood cell count decreased	5 (1.6)	0	0	17 (5.3)	2 (0.6)	0
General disorders and administration site conditions	177 (55.3)	22 (6.9)	0	188 (58.8)	26 (8.1)	0
Fatigue	86 (26.9)	8 (2.5)	0	97 (30.3)	12 (3.8)	0
Mucosal inflammation	61 (19.1)	3 (0.9)	0	80 (25.0)	8 (2.5)	0
Asthenia	57 (17.8)	10 (3.1)	0	48 (15.0)	7 (2.2)	0
Malaise	10 (3.1)	1 (0.3)	0	16 (5.0)	0	0
Metabolism and nutrition disorders	153 (47.8)	49 (15.3)	0	105 (32.8)	24 (7.5)	0
Decreased appetite	65 (20.3)	4 (1.3)	0	53 (16.6)	2 (0.6)	0
Hyponatraemia	38 (11.9)	22 (6.9)	0	19 (5.9)	14 (4.4)	0
Hypophosphataemia	38 (11.9)	17 (5.3)	0	15 (4.7)	3 (0.9)	0
Hypomagnesaemia	32 (10.0)	1 (0.3)	0	9 (2.8)	0	0
Endocrine disorders	123 (38.4)	10 (3.1)	0	94 (29.4)	1 (0.3)	0
Hypothyroidism	107 (33.4)	1 (0.3)	0	90 (28.1)	1 (0.3)	0
Hyperthyroidism	29 (9.1)	2 (0.6)	0	6 (1.9)	0	0
Nervous system disorders	115 (35.9)	4 (1.3)	0	105 (32.8)	1 (0.3)	0
Dysgeusia	69 (21.6)	0	0	65 (20.3)	0	0
Headache	20 (6.3)	0	0	13 (4.1)	0	0
Vascular disorders	107 (33.4)	39 (12.2)	0	111 (34.7)	40 (12.5)	0
Hypertension	97 (30.3)	35 (10.9)	0	107 (33.4)	39 (12.2)	0
Respiratory, thoracic and mediastinal disorders	97 (30.3)	15 (4.7)	0	65 (20.3)	5 (1.6)	1 (0.3)
Dysphonia	37 (11.6)	1 (0.3)	0	8 (2.5)	0	0
Epistaxis	13 (4.1)	0	0	25 (7.8)	0	0
Musculoskeletal and connective tissue disorders	77 (24.1)	4 (1.3)	0	48 (15.0)	2 (0.6)	0
Arthralgia	29 (9.1)	0	0	12 (3.8)	0	0
Muscle spasms	25 (7.8)	0	0	2 (0.6)	0	0
Blood and lymphatic system disorders	66 (20.6)	6 (1.9)	0	129 (40.3)	33 (10.3)	0
Anaemia	32 (10.0)	3 (0.9)	0	61 (19.1)	8 (2.5)	0
Thrombocytopenia	19 (5.9)	1 (0.3)	0	61 (19.1)	14 (4.4)	0
Neutropenia	14 (4.4)	2 (0.6)	0	47 (14.7)	11 (3.4)	0
Leukopenia	4 (1.3)	0	0	23 (7.2)	1 (0.3)	0
Hepatobiliary disorders	45 (14.1)	17 (5.3)	0	31 (9.7)	3 (0.9)	0
Hepatotoxicity	18 (5.6)	8 (2.5)	0	10 (3.1)	1 (0.3)	0
Renal and urinary disorders	45 (14.1)	14 (4.4)	0	36 (11.3)	8 (2.5)	0
Proteinuria	26 (8.1)	9 (2.8)	0	21 (6.6)	7 (2.2)	0

MedDRA Version: 22.1, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.5-2 of the CA2099ER Final CSR[2]

Selection of specific adverse reactions from study CA2099ER to be presented in the proposed SmPC (Sections 4.4 and 4.8) for nivo+cabo was based on clinical relevance as determined by the Sponsor's medical reviewer. PTs considered to be related to either nivolumab or cabozantinib monotherapy as shown in the respective SmPCs, and found to be related events (or not assessed) by the investigator for the combination of nivo+cabo, were selected for inclusion into the tabulated list for nivo+cabo in Section

4.8 of the SmPC. Certain terms were excluded from the list of related events. These were events which were overly general/non-specific, events where the sponsor's medical reviewer did not suspect causal relationship to cabozantinib or nivolumab, and events which were captured under a different term.

In addition, laboratory values worsening from baseline for PTs in which laboratory testing was performed routinely in CA2099ER per protocol were considered for inclusion.

Updated safety data DBL Sep-2020

The median duration (defined as last dose date - start dose date + 1 day) of nivo+cabo was 17.99 months (16.13 months for nivolumab; 17.30 months for cabozantinib), and 9.15 months for sunitinib at the Sep-2020 DBL. Study treatment was ongoing in 45.0% of subjects treated with nivo+cabo and 22.2% with sunitinib. The median number of doses received during the treatment period was as follows nivo+cabo arm: 34.0 doses nivolumab, 417.5 doses cabozantinib, sunitinib arm: 166.0 doses sunitinib.

Dose delays of study drug (proportion of subjects with ≥1 dose delay) were as follows, as reported on the exposure page of the CRF:

- Nivo+cabo arm: 73.1% of subjects had delays for nivolumab only, 81.9% for cabozantinib only, and 89.4% for either nivolumab or cabozantinib
- Sunitinib arm: 72.8% had dose delays

Dose reductions (subjects with ≥1 dose reduction) were as follows, as reported on the exposure page of the CRF:

- Nivo+cabo arm: 59.4% had dose reductions of cabozantinib
- Sunitinib arm: 52.5% had dose reductions of sunitinib.

As of the Sep-2020 lock, there remained only one death reported due to study drug in the nivo+cabo treatment arm; the verbatim term for the cause of death per investigator was small intestine perforation.

The proportion of patients experiencing all causality AEs leading to discontinuation was 31.6% (drug-related 23.4%). In the below table a summary of safety data from the March 2020 and September 2020 cut-off is shown.

Table 30. CA2099ER Summary of Safety - All Treated Subjects - Mar-2020 and Sep-2020

Safety Parameters	No. of Subjects (%)							
	Mar-2020				Sep-2020			
	Nivo+Cabo (N =320)		Sunitinib (N =320)		Nivo+Cabo (N =320)		Sunitinib (N =320)	
Deaths (at any time during the study)	67 (20.9)		99 (30.9)		86 (26.9)		116 (36.3)	
Primary Reason for Death								
Disease	51 (15.9)		74 (23.1)		67 (20.9)		87 (27.2)	
Study Drug Toxicity[a]	1 (0.3)		2 (0.6)		1 (0.3)		2 (0.6)	
Unknown	3 (0.9)		6 (1.9)		3 (0.9)		10 (3.1)	
Other [b]	12 (3.8)		17 (5.3)		15 (4.7)		17 (5.3)	
	Adverse Event Grades				Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	148 (46.3)	109 (34.1)	127 (39.7)	94 (29.4)	155 (48.4)	115 (35.9)	131 (40.9)	96 (30.0)
Drug-related SAEs	78 (24.4)	66 (20.6)	41 (12.8)	31 (9.7)	80 (25.0)	60 (18.8)	41 (12.8)	31 (9.7)
All-causality AEs leading to DC (of any study drugs)	63 (19.7)[c]	34 (10.6)	54 (16.9)	32 (10.0)	101 (31.6)[c]	69 (21.6)	62 (19.4)	44 (13.8)
Drug-Related AEs leading to DC (of any study drugs)	49 (15.3)[d]	28 (8.8)	28 (8.8)	21 (6.6)	75 (23.4)[d]	48 (15.0)	29 (9.1)	24 (7.5)
All-causality AEs leading to dose delay or reduction (of any study drugs)[e]	267 (83.4)[f]	NA	232 (72.5)	NA	267 (83.4)[f]	NA	230 (71.9)	NA
Drug-Related AEs leading to dose delay or reduction (of any study drugs)[e]	250 (78.1)[g]	NA	207 (64.7)	NA	254 (79.4)[g]	NA	209 (65.3)	NA
All-causality AEs (PT)	319 (99.7)	225 (70.3)	317 (99.1)	209 (65.3)	319 (99.7)	251 (78.4)	317 (99.1)	234 (73.1)
≥ 20% of Subjects in Any Treatment Group								
Diarrhea	204 (63.8)	22 (6.9)	151 (47.2)	14 (4.4)	207 (64.7)	27 (8.4)	157 (49.1)	14 (4.4)
Palmar-plantar erythrodysaesthesia syndrome	128 (40.0)	24 (7.5)	130 (40.6)	24 (7.5)	128 (40.0)	24 (7.5)	132 (41.3)	26 (8.1)
Hypertension	111 (34.7)	40 (12.5)	119 (37.2)	42 (13.1)	116 (36.3)	43 (13.4)	120 (37.5)	42 (13.1)
Hypothyroidism	109 (34.1)	1 (0.3)	94 (29.4)	1 (0.3)	114 (35.6)	1 (0.3)	98 (30.6)	1 (0.3)
Fatigue	103 (32.2)	11 (3.4)	111 (34.7)	15 (4.7)	105 (32.8)	11 (3.4)	114 (35.6)	17 (5.3)
Alanine aminotransferase increased	90 (28.1)	17 (5.3)	27 (8.4)	7 (2.2)	95 (29.7)	18 (5.6)	29 (9.1)	8 (2.5)
Decreased appetite	90 (28.1)	6 (1.9)	65 (20.3)	4 (1.3)	97 (30.3)	6 (1.9)	66 (20.6)	4 (1.3)
Nausea	85 (26.6)	2 (0.6)	98 (30.6)	1 (0.3)	92 (28.8)	2 (0.6)	101 (31.6)	1 (0.3)
Aspartate aminotransferase increased	81 (25.3)	11 (3.4)	35 (10.9)	4 (1.3)	88 (27.5)	12 (3.8)	38 (11.9)	4 (1.3)
Dysgeusia	76 (23.8)	0	69 (21.6)	0	76 (23.8)	0	70 (21.9)	0
Asthenia	71 (22.2)	14 (4.4)	59 (18.4)	10 (3.1)	72 (22.5)	14 (4.4)	60 (18.8)	11 (3.4)
Rash	69 (21.6)	6 (1.9)	26 (8.1)	0	73 (22.8)	7 (2.2)	26 (8.1)	0
Mucosal inflammation	66 (20.6)	3 (0.9)	81 (25.3)	8 (2.5)	70 (21.9)	3 (0.9)	83 (25.9)	8 (2.5)
Vomiting	55 (17.2)	6 (1.9)	66 (20.6)	1 (0.3)	59 (18.4)	6 (1.9)	66 (20.6)	2 (0.6)
Stomatitis	54 (16.9)	8 (2.5)	79 (24.7)	7 (2.2)	58 (18.1)	8 (2.5)	81 (25.3)	8 (2.5)
Anemia	48 (15.0)	6 (1.9)	81 (25.3)	12 (3.8)	53 (16.6)	7 (2.2)	82 (25.6)	14 (4.4)
Pruritis	60 (18.8)	1 (0.3)	14 (4.4)	0	66 (20.6)	1 (0.3)	14 (4.4)	0
Back pain	58 (18.1)	5 (1.6)	40 (12.5)	6 (1.9)	65 (20.3)	6 (1.9)	40 (12.5)	6 (1.9)
Thrombocytopenia	25 (7.8)	2 (0.6)	62 (19.4)	15 (4.7)	26 (8.1)	2 (0.6)	64 (20.0)	15 (4.7)
Drug-related AEs	309 (96.6)	194 (60.6)	298 (93.1)	162 (50.6)	310 (96.9)	199 (62.2)	298 (93.1)	167 (52.2)
≥ 15% of Subjects in Any Treatment Group								
Diarrhea	182 (56.9)	18 (5.6)	136 (42.5)	14 (4.4)	187 (58.4)	21 (6.6)	143 (44.7)	14 (4.4)
Palmar-plantar erythrodysaesthesia syndrome	122 (38.1)	24 (7.5)	129 (40.3)	24 (7.5)	122 (38.1)	24 (7.5)	132 (41.3)	26 (8.1)
Hypothyroidism	107 (33.4)	1 (0.3)	90 (28.1)	1 (0.3)	112 (35.0)	1 (0.3)	94 (29.4)	1 (0.3)
Hypertension	97 (30.3)	35 (10.9)	107 (33.4)	39 (12.2)	100 (31.3)	37 (11.6)	107 (33.4)	39 (12.2)
Fatigue	86 (26.9)	8 (2.5)	97 (30.3)	12 (3.8)	86 (26.9)	8 (2.5)	101 (31.6)	14 (4.4)
Alanine aminotransferase increased	80 (25.0)	15 (4.7)	20 (6.3)	2 (0.6)	86 (26.9)	16 (5.0)	22 (6.9)	3 (0.9)
Aspartate aminotransferase increased	75 (23.4)	10 (3.1)	28 (8.8)	2 (0.6)	81 (25.3)	11 (3.4)	31 (9.7)	2 (0.6)
Dysgeusia	69 (21.6)	0	65 (20.3)	0	69 (21.6)	0	66 (20.6)	0

	No. of Subjects (%)							
	Mar-2020				Sep-2020			
Safety Parameters	Nivo+Cabo (N =320)		Sunitinib (N =320)		Nivo+Cabo (N =320)		Sunitinib (N =320)	
Nausea	68 (21.3)	2 (0.6)	81 (25.3)	0	72 (22.5)	1 (0.3)	85 (26.6)	0
	Adverse Event Grades				Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Decreased appetite	65 (20.3)	4 (1.3)	53 (16.6)	2 (0.6)	68 (21.3)	4 (1.3)	55 (17.2)	2 (0.6)
Rash	62 (19.4)	5 (1.6)	22 (6.9)	0	65 (20.3)	6 (1.9)	21 (6.6)	0
Mucosal inflammation	61 (19.1)	3 (0.9)	80 (25.0)	8 (2.5)	65 (20.3)	3 (0.9)	82 (25.6)	8 (2.5)
Asthenia	57 (17.8)	10 (3.1)	48 (15.0)	7 (2.2)	58 (18.1)	10 (3.1)	49 (15.3)	8 (2.5)
Pruritus	52 (16.3)	1 (0.3)	13 (4.1)	0	55 (17.2)	1 (0.3)	13 (4.1)	0
Stomatitis	50 (15.6)	7 (2.2)	74 (23.1)	7 (2.2)	52 (16.3)	7 (2.2)	75 (23.4)	8 (2.5)
Lipase increased	48 (15.0)	17 (5.3)	35 (10.9)	15 (4.7)	52 (16.3)	20 (6.3)	36 (11.3)	15 (4.7)
Vomiting	36 (11.3)	4 (1.3)	52 (16.3)	1 (0.3)	41 (12.8)	4 (1.3)	52 (16.3)	2 (0.6)
Anemia	32 (10.0)	3 (0.9)	61 (19.1)	8 (2.5)	32 (10.0)	2 (0.6)	63 (19.7)	10 (3.1)
Thrombocytopenia	19 (5.9)	1 (0.3)	61 (19.1)	14 (4.4)	20 (6.3)	1 (0.3)	62 (19.4)	14 (4.4)
Platelet count decreased	17 (5.3)	0	59 (18.4)	14 (4.4)	17 (5.3)	0	60 (18.8)	14 (4.4)
Neutropenia	14 (4.4)	2 (0.6)	47 (14.7)	11 (3.4)	15 (4.7)	2 (0.6)	50 (15.6)	13 (4.1)

[a] As reported in the Final CSR, the causes of death per investigator were as follows: in the nivo+cabo arm: 1 event of small intestine perforation; in the sunitinib arm: 2 events of respiratory distress and pneumonia

[b] As reported in the Final CSR, the verbatim terms reported for the 12 'other' reasons for death are: in the nivo+cabo arm: body ache (pain after a fall), cardiac embolism, AE (cardio-respiratory arrest), atrioventricular block with asystole, upper gastrointestinal bleeding, intestinal perforation, , septic shock secondary to pneumonia, heart failure, AE not related to study drug (intestinal perforation), cardiac arrest, hypoglycemia, and 1 not specified cause of death (updated to pneumonia at Sep-2020 DBL). The verbatim terms reported for the 3 additional 'other' reasons for death in the nivo+cabo arm reported at the Sep-2020 DBL are: bacteremia, bacterial infection, and acute hepatic failure (this subject death was previously captured at the Mar-2020 DBL, but the reason had been changed from 'Unknown' to 'Other' at the Sep-2020 DBL). As reported in the Final CSR, the verbatim terms reported for the 17 'other' reasons for death are: in the sunitinib arm: respiratory failure, cardiorespiratory arrest, respiratory infection, urinary infection which resulted in death, probable cardiopathy ischemic, ischemic heart disease, sepsis, acute heart attack, heart failure, necrotic bowel, gastrointestinal bleeding, pneumonia (2 events), progression of disease (2 events), and respiratory insufficiency (2 events).

[c] All-causality (any grade) AE led to dc of:
Mar-2020: only cabo in 24 (7.5%), only nivo in 21 (6.6%), both nivo and cabo at the same time in 18 (5.6%) subjects.

Sep-2020: only cabo in 31 (9.7%), only nivo in 32 (10.0%), both nivo and cabo at the same time in 27 (8.4%) subjects.

[d] Drug-related (any grade) AE led to dc of:
Mar-2020: only cabo in 21 (6.6%), only nivo in 18 (5.6%), both nivo and cabo at the same time in 10 (3.1%) subjects.
Sep-2020: only cabo in 23 (7.2%), only nivo in 31 (9.7%), both nivo and cabo at the same time in 16 (5.0%) subjects.

