25 February 2021
EMA/CHMP/159169/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0092

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
ADA	anti-drug antibody
ADaM	Analysis Data Model
ADR	adverse reaction
AE(s)	adverse event(s)
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BID	twice daily
BLA	biologics licensing application
BMS	Bristol-Myers Squibb Company
BOR	best overall response
cc	clear cell
ccRCC	clear cell renal cell carcinoma
Cavg/Cavdg28	time-averaged concentration/ time-averaged concentration at Day 28
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CL/F	apparent clearance
CLS	capillary leak syndrome;
Cmax	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CoC	Contribution of Components
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events

DBL	database lock
DC/D	discontinuation or death
DILI	drug-induced liver injury
DLTs	dose-limiting toxicities
DMC	Data Monitoring Committee
DoR	duration of response
EAU	European Association of Urology
EBE	empirical Bayes estimates
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
E-R	exposure-response
ESMO	European Society for Medical Oncology
ETM	event to monitor
EQ-5D-3L	EuroQoL Group's instrument to measure general health status
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FKSI-19	Functional Assessment of Cancer Therapy-Kidney Symptom Index
GB	glioblastoma multiforme
GCP	Good Clinical Practice
GI	gastrointestinal
HA	health authority
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQoL	health related quality of life
IA	interim analysis
ICI(s)	immune checkpoint inhibitor(s)
ICF	informed consent form
IMAE(s)	immune-mediated adverse event(s)
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IMM(s)	immune modulating medication(s)
IND	Investigational New Drug
I/P	intermediate and/or poor

IRT	interactive response technology
ISE	Integrated Summary of Effectiveness
ISR	investigator sponsored research
ISS	Integrated Safety Summary
ITT	intent-to-treat
IU	International Unit
IV	intravenous(ly)
KM	Kaplan-Meier
KPS	Karnofsky performance status
LC-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
MTC	medullary thyroid cancer
mTOR	mammalian target of rapamycin
mUC	metastatic urothelial cancer
NA	not applicable
NAb	neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institute of Health
NR	not reached
NSCLC	non-small cell lung cancer
OESI	other events of special interest
ORR	objective response rate
OS	overall survival
PROs	patient-reported outcomes
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
PFS	progression-free survival
PID	patient identification
PK	pharmacokinetic
PO	per os, i.e. by mouth
POPPK	population pharmacokinetics
PR	partial response
PRP	PD1- Blockade Durable Response Predictive (biomarker model)
PT	preferred term
P-Y	person-years
QxW	every x weeks
QD	once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
ROW	rest of the world
RP2D	recommended phase 2 dose
RSI	Request for Supplementary Information
RTK(s)	receptor tyrosine kinase(s)
RTOR	Real-Time Oncology Review
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease; standard deviation
SDTM	Study Data Tabulation Model Implementation Guide
sNDA	supplemental New Drug Application
SOC	system organ class
SDTM	Study Data Tabulation Model
SI	International System of Units

TAM	tumour-assisted macrophages
TKI(s)	tyrosine kinase inhibitor(s)
TTR	time to response
UC	urothelial cancer
ULN	Upper limit of normal
US	United States
UTD	unable to determine
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG 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 cabozantinib for the first line treatment of advanced renal cell carcinoma for Opdivo; 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 19.0 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 P/0026/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0026/2020 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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: N/A Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	25 August 2020
Start of procedure:	12 September 2020
CHMP Co-Rapporteur's preliminary assessment report circulated on:	6 November 2020
PRAC Rapporteur's preliminary assessment report circulated on:	11 November 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	26 November 2020
Updated CHMP Co-Rapporteur's assessment report circulated on:	3 December 2020
Request for supplementary information adopted by the CHMP on:	10 December 2020
MAH's responses submitted to the CHMP on:	21 December 2020
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 January 2021
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 January 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	11 February 2021
Updated CHMP Co-Rapporteur's assessment report on the MAH's responses circulated on:	18 February 2021
CHMP Opinion adopted on:	25 February 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This application concerns an extension of indication to include the use of Opdivo in combination with cabozantinib in 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 section 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.