[e] Based on data reported on AE page of CRF. The term dose delay includes delay and interruption reported on the AE page because delay and interruption are used interchangeably for the oral drugs.

[f] All-causality (any grade) AE led to dose delay or reduction of:
Mar-2020: only cabo in 148 (46.3%), only nivo [delay; dose reduction not permitted] in 10 (3.1%), both nivo and cabo at the same time in 68 (21.3%), sequentially in 20 (6.3%), and unassigned in 21 (6.6%) subjects.
Sep-2020: only cabo in 125 (39.1%), only nivo [delay; dose reduction not permitted] in 6 (1.9%), both nivo and cabo at the same time in 85 (26.6%), sequentially in 50 (15.6%), and unassigned in 1 (0.3%) subjects (unassigned = unassigned to any of the other categories due to a lack of information on the CRF).

[g] Drug-related (any grade) AE led to dose delay or reduction of:
Mar-2020: only cabo in 139 (43.4%), only nivo [delay; dose reduction not permitted] in 8 (2.5%), both nivo and cabo at the same time in 65 (20.3%), sequentially in 20 (6.3%), and unassigned in 18 (5.6%) subjects.
Sep-2020: only cabo in 142 (44.4%), only nivo [delay; dose reduction not permitted] in 8 (2.5%), both nivo and cabo at the same time in 70 (21.9%), sequentially in 32 (10.0%), and unassigned in 2 (0.6%) subjects (unassigned = unassigned to any of the other categories due to a lack of information on the CRF).

MedDRA version 22.1 CTCAE version 4.0. All events are within 30 days of the last dose of study drug.

Abbreviations: AEs = adverse events; CTC = Common Toxicity Criteria; DC = discontinuation, PT - preferred term SAEs - serious adverse events.

Source: **Mar-2020 DBL:** Table 8.1-1 (overall safety summary), Table 6.1.3.1 (all-causality AEs), Table 6.1.3.2 (drug-related AEs), Table 6.4.1new.1 (all-causality AEs leading to DC), Table 6.4.1new.2 (drug-related AEs leading to DC), Table 6.4.1new.3 (all-causality AEs leading to dose delay or reduction), and Table 6.4.1new.4 (drug-related AEs leading to dose delay or reduction) in the CA2099ER Final CSR[1].
Sep-2020 DBL: Table 6.15 (deaths), Appendix 6.16 (deaths listing), Table 6.3.1.2.1 (all-causality SAEs), Table 6.3.1.2.2 (drug-related SAEs), Table 6.4.1.1 (all-causality AEs leading to DC), Table 6.4.1.2 (drug-related AEs leading to DC), Table 6.4.1.3 (all-causality AEs leading to dose delay or reduction), Table 6.4.1.4 (drug-related AEs leading to dose delay or reduction), Table 6.1.3.1 (all-causality AEs), Table 6.1.3.2 (drug-related AEs), in Appendix 18.

Table 31. Dose Reduction Summary for Cabozantinib – All Treated Subjects (DBL Sep 2020)

	Nivo + Cabo N = 320
	Cabo N = 320
SUBJECTS TREATED	320
SUBJECTS WITH ANY DOSE REDUCTION DUE TO AE	173 (54.1)
EVER RECEIVED [40 MG DAILY] (ASSIGNED DOSE LEVEL)	320 (100.0)
EVER RECEIVED [20 MG DAILY], RESULTING FROM AE	168 (52.5)
EVER RECEIVED [20 MG EVERY OTHER DAY], RESULTING FROM AE	30 (9.4)
LOWEST DOSE LEVEL RECEIVED (EXCLUDING DOSE HOLDS)	
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	146 (45.6)
[20 MG DAILY], RESULTING FROM AE	137 (42.8)
[20 MG EVERY OTHER DAY], RESULTING FROM AE	37 (11.6)
LAST DOSE LEVEL RECEIVED (EXCLUDING DOSE HOLDS)	
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	157 (49.1)
[20 MG DAILY], RESULTING FROM AE	126 (39.4)
[20 MG EVERY OTHER DAY], RESULTING FROM AE	37 (11.6)
LAST DOSE LEVEL RECEIVED (INCLUDING DOSE HOLDS)	
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	93 (29.1)
[20 MG DAILY], RESULTING FROM AE	45 (14.1)
[20 MG EVERY OTHER DAY], RESULTING FROM AE	21 (6.6)
0 MG, RESULTING FROM AE	161 (50.3)
TIME ON TREATMENT [MEDIAN (RANGE)] (DAYS) [1] AT:	
MORE THAN 0 MG	463.0 (5 - 968)
[40 MG DAILY] (ASSIGNED DOSE LEVEL)	129.0 (3 - 867)
[20 MG DAILY], RESULTING FROM AE	261.0 (8 - 943)
[20 MG EVERY OTHER DAY], RESULTING FROM AE	135.0 (7 - 637)
0 MG, RESULTING FROM AE	30.0 (1 - 314)
TIME TO FIRST DOSE LEVEL (20 MG) REDUCTION DUE TO AE (DAYS) [2]	
N	168
MEAN (SD)	154.6 (141.1)
MEDIAN (RANGE)	106.0 (9 - 814)
25TH, 75TH PERCENTILES	64.5, 197.0
TIME TO SECOND DOSE LEVEL (20 MG EVERY OTHER DAY) REDUCTION DUE TO AE (DAYS) [3]	
N	30
MEAN (SD)	256.1 (179.5)
MEDIAN (RANGE)	181.5 (65 - 613)
25TH, 75TH PERCENTILES	125.0, 403.0

[1] Time on treatment = sum of total days subject actually received the specified dose level; in each row, include all and only subjects who received treatment at that level, regardless of reason (exclude subjects who never received treatment at that level)
[2] Only subjects who had dose reduction due to AE were considered.
[3] Only subjects who had second dose reduction due to AE were considered.
Program Source: /opt/zfs001/prd/bms237293/stats/ebr2540/prog/tables/rt-ex-red-cabo.sas 02FEB2021:06:32:26

Table 32. Dose Delay Summary for Cabozantinib – All Treated Subjects (DBL Sep 2020)

	Nivo + Cabo N = 320
	Cabo N = 320
SUBJECTS WITH:	
ANY DOSE HOLD DUE TO AE	235 (73.4)
DOSE HOLD >= 7D DUE TO AE	218 (68.1)
DOSE HOLD >=14D DUE TO AE	168 (52.5)
DOSE HOLD >=21D DUE TO AE	80 (25.0)
DOSE HOLD > 42D DUE TO AE	19 (5.9)
NUMBER OF DOSE HOLDS PER SUBJECT DUE TO AE	
N	235
MEAN (SD)	4.2 (8.5)
MEDIAN (RANGE)	3.0 (1 - 120)
1	60 (18.8)
2	46 (14.4)
3	39 (12.2)
>3	90 (28.1)
TOTAL DURATION OF ALL DOSE HOLDS PER SUBJECT DUE TO AE (DAYS) [1]	
N	235
MEAN (SD)	44.8 (42.7)
MEDIAN (RANGE)	30.0 (1 - 314)
>= 7D	221 (94.0)
>=14D	193 (82.1)
>=21D	158 (67.2)
> 42D	94 (40.0)
DURATION OF EACH DOSE HOLDS PER THE NUMBER OF DOSE HOLDS DUE TO AE (DAYS) [2]	
TOTAL #	989
MEAN (SD)	10.7 (11.8)
MEDIAN (RANGE)	7.0 (1 - 114)
>= 7D	599 (60.6)
>=14D	348 (35.2)
>=21D	103 (10.4)
> 42D	23 (2.3)
MEDIAN (RANGE) TIME (DAYS) TO FIRST [3]	
DOSE HOLD DUE TO AE	68.0 (3 - 745)
DOSE HOLD >= 7D DUE TO AE	70.0 (3 - 700)
DOSE HOLD >=14D DUE TO AE	97.0 (3 - 738)
DOSE HOLD >=21D DUE TO AE	132.0 (10 - 759)
DOSE HOLD > 42D DUE TO AE	167.0 (19 - 700)
MEDIAN (RANGE) TIME (DAYS) TO SECOND [4]	
DOSE HOLD DUE TO AE	134.0 (14 - 738)
DOSE HOLD >= 7D DUE TO AE	152.0 (28 - 766)
DOSE HOLD >=14D DUE TO AE	208.0 (28 - 759)
DOSE HOLD >=21D DUE TO AE	178.5 (61 - 503)
DOSE HOLD > 42D DUE TO AE	354.0 (317 - 376)

[1] Duration of each dose hold = hold stop date - hold start date + 1; n = number of subjects who had dose holds due to AE. Total dose hold due to AE = summation of all dose holds due to AE.
[2] Summary of dose holds, where Total # = total number of dose holds due to AE (a subject may have more than 1 dose hold).
[3] Only subjects who had a dose hold due to AE were considered.
[4] Only subjects who had a second dose hold due to AE were considered.
Program Source: /opt/zfs001/prd/bms237293/stats/ebr2540/prog/tables/rt-ex-delay-cabo.sas 02FEB2021:06:31:37

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 33. Serious Adverse Events Reported in ≥1% of Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	148 (46.3)	109 (34.1)	16 (5.0)	127 (39.7)	94 (29.4)	17 (5.3)
Gastrointestinal disorders	33 (10.3)	18 (5.6)	2 (0.6)	14 (4.4)	8 (2.5)	1 (0.3)
Diarrhoea	15 (4.7)	6 (1.9)	0	0	0	0
Infections and infestations	31 (9.7)	27 (8.4)	1 (0.3)	19 (5.9)	16 (5.0)	1 (0.3)
Pneumonia	7 (2.2)	5 (1.6)	0	8 (2.5)	6 (1.9)	1 (0.3)
Urinary tract infection	6 (1.9)	5 (1.6)	0	5 (1.6)	4 (1.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (7.2)	12 (3.8)	8 (2.5)	20 (6.3)	13 (4.1)	4 (1.3)
Malignant neoplasm progression	13 (4.1)	5 (1.6)	8 (2.5)	13 (4.1)	7 (2.2)	4 (1.3)
Respiratory, thoracic and mediastinal disorders	23 (7.2)	17 (5.3)	0	22 (6.9)	15 (4.7)	4 (1.3)
Pneumonitis	9 (2.8)	5 (1.6)	0	0	0	0
Pulmonary embolism	9 (2.8)	9 (2.8)	0	3 (0.9)	3 (0.9)	0
Pleural effusion	2 (0.6)	2 (0.6)	0	8 (2.5)	6 (1.9)	0
Respiratory failure	1 (0.3)	1 (0.3)	0	4 (1.3)	2 (0.6)	2 (0.6)
General disorders and administration site conditions	13 (4.1)	7 (2.2)	2 (0.6)	18 (5.6)	9 (2.8)	3 (0.9)
Pyrexia	4 (1.3)	1 (0.3)	0	4 (1.3)	1 (0.3)	0
Metabolism and nutrition disorders	13 (4.1)	12 (3.8)	0	11 (3.4)	11 (3.4)	0
Hyponatraemia	7 (2.2)	7 (2.2)	0	4 (1.3)	4 (1.3)	0
Endocrine disorders	12 (3.8)	9 (2.8)	0	0	0	0
Adrenal insufficiency	6 (1.9)	5 (1.6)	0	0	0	0
Musculoskeletal and connective tissue disorders	12 (3.8)	10 (3.1)	0	15 (4.7)	12 (3.8)	0
Back pain	2 (0.6)	2 (0.6)	0	4 (1.3)	2 (0.6)	0
Renal and urinary disorders	6 (1.9)	3 (0.9)	0	12 (3.8)	9 (2.8)	0
Acute kidney injury	2 (0.6)	1 (0.3)	0	6 (1.9)	4 (1.3)	0
Blood and lymphatic system disorders	2 (0.6)	2 (0.6)	0	14 (4.4)	10 (3.1)	0
Anaemia	2 (0.6)	2 (0.6)	0	8 (2.5)	4 (1.3)	0

MedDRA Version: 22.1. CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.3-1 of the CA2099ER Final CSR[2]

Table 34. Drug-related Serious Adverse Events Reported in ≥1% of Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	78 (24.4)	66 (20.6)	0	41 (12.8)	31 (9.7)	1 (0.3)
Gastrointestinal disorders	20 (6.3)	13 (4.1)	0	7 (2.2)	4 (1.3)	0
Diarrhoea	11 (3.4)	6 (1.9)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	15 (4.7)	10 (3.1)	0	5 (1.6)	3 (0.9)	1 (0.3)
Pneumonitis	9 (2.8)	5 (1.6)	0	0	0	0
Pulmonary embolism	6 (1.9)	6 (1.9)	0	1 (0.3)	1 (0.3)	0
Endocrine disorders	10 (3.1)	8 (2.5)	0	0	0	0
Adrenal insufficiency	6 (1.9)	5 (1.6)	0	0	0	0
Metabolism and nutrition disorders	7 (2.2)	7 (2.2)	0	5 (1.6)	5 (1.6)	0
Hyponatraemia	4 (1.3)	4 (1.3)	0	3 (0.9)	3 (0.9)	0
Blood and lymphatic system disorders	1 (0.3)	1 (0.3)	0	9 (2.8)	7 (2.2)	0
Anaemia	1 (0.3)	1 (0.3)	0	5 (1.6)	3 (0.9)	0

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.3-2 of the CA2099ER Final CSR[2]

Table 35. Time to Resolution of Serious Adverse Event Summary - All Treated Subjects in CA2099ER

	Nivo + Cabo		Sun	
	Any Grade N = 148	Grade 3-5 N = 125	Any Grade N = 127	Grade 3-5 N = 111
NUMBER OF SUBJECTS WHO RESOLVED (%)	109 (73.6)	88 (70.4)	83 (65.4)	70 (63.1)
TIME TO RESOLUTION (WEEKS)				
MEDIAN(A)	2.00	2.00	1.57	1.71
(95% CI)	(1.57, 2.57)	(1.43, 2.29)	(1.14, 2.43)	(1.14, 2.86)
RANGE(B) (MIN - MAX)	0.1 - 107.9+	0.1 - 107.9+	0.1 - 65.6+	0.1+ - 65.6+

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced serious adverse event without worsening from baseline grade were excluded from time to resolution analysis.
Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.
Program Source: /opt/zfs001/prd/bms237293/stats/ebr2407_fa01/prog/tables/rt-ae-trsae.sas 19NOV2020:14:59:56

Deaths

Table 36. Death Summary

	Nivo + Cabo N = 320	Sun N = 320
NUMBER OF SUBJECTS WHO DIED (%)	67 (20.9)	99 (30.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	51 (15.9)	74 (23.1)
STUDY DRUG TOXICITY	1 (0.3)	2 (0.6)
UNKNOWN	3 (0.9)	6 (1.9)
OTHER	12 (3.8)	17 (5.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	22 (6.9)	30 (9.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE	12 (3.8)	15 (4.7)
STUDY DRUG TOXICITY	0	2 (0.6)
UNKNOWN	2 (0.6)	2 (0.6)
OTHER	8 (2.5)	11 (3.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	48 (15.0)	56 (17.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	35 (10.9)	37 (11.6)
STUDY DRUG TOXICITY	1 (0.3)	2 (0.6)
UNKNOWN	2 (0.6)	3 (0.9)
OTHER	10 (3.1)	14 (4.4)

Source: Refer to Table 8.2-1 of the CA2099ER Final CSR[2]

Death in one (0.3%) subject due to small intestine perforation in the nivo+cabo arm, and two (0.6%) subjects (due to respiratory distress and pneumonia/acute respiratory failure) in the sunitinib arm were considered as related to study drug by the investigator.

Table 37. Deaths attributed to "Other" Reasons

Verbatim Term for cause of Death	PT (Relationship)	Days since last dose
Nivo+cabo arm		
Body ache (after a fall)	Pain (not related)	51
Cardiac embolism	Not available	282
AE (cardio-respiratory arrest)	Cardio-respiratory arrest (not related)	7
Not specified[a]	Unknown	Unknown
Atrioventricular block with asystole	Hyponatraemia (not related)	16
Upper gastrointestinal bleeding	Upper gastrointestinal haemorrhage (not related)	23
Intestinal perforation	Radiation injury (not related)	6
Septic shock secondary to pneumonia	Septic shock (not related)	13
Heart failure	Not available	173
AE not related to study drug (intestinal perforation)	Intestinal perforation (not related)	17
Cardiac arrest	Cardiac arrest (not related)	12
Patient died due to hypoglycemia (SAE)	Hypoglycaemia (not related)	59
Sunitinib arm		
Respiratory failure	Respiratory failure (not related)	16
Progression of disease	Dyspnoea (not related)	2
Cardiorespiratory arrest	Cardio-respiratory arrest (not related)	45
Respiratory infection	Respiratory tract infection (not related)	21
Pneumonia	Pneumonia (not related)	22
Respiratory insufficiency	Respiratory failure (not related)	76
Respiratory insufficiency	Respiratory failure (not related)	73
Urinary infection, which resulted in death	Urinary tract infection (not related)	26
Probable cardiopathy ischemic	Myocardial ischaemia (not related)	2
Ischemic heart disease	Myocardial ischaemia (not related)	9
Sepsis	Not available	207
Progression	Malignant neoplasm progression (not related)	25
Acute heart attack	Myocardial infarction (not related)	14
Heart failure	Cardio-respiratory arrest (not related)	26
Necrotic bowel	Not available	166
Gastrointestinal bleeding	Gastrointestinal haemorrhage (not related)	9
Pneumonia	Not available	129

[a] This subject had a missing death date, which according to project convention was imputed by last known alive date of "2020-03-16". It was found out after DBL that the subjects died on 13-Jun-2020, and should not be included in this listing.
Not available: No relevant AE/SAEs were reported at the time when death occurred.