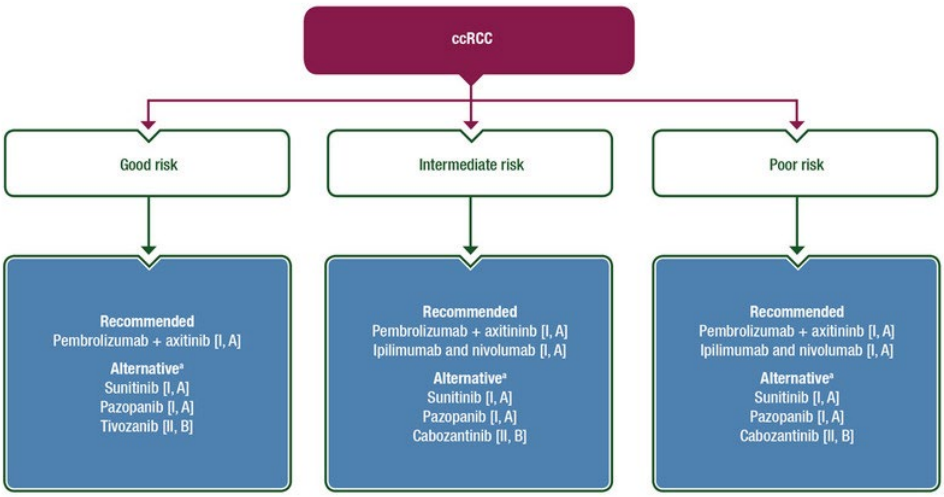
Patients with none (0) of these risk factors are considered good risk, those with one or two (1-2) are considered intermediate risk, and those with three or more (≥3) are considered poor risk. The estimated median overall survival (OS) for the patients in these risk groups is 43.2 months, 22.5 months,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



[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

Opdivo (nivolumab)

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Currently, Opdivo (nivolumab) is approved in the EU (Opdivo SmPC):

- as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults;
- as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection;
- as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults;
- **as monotherapy for the treatment of advanced RCC after prior therapy in adults;**
- **in combination with ipilimumab for the 1L treatment of adult patients with intermediate/poor-risk advanced RCC;**
- as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin;
- as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy; and
- as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Cabometyx (cabozantinib)

Cabozantinib (XL184) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib has been evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.

Currently, cabozantinib as Cabometyx is approved in the EU for (Cabometyx SmPC):

- **the treatment of advanced RCC:**
    - **in treatment-naïve adults with intermediate or poor risk;**
    - **in adults following prior VEGF-targeted therapy**; and

- the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

As Cometriq, cabozantinib is approved for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (Cometriq SmPC).

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

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 (see next paragraph) 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.

CA2099ER (NCT03141177), a phase 3, randomized trial of nivo+cabo vs sunitinib in patients with previously untreated advanced RCC is the pivotal study for the current application, see 2.4.2. Main study.

A summary highlighting the key aspects of the studies investigating nivolumab and cabozantinib in advanced RCC that are included or referenced in this application is provided in Table 1, see 2.3.1. Introduction.

2.1.4. General comments on compliance with GCP

The MAH has provided a statement that the clinical trials included in this submission were performed in accordance with the principles of Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH). The clinical trials carried out outside the European Union (EU) 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.

2.2.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not represent a significant risk. As a protein, nivolumab is exempt from submission of

Environmental Risk Assessment studies under the 1 June 2006 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00). Nivolumab is not considered to pose a significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

Nivolumab as a protein is exempt from the need for ERA studies and is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The current submission concerns the extension of the indication for nivolumab in combination with cabozantinib for the treatment of subjects with advanced renal cell carcinoma (RCC). The basis of this submission is study CA2099ER, a phase 3, randomized (1:1), open-label study, in which patients received nivolumab 240 mg Q2W in combination with 40 mg QD oral cabozantinib compared with sunitinib treatment. Exposure-response analyses were conducted to support cabozantinib's contribution of components justification for the combination of nivolumab and cabozantinib (nivo+cabo) in study CA2099ER compared with previous nivolumab monotherapy studies and to provide a model-based bridge from nivolumab 240 mg Q2W + cabozantinib 40 mg QD (the dose and regimen evaluated in study CA2099ER) to 480 mg Q4W + cabozantinib 40 mg QD. Nivolumab immunogenicity data are also presented from study CA2099ER.

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

Table 1 Key aspects of studies investigating nivolumab and cabozantinib in advanced RCC

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	Cabozantinib 60 mg PO QD or sunitinib 50 mg PO QD for	**Primary:** Compare BICR-assessed PFS[c,d] of cabozantinib with that of sunitinib.

Study ID	Study Design	Dosing Regimen	Objectives
	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)	4 weeks, followed by a 2-week break.	**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 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 clinical pharmacology of nivolumab and cabozantinib have been described in previously submitted clinical pharmacology packages and included single- and multiple-dose pharmacokinetic parameters, drug-drug interaction potential, pharmacodynamics, QT prolongation potential, popPK analyses for the various tumour indications and exposure-response analyses. Nivolumab and cabozantinib pharmacokinetics from study CA2099ER were analysed and compared with historical pharmacokinetic monotherapy data. PopPK analyses were performed for both nivolumab and cabozantinib, adding data from the CA2099ER study into the existing popPK models for each drug with the combination effect added as a covariate, respectively.

In this report the pharmacokinetics of nivolumab will be discussed with cabozantinib as covariate while in procedure **EMEA/H/C/004163/II/0017** the pharmacokinetics of cabozantinib are discussed with nivolumab as covariate.

Bioanalytical methods

The pharmacokinetic samples from subjects in study CA2099ER were analysed by the same validated assay as used previously. The bioanalytical methods for the assessment of (neutralizing) antibodies against nivolumab were also the same as presented in the previously submitted marketing application for nivolumab.

Population pharmacokinetics (popPK)

The purpose of the popPK analyses was to characterize the effect of cabozantinib on the pharmacokinetics of nivolumab in subjects with RCC, to determine the effect of key covariates on nivolumab pharmacokinetics and exposure, and to compare summary measures of nivolumab exposure for nivolumab 240 mg every 2 weeks (Q2W) and for the proposed 480 mg every 4 weeks (Q4W) posology in subjects with RCC when used with cabozantinib combination therapy.

In study CA2099ER nivolumab pharmacokinetic samples were collected on Day 1: pre-dose, end of infusion (0.5 h), and prior to dosing on Weeks 7, 13, 29, 45, and every 16 weeks thereafter up to 2 years.