Source: Refer to Table 8.2.2-1 of the CA2099ER Final CSR[2]

Other Significant Events

Select Adverse Events, Immune-mediated Adverse Events and Other Adverse Events of Special Interest for nivolumab

To characterise adverse events of special clinical interest that may be associated with nivolumab, the MAH has defined and analysed several categories of AEs: Select AEs, Immune-mediated AEs (IMAEs), Other events of special interest (OESI).

Select adverse events (endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, rash, hypersensitivity/infusion reactions) are currently considered as select AEs, based on the following principles: AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies; AEs that may require immunosuppression (eg, corticosteroids) as part of their management; AEs whose early recognition and management may mitigate severe toxicity; AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization. Hypersensitivity/infusion reactions were analyzed along with the select AE categories

because multiple event terms may be used to describe such events and pooling of terms was, therefore, necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs. Events occurring within 30 days of the last dose were included.

Analysis of **immune-mediated adverse events** (IMAEs) included events (regardless of causality) for which subjects received immune-modulating medicines for treatment of the event, except for endocrine events which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. The analysis also included events where the investigator identified them as IMAEs due to no clear alternate pathology and an immune mediated component was present. Events occurring within 100 days of the last dose were included.

In order to capture **Other events of special interest** (OESI) that do not fulfill all criteria to qualify as IMAEs or Select AEs, and which may be associated with the use of cancer immunotherapy and require immunosuppression as part of their management, the following categories of AEs were defined: demyelination, encephalitis, Gullain-Barré syndrome, myasthenic syndrome, pancreatitis, uveitis, myositis, myocarditis, and rhabdomyelosis. Events occurring within 100 days of the last dose were included.

Table 38. Summary of Select Adverse Events, Immune-Mediated Adverse Events and Other Events of Special Interest – CA2099ER ()

Safety Parameters	No. of Subjects (%)			
	Nivo+Cabo (N =320)		Sunitinib (N =320)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality Select AEs				
Endocrine	142 (44.4)	8 (2.5)	113 (35.3)	1 (0.3)
Gastrointestinal	206 (64.4)	23 (7.2)	151 (47.2)	14 (4.4)
Hepatic	141 (44.1)	36 (11.3)	83 (25.9)	17 (5.3)
Pulmonary	17 (5.3)	5 (1.6)	2 (0.6)	2 (0.6)
Renal	59 (18.4)	7 (2.2)	52 (16.3)	4 (1.3)
Skin	216 (67.5)	35 (10.9)	159 (49.7)	24 (7.5)
Hypersensitivity/Infusion Reactions	11 (3.4)	0	6 (1.9)	2 (0.6)
Drug-related Select AEs				
Endocrine	137 (42.8)	8 (2.5)	106 (33.1)	1 (0.3)
Gastrointestinal	184 (57.5)	19 (5.9)	136 (42.5)	14 (4.4)
Hepatic	128 (40.0)	33 (10.3)	70 (21.9)	11 (3.4)
Pulmonary	17 (5.3)	5 (1.6)	1 (0.3)	1 (0.3)
Renal	31 (9.7)	4 (1.3)	26 (8.1)	1 (0.3)
Skin	199 (62.2)	34 (10.6)	151 (47.2)	24 (7.5)
Hypersensitivity/Infusion Reactions	8 (2.5)	0	1 (0.3)	0
All-causality IMAEs within 100 days of last dose Treated with Immune Modulating Medication				
Hepatitis	32 (10.0)	19 (5.9)	7 (2.2)	2 (0.6)
Rash	32 (10.0)	6 (1.9)	2 (0.6)	0
Diarrhea/Colitis	17 (5.3)	5 (1.6)	1 (0.3)	0
Pneumonitis	10 (3.1)	3 (0.9)	0	0
Nephritis/Renal Dysfunction	5 (1.6)	2 (0.6)	2 (0.6)	0
Hypersensitivity/Infusion Reactions	2 (0.6)	0	0	0
All-causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication				
Hypothyroidism/Thyroiditis	81 (25.3)	2 (0.6)	31 (9.7)	1 (0.3)
Hyperthyroidism	30 (9.4)	2 (0.6)	1 (0.3)	0
Adrenal Insufficiency	11 (3.4)	6 (1.9)	0	0
Hypophysitis	2 (0.6)	1 (0.3)	0	0
Diabetes Mellitus	0	0	0	0
All-causality OESIs within 100 days of last dose With or Without Immune Modulating Medication				
Pancreatitis	2 (0.6)	1 (0.3)	0	0
Encephalitis	2 (0.6)	1 (0.3)	0	0
Myositis	0	0	0	0
Myasthenic Syndrome	1 (0.3)	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	1 (0.3)	1 (0.3)	0	0
Uveitis	1 (0.3)	1 (0.3)	1 (0.3)	0
Myocarditis	1 (0.3)	1 (0.3)	0	0
Rhabdomyolysis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

Abbreviations: AE: adverse event; ALT: alanine amino transferase; AST: aspartate amino transferase; CTC: Common Toxicity Criteria; DC: discontinuation, IMAEs: immune-mediated adverse events; IMM: immune modulating medication; MedDRA: Medical Dictionary for Regulatory Activities; OESI: other events of special interest; SAE: serious adverse event

Source: Refer to Table 8.1-1 of the CA2099ER Final CSR[2]

Table 39. Onset, Management and Resolution of Drug-Related Select AEs – Nivolumab+Cabozantinib Treated Subjects (N=320)

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE (range), wks[c, d, e]	% Subj. with Drug-related Select AE that Resolved[d, e]
Endocrine	42.8 / 2.5	12.14 (2.0 - 84.7)	1.6	10.9 / 4.4	N.A. (0.9 - 101.4+)	34.3
Gastrointestinal	57.5 / 5.9	12.36 (0.3 - 75.7)	0.9	10.9 / 8.2	11.14 (0.1 - 109.1+)	69.4
Hepatic	40.0 / 10.3	8.14 (0.1 - 88.3)	3.1	27.3 / 23.4	9.14 (0.1 - 65.7+)	77.3
Pulmonary	5.3 / 1.6	24.00 (12.3 - 74.3)	0.9	52.9 / 47.1	6.36 (0.1+ - 36.9+)	70.6
Renal	9.7 / 1.3	14.14 (2.1 - 86.0)	0.3	19.4 / 9.7	3.50 (0.6 - 83.9+)	70.0
Skin	62.2 / 10.6	6.14 (0.1 - 92.3)	1.3	37.2 / 7.5	17.71 (0.1 - 106.6+)	65.8
Hypersensitivity/ Infusion Reaction	2.5 / 0	3.14 (0.1 - 18.0)	0	12.5 / 0	0.86 (0.1 - 10.9)	100.0

Includes events reported between first dose and 30 days after last dose of study therapy.

[a] Denominator is based on the number of subjects who experienced the event

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

[d] Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

Abbreviations: AE - adverse event, DC - discontinuation, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Source: Refer to Table 8.7-1 of the CA2099ER Final CSR[2]

Table 40. Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose – Nivolumab+Cabozantinib treated subjects (N=320)

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay[a] or Dose Reduction	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[b]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[c,d]	Median[e] Time to Resolution (range), wks [c,d,f,]	% Subj. with Recurrence after Reinitiation [g]
Pneumonitis	3.1/ 0.9	33.93 (12.3 - 61.0)	0.9 / 2.2	100.0 / 80.0	6.07 (1.6 - 56.3)	70.0	11.93 (2.9 - 32.6)	25.0 (1/4)
Diarrhea/Colitis	5.3 / 1.6	29.29 (4.1 - 87.1)	0.3 / 3.4	100.0 / 76.5	5.43 (0.1 - 75.4)	82.4	6.14 (0.6 - 62.3+)	33.3 (1/3)
Hepatitis	10.0 / 5.9	10.07 (4.0 - 46.7)	1.9 / 9.1	100.0 / 87.5	5.50 (1.0 - 81.1)	96.9	4.07 (0.9 - 37.4)	58.8 (10/17)
Nephritis/Renal Dysfunction	1.6 / 0.6	11.86 (4.0 - 41.9)	0 /1.3	100.0 / 40.0	6.00 (1.0 - 25.0)	80.0	1.14 (0.9 - 8.0+)	0 (0/3)
Rash	10.0 / 1.9	12.43 (0.7 - 99.3)	0.3 / 3.4	100.0 / 34.4	10.93 (0.6 - 100.1)	78.1	8.14 (0.1 - 55.0+)	0 (0/2)
Hypersensitivity/ Infusion Reactions	0.6 / 0	2.14 (0.1 - 4.1)	0 /0	100.0 / 50.0	2.07 (0.1 - 4.0)	100.0	3.07 (0.1 - 6.0)	N.A. (0 /0)
Endocrine IMAEs								
Adrenal Insufficiency	3.4 / 1.9	37.29 (4.1 - 76.7)	0.9 / 2.5	81.8 / 27.3	45.14 (16.9 - 82.1)	27.3	N.A. (0.9 - 82.1+)	66.7 (2/3)
Hypophysitis	0.6 / 0.3	47.93 (18.1 - 77.7)	0 / 0.6	50.0 / 50.0	58.00 (58.0 - 58.0)	50.0	N.A. (1.3 - 59.1+)	N.A. (0 /0)
Hypothyroidism/ Thyroiditis	25.3 / 0.6	18.14 (2.0 - 75.3)	0.3 / 1.6	3.7 / 1.2	1.00 (0.3 - 70.7)	37.0	N.A. (0.4 - 95.4+)	33.3 (1/3)
Hyperthyroidism	9.4 / 0.6	9.50 (2.1 - 77.9)	0.3 / 3.1	10.0 / 10.0	0.29 (0.1 - 1.1)	86.7	7.71 (0.3 - 70.0+)	0 (0/4)
Diabetes Mellitus	0 / 0	N.A.	0 / 0	N.A.	N.A.	N.A.	N.A.	N.A. (0/0)

[a] For oral drugs, dose delay include dose delays and dose interruptions.

[b] Denominator is based on the number of subjects who experienced the event.

[c] Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

[d] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

[e] From Kaplan-Meier estimation.

[f] Symbol + indicates a censored value.

[g] Percentages are based on subjects who were re-challenged. Numerator is the number of subjects who had a recurrence (or a positive re-challenge) and denominator is the number of subjects who were re-challenged. A positive re-challenge/recurrence is defined as any occurrence of new event(s) or worsening of any severity grade IMAE on or after study therapy re-initiation.

Abbreviations: DC - discontinuation, IMAE - immune-mediated adverse events, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Source: Refer to Table 8.8-1 of the CA2099ER Final CSR[2]

Table 41. Treatment, Onset, and Resolution Information for Other Events of Special Interest by Subject -All Treated Subjects

Event Description	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Nivolumab+cabozantinib				
Myasthenic syndrome				
Grade 2 drug-related AE of myasthenic syndrome	dexamethasone	27-Dec-2018 (21)	26	Yes
Grade 1 drug-related AE of myasthenic syndrome	dexamethasone	22-Jan-2019 (47)	121	Yes
Guillain-Barre syndrome				
Grade 3 drug-related SAE of Guillain-Barre syndrome	none	16-Nov-2018 (24)	12	Yes
Pancreatitis				
Grade 4 drug-related SAE of acute pancreatitis	methylprednisolone	19-Jun-2019 (252)	ongoing	No
Grade 2 drug-related SAE of pancreatitis	none	02-Jul-2019 (99)	ongoing	No
Uveitis				
Grade 2 drug-related AE of uveitis	none	07-Aug-2019 (211)	14	Yes
Grade 1 drug-related AE of uveitis	none	21-Aug-2019 (225)	43	Yes
Grade 3 drug-related AE of uveitis	dexamethasone	03-Oct-2019 (268)	28	Yes
Encephalitis				
Grade 3 drug-related SAE of encephalitis	corticosteroids	20-Jun-2019 (270)	33	Yes
Grade 1 drug-related AE of autoimmune encephalitis	none	26-Apr-2018 (24)	21	Yes
Myocarditis				
Grade 3 drug-related SAE of myocarditis	methylprednisolone	06-Aug-2019 (225)	7	Yes
Grade 3 drug-related AE of myocarditis	methylprednisolone	12-Aug-2019 (231)	8	Yes
Grade 2 drug-related AE of myocarditis	methylprednisolone	19-Aug-2019 (238)	43	Yes
Grade 1 drug-related AE of myocarditis	none	30-Sep-2019 (280)	ongoing	No
Sunitinib				
Uveitis				
Grade 2 unrelated AE of uveitis	dexamethasone	29-Jun-2018 (137)	14	Yes

Abbreviations: AE: adverse event, OESI: other events of special interest, SAE: serious adverse event

Source: Refer to Table 8.9-1 of the CA2099ER Final CSR[2]

Events to Monitor for Cabozantinib

To track events likely to be associated with the use of cabozantinib, a set of events to monitor (ETMs) were defined that are known to be associated with the use of tyrosine kinase inhibitors or vascular endothelial growth factor pathway inhibition and that may have potentially serious consequences or that have been determined to warrant ongoing routine surveillance.

These comprise GI perforation, abscess, intra-abdominal and pelvic abscess, fistula, wound complication, osteonecrosis, Grade ≥3 hemorrhage, hypertension, proteinuria, palmar-plantar erythrodysesthesia syndrome (PPES), posterior reversible encephalopathy syndrome (PRES), arterial thromboembolic events, venous and mixed thromboembolic events, QT prolongation, renal failure, and hepatotoxicity.

Each ETM is a grouped clinical term comprising a broad set of AEs that are related pathophysiologically. The search methods used to identify the AEs grouped within each ETM vary between ETMs and may include one or more of the following: standardized MedDRA queries (SMQs), keyword searches of MedDRA PTs, and predefined lists of relevant PTs. ETMs for cabozantinib are shown in Table 42 (modified

to show only associated PTs occurring in ≥2 subjects in the nivo+cabo treatment arm). Not all PTs for a given ETM have been reported for subjects receiving cabozantinib.

Table 42. Adverse Events to Monitor by Grade Sorted in Descending Difference in Percentages in Any Grade – (Lists associated PTs occurring in ≥2 subjects in the nivo+cabo treatment arm - modified by thereviewer)

Group Term (%) / Preferred Term (%)	Nivo + Cabo N = 320				Sun N = 320			
	Any Grade	Grade 3-4	Grade 4	Grade 5	Any Grade	Grade 3-4	Grade 4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	250 (78.1)	110 (34.4)	10 (3.1)	5 (1.6)	233 (72.8)	94 (29.4)	6 (1.9)	4 (1.3)
PPES	128 (40.0)	24 (7.5)	0	0	130 (40.6)	24 (7.5)	0	0
Palmar-plantar erythrodysaesthesia syndrome	128 (40.0)	24 (7.5)	0	0	130 (40.6)	24 (7.5)	0	0
HYPERTENSION	115 (35.9)	44 (13.8)	1 (0.3)	0	125 (39.1)	46 (14.4)	0	0
Hypertension	111 (34.7)	40 (12.5)	1 (0.3)	0	119 (37.2)	42 (13.1)	0	0
Blood pressure increased	6 (1.9)	3 (0.9)	0	0	7 (2.2)	4 (1.3)	0	0
HAEMORRHAGE	68 (21.3)	4 (1.3)	2 (0.6)	1 (0.3)	67 (20.9)	12 (3.8)	1 (0.3)	1 (0.3)
Epistaxis	22 (6.9)	0	0	0	32 (10.0)	0	0	0
Haematuria	9 (2.8)	1 (0.3)	0	0	14 (4.4)	4 (1.3)	0	0
Contusion	8 (2.5)	0	0	0	1 (0.3)	0	0	0
Gingival bleeding	8 (2.5)	0	0	0	2 (0.6)	0	0	0
Haemoptysis	5 (1.6)	0	0	0	8 (2.5)	2 (0.6)	0	0
Haematochezia	3 (0.9)	0	0	0	1 (0.3)	0	0	0
Haemorrhoidal haemorrhage	3 (0.9)	0	0	0	0	0	0	0
Anal haemorrhage	2 (0.6)	0	0	0	0	0	0	0
Haematoma	2 (0.6)	1 (0.3)	0	0	1 (0.3)	0	0	0
Increased tendency to bruise	2 (0.6)	0	0	0	1 (0.3)	0	0	0
Petechiae	2 (0.6)	0	0	0	1 (0.3)	0	0	0
PROTEINURIA	36 (11.3)	10 (3.1)	0	0	25 (7.8)	7 (2.2)	0	0
Proteinuria	33 (10.3)	9 (2.8)	0	0	25 (7.8)	7 (2.2)	0	0
Urine protein/creatinine ratio increased	5 (1.6)	0	0	0	0	0	0	0
VENOUS AND MIXED/UNSPECIFIED THROMBOTIC EVENTS	36 (11.3)	23 (7.2)	5 (1.6)	0	19 (5.9)	8 (2.5)	2 (0.6)	0
Pulmonary embolism	20 (6.3)	17 (5.3)	2 (0.6)	0	6 (1.9)	4 (1.3)	1 (0.3)	0
Deep vein thrombosis	8 (2.5)	2 (0.6)	1 (0.3)	0	2 (0.6)	0	0	0
Thrombosis	4 (1.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0	0
Embolism	2 (0.6)	2 (0.6)	0	0	2 (0.6)	1 (0.3)	1 (0.3)	0
Portal vein thrombosis	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0	0	0
Venous thrombosis limb	2 (0.6)	1 (0.3)	0	0	0	0	0	0
HEPATOTOXICITY	29 (9.1)	14 (4.4)	1 (0.3)	0	15 (4.7)	4 (1.3)	1 (0.3)	0
Hepatotoxicity	18 (5.6)	8 (2.5)	1 (0.3)	0	10 (3.1)	1 (0.3)	0	0
Hepatitis	6 (1.9)	3 (0.9)	0	0	1 (0.3)	0	0	0
Autoimmune hepatitis	2 (0.6)	2 (0.6)	0	0	0	0	0	0
RENAL FAILURE	22 (6.9)	3 (0.9)	0	0	21 (6.6)	4 (1.3)	2 (0.6)	0
Renal failure	10 (3.1)	1 (0.3)	0	0	4 (1.3)	0	0	0
Acute kidney injury	8 (2.5)	2 (0.6)	0	0	12 (3.8)	4 (1.3)	2 (0.6)	0
Renal impairment	4 (1.3)	0	0	0	2 (0.6)	0	0	0
Nephropathy toxic	3 (0.9)	0	0	0	4 (1.3)	0	0	0
OSTEONECROSIS	18 (5.6)	2 (0.6)	0	0	12 (3.8)	1 (0.3)	0	0
Tooth abscess	8 (2.5)	0	0	0	3 (0.9)	0	0	0
Tooth infection	7 (2.2)	1 (0.3)	0	0	8 (2.5)	1 (0.3)	0	0
Osteonecrosis of jaw	2 (0.6)	1 (0.3)	0	0	0	0	0	0
ABSCESS	13 (4.1)	3 (0.9)	0	0	4 (1.3)	0	0	0
Tooth abscess	8 (2.5)	0	0	0	3 (0.9)	0	0	0
Lung abscess	3 (0.9)	3 (0.9)	0	0	0	0	0	0
QT PROLONGATION	9 (2.8)	2 (0.6)	0	3 (0.9)	9 (2.8)	1 (0.3)	0	2 (0.6)
Syncope	5 (1.6)	2 (0.6)	0	0	4 (1.3)	1 (0.3)	0	0
WOUND COMPLICATION	9 (2.8)	1 (0.3)	0	0	4 (1.3)	1 (0.3)	0	0
Wound	4 (1.3)	1 (0.3)	0	0	1 (0.3)	0	0	0
ARTERIAL THROMBOTIC EVENTS	7 (2.2)	3 (0.9)	0	0	3 (0.9)	0	0	1 (0.3)
Ischaemic stroke	2 (0.6)	1 (0.3)	0	0	0	0	0	0
Myocardial infarction	2 (0.6)	2 (0.6)	0	0	2 (0.6)	0	0	1 (0.3)
GI PERFORATION	4 (1.3)	3 (0.9)	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	0	0
Appendicitis perforated	2 (0.6)	2 (0.6)	1 (0.3)	0	0	0	0	0
FISTULA	3 (0.9)	0	0	0	0	0	0	0
Anal fistula	2 (0.6)	0	0	0	0	0	0	0