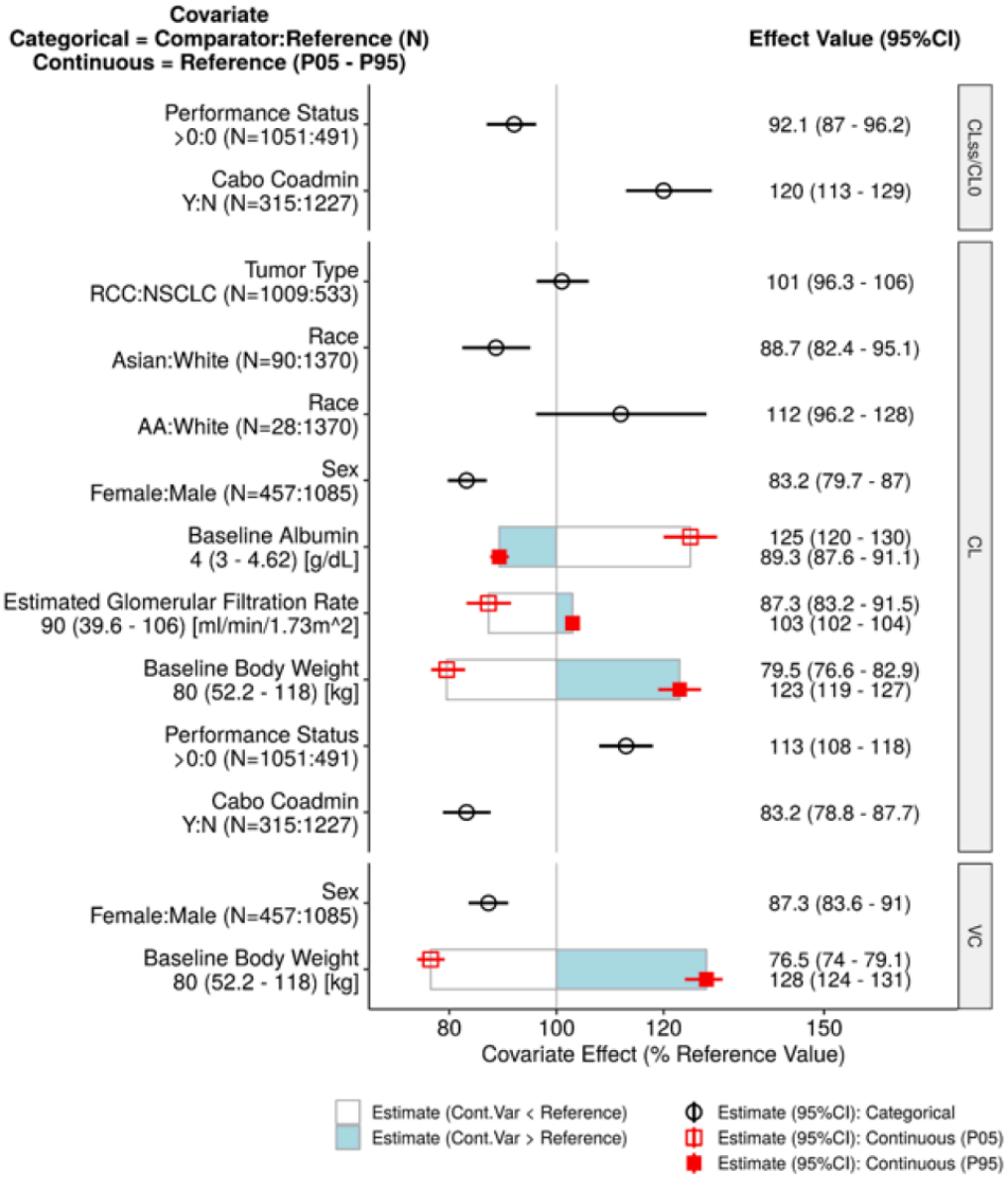
The nivolumab popPK analysis dataset included a total of 7 clinical studies, 9,263 nivolumab concentration values (1,407 nivo+cabo) from 1,542 subjects (315 nivo+cabo) with RCC and NSCLC who received nivolumab monotherapy and nivo+cabo (study CA2099ER). NSCLC data were included since this tumour type was the reference used in prior nivolumab popPK analyses, and it was previously demonstrated that subjects with NSCLC and RCC have similar nivolumab CL. The data included are from one Phase 1 study (CA209003 [multiple tumour types, only RCC and NSCLC included]), two phase 2 studies (CA209009 [RCC] and CA209010 [RCC]), and four phase 3 studies (CA2099ER Arm A [RCC], CA209017 [SQ-NSCLC], CA209025 [RCC], and CA209057 [NSQ-NSCLC]). The Arm B (nivolumab + ipilimumab + cabozantinib) from study CA2099ER was not included in this analysis as this arm was terminated.

Model development consisted of re-estimating parameters of the previously developed final model (Zhang et al 2019, see also Procedure EMEA/H/C/003985/II/0019) excluding the effect of combination

regimen with ipilimumab and tumour type. The model was a 2-compartment, zero-order infusion model with time-varying total CL described using a sigmoidal Emax function with a proportional residual error model, random effect on CL, intercompartmental clearance (Q), VC, volume of distribution of peripheral compartment (VP), and EMAX and correlation of random effect between CL and VC. The full model was developed from the base model by incorporating additional covariates to assess the impact of combination with cabozantinib and tumour type (RCC versus NSCLC) on nivolumab CL. The following covariates were already included in the base model: for CL body weight, estimated glomerular filtration rate (eGFR), performance status, sex, race, albumin, lactate dehydrogenase, and tumour size, and covariates for the volume of distribution of the VC were body weight and sex.

Figure 3 shows that the nivolumab CL was 17% lower in subjects receiving nivolumab with cabozantinib 40 mg QD compared to nivolumab monotherapy after accounting for the effects of other covariates with CL values of 8.95 mL/h vs 11.1 mL/h, respectively from post-hoc estimates. Nivolumab CL at steady state was ~7% lower for nivo+cabo compared with nivolumab monotherapy, 8.12 mL/h vs 8.76 mL/h, respectively from post-hoc estimates. The estimated effect of eGFR, race (Asian), PS, body weight, albumin, and sex on nivolumab CL were consistent with the previous analyses; the magnitudes of the effects on the parameters (CL and VC) were less than 20% for all other covariates except body weight and albumin.

Figure 2 Covariate effects on nivolumab pharmacokinetic model parameters (full model)



Analysis-Directory: /global/pkms/data/CA/209/rcc-combo-cabo-submission/prd/ppk/final/

Program Source: Analysis-Directory/R/scripts/nivoppk.Rmd

Source: Analysis-Directory/R/plots/ggcoveff_plot

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, white/other race, BBWT = 80 kg, PS = 0, BALB = 4 g/dL, eGFR = 90 mL/min/1.73 m^2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.

Note 5: PS appeared twice in the figure. Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 13%, whereas the reduction of nivolumab CL over time was more significant in subjects with PS > 0 than subjects with PS = 0 by 8%.

Note 6: Cabo Coadmin appeared twice in the figure. Baseline CL of nivolumab in subjects with cabozantinib coadministration was lower than subjects with monotherapy by 17%, whereas the reduction of nivolumab CL over time was less significant in subjects with cabozantinib coadministration than subjects with monotherapy by 20%.

Note 7: CLss/CL0 = e^{EMAX}

Note 8: For two subjects with missing race, it was imputed as reference race 'White' in the PPK analysis.

Despite the lower baseline CL with cabozantinib administration, this did not result in meaningful differences in nivolumab exposures in patients with RCC (see Table 2), indicating cabozantinib did not have a clinically meaningful impact on nivolumab exposures.

Table 2 Comparison of nivolumab exposures at 240 mg every 2 weeks for renal cell carcinoma combination therapy with cabozantinib, renal cell carcinoma monotherapy

Exposure (µg/mL)	RCC Nivo+Cabo Geo. Mean (CV%) (N = 315, GI[a])	RCC Nivo Mono Geo. Mean (CV%) (N = 694, G2[b])	% Diff GM (G1-G2)[c]
Cmin1	20.6 (23.0)	17.2 (40.7)	19.8
Cmax1	58.9 (38.9)	55.5 (47.4)	6.13
Cavg1	29.4 (21.6)	26.4 (36.4)	11.4
Cminss	68.7 (37.2)	63.0 (52.8)	9.05
Cmaxss	129 (31.6)	121 (44.1)	6.61
Cavgss	87.9 (32.4)	81.7 (46.8)	7.59

a Nivolumab 240 mg Q2W + cabozantinib 40 mg QD in RCC subjects, which includes data from study CA2099ER.
b Nivolumab monotherapy in RCC subjects (0.3, 1, 2, 3, 10 mg/kg), which includes data from Studies CA209003, CA209009, CA209010, and CA209025.
c Percent difference in geometric mean of RCC Nivo+Cabo (G1) relative to RCC Nivo Mono (G2).

2.3.3. Pharmacodynamics

Nivolumab exposure response analyses were conducted to support the administration of nivolumab 240 mg Q2W or 480 mg Q4W and cabozantinib 40 mg QD in subjects with previously untreated advanced RCC.

Further, immunogenicity of nivolumab was assessed in study CA2099ER and this is discussed in the safety section (section **2.5. Clinical safety**).

Exposure-response analyses

Nivolumab exposure-response analyses for efficacy in RCC

PFS was selected as the response endpoint since this was the primary endpoint in study CA2099ER and PFS determined by investigator was used for previous nivolumab monotherapy studies. Nivolumab time-averaged concentration during the first dosing interval (Cavg1) was used as the exposure measure, due to nivolumab time-varying CL, to avoid biasing the exposure-response analysis with exposure measurements from later treatment cycles when treatment outcomes affect disease related changes in exposure.