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Subject is counted once if the subject reported one or more events.
Source: Refer to Table 8.10-1 of the CA2099ER Final CSR[2]

Table 43. Time to Resolution of ETM per Group Term - Treated Subjects Who Experienced at Least One ETM from the Group Term

	Nivo + Cabo Number of subjects with an Event (N = 250)	Sunitinib Number of subjects with an Event (N = 233)
Group term: Abscess		
Number (%) of subjects who resolved	12 (92%)	4 (100%)
Median Time to resolution (days) (95% CI) [A]	11.0 (6.0, 25.0)+	16.0 (5.0, 74.0)
Min, Max [B]	1.0, 55.0+	5.0, 74.0
Group term: Arterial thrombotic events		
Number (%) of subjects who resolved	6 (86%)	0
Median Time to resolution (days) (95% CI) [A]	21.0 (1.0, 62.0)	NE (NE, NE)
Min, Max [B]	1.0, 398.0+	1.0+, 412.0+
Group term: Fistula		
Number (%) of subjects who resolved	3 (100%)	0
Median Time to resolution (days) (95% CI) [A]	14.0 (1.0, 58.0)	
Min, Max [B]	1.0, 58.0	
Group term: GI perforation		
Number (%) of subjects who resolved	2 (50%)	0
Median Time to resolution (days) (95% CI) [A]	16.0 (10.0, NE)	NE (NE, NE)
Min, Max [B]	1.0+, 46.0+	31.0+, 31.0+
Group term: Haemorrhage		
Number (%) of subjects who resolved	4 (80%)	10 (77%)
Median Time to resolution (days) (95% CI) [A]	6.0 (1.0, 13.0)	8.0 (3.0, 20.0)
Min, Max [B]	1.0, 13.0	1.0+, 497.0
Group term: Hepatotoxicity		
Number (%) of subjects who resolved	26 (90%)	13 (87%)
Median Time to resolution (days) (95% CI) [A];	24.0 (15.0, 32.0)	22.5 (8.0, 64.0)
Min, Max [B]	6.0, 366.0+	3.0+, 168.0
Group term: Hypertension		
Number (%) of subjects who resolved	63 (55%)	65 (52%)
Median Time to resolution (days) (95% CI) [A]	212.0 (80.0, NE)	273.0 (63.0, NE)
Min, Max [B]	1.0, 756.0+	1.0, 632.0+
Group term: Osteonecrosis		
Number (%) of subjects who resolved	15 (83%)	10 (83%)
Median Time to resolution (days) (95% CI) [A]	7.5 (6.0, 11.0)	12.0 (7.0, 17.0)

	Nivo + Cabo Number of subjects with an Event (N = 250)	Sunitinib Number of subjects with an Event (N = 233)
Min, Max [B]	1.0, 275.0+	4.0+, 461.0+
Group term: PPES		
Number (%) of subjects who resolved	79 (62%)	70 (54%)
Median Time to resolution (days) (95% CI) [A]	140.0 (93.0, 235.0)	155.0 (74.0, NE)
Min, Max [B]	5.0, 666.0	4.0+, 587.0+
Group term: Proteinuria		
Number (%) of subjects who resolved	19 (53%)	13 (52%)
Median Time to resolution (days) (95% CI) [A];	204.0 (84.0, NE);	183.0 (42.0, NE);
Min, Max [B]	9.0, 736.0+	8.0, 576.0+
Group term: QT prolongation		
Number (%) of subjects who resolved	6 (67%)	7 (78%)
Median Time to resolution (days) (95% CI) [A];	1.0 (1.0, 9.0);	34.0 (1.0, 168.0);
Min, Max [B]	1.0, 9.0	1.0, 168.0
Group term: Renal failure		
Number (%) of subjects who resolved	13 (59%)	16 (76%)
Median Time to resolution (days) (95% CI) [A];	28.0 (15.0, NE)	24.0 (8.0, 36.0)
Min, Max [B]	1.0, 486.0+	2.0, 161.0+
Group term: Venous and mixed/unspecified thrombotic events		
Number (%) of subjects who resolved	14 (39%)	12 (63%)
Median Time to resolution (days) (95% CI) [A];	NE (44.0, NE);	75.0 (13.0, NE);
Min, Max [B]	2.0, 675.0+	1.0, 472.0+
Group term: Wound complication		
Number (%) of subjects who resolved	4 (44%)	3 (75%)
Median Time to resolution (days) (95% CI) [A];	NE (5.0, NE);	80.5 (28.0, NE);
Min, Max [B]	5.0, 568.0+	28.0, 197.0+

NE=not evaluable.

Includes events reported between first dose and 30 days after last dose of study therapy.

[A] From Kaplan-Meier estimation.

[B] Symbol + indicates a censored value.

Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis. Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

Source: Table 5 in Appendix 22

Table 44. Recurrence After Reinitiating Either Nivolumab or Cabozantinib Alone or Nivo+Cabo Therapy for ETM

Group term	No (N, %)	Yes (N, %)
Abscess	13 (100.00)	0
Arterial thrombotic events	7 (100.00)	0
Fistula	3 (100.00)	0
GI perforation	4 (100.00)	0
Haemorrhage	5 (100.00)	0
Hepatotoxicity	18 (62.07)	11 (37.93)
Hypertension	93 (80.87)	22 (19.13)
Osteonecrosis	18 (100.00)	0
PPES	98 (76.56)	30 (23.44)
Proteinuria	31 (86.11)	5 (13.89)
QT prolongation	8 (88.89)	1 (11.11)
Renal failure	19 (86.36)	3 (13.64)
Venous and mixed/unspecified thrombotic events	34 (94.44)	2 (5.56)
Wound complication	8 (88.89))	1 (11.11)

Source: Table 6 in Appendix 22.

Overlapping AEs

Hepatotoxicity (ALT/AST increases, and select hepatic events), diarrhea, hypothyroidism, and rash are part of the known safety profiles of both nivolumab and cabozantinib (ie, overlapping AEs). The higher frequencies and/or severities of these AEs with nivo+cabo observed in CA2099ER in comparison with the nivolumab and cabozantinib as monotherapies (and higher vs the sunitinib arm within CA2099ER), acknowledging the different doses of cabozantinib among the compared studies, suggest potentially additive effects of the two drugs when used in combination; these 4 terms are therefore assessed in more detail below.

Hepatotoxicity

Hepatotoxicity in CA2099ER was assessed by several methods including the Select hepatic AE category which comprises the following PTs: hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gammaglutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure. Unlike the ETM of hepatotoxicity, the Select hepatic AE category definition accounts for increases in transaminases, among other types of hepatic events, and may more comprehensively represent the incidence of hepatotoxicity than an all-causality SOC of hepatobiliary disorders or laboratory test results independently. The assessment of hepatotoxicity with the nivo+cabo combination in relation to the monotherapy components took into consideration the differences among nivolumab and cabozantinib monotherapy studies and the fact that the comprehensive hepatic 'select AE' grouping was not utilized across monotherapy studies, but only for nivolumab monotherapy in 2L+ RCC (CA209025). Laboratory test abnormalities (worsening from baseline) (ie, increased ALT and AST lab values) may be the most direct and objective measurements of hepatotoxicity, and therefore most relevant in relation to assessing the hepatic safety profile of the combination and the handling of dose modifications by the investigator for severe events.

Table 45. Any Hepatic Select Adverse Events Summary by Worst CTC grade – CA2099ER (modified by the assessor)

Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	141 (44.1)	36 (11.3)	0	83 (25.9)	17 (5.3)	0
Alanine aminotransferase increased	90 (28.1)	17 (5.3)	0	27 (8.4)	7 (2.2)	0
Aspartate aminotransferase increased	81 (25.3)	11 (3.4)	0	35 (10.9)	4 (1.3)	0
Blood alkaline phosphatase increased	37 (11.6)	3 (0.9)	0	26 (8.1)	2 (0.6)	0
Blood bilirubin increased	18 (5.6)	1 (0.3)	0	13 (4.1)	3 (0.9)	0
Hepatotoxicity	18 (5.6)	8 (2.5)	0	10 (3.1)	1 (0.3)	0
Gamma-glutamyltransferase increased	13 (4.1)	3 (0.9)	0	7 (2.2)	3 (0.9)	0
Transaminases increased	12 (3.8)	2 (0.6)	0	7 (2.2)	2 (0.6)	0
Hepatic enzyme increased	7 (2.2)	0	0	2 (0.6)	0	0
Hepatitis	6 (1.9)	3 (0.9)	0	1 (0.3)	0	0
Hyperbilirubinaemia	6 (1.9)	1 (0.3)	0	8 (2.5)	1 (0.3)	0
Liver function test increased	3 (0.9)	0	0	1 (0.3)	0	0
Autoimmune hepatitis	2 (0.6)	2 (0.6)	0	0	0	0
Liver function test abnormal	1 (0.3)	0	0	0	0	0
Drug-induced liver injury	0	0	0	1 (0.3)	1 (0.3)	0
Hepatic failure	0	0	0	1 (0.3)	1 (0.3)	0

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Endocrine Adverse Events are not included in this table.
Program Source: /opt/zfs001/prd/bms237293/stats/interim/prog/tables/rt-ae-slaegr.sas 14MAY2020:09:01:18

Diarrhoea

In CA2099ER, all-causality AEs in the PT 'diarrhea' occurred in the nivo+cabo treatment arm with a frequency of 63.8% (any grade); 6.9% (Grade 3-4) (Table 27). In comparison, in the nivolumab monotherapy trials CA209205 and CA209669 and the cabozantinib monotherapy trials METEOR and CABOSUN, all-causality AEs of diarrhoea occurred with a frequency of 23.6%, 30.9%, 74% and 73%, respectively; grade 3-4: 1.2%, 3,3%, 11% and 10%, respectively.

Most all causality AEs of diarrhoea with nivo+cabo were considered drug-related (56.9%) by the investigator (Table 29). Very few diarrhoea events (0.6%) led to discontinuation of treatment (Table 56). 11 subjects (3.4%) in the nivo+cabo arm had a serious drug-related select AE of diarrhea (Table 34). The incidence of diarrhoea/colitis requiring immune modulating medication (IMAEs) was 5.3% (Table 40).

Hypothyroidism

In CA2099ER, all-causality AEs in the PT 'hypothyroidism' with nivo+cabo were reported more frequently with nivo+cabo (34.1% any grade; 0.3% Grade 3-4) compared with sunitinib (29.4% any grade; 0.3% Grade 3-4; Table 27). In comparison, in the nivolumab monotherapy trials CA209205 and CA209669 and the cabozantinib monotherapy trials METEOR and CABOSUN, all-causality AEs of hypothyroidism occurred with a frequency of 6.9%, 17.1%, 21% and 23%, respectively; grade 3-4: 0.2%, 0%, 0% and 0%, respectively.

Almost all causality AEs of hypothyroidism with nivo+cabo were considered drug-related (33.4%) by the investigator (Table 29). When reported as on-treatment thyroid function laboratory abnormalities (see below), 63.4% of subjects had normal baseline but elevated post-baseline TSH levels with nivo+cabo, and 30.6% of subjects had elevated TSH as well as at least one FT3/FT4 < LLN, consistent with hypothyroidism (Table 52).

Very few (0.3%) events of hypothyroidism in the nivo+cabo arm led to discontinuation of treatment. One subject (0.3%) in the nivo+cabo arm had a serious drug-related AE of hypothyroidism (data not shown).

Hypothyroidism/thyroiditis is within the category of endocrine IMAEs, which do not have a requirement of immune modulating medication, and the incidence was 25.3% (grade 3-4 0.6%) in the nivo+cabo arm (Table 40).

Rash

In CA2099ER, all-causality any grade AEs in the PT 'rash' (21.6% any grade; 1.9% Grade 3-4) were mainly Grade 1-2 in severity with nivo+cabo (Table 27). In comparison, in the nivolumab monotherapy trials CA209205 and CA209669 and the cabozantinib monotherapy trials METEOR and CABOSUN, all-causality AEs of rash occurred with a frequency of 15.8%, 32.5%, 15%, 15%, respectively; grade 3-4: 0.7%, 3.3%, 0.6%, 0%, respectively.

In CA2099ER, most all causality AEs of rash with nivo+cabo were considered drug-related (19.4%) by the investigator. One subject (0.3%) in the nivo+cabo arm had a serious drug-related AE of rash. The incidence of IMAEs of rash in the nivo+cabo arm (10.0%) indicates the requirement of immune modulating medication for rash in CA2099ER.

Adverse Events Leading to Dose Delay/Interruption or Reduction

AEs leading to dose delays or reductions

The numbers and percentages of patients with any-Grade all-causality AEs leading to dose delays or reductions as of the 30-Mar-2020 DBL were as follows:

- Nivo+cabo arm: 267 patients (83.4%) with AEs leading to delays or reductions *of any study drugs*
  - Nivolumab only: 10 patients (3.1%) with AEs leading to delays of nivolumab only
  - Cabozantinib only: 148 patients (46.3%) with AEs leading to delays or reductions of cabozantinib only
  - Both nivolumab and cabozantinib: 68 patients (21.3%) with AEs leading to delays or reductions of both nivolumab and cabozantinib due to the same AE at the same time
  - Sequential: 20 patients (6.3%) with AEs leading to sequential delays or reductions of nivolumab and cabozantinib
  - Unassigned: 21 patients (6.6%) were unassigned to any of the above categories due to lack of information on the study drug exposure CRF page
- Sunitinib arm: 232 patients (72.5%) with AEs leading to delays or reductions of sunitinib

The most frequently reported all-causality AEs leading to dose delays or reductions *of any study drugs* were:

- Nivo+cabo: diarrhoea (24.4%), PPES (19.1%), and hypertension (10.6%), ALT increased (10.0%)
- Sunitinib: PPES (15.0%), diarrhoea (11.3%), hypertension (10.6%), thrombocytopenia (9.7%)

Most AEs leading to dose delays or reductions were treatment-related AEs.

All-causality AEs leading to dose delays:

Any-grade all-causality AEs leading to dose delays of any study drug reported as of the 30-Mar-2020 DBL were as follows:

- Nivo+cabo arm: Any-grade and Grade 3-4 all-causality AEs leading to dose delays due to an AE of either nivolumab and/or cabozantinib occurred in 252 (78.8%) and 159 (49.7%) subjects, respectively.
- Sunitinib arm: Any-grade and Grade 3-4 all-causality AEs leading to dose delays due to an AE occurred in 209 (65.3%) and 148 (46.3%) subjects, respectively.

The most frequently reported any-grade all-causality AEs leading to dose delays (of any study drugs) were as follows:

- Nivo+cabo: diarrhoea (20.6%), palmar-plantar erythrodysaesthesia syndrome (PPES) (15.9%), hypertension (10.0%), ALT increased (9.1%)
- Sunitinib: PPES (10.9%), diarrhoea (9.4%), hypertension (8.8%), thrombocytopenia (8.4%)

All-causality AEs leading to dose reductions as of the 30-Mar-2020 DBL:

- Nivo+cabo arm: Any-grade and Grade 3-4 all-causality AEs leading to dose reductions of cabozantinib occurred in 126 (39.4%) and 29 (9.1%) subjects, respectively.
- Sunitinib arm**:** Any-grade and Grade 3-4 all-causality AEs leading to dose reductions occurred in 90 (28.1%) and 28 (8.8%) subjects, respectively.

The most frequently reported any-grade all-causality AEs leading to dose reductions (of any study drugs) were as follows:

- Nivo+cabo: PPES (7.8%), diarrhoea (5.6%), proteinuria (3.1%), hypertension (2.8%)
- Sunitinib: PPES (6.3%), hypertension (3.1%), platelet count decreased (2.8%), diarrhea (2.5%).

Laboratory findings

Laboratory result abnormalities that were recorded regardless of causality and reported after first dose and within 30 days of last dose of study therapy as of the 30-Mar-2020 DBL are presented below for all patients treated with nivo+cabo or sunitinib in CA2099ER.

Table 46. Summary of On-Treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters that Worsened Relative to Baseline - SI Units with 30 Days Follow Up - All Treated Patients

	Number of Subjects (%)					
	Nivo + Cabo			Sun		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	316	117 (37.0)	8 (2.5)	311	190 (61.1)	15 (4.8)
PLATELET COUNT	316	129 (40.8)	1 (0.3)	310	216 (69.7)	30 (9.7)
LEUKOCYTES, LOCAL LAB	316	116 (36.7)	1 (0.3)	311	206 (66.2)	16 (5.1)
LYMPHOCYTES (ABSOLUTE), LOCAL LAB	228	95 (41.7)	15 (6.6)	225	102 (45.3)	23 (10.2)
ABSOLUTE NEUTROPHIL COUNT	316	112 (35.4)	10 (3.2)	311	209 (67.2)	36 (11.6)
ALKALINE PHOSPHATASE, LOCAL LAB	317	131 (41.3)	9 (2.8)	310	115 (37.1)	5 (1.6)
ASPARTATE AMINOTRANSFERASE, LOCAL LAB	317	245 (77.3)	25 (7.9)	310	177 (57.1)	8 (2.6)
ALANINE AMINOTRANSFERASE, LOCAL LAB	316	249 (78.8)	31 (9.8)	310	121 (39.0)	11 (3.5)
BILIRUBIN, TOTAL, LOCAL LAB	316	54 (17.1)	3 (0.9)	309	68 (22.0)	3 (1.0)
CREATININE, LOCAL LAB	317	121 (38.2)	4 (1.3)	311	135 (43.4)	2 (0.6)
HYPERNATREMIA	317	34 (10.7)	0	310	24 (7.7)	0
HYPONATREMIA	317	140 (44.2)	37 (11.7)	310	113 (36.5)	37 (11.9)
HYPERKALEMIA	317	113 (35.6)	15 (4.7)	309	83 (26.9)	3 (1.0)
HYPOKALEMIA	317	61 (19.2)	10 (3.2)	309	37 (12.0)	6 (1.9)
HYPERCALCEMIA	314	28 (8.9)	1 (0.3)	309	41 (13.3)	3 (1.0)
HYPOCALCEMIA	314	172 (54.8)	6 (1.9)	309	74 (23.9)	2 (0.6)
HYPERMAGNESEMIA	308	44 (14.3)	10 (3.2)	304	32 (10.5)	7 (2.3)
HYPOMAGNESEMIA	308	153 (49.7)	5 (1.6)	304	88 (28.9)	1 (0.3)
HYPERPHOSPHATEMIA	307	0	0	307	0	0
HYPOPHOSPHATEMIA	307	210 (68.4)	63 (20.5)	307	146 (47.6)	22 (7.2)
HYPERGLYCEMIA	170	74 (43.5)	6 (3.5)	173	76 (43.9)	3 (1.7)
HYPOGLYCEMIA	262	67 (25.6)	2 (0.8)	270	37 (13.7)	1 (0.4)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Patients with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as a denominator.
(B) Per Anemia criteria in CTC Version 4.0 there is no Grade 4 for hemoglobin.
Source: Appendix L.7b.USPI.3

Table 47. Summary of On-Treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters amylase and lipase

	Number of Subjects (%)					
	Nivo + Cabo			Sun		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
AMYLASE LOCAL LAB	285	117 (41.1)	28 (9.8)	277	77 (27.8)	16 (5.8)
LIPASE, TOTAL	308	127 (41.2)	42 (13.6)	300	114 (38.0)	40 (13.3)

Liver Function Tests

Table 48. Summary of On-Treatment Worst CTC Grade Liver Function Tests that Worsened Relative to Baseline (SI units)

	Number of Subjects (%)					
	Nivo+cabo			Sunitinib		
Lab Test Description	N(A)	Grade 1-4	Grade 3-4	N(A)	Grade 1-4	Grade 3-4
ALKALINE PHOSPHATASE	317	131 (41.3)	9 (2.8)	310	115 (37.1)	5 (1.6)
ASPARTATE AMINOTRANSFERASE	317	245 (77.3)	25 (7.9)	310	177 (57.1)	8 (2.6)
ALANINE AMINOTRANSFERASE	316	249 (78.8)	31 (9.8)	310	121 (39.0)	11 (3.5)
BILIRUBIN, TOTAL	316	54 (17.1)	3 (0.9)	309	68 (22.0)	3 (1.0)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as a denominator.
Source: Appendix L.7b.USPI.3 [SI]

Table 49. On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units)

Abnormality (%)	Nivo + Cabo N = 320	Sun N = 320
	N = 317	N = 311
ALT OR AST > 3XULN	83 (26.2)	37 (11.9)
ALT OR AST > 5XULN	35 (11.0)	15 (4.8)
ALT OR AST > 10XULN	12 (3.8)	4 (1.3)
ALT OR AST > 20XULN	2 (0.6)	2 (0.6)
	N = 317	N = 311
TOTAL BILIRUBIN > 2XULN	7 (2.2)	10 (3.2)
	N = 317	N = 311
ALP > 1.5XULN	90 (28.4)	62 (19.9)
	N = 317	N = 311
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	5 (1.6)	5 (1.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	5 (1.6)	7 (2.3)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	4 (1.3)	4 (1.3)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	4 (1.3)	6 (1.9)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter

Source: Refer to Table 8.1.2.1-1 of the CA2099ER Final CSR[2]

Table 50. Time to Resolution of Abnormalities in Specific Liver Tests (AST or ALT)

	Nivo + Cabo				Sun			
	> 3XULN N = 83	> 5XULN N = 35	> 10XULN N = 12	> 20XULN N = 2	> 3XULN N = 37	> 5XULN N = 15	> 10XULN N = 4	> 20XULN N = 2
NUMBER OF SUBJECTS WHO RESOLVED (%)	74 (89.2)	29 (82.9)	9 (75.0)	1 (50.0)	32 (86.5)	10 (66.7)	2 (50.0)	0
TIME TO RESOLUTION (WEEKS)								
MEDIAN(A) (95%CI)	2.14 (2.14, 2.71)	3.00 (2.00, 3.14)	3.14 (1.29, 6.14)	5.00 (N.A., N.A.)	3.21 (3.14, 3.86)	3.93 (1.43, 7.00)	4.14 (3.43, N.A.)	N.A. (N.A., N.A.)
RANGE(B) (MIN - MAX)	0.4 - 83.6+	0.4 - 81.6+	0.7+ - 74.7+	0.4+ - 5.0	0.4+ - 23.9+	0.4+ - 21.0+	0.4+ - 15.3+	0.4+ - 15.3+

Table 51. Summary of Subjects who Were Re-challenged with Nivolumab or Cabozantinib Defined by Abnormalities in Specific Liver Tests (AST or ALT) – Nivo+Cabo treatment arm- All treated subjects Who Experienced at Least One Abnormality- modified by the Reviewer

ALT/AST > 3XULN

	Number of Subjects (%)
	NIVO + CABO N = 83
SUBJECTS WITH STUDY THERAPY WITHHELD	35 (42.2)
SUBJECTS WHO WERE RE-CHALLENGED (A)	32 (91.4)
NIVOLUMAB ONLY	8 (22.9)
CABOZANTINIB ONLY	6 (17.1)
BOTH	18 (51.4)
POSITIVE RE-CHALLENGE/RECURRENCE (B)	10 (28.6)
NEGATIVE RE-CHALLENGE/RECURRENCE (B)	22 (62.9)

Subjects who were re-challenged: Subjects with study therapy re-initiated on or after abnormality resolution (AST and ALT <= 3XULN).
(A) Percentages are based on subjects with study therapy withheld.
A positive re-challenge/recurrence is defined as any occurrence of new abnormality (AST or ALT > 3XULN) on or after study therapy re-initiation.
If there was no new occurrence on or after study therapy re-initiation, this is a negative re-challenge.
(B) Percentages are based on subjects who were re-challenged.
Program Source: /opt/zfs001/prd/bms237293/stats/ebr2120/prog/tables/rt-lb-liversirech.sas 15JUL2020:09:53:16

Brief narratives of the 5 subjects in the nivo+cabo arm who had concurrent ALT or AST > 3X ULN with TBili > 2X ULN are provided below :

- Subject CA2099ER-45-740 was a 73 year old male who experienced Grade 3 hepatotoxicity (related) on Day 50; his lab test results showed elevated liver function tests (LFTs) wit ALT/AST > 3X ULN and TBili > 2X ULN (ALT of 611 U/L, AST of 466 U/L, and TBili of 47 umol/L). Treatment with corticosteroids was given, and both study drugs were delayed. By Day 64, the hepatotoxicity improved to Grade 2, and cabozantinib and nivolumab were restarted. Grade 3 hepatotoxicity recurred on Day 78; steroid therapy was given, and both study drugs were delayed again. By Day 92, hepatotoxicity improved to Grade 1, and cabozantinib and nivolumab were restarted on Day 93. The event of hepatotoxicity resolved (with improved levels of ALT [59 U/L], AST [28 U/L] and TBili [29 umol/L]) by Day 113.
- Subject CA2099ER-50-194 was a 69-year-old female who developed Grade 3 increased ALT (related; lab ALT of 186 U/L) on Day 28. The subject received treatment with corticosteroids, and both study drugs were delayed. On Day 35, lab test results showed elevated LFTs with ALT/AST > 3X ULN and TBili > 2X ULN (ALT of 166 U/L, AST of 71 U/L and Tbili of 41 umol/L), and Grade 2 increased in blood bilirubin (related). The events of increased ALT and increased blood bilirubin resolved on Day 49, and cabozantinib and nivolumab were restarted on Day 58. On Days 146, 188, and 196, lab test results showed elevated LFTs with ALT/AST > 3X ULN and TBili > 2X ULN. The subject had malignant neoplasm progression on Day 206 and the study therapies were discontinued.

- Subject CA2099ER-54-170 was a 60 year old male whose lab test results showed elevated LFTs with ALT/AST > 3X ULN and TBili > 2X ULN (ALT of 415 U/L, AST of 384 U/L, TBili of 48 umol/L) on Day 44, and was hospitalized on Day 46 due to Grade 4 hepatotoxicity (related). The lab test results on Day 46 showed elevated LFTs with ALT/AST > 3X ULN and TBili > 2X ULN (ALT of 463 U/L, AST of 329 U/L, and TBili of 7.4 mg/dL). The subject received treatment with corticosteroids; the study therapy with cabozantinib was discontinued, and nivolumab was delayed. Hepatotoxicity resolved on Day 52, and nivolumab restarted on Day 71. Subject developed Grade 3 renal failure (related) on Day 151; the event improved to Grade 2 with steroid treatment. On Day 204, study therapy with nivolumab was discontinued due to worsening of hepatotoxicity.
- Subject CA2099ER-70-798 was a 54-year-old male whose lab test results showed ALT of 98 U/L, AST of 88 U/L, and TBili of 14 umol/L on Day 43, and was hospitalized on Day 57 due to Grade 3 hepatotoxicity (related). Study drugs were discontinued, and the subject received treatment with steroids, sulfamethoxazole/trimethoprim, and cholecalciferol. Imaging did not show biliary obstruction, and he was discharged as steroid treatment had reduced the toxicity. The subject was re-hospitalized as his liver function tests increased again on Day 63. The subject was treated with corticosteroids and mycophenolate, and the event resolved on Day 83. The subject lab test results showed elevated LFTs with ALT/AST > 3X ULN and TBili > 2X ULN (ALT of 152 U/L, AST of 61 U/L, TBili of 62 umol/l) on Day 148; the event did not resolve. The subject had progression of disease on Day 189.
- Subject CA2099ER-106-940 was a 52-year-old male who had Grade 2 blood bilirubin increased (related; lab TBili of 34 umol/L) at Day 155. Treatment with steroids was given, and both study drugs were delayed; the event resolved on Day 164. On Day 167, the subject developed Grade 2 AST increased (lab AST of 330 U/L). On Day 169, the subject was diagnosed with Grade 2 events of ALT increased and blood bilirubin increased (both related); the lab test results showed elevated LFTs with ALT/AST > 3X ULN and TBili > 2X ULN (ALT of 424 U/L, AST of 411 U/L, and TBili of 39 umol/L). Both study drugs were discontinued per protocol. The events of increased ALT, increased AST, and increased blood bilirubin resolved on Day 183.

Thyroid Function Tests

Table 52. On-treatment Laboratory Abnormalities in Specific Thyroid Tests (SI units) (Subjects With at Least One On-Treatment TSH Measurement)

Abnormality (%)	Nivo + Cabo N = 317	Sun N = 306
TSH > ULN	238 (75.1)	206 (67.3)
TSH > ULN WITH TSH <= ULN AT BASELINE	201 (63.4)	159 (52.0)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	97 (30.6)	94 (30.7)
TSH > ULN WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	97 (30.6)	79 (25.8)
TSH > ULN WITH FT3/FT4 TEST MISSING (A) (B)	44 (13.9)	33 (10.8)
TSH < LLN	103 (32.5)	66 (21.6)
TSH < LLN WITH TSH >= LLN AT BASELINE	95 (30.0)	58 (19.0)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	65 (20.5)	37 (12.1)
TSH < LLN WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	30 (9.5)	21 (6.9)
TSH < LLN WITH FT3/FT4 TEST MISSING (A) (B)	8 (2.5)	8 (2.6)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

(A) Within a 2-week window after the abnormal TSH test date.

(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Source: Refer to Table 8.1.2.3-1 of the CA2099ER Final CSR[2]

Haematology

Haematologic abnormalities were mostly grade 1-2. The only Grade 3-4 haematologic abnormality reported in ≥5% of subjects in the nivo+cabo arm was decreased absolute lymphocytes (6.9% Grade 3). In the sunitinib arm, the following Grade 3-4 haematologic abnormality were reported in ≥5% of subjects: decreased absolute neutrophil count (10.3% Grade 3), decreased absolute lymphocytes (10.0% Grade 3), decreased platelet count (7.4% Grade 3), and decreased leukocytes (5.1% Grade 3). On-treatment worsening of haematology parameters to grade 3-4 relative to baseline was reported more frequently with sunitinib compared to nivo+cabo.

Kidney Function Tests

In the nivo+cabo and sunitinib arms, overall 31.5% of subjects with at least 1 on-treatment measurement had normal (Grade 0) creatinine values during the treatment reporting period.

In both treatment arms, the majority of reported abnormalities in creatinine (increased) were Grade 1 or 2: 50.8% were Grade 1, 16.7% were Grade 2. 4 (1.3%) subjects in the nivo+cabo arm and 2 (0.6%) subjects in the sunitinib arm had a Grade 3-4 increased creatinine level.

Table 53. Laboratory Test Results Summary of Worst CTC Grade - SI Units All Treated Patients

Lab Test Group Lab Test Description Toxicity Grade (%)	Nivo + Cabo N = 320	Sun N = 320
CREATININE, LOCAL LAB	N = 317	N = 311
GRADE 0	96 (30.3)	102 (32.8)
GRADE 1	169 (53.3)	150 (48.2)
GRADE 2	48 (15.1)	57 (18.3)
GRADE 3	4 (1.3)	1 (0.3)
GRADE 4	0	1 (0.3)
NOT REPORTED	3	9

Electrolytes

- **Table 54. Summary of On-Treatment Worst CTC Grade Electrolyte Levels That Worsened Relative to Baseline**

	Number of Subjects (%)					
	Nivo+Cabo			Sunitinib		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
SODIUM						
HYPERNATREMIA	317	34 (10.7)	0	310	24 (7.7)	0
HYPONATREMIA	317	140 (44.2)	37 (11.7)	310	113 (36.5)	37 (11.9)
POTASSIUM						
HYPERKALEMIA	317	113 (35.6)	15 (4.7)	309	83 (26.9)	3 (1.0)
HYPOKALEMIA	317	61 (19.2)	10 (3.2)	309	37 (12.0)	6 (1.9)
CALCIUM						
HYPERCALCEMIA	314	28 (8.9)	1 (0.3)	309	41 (13.3)	3 (1.0)
HYPOCALCEMIA	314	172 (54.8)	6 (1.9)	309	74 (23.9)	2 (0.6)
MAGNESIUM						
HYPERMAGNESEMIA	308	44 (14.3)	10 (3.2)	304	32 (10.5)	7 (2.3)
HYPOMAGNESEMIA	308	153 (49.7)	5 (1.6)	304	88 (28.9)	1 (0.3)
Phosphate						
HYPERPHOSPHATEMIA	307	0	0	307	0	0
HYPOPHOSPHATEMIA	307	210 (68.4)	63 (20.5)	307	146 (47.6)	22 (7.2)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as a denominator.

Source: Appendix L.7b.USPI.3 (SI)

ECG abnormalities

ECG abnormalities at baseline and on-treatment are shown in below table. The treatment emergent abnormalities with potential clinical significance under 'Other' were summarized in the following categories: 1) QT prolongation in 6 subjects with nivo + cabo and 3 with sunitinib; 2) Infarct/MI in 4 subjects with nivo+cabo and 4 with sunitinib; 3) LAFB/LBBB/BIFASCICULAR in 7 subjects with nivo+cabo and 5 with sunitinib.

Table 55. Electrocardiogram Abnormality Frequencies - All Treated Subjects in CA2099ER

	Number of Subjects (%)			
	Nivo + Cabo N = 320		Sun N = 320	
	Baseline	On-Treatment	Baseline	On-Treatment
TOTAL SUBJECTS WITH AN EVENT	81 (25.3)	130 (40.6)	66 (20.6)	112 (35.0)
1ST DEGREE AV BLOCK	4 (1.3)	15 (4.7)	5 (1.6)	8 (2.5)
ATRIAL FIBRILLATION	2 (0.6)	4 (1.3)	1 (0.3)	2 (0.6)
LEFT BUNDLE BRANCH BLOCK	1 (0.3)	3 (0.9)	2 (0.6)	5 (1.6)
LEFT ATRIAL ABNORMALITY	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.9)
Q AXIS, LEFT AXIS DEVIATION	6 (1.9)	22 (6.9)	4 (1.3)	13 (4.1)
LEFT VENTRICULAR HYPERTROPHY	1 (0.3)	5 (1.6)	4 (1.3)	7 (2.2)
MYOCARDIAL ISCHEMIA	0	2 (0.6)	0	2 (0.6)
OLD INFARCTION	2 (0.6)	9 (2.8)	1 (0.3)	5 (1.6)
OTHER INTRAVENTRICULAR CONDUCTION DEFECT	1 (0.3)	7 (2.2)	0	7 (2.2)
OTHER NON-SPECIFIC ST/T	3 (0.9)	16 (5.0)	3 (0.9)	13 (4.1)
OTHER RHYTHM ABNORMALITIES	0	5 (1.6)	2 (0.6)	4 (1.3)
PACED RHYTHM	0	1 (0.3)	0	1 (0.3)
PRE-EXCITATION	0	1 (0.3)	0	1 (0.3)
RIGHT BUNDLE BRANCH BLOCK	5 (1.6)	13 (4.1)	4 (1.3)	10 (3.1)
RIGHT VENTRICULAR HYPERTROPHY	0	1 (0.3)	0	0
SINUS BRADYCARDIA	7 (2.2)	39 (12.2)	8 (2.5)	30 (9.4)
SINUS TACHYCARDIA	7 (2.2)	9 (2.8)	4 (1.3)	10 (3.1)
PREMATURE ATRIAL COMPLEXES	1 (0.3)	3 (0.9)	1 (0.3)	1 (0.3)
SUPRAVENTRICULAR TACHYCARDIA	0	1 (0.3)	0	0
PREMATURE VENTRICULAR COMPLEX	3 (0.9)	5 (1.6)	1 (0.3)	1 (0.3)
VENTRICULAR TACHYCARDIA	0	1 (0.3)	0	0
OTHER	37 (11.6)	66 (20.6)	25 (7.8)	59 (18.4)

Baseline is defined as last non-missing result with a collection date-time less than the date-time of the first active dose of study medication.
Program Source: /opt/zfs001/prd/bms237293/stats/ebr2407 fa01/prog/tables/rt-eg-freq.sas 18NOV2020:05:36:13

Safety in special populations

Overall, as of the 30-Mar-2020 DBL the safety profile of nivo+cabo among subgroups of race and geographic region was generally similar to the total nivo+cabo treated population. However, very low numbers of non-whites participated in the pivotal trial, so results are not interpretable with respect to race.

The following numerical differences were observed in the subgroups of gender within the Endocrine Disorder SOC: female patients reported more all-causality any Grade AEs than male patients for both treatment arms (nivo+cabo: 36.8% for males and 50.7% for females; sunitinib: 28.2% for males and 38.7% for females). Drug-related AEs also showed a higher incidence for female patients in Endocrine Disorders SOC.

With regard to age, more SAEs were observed in older subjects (≥65, ≥65 and <75, and 75 years) compared with younger subjects (< 65 years) in both treatment arms. In the nivo+cabo treatment arm, frequencies of AEs leading to discontinuation were higher in the 75-84 and ≥ 85 years age group compared with the < 65 years and 65-74 years age group; this difference was not seen in the sunitinib treatment arm. However, the interpretation is limited by small number of subjects in the 75 to 84 years of age (n = 27 in the nivo+cabo arm and n = 25 in the sunitinib arm) and ≥ 85 years of age (n = 2 in the nivo+cabo arm and n = 4 in the sunitinib arm) subgroups.

Subgroup analyses comparing favourable risk patients with of patients with intermediate/poor risk were reported. These data indicate that there are no large differences in all-causality (Any Grade, Grade 3-4) AEs, SAEs and AEs leading to discontinuation between subjects with favourable risk versus the subgroup of subject with intermediate/poor risk for the nivo+cabo arm.

Safety related to drug-drug interactions and other interactions

Multiple drug interaction studies have been conducted with cabozantinib, the results of which are reflected in the current product SmPC. No new information has been generated in support of this submission. However, pharmacokinetic analysis to evaluate whether nivolumab may influence the PK of cabozantinib has been performed (please refer to section 2.3.2).

No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. No new information has been generated in support of this submission.

Discontinuation due to adverse events

Table 56. Adverse Events Leading to Discontinuation in ≥2 subjects

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	63 (19.7)	34 (10.6)	5 (1.6)	54 (16.9)	32 (10.0)	13 (4.1)
Gastrointestinal disorders	8 (2.5)	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.3)	1 (0.3)
Diarrhoea	2 (0.6)	1 (0.3)	0	0	0	0
Infections and infestations	8 (2.5)	6 (1.9)	1 (0.3)	3 (0.9)	2 (0.6)	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	1 (0.3)
Investigations	7 (2.2)	5 (1.6)	0	8 (2.5)	7 (2.2)	0
Alanine aminotransferase increased	6 (1.9)	4 (1.3)	0	3 (0.9)	3 (0.9)	0
Aspartate aminotransferase increased	5 (1.6)	3 (0.9)	0	3 (0.9)	2 (0.6)	0
Transaminases increased	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Blood bilirubin increased	1 (0.3)	0	0	3 (0.9)	2 (0.6)	0
Renal and urinary disorders	7 (2.2)	3 (0.9)	0	7 (2.2)	4 (1.3)	0
Proteinuria	5 (1.6)	2 (0.6)	0	6 (1.9)	3 (0.9)	0
Endocrine disorders	5 (1.6)	1 (0.3)	0	0	0	0
Adrenal insufficiency	3 (0.9)	1 (0.3)	0	0	0	0
Hepatobiliary disorders	5 (1.6)	4 (1.3)	0	4 (1.3)	3 (0.9)	0
Hepatotoxicity	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.6)	2 (0.6)	2 (0.6)	9 (2.8)	5 (1.6)	3 (0.9)
Malignant neoplasm progression	3 (0.9)	1 (0.3)	2 (0.6)	7 (2.2)	4 (1.3)	3 (0.9)
Neoplasm progression	2 (0.6)	1 (0.3)	0	0	0	0
Metastases to central nervous system	0	0	0	2 (0.6)	1 (0.3)	0
Skin and subcutaneous tissue disorders	5 (1.6)	3 (0.9)	0	3 (0.9)	2 (0.6)	0
Palmar-plantar erythrodysaesthesia syndrome	2 (0.6)	1 (0.3)	0	3 (0.9)	2 (0.6)	0
Musculoskeletal and connective tissue disorders	4 (1.3)	1 (0.3)	0	0	0	0
Arthralgia	2 (0.6)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (1.3)	2 (0.6)	0	8 (2.5)	4 (1.3)	4 (1.3)
Pneumonitis	3 (0.9)	1 (0.3)	0	0	0	0
Respiratory failure	0	0	0	2 (0.6)	0	2 (0.6)
Cardiac disorders	3 (0.9)	1 (0.3)	1 (0.3)	5 (1.6)	1 (0.3)	4 (1.3)
Myocardial ischaemia	0	0	0	2 (0.6)	0	2 (0.6)
General disorders and administration site conditions	3 (0.9)	1 (0.3)	0	5 (1.6)	3 (0.9)	0
Mucosal inflammation	0	0	0	2 (0.6)	2 (0.6)	0
Pain	0	0	0	2 (0.6)	0	0
Metabolism and nutrition disorders	0	0	0	3 (0.9)	3 (0.9)	0
Hyponatraemia	0	0	0	2 (0.6)	2 (0.6)	0

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.4-1 of the CA2099ER Final CSR[2]

Table 57. Drug-Related Adverse Events Leading to Discontinuation in ≥2 Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320			Sun N = 320		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	49 (15.3)	28 (8.8)	0	28 (8.8)	21 (6.6)	1 (0.3)
Gastrointestinal disorders	7 (2.2)	3 (0.9)	0	1 (0.3)	1 (0.3)	0
Diarrhoea	2 (0.6)	1 (0.3)	0	0	0	0
Investigations	7 (2.2)	5 (1.6)	0	7 (2.2)	6 (1.9)	0
Alanine aminotransferase increased	6 (1.9)	4 (1.3)	0	2 (0.6)	2 (0.6)	0
Aspartate aminotransferase increased	5 (1.6)	3 (0.9)	0	2 (0.6)	1 (0.3)	0
Transaminases increased	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Blood bilirubin increased	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0
Renal and urinary disorders	7 (2.2)	3 (0.9)	0	6 (1.9)	3 (0.9)	0
Proteinuria	5 (1.6)	2 (0.6)	0	6 (1.9)	3 (0.9)	0
Endocrine disorders	5 (1.6)	1 (0.3)	0	0	0	0
Adrenal insufficiency	3 (0.9)	1 (0.3)	0	0	0	0
Hepatobiliary disorders	5 (1.6)	4 (1.3)	0	3 (0.9)	2 (0.6)	0
Hepatotoxicity	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Skin and subcutaneous tissue disorders	5 (1.6)	3 (0.9)	0	3 (0.9)	2 (0.6)	0
Palmar-plantar erythrodysaesthesia syndrome	2 (0.6)	1 (0.3)	0	3 (0.9)	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	4 (1.3)	2 (0.6)	0	2 (0.6)	1 (0.3)	1 (0.3)
Pneumonitis	3 (0.9)	1 (0.3)	0	0	0	0
Blood and lymphatic system disorders	1 (0.3)	1 (0.3)	0	3 (0.9)	3 (0.9)	0
Thrombocytopenia	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0

MedDRA Version: 22.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.4-2 of the CA2099ER Final CSR[2]

Post marketing experience

Cabozantinib was first approved on 25-Apr-2016 in the US for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy, and on 09-09-2016 in the EU for the treatment of adults with advanced RCC who have received prior vascular endothelial growth factor (VEGF)-targeted therapy. Since then, cabozantinib has been approved for use in previously untreated patients with RCC and patients with HCC who have received prior sorafenib.

According to the MAH, based on worldwide pharmacovigilance activities, review of postmarketing safety data is consistent with, and confirms the clinical trial safety data for cabozantinib.

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and in the EU, and for other indications as monotherapy.

Based on pharmacovigilance activities, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab.

2.5.1. Discussion on clinical safety

The safety profile for nivolumab (240 mg IV Q2W) and cabozantinib (40 mg PO QD) combination therapy has not been described previously. The safety data in support of the sought indication extension for cabozantinib in combination with nivolumab (nivo+cabo) for first line treatment of adults with advanced RCC, is based on the pivotal **CA2099ER** study, which is an ongoing, phase 3, randomized, open-label, multicenter study vs. sunitinib (database lock date 30 March 2020, updated safety database lock date 10 September 2020). The contribution of each drug to the safety profile of the combination nivo+cabo was derived from cross-study comparisons of trials with the monocomponents in advanced RCC indications.

Some important differences to note between the monotherapy studies and the pivotal study CA2099ER include different doses of cabozantinib (60 mg in the monotherapy studies vs. 40 mg in CA2099ER), differences in study populations (lines of therapy, prognosis risk groups included), as well as differences in the methods used to capture and report safety events. Although recognizing the caveats of cross-trial comparisons, it is considered that the contextualization of the nivo+cabo safety profile with the monotherapies is of value, as it gives a broad impression of the contribution of each drug to the safety profile of the combination. It should also be noted that the pivotal CA2099ER study was performed open-label, which is a potential source of bias.

Median follow-up was 15.70 months for the nivo+cabo arm and 14.59 months for the sunitinib arm at 30-Mar-2020 DBL. Overall median **duration of therapy** was longer in the nivo+cabo arm (14.26 months) compared to the sunitinib arm (9.23 months). In relation to the proposed target population the extent of exposure in the nivo+cabo arm is considered acceptable for the assessment of the B/R. The long-term safety of the combination of nivo+cabo is not known, however this is considered acceptable considering the prognoses of these patients and the fact that many patients will receive subsequent therapies. The median number of cabozantinib doses received was 352.5, corresponding to approximately 12 months of treatment regardless of dose delays. At the time of database lock (30-Mar-2020), median time on treatment for the combination arm was not reached (55.6% of the patients still on treatment). It is likely that the longer time on treatment seen with nivo+cabo is reflective of the improved efficacy over the control arm, as most patients who discontinued treatment did so due to disease progression (27.8% in the nivo+cabo arm vs 48.1% in the sunitinib arm). Overall, 29.4% of patients discontinued the study (24.4% in the nivo+cabo treatment arm, 34.4% in the sunitinib arm). The most common reason for discontinuation was death: 22.8% of subjects (19.4% in the nivo+cabo arm and 26.3% in the sunitinib arm).

The MAH submitted updated safety data with a 10-Sep-2020 DBL indicating comparable safety data to the March 2020 DBL. Nevertheless, the following were noted: a longer exposure in the nivo+cabo arm, a higher proportion of subjects requiring at least one dose delay of cabozantinib (81.9% vs 68.11%) and sunitinib (72.8% vs 51.9%), more deaths due to disease progression in both arms and more discontinuations due to AEs in both arms (for nivo+cabo 31.6% vs 19.7%; for sunitinib 16.9% vs 19.4%), all of which were to be expected and are considered acceptable.

No study report has been submitted to support **dose selection** in the CA2099ER study, which was based on safety data from an investigator-initiated phase I dose escalation study (see Section 2.4.1). The dose finding study concluded on the 40 mg cabozantinib dose over the 60 mg dose, based on a trend towards less treatment related AEs and fewer dose reductions in the 40 mg dose groups (n=12) compared to the 60 mg dose groups (n=12). Lower doses of cabozantinib were not investigated, and there is a potential for ameliorated tolerability at even lower initial dose levels, which is also supported by previous cabozantinib exposure-safety modelling in RCC monotherapy (see section 2.3.5). It is possible, but remains unknown, that efficacy could be maintained at a lower cabozantinib starting dose. The MAH is recommended to prospectively investigate lower dose levels for cabozantinib in future studies.

In CA2099ER, **dose delay** (delays and interruptions) criteria for the management of AEs during nivolumab, cabozantinib, or sunitinib treatment were established. Dosing of nivolumab could be delayed without concomitant delay of cabozantinib dosing if toxicity was assessed to be related to only nivolumab, and *vice versa*. As a main rule, dosing was to be resumed at a lower dose when re-treatment criteria were met (cabozantinib and sunitinib only). Dose delays or dose reductions (all causes) were more common in the nivo+cabo treatment arm (83.4% overall) compared to the sunitinib treatment arm (51.9% in addition to the planned 2 weeks off treatment). A total of 71.9% of subjects had dose delays for nivolumab only, while 68.1% of patients had dose delays for cabozantinib only. Any-grade all-causality AEs leading to dose delays occurred in 78.8% of the patients in the nivo+cabo arm, versus 65.3% patients in the sunitinib arm. No **dose reductions** were allowed for nivolumab. Dose reductions of

cabozantinib (all reasons) occurred in 56.3% of patients. Dose reductions of cabozantinib due to an AE occurred in 50.6% of patients. Median daily dose cabozantinib was 29.55 mg, which is about 10 mg lower than the planned dose of 40 mg. In comparison, the median daily dose of sunitinib was 28.42 mg, or about 5 mg lower than the planned dose of 33.33 mg/day (50 mg QD for 4 weeks followed by no treatment for 2 weeks). Relative dose intensity for cabozantinib was low; 48% of patients had less than 70% relative dose intensity, and 17% of patients had lower than 50% relative dose intensity. The high frequency of dose modifications indicates poor tolerability of the nivo+cabo combination, which is handled by dose reductions (for cabozantinib) and delays of one or both medicinal products. Recommendations for dose reductions in the cabozantinib SmPC ("reduce the dose to 20 mg of CABOMETYX once daily, and then to 20 mg every other day") are based on the CA2099ER study and are considered acceptable.

Almost all patients in both treatment arms experienced **adverse events** (AEs) in the pivotal study (99.7% in the nivo+cabo arm and 99.1% in the sunitinib arm). When incidence rates were exposure-adjusted, all-causality AE incidence rates (events per 100 person-years) were 1705.2 in the nivo+cabo treatment arm and 1852.6 in the sunitinib arm. The most frequently reported **any grade, all causality AEs** (≥30%) in the nivo+cabo arm and/or the sunitinib arm were diarrhoea (63.8% vs 47.2%), PPES (40.0% vs 40.6%), hypertension (34.7% vs 37.2%), hypothyroidism (34.1% vs 29.4%) fatigue (32.2% vs 34.7%) and nausea (26.6% vs 30.6%, respectively). **All causality grade ≥ 3 AEs** were reported with higher frequency in the nivo+cabo treatment arm (70.3%) compared to the sunitinib arm (65.3%). The most frequently reported Grade 3-4 all-causality AEs (≥ 5%) in the nivo+cabo arm and/or the sunitinib arm were hypertension (12.5% vs 13.1%), hyponatraemia (9.4% vs 5.9%), PPES (7.5% in both treatment arms), diarrhea (6.9% vs 4.4%), lipase increased (6.3% vs 4.7%), hypophosphatemia (5.9% vs 1.3%) , ALT increased (5.3% vs 2.2%) and neutrophil count decreased (0.3% vs 5.0%).

The large majority of subjects had at least one **drug-related AE** reported: 96.6% of patients in the nivo+cabo arm, and 93.1% in the sunitinib arm; the most common (≥25% in either treatment arm) being diarrhoea (56.9% vs 42.5%), PPES (38.1% vs 40.3%), hypothyroidism (33.4% vs 28.1%), hypertension (30.3% vs 33.4%), fatigue (26.9% vs 30.3%), ALT increased (25.0% vs 6.0%), and nausea (21.3% vs 23.3%). **Grade 3-4 drug-related AEs** were reported in 60.6% of patients in the nivo+cabo arm, and 50.6% in the sunitinib arm. The most frequently reported grade 3-4 drug-related AEs (≥5% in the nivo+cabo treatment arm) were hypertension (10.9% vs 12.2%), PPES (7.5% in both arms), hyponatraemia (6.9% vs 4.4%), diarrhoea (5.6% vs 4.4%), lipase increased (5.3% vs 4.7%), hypophosphataemia (5.3% vs 4.7%). In general, frequencies of drug-related AEs with the nivo+cabo combination were comparable to frequencies previously reported for the drugs used in monotherapy. Drug-related adverse events within the SOCs GI disorders, Endocrine disorders, Skin and Subcutaneous disorders, and Hepatobiliary disordes, were more frequently reported for nivo+cabo compared to sunitinib. Events within these SOCs show potential additive toxicity with nivo+cabo (hepatotoxicity, diarrhoea, hypothyroidism, rash), and were therefore further assessed. Haematological toxicity was less frequently observed with nivo+cabo treatment compared to sunitinib.

No new terms were identified for nivo+cabo that have not been seen previously with either cabozantinib or nivolumab monotherapy. The method for considering which ADRs to include in the tabulated list of Section 4.8 of the Cabometyx SmPC was based on clinical relevance as determined by the sponsor's medical reviewer. For non-included events assessed as related by the investigator, the MAH has provided rationales for evaluation which is considered acceptable.

Treatment-related SAEs were more frequently reported in the nivo+cabo arm (24.4% vs 12.8%). The most frequently reported drug-related SAEs in (≥ 1% of subjects in the nivo+cabo arm) were diarrhoea (3.4% in the nivo+cabo arm vs 0% in the sunitinib arm), pneumonitis (2.8% vs 0%), pulmonary embolism (1.9% vs 0.3%), adrenal insufficiency (1.9% vs 0%), and hyponatraemia (1.3% vs 0.9%).

Overall, as of DCO (Mar-2020), more patients had died in the sunitinib arm (99; 30.9%) compared to the nivo+cabo arm (67; 20.9%). Most **deaths** were due to disease (51[23.1%] patients in the sunitinib arm, 74 patients [15.9%] in the nivo+cabo arm arm, respectively). The frequency of death from drug toxicity was low in both treatment arms. There was one death in the nivo+cabo treatment arm attributed to study drug toxicity vs. two deaths in the sunitinib arm. The treatment-related fatal event in the nivo+cabo arm was due to small intestine perforation, which is a known ADR for cabozantinib. Deaths attributed to other reasons were reported in 12 (3.8%) of subjects in the nivo+cabo arm and 17 (5.3%) of subjects in the sunitinib arm. For three of these deaths attributed to other reasons (a patient who died from a GI bleeding and two from intestinal perforation) a causal role of study therapy cannot be excluded or ascertained due to limited available information. A warning/precautionary statement in section 4.4 of the current Cabometyx SmPC is included for serious GI perforations and fistulas (including fatal cases), which is considered adequate. .

Analyses of **Select AEs**, Immune-related AEs (**IMAEs**) and Other events of special interest (**OESI**) were conducted in order to further characterize AEs of special clinical interest (potentially) associated with the use of nivolumab. All grade and grade 3-4 Select AEs (except grade 3 or 4 hypersensitivity reactions), IMAEs and OESIs categories occurred more frequently with nivo+cabo compared to sunitinib.

The total number patients with select AEs was 164 (57.5%) in the nivo+cabo arm and 136 (42.5%) in the sunitinib arm (data not shown). The majority of Select AEs were Grade 1-2 and most were considered drug-related by the investigator. The most commonly occurring grade 3-4 drug-related Select AE category was skin and hepatic, which occurred in 10.6% and 10.3% of patients in the nivo+cabo treatment arm, respectively, compared to 7.5% and 3.4% in the sunitinib arm, respectively. Immune-related management algorithms were included in the protocol for CA2099ER. These guidelines included treatment with systemic corticosteroids for immuno-oncology related adverse events. The proportion of patients with drug-related Select AEs who were treated with immune-modulating medication (mainly corticosteroids) ranged from 10.9% for endocrine and gastrointestinal Select AEs to 52.9% for pulmonary Select AEs. Most drug-related non-endocrine select AEs (GI, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reactions) with nivo+cabo treatment had resolved (ranging from 65.8% to 100% across non-endocrine select AE categories) at the time of DBL. In total, 34.3% of the drug-related endocrine select AEs with nivo+cabo were resolved, with the median time to resolution of not evaluable. Some drug-related endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

The majority of IMAEs were grade 1-2. The most frequently reported grade 3-4 IMAE in the nivo+cabo treatment arm was hepatitis (5.9%). Almost all (96.9%) patients with an IMAE of hepatitis resolved, with median time to resolution 4.1 weeks. The majority, 10/17 (58.8%) of patients who had a rechallenge after resolution of IMAE hepatitis, experienced recurrence after reinitiation. Non-endocrine IMAEs occurred infrequently in the sunitinib arm.

Overall, a higher proportion of patients in the nivo+cabo treatment arm experienced OESI compared to the sunitinib treatment (8/320; 2.5% vs. 1/320; 0.3%, respectively). 14 OESI events were experienced in the nivo+cabo treatment arm; all these were assessed as related to study drug. In the nivo+cabo arm, the OESIs reported were myasthenic syndrome (1 subject [2 events]), Guillain Barré syndrome (1 subject [1 event]), pancreatitis (2 subjects [1 event each]), uveitis (1 subject [3 events]), encephalitis (2 subjects [1 event each]), and myocarditis (1 subject [4 events]). Over half of these events (8/14) were grade 3-4 and five were SAEs. Three events are ongoing at the 30 March 2020 DCO date, these are two unresolved/ongoing events of acute pancreatitis/pancreatitis and one event of myocarditis. Pancreatitis is also an uncommonly reported ADR in cabozantinib monotherapy trials.

There were no OESI events in the categories of myositis, demyelination, rhabdomyolysis, and graft versus host disease.

Overall, any grade **Events To Monitor (ETM) for cabozantinib** occurred with a somewhat higher frequency in the nivo+cabo treatment arm (78%, grade 3-4: 34.4%) compared to the sunitinib treatment arm (72.8%, grade 3-4: 29.4%). However, considering the differences in time exposure between the treatment arms, the observed differences are of uncertain relevance. The most frequently reported (≥ 20%) all-causality ETMs were PPES, hypertension and haemorrhage, all of which were reported with similar frequencies in both treatment arms (40.0%, 35.9% and 21.3% respectively in the nivo+cabo arm, and 40.6%, 39.1% and 20.9% respectively in the sunitinib arm). The most frequently reported **grade 3-4 ETMs** in the nivo+cabo arm were hypertension (13.8%), PPES (7.5%) and venous and mixed thrombotic events (7.2%). Of these grade 3-4 ETMs, venous and mixed thrombotic events were the only events less commonly reported in the sunitinib treatment arm (2.5%). Most of the PTs in the ETM of venous and mixed thrombotic events were pulmonary embolism (20/36 events, of which grade 3-4: 17/20). There were five events of severity grade 4 in this ETM category. These events were reported as generally successfully treated with low molecular weight heparins, and had a short time (within 10 days) to event resolution. Pulmonary embolism is a commonly occurring event with cabozantinib, and is adequately reflected in the SmPC.

Similar rates of grade 5 ETMs were reported in both treatment arm. There were five (1.6%) grade 5 ETMs in the nivo+cabo arm, all assessed as unrelated to study drug. The grade 5 ETMs in the nivo+cabo arm were: GI perforation, upper GI haemorrhage, sudden death, cardiorespiratory arrest, cardiac arrest.

The ETM of hepatotoxicity includes the SMQs "Drug related hepatic disorders- severe events only". Transaminase elevations, commonly observed during cabozantinib treatment, are apparently not included in the hepatotoxicity ETM. Hepatotoxicity ETM of all grades and grade 3-4 was reported more frequently in the nivo+cabo treatment arm (9.1% and 4.4%, respectively) compared to the sunitinib arm (4.7% and 1.3%, respectively). Under the hepatotoxicity ETM, the PTs reported for ≥2 subjects in the nivo+cabo arm were hepatotoxicity (all grades 5.6%, grade 3-4 2.5%) hepatitis (all grade 1.9%, grade 3-4 0.9%) and autoimmune hepatitis (all grades 0.6%, grade 3-4 0.6%). The PT of hepatotoxicity has not been included in the ADR table of Cabometyx SmPC, however it is considered sufficient to have the term of hepatitis (including autoimmune hepatitis), increased ALT, increased AST, increased alkaline phosphatase, and increased total bilirubin in the Investigations SOC included in the SmPC.

No new safety signals were identified with nivo+cabo, relative to the type of AEs typically observed for each agent in monotherapy trials. The most common all-causality AEs with nivo+cabo in CA2099ER are generally reflected in the commonly reported all-causality AEs for each individual agent in the previous RCC monotherapy studies for these drugs, but some differences were noted. ALT increased, AST increased (*hepatotoxicity*), *diarrhoea*, *hypothyroidism*, and *rash* appeared to occur more frequently with the nivo+cabo combination compared to the monotherapies, and they occurred more frequently compared to the sunitinb arm in CA2099ER, as well. The majority of these four types of AEs were considered drug-related by the investigator. The higher frequencies and/or severities of these AEs with nivo+cabo observed in CA2099ER compared to nivolumab and cabozantinib as monotherapies, suggests *potentially additive effects* of the two drugs when used in combination. These four toxicities were therefore further assessed.

Hepatotoxicity: Laboratory abnormalities of ALT and AST increases were reported more frequently with nivo+cabo (78.8% and 77.3%, respectively) compared to sunitinib (39.0% and 57.1%, respectively), including grade 3 or 4 ALT and AST abnormalities (9.8% and 7.9% vs 3.5% and 2.6%, respectively). Grade ≥3 ALT and AST abnormalities with nivo+cabo were also more frequent compared to the nivolumab (3.2% ALT and 2.8% AST) and cabozantinib (3.3% ALT and 3.3% AST) monotherapies, indicating additive hepatotoxicity with nivo+cabo. Overall, characteristics of drug-related hepatic select AEs were congruent with those of ALT and AST elevations ≥ 3XULN in terms of time to onset, requirement for immune-modulating medication, outcome and time to resolution. A warning has been included in section 4.4 of the SmPC that when cabozantinib is given in combination with nivolumab,

higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to cabozantinib monotherapy in patients with advanced RCC. Liver enzymes should be monitored before initiation of and periodically throughout treatment.

Diarrhoea: The frequencies of all-causality diarrhoea in the nivo+cabo treatment arm of CA2099ER (63.8% any grade; 6.9% Grade 3-4), were higher than in the nivolumab monotherapy studies CA209205 and CA209669 (all-causality 23.6% and 30.9%; grade 3-4 1.2% and 3,3%, respectively), but lower than seen in the cabozantinib monotherapy studies METEOR and CABOSUN (all-causality 74% and 73%; grade 3-4 11% and 10%, respectively), acknowledging the higher doses of cabozantinib in METEOR and CABOSUN vs CA2099ER (60 mg vs. 40 mg), overall suggesting potential small additive toxicity. Most events of diarrhoea with nivo+cabo were of low grade and manageable using standard AE management practices. The SmPC for Cabometyx includes a warning/precautionary statement for gastrointestinal disorders, including diarrhoea, which is considered sufficient.

Hypothyroidism: TSH increases (> ULN) from baseline (≤ ULN) were reported more frequently in subjects in the nivo+cabo arm (201/317; 63.4%), compared to the sunitinib arm (159/306; 52.0%). The frequency of all causality any grade AEs of hypothyroidism noted with nivo+cabo was higher than seen in the monotherapy studies: 34.1% with nivo+cabo, vs 7-17% with nivolumab monotherapy and 21-23% with cabozantinib monotherapy, suggesting potential additive toxicity. The frequency of all causality Grade 3-4 AEs of hypothyroidism noted with nivo+cabo was low and similar to what is seen in the monotherapy studies: 0.3% with nivo+cabo vs 0-0.2% with nivolumab monotherapy and 0% with cabozantinib monotherapy, indicating that there may not be additive toxicity for severe events of hypothyroidism. Most events of hypothyroidism with nivo+cabo were manageable using standard AE management practices. Considering the high frequency observed in monotherapy trials with cabozantinib and with the combination, a warning has been included in section 4.4. of the SmPC. *Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of cabozantinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during cabozantinib treatment. Thyroid function should be monitored periodically throughout treatment with cabozantinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice.*

Rash: The frequencies of all causality any grade AEs rash noted with nivo+cabo (21.6% any grade; 1.9% grade 3-4), were generally higher than with the monotherapies Most rash events were of low grade and manageable using standard AE management practices. There was one related SAE of rash with nivo+cabo in CA2099ER. The SmPC Section 4.4 for Cabometyx does not contain any warning/precautionary statement concerning severe rash, however PPES is mentioned in Section 4.4. Considering the low grade of rash events for the majority of reported cases, and the general drug toxicity management guidelines already in place, further warning/precautionary statement for rash is not warranted at this time.

Nivo+cabo and sunitinib have a different pattern of worsening of **laboratory abnormalities** relative to baseline. In the sunitinib arm haematology abnormalities were more frequent, while in the nivo+cabo arm liver function abnormalities, thyroid function abnormalities and certain electrolyte abnormalities (hypocalcemia, hypomagnesia, hypophosphatemia) occurred more frequently. Grade 3-4 electrolyte abnormalities were similar between the two study arms, except for Grade 3-4 hypophosphatemia (20.6% vs 6.8%) which occurred more frequently in the nivo+cabo arm. There are no large differences in the number of patients with ECG abnormalities on treatment in the nivo+cabo arm (40.6%) compared to the sunitinib arm (35%).

Any grade all-causality **AEs leading to discontinuation of any study** drug occurred in 19.7% of subjects in the nivo+cabo arm, which is higher than in the sunitinib arm (16.9%, Table 47). However, a lower proportion discontinued both drugs simultaneously in the nivo+cabo arm (5.6%) compared to

sunitinib. Cabozantinib only was discontinued in 7.5% of subjects, and nivolumab only in 6.6% of subjects due to AEs (data not shown). The most common all-causality AE leading to study drug discontinuation in the nivo+cabo arm was ALT elevation (1.9%), while in the sunitinib arm, it was malignant neoplasm progression (2.2%). Treatment discontinuation due to all-causality AEs in the nivo+cabo arm in CA2099ER was comparable to what was reported for cabozantinib in the CABOSUN study (21%), but higher than the METEOR study, where 10% discontinued due to AEs (refer to EPAR EMEA/H/C/004163/0000 and EMEA/H/C/004163/II/0003). Most AEs who led to any study drug discontinuation in the nivo+cabo arm were considered drug-related (15.3% of the patients discontinued any drug due to drug-related AE; 5.6% discontinued nivolumab only; 6.6% discontinued cabozantinib only; and 3.1% discontinued both), while in the sunitinib arm, a lower proportion of drug-related AEs (8.8%) led to discontinuation. The most commonly reported drug-related AEs leading to discontinuation of any drug in the nivo+cabo arm were ALT increased (1.9%), AST increased (1.6%), proteinuria (1.6%), adrenal insufficiency (0.9%), and pneumonitis (0.9%). In the sunitinib arm, the most commonly reported drug-related AEs leading to discontinuation was proteinuria (1.9%) and PPES (0.9%). The drug-related AEs leading to discontinuation in ≥2 patients with nivo+cabo, are all known ADRs with cabozantinib and/or nivolumab.

2.5.2. Conclusions on clinical safety

In the 1L treatment setting of advanced RCC patients no new safety concerns have arisen for nivolumab and cabozantinib combination therapy. ALT and AST increases and hypothyroidism appear to occur more frequently with nivo+cabo than with the monotherapies, diarrhoea was observed more frequently compared to nivolumab monotherapy, and rash was observed more frequently compared to cabozantinib monotherapy. This is likely because these are both overlapping toxicities for nivolumab and cabozantinib. The assessment is complicated by the lack of direct comparison in the pivotal study, and by the lower dose of cabozantinib (40 mg) employed with the combination compared to the cross-referenced monotherapy trials.

The toxicity of treatment with nivo+cabo is slightly worse compared to treatment with sunitinib with slightly higher rates of severe AEs, SAEs, dose modifications and discontinuations. The most important differences in toxicity profile pertain to the AEs of diarrhoea, elevated liver enzymes (AST and ALT) and rash, that were more frequently observed in the nivo+cabo arm compared to the sunitinib arm, while haematological toxicity was observed less frequently. The toxicity profile for nivo+cabo appears manageable with dose delays, dose reductions and, in case of immune-related AEs, immune modulating therapies.

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 endorsed the Risk Management Plan version 5.1 with the following content:

Safety concerns

Table 58. Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal perforation • Gastrointestinal and non-gastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Posterior reversible encephalopathy syndrome (PRES) • Osteonecrosis
Important potential risks	• Renal Failure • Hepatotoxicity • Embryotoxicity • Carcinogenicity
Missing information	None

Pharmacovigilance plan

59. Ongoing and Planned Additional Pharmacovigilance Activities in the Pharmacovigilance Plan

Category 3- Study				
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/ongoing	**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 2. Protocol approval 3. Study start 4. Study finish 5. Progress report submission 6. Interim report 7. Final report	1. Submitted 24 April 2017 2. 12 October 2017 3. 24 April 2018 4. Planned December 2021 (LPO) 5. 25 October 2019 6. Planned December 2020 7. Planned September 2022

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

Risk minimisation measures

60. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
Posterior reversible encephalopathy syndrome (PRES)	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
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	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
Embryotoxicity	**Routine risk minimisation measures:** SmPC Section 4.5 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.
Carcinogenicity	**Routine risk minimisation measures:** SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: PASS.

ATE=arterial thromboembolic event; PL=Patient Information Leaflet; PRES=posterior reversible encephalopathy syndrome; SmPC=summary of product characteristics.
a data in this section relate to events of pulmonary embolism, venous thrombosis and arterial thrombosis.

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. The Package Leaflet has been updated accordingly.

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 MAH and has been found acceptable for the following reasons:

In the current variation, the addition of the proposed indication in renal cell carcinoma (RCC) in combination with nivolumab, the design, layout and format of the leaflet is not impacted. The modifications in the leaflet relate to slight changes in the safety profile and current writing style is followed. In the context of user testing, the updates are considered non-significant.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application concerns an extension of indication to include the use of Cabometyx in combination with nivolumab the first-line (1L) treatment of advanced renal cell carcinoma.

3.1.2. Available therapies and unmet medical need

The medicinal products and combinations of medicinal products that are currently approved in the EU for first-line (1L) systemic treatment in ccRCC are the following: pembrolizumab + axitinib, sunitinib, pazopanib, tivozanib, nivolumab + ipilimumab, and cabozantinib. In spite of available therapies, both (median) progression-free survival (PFS) and overall survival (OS) for patients with advanced RCC are still rather limited, especially for patients in the intermediate and poor risk groups.

In particular, RCC with sarcomatoid features is characterised by limited therapeutic options due to its relative resistance to established systemic targeted therapy. Most trials report on a poor median overall survival of 5 to 12 months. Studies have shown that sarcomatoid RCC express programmed death 1 (PD-1) and its ligand (PD-L1) at a much higher level than non-sarcomatoid RCC, suggesting that blockade of the PD-1/PD-L1 axis may be an attractive new therapeutic strategy (Pichler et al, 2019).

Therefore, an unmet medical need remains.

3.1.3. Main clinical studies

The single pivotal study in this application is **CA2099ER** (NCT03141177), a phase 3, open-label, (1:1) randomized trial of nivolumab combined with cabozantinib (nivo+cabo, doublet regimen, Arm A) vs sunitinib (Arm C) in patients with previously untreated (1L) advanced RCC.

3.2. Favourable effects

Study CA2099ER met its primary endpoint at a pre-planned final analysis for **PFS**. Nivo+cabo demonstrated a statistically significant improvement in PFS per BICR (primary definition) compared with sunitinib: HR = 0.51 (95% CI: 0.41, 0.64); p <0.0001. Median PFS was longer with nivo+cabo compared with sunitinib: 16.59 (95% CI: 12.45, 24.94) vs 8.31 (95% CI: 6.97, 9.69) months, respectively (an increase of 8.28 months) (data cutoff 30 March 2020).

The results of all sensitivity analyses were consistent with the pre-planned final PFS analysis, and so were the results of PFS per BICR using the secondary definition of PFS in accordance with EMA/CHMP guideline: HR = 0.54; 95% CI: 0.44, 0.67; median PFS 14.29 (95% CI: 12.29, 19.84) vs 8.31 (95% CI: 7.00, 9.69) months. In a subgroup analysis, PFS HRs for almost all subgroups favoured nivo+cabo vs sunitinib (HR <1).

Nivo+cabo demonstrated a statistically significant improvement in the secondary endpoint **OS** compared with sunitinib: HR = 0.60 (98.89% CI: 0.40, 0.89); p = 0.0010. Median OS was not reached in either

treatment group. In a subgroup analysis, OS HRs for almost all subgroups favoured nivo+cabo vs sunitinib (HR <1).

The secondary endpoint **ORR** per BICR was statistically significantly higher with nivo+cabo than with sunitinib: 55.7% (95% CI: 50.1, 61.2) vs 27.1% (95% CI: 22.4, 32.3); difference +28.6% (95% CI: 21.7, 35.6); odds ratio = 3.52 (95% CI: 2.51, 4.95); p <0.0001). In the nivo+cabo arm compared with the sunitinib arm, a numerically higher proportion of patients had a BOR of CR (8.0% vs 4.6%) or PR (47.7% vs 22.6%). The median duration of response (**DoR**) tended to be longer with nivo+cabo than with sunitinib: 20.17 (95% CI: 17.31, N.A.) vs 11.47 (95% CI: 8.31, 18.43) months. The median time to response (TTR) per BICR for all confirmed responders was 2.83 (95% CI: 1.0, 19.4) months with nivo+cabo vs 4.17 (95% CI: 1.7, 12.3) months with sunitinib. In a subgroup analysis, the difference in unweighted ORRs favoured nivo+cabo vs sunitinib in all subgroups.

An efficacy benefit of nivo+cabo vs sunitinib was observed regardless of baseline IMDC prognostic score and tumour cell PD-L1 expression status (<1%, ≥1%).

Updated results (10-Sep-2020 DBL) with approximately 5.5 months additional follow-up were confirmative.

3.3. Uncertainties and limitations about favourable effects

Notwithstanding the statistically significant improvement in PFS, OS, and ORR observed (data cutoff 30 March 2020) for nivo+cabo compared with sunitinib that were confirmed by the updated results, efficacy data in terms of OS remains overall somewhat immature. In the updated results the death rate in the nivo+cabo arm was 26.6% vs 35.4% in the sunitinib arm, with median OS only reached in the sunitinib arm (29.47 [28.35, NA] months). Therefore, some uncertainty remains regarding an OS benefit particularly in the subgroup of IMDC favourable-risk patients.

3.4. Unfavourable effects

Similar frequencies of any-Grade all-causality AEs were reported in the nivo+cabo arm (99.7%) and in the sunitinib arm (99.1%). The overall incidence of Grade 3-4 AEs (respectively 70.3% vs 65.3%), SAEs (46.3% vs 39.7%) and treatment-related SAEs (24.4% vs 12.8%) was higher in the nivo+cabo vs the sunitinib arm.

The most frequently reported **any-Grade all-causality AEs** in the nivo+cabo arm were diarrhoea (63.8%), palmar-plantar erythrodysaesthesia syndrome (PPES; 40.0%), hypertension (34.7%), hypothyroidism (34.1%), fatigue (32.2%), ALT increased (28.1%), decreased appetite (28.1%), nausea (26.6%) and AST increased (25.3%). Most of these AEs were considered to be treatment-related in the nivo+cabo arm.

Of the any-Grade all-causality AEs occurring in ≥20% of patients, diarrhoea (63.8% vs 47.2%), increased ALT (28.1% vs 8.4%), increased AST (25.3% vs 10.9%) and rash (21.6% vs 8.1%) were observed much more frequently in the nivo+cabo arm compared to the sunitinib arm.

Increases in ALT and AST (except in CABOSUN where these were solicited) and hypothyroidism were observed more frequently with nivo+cabo treatment compared to both nivolumab (study CA209205 and CA209669) and cabozantinib monotherapy (METEOR and CABOSUN studies). Frequencies of diarrhoea noted with nivo+cabo were higher compared to nivolumab monotherapy, but lower compared to cabozantinib monotherapy. Frequencies of rash reported with nivo+cabo were higher compared to cabozantinib monotherapy, but lower compared to nivolumab monotherapy.

The most frequently reported **Grade 3-4 all-causality AEs** in the nivo+cabo arm were hypertension (12.5%), hyponatraemia (9.4%), PPES (7.5%), diarrhoea (6.9%), lipase increased (6.3%). There was no large difference in frequencies of Grade 3-4 AEs between the nivo+cabo and sunitinib arm.

The most frequently reported all-causality **SAEs** in the nivo+cabo arm were diarrhoea (4.7%), malignant neoplasm progression (4.1%), pneumonitis (2.8%), pulmonary embolism (2.8%), pneumonia (2.2%) and hyponatraemia (2.2%). There were no large differences in frequencies of SAEs between the two study arms, except for diarrhoea (4.7% in the nivo+cabo arm vs 0% in the sunitinib arm).

In the nivo+cabo arm a single (0.3%) **death** due to small intestine perforation was considered related to treatment by the investigator, in the sunitinib arm two (0.6%) deaths due to respiratory distress and pneumonia/acute respiratory failure were considered related to treatment.

Discontinuation of (any) study medication due to AEs occurred at a slightly higher rate in the nivo+cabo arm (19.7%: 6.6% nivolumab only; 7.5% cabozantinib only; 5.6% both medicinal products [at the same time, for the same AE]) compared to the sunitinib arm (16.9%). In the nivo+cabo arm ALT increased (1.9%), AST increased (1.6%) and proteinuria (1.6%) were the most frequent reasons for discontinuation.

AEs with potential immune-related aetiology occurred more frequently in the nivo+cabo arm vs the sunitinib arm. The most frequently reported drug-related select AEs in the nivo+cabo arm (vs the sunitinib arm) were in the categories skin (62.2% vs 47.2%), gastrointestinal (57.5% vs 42.5%), endocrine (42.8% vs 33.1%), and hepatic (40.0% vs 21.9%). The majority of these AEs were low Grade and most AEs resolved with dose delays and/or immune modulating medication. An exception was endocrine select AEs, in this category most AEs were not considered resolved due to the continuing need for hormone replacement therapy.

AEs potentially associated with TKIs or VEGF inhibition ("event to monitor" [ETMs]) were observed at comparable rates in the nivo+cabo arm (78.1%) vs the sunitinib arm (72.8%). Grade 3 or higher ETM rates for nivo+cabo which were higher than in the sunitinib treatment arm were venous and mixed thrombotic events (7.2% vs 2.5%, respectively) and hepatotoxicity (4.4% vs 1.3%).

3.5. Uncertainties and limitations about unfavourable effects

Median follow-up was 15.70 months for the nivo+cabo arm and 14.59 months for the sunitinib arm. Follow-up was relatively short in relation to establishing the long-term safety of the combination of nivo+cabo, even with the new safety DBL of 10 September 2020.

It cannot be excluded that the open-label design of the pivotal study may have affected safety reporting.

The contribution of each drug to the safety profile of the combination nivo+cabo was derived from cross-study comparisons of trials with the monocomponents in advanced RCC indications. Some important differences to these studies include different doses of cabozantinib (60 mg in the monotherapy studies vs. 40 mg in CA2099ER), differences in study populations and different methods to capture and report safety events.

Longer duration of therapy in the nivo+cabo treatment arm (14.26 months) compared to sunitinib (9.23 months) could result in over-estimation of the magnitude of worse grade 3-4 event and SAE profile seen in the nivo+cabo arm relative to sunitinib.

Few older subject ≥ 75 years participated in the pivotal trial, precluding any interpretation of possible differences in the safety profile between patients ≥ 75 years.

3.6. Effects Table

Effects Table for Cabometyx, first line treatment of advanced renal cell carcinoma in combination with Opdivo (database lock: 30 March 2020)

Effect	Short description	Unit	Treatment Cabozantinib+ nivolumab	Control Sunitinib	Uncertainties / Strength of evidence
Favourable Effects					
PFS per RECIST 1.1 by BICR (ITT)	Time from randomisation to first PD (per RECIST 1.1 by BICR) or death due to any cause, whichever occurs first	Months (95% CI) HR (95% CI)	16.59 vs 8.31 (12.45, 24.94) (6.97, 9.69) HR 0.51 (0.41, 0.64; p < 0.0001)		A statistically significant benefit in favour of the combination therapy is observed for PFS, OS and ORR. Updated efficacy results are confirmatory. Median OS has not been reached in either of treatment arms; thus, long term benefit is uncertain. Even updated results are somewhat immature regarding OS However, no apparent detrimental effect is seen in OS.
OS (ITT)	Time from to randomisation to death due to any cause (secondary endpoint)	Months (95% CI) HR (98.89% CI)	NR vs NR (NR, NR) (22.60, NR) HR 0.60 (0.40, 0.89; p = 0.0010)		
ORR per RECIST 1.1 by BICR (ITT)	Proportion of patients who achieved complete or partial response (secondary endpoint)	%	55.7	27.1	
Unfavourable Effects					
Drug-related AEs	Grade 3-4 AEs	%	60.6	50.6	Real effect size difference uncertain due to longer treatment duration in nivo+cabo arm. Long-term safety unknown. Safety reporting may be influenced by open-label study design.
	SAEs		24.4	12.8	
	AEs leading to discontinuation of **any** study drug		15.3	8.8	

Abbreviations: NR=not reached; AE= adverse event; SAE= serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the single pivotal study CA2099ER, the nivo+cabo combination demonstrated a clinically relevant and statistically significant improvement in PFS per BICR (primary definition) compared with sunitinib treatment. This result was robust as the results of all sensitivity analyses and of the PFS analysis using the secondary definition were consistent with the primary analysis. Nivo+cabo also demonstrated a statistically significant improvement in the secondary endpoints OS and ORR (per BICR) compared with sunitinib. An efficacy benefit was observed regardless of baseline IMDC prognostic score and tumour cell PD-L1 expression status.

Updated results were confirmative, but remain somewhat immature regarding OS. There thus remains some uncertainty regarding an OS benefit, particularly in the subgroup of IMDC favourable-risk patients. This is, however, acceptable as there is no apparent detrimental effect on OS in any subgroup, including the subgroup of IMDC favourable-risk patients that has clearly favourable PFS results with support from ORR.

Regarding the contribution of the individual components, the additive efficacy of both individual components has been shown in a qualitative sense based primarily on an increase in ORR over the individual agents.

This is to be weighed against the toxicity profile for nivo+cabo which is only slightly worse compared to sunitinib, reflected by only slightly higher percentages of Grade 3-4 AEs, SAEs and dose modifications in the nivo+cabo arm. The most important differences in toxicity profile pertain to the AEs of diarrhoea, elevated liver enzymes (AST and ALT) and rash that were more frequently observed in the nivo+cabo arm compared to the sunitinib arm, while haematological toxicity was observed less frequently.

No new safety concerns were raised for nivolumab or cabozantinib, though increases in ALT and AST, and hypothyroidism appear to occur more frequently with nivo+cabo combination therapy compared to the monotherapy components separately. With nivo+cabo treatment diarrhoea was observed more frequently compared to nivolumab monotherapy, and rash was observed more frequently compared to cabozantinib monotherapy. The toxicity profile for nivo+cabo appears manageable with dose delays, dose reductions and, in case of immune-related AEs, immune modulating therapies.

The high frequency of dose modifications indicates poor tolerability of the combination therapy. The tolerability profile and benefit/risk balance may be improved with lower initial cabozantinib doses. However, as lower doses have not been prospectively tested, and the dose-response relationship is not characterised, it is unknown whether lower initial doses would maintain similar clinical benefit. The MAH is recommended to explore lower doses in future studies.

3.7.2. Balance of benefits and risks

The nivo+cabo combination demonstrated a statistically significant improvement in efficacy (PFS, OS, and ORR) compared with sunitinib treatment. This combination of an efficacy benefit across all three endpoints (PFS, OS, and ORR) is regarded as being clinically relevant. Even though an OS benefit is not yet established for all subgroups, this is acceptable since there is no apparent detrimental effect on OS in any subgroup. Treatment with nivo+cabo resulted in a slightly worse toxicity profile compared to sunitinib. No new safety concerns have arisen for the nivo+cabo combination and the toxicity profile for nivo+cabo appears manageable. It can be concluded that the benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Cabometyx in combination with nivolumab for the first-line treatment of advanced RCC in adults 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 in combination with nivolumab first line treatment of advanced renal cell carcinoma 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 is updated in accordance. Version 5.1 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.