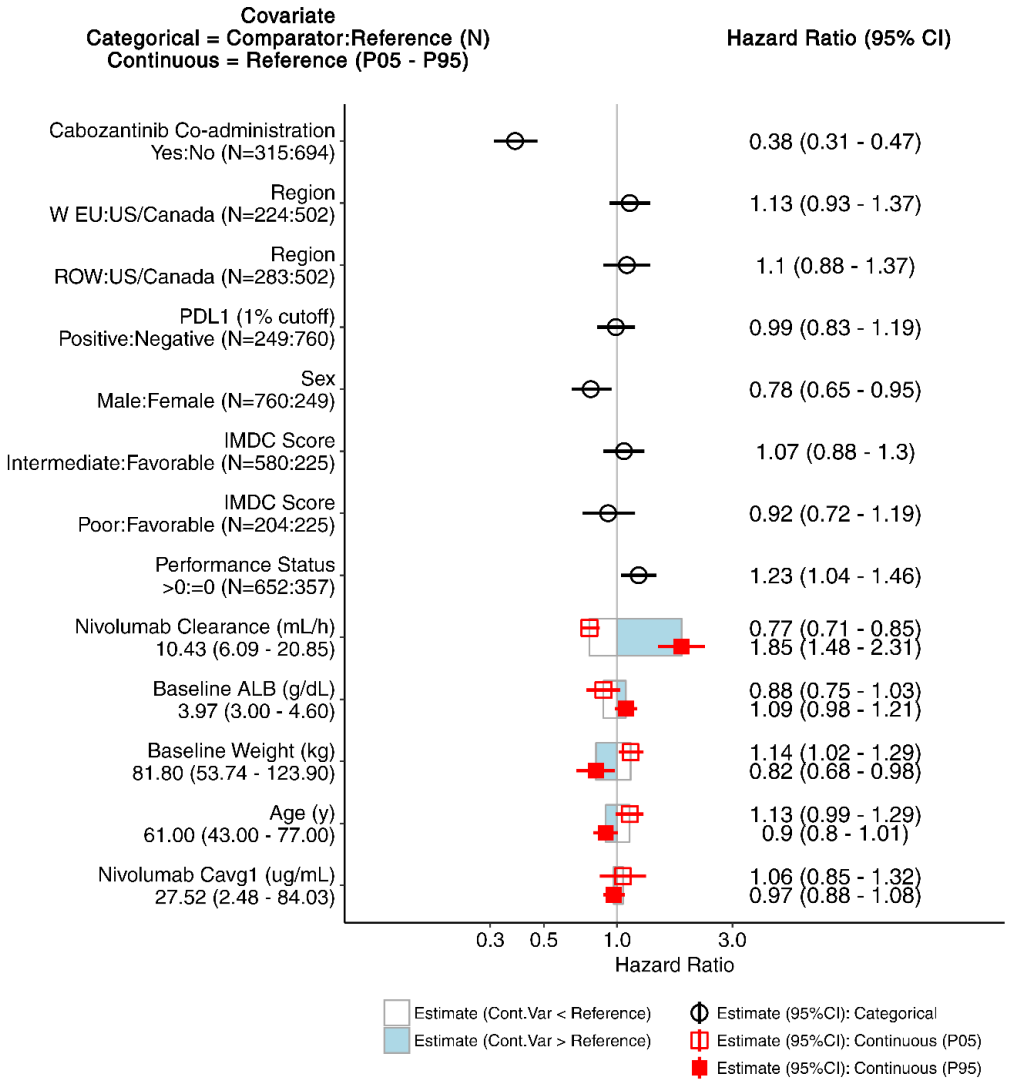
The exposure-response analysis of PFS included 1009 subjects with RCC from studies CA209003, CA209009, CA209010, CA209025, and CA2099ER including 315 subjects with mRCC treated with nivo+cabo in study CA2099ER and for whom estimates of nivolumab exposure (Cavg1) were available. A semi-parametric Cox-proportional hazards (CPH) model was used to characterize exposure-response

PFS. The model with nivolumab Cavg1 as a log-linear function had a lower BIC relative to the linear model of Cavg1 and this effect was included in the full model.

Figure 4 is a graphical presentation of all the estimated effects in the full model, showing the HRs of PFS across the predictor ranges and the associated 95% CIs. Cabozantinib coadministration had an additive favourable effect on PFS compared with nivolumab single agent studies. Subjects with lower than the reference baseline CL (10.4 mL/h), higher than the reference BBWT (81.8 kg) or male subjects had up to 20% reduction in the risk of disease progression or death, while subjects with PS > 0 (KPS ≤ 90) had approximately 20% increased risk. In addition, cabozantinib coadministration interactions with the significant predictors in the full model were not significant, suggesting that the covariate effects were consistent across nivolumab monotherapy and nivo+cabo combination therapy. The 95% CI of the HR for other potential predictor/prognostic variables evaluated (age, baseline albumin, IMDC score, PD-L1 status, and region) included 1, indicating a lack of evidence for the effect of these variables on the risk of tumour progression or death.

In addition, a sensitivity analysis of the full model evaluating line of therapy was performed. Line of therapy was not found to be significant and was highly correlated with cabozantinib coadministration given that nearly all of the first-line treated subjects were also administered cabozantinib.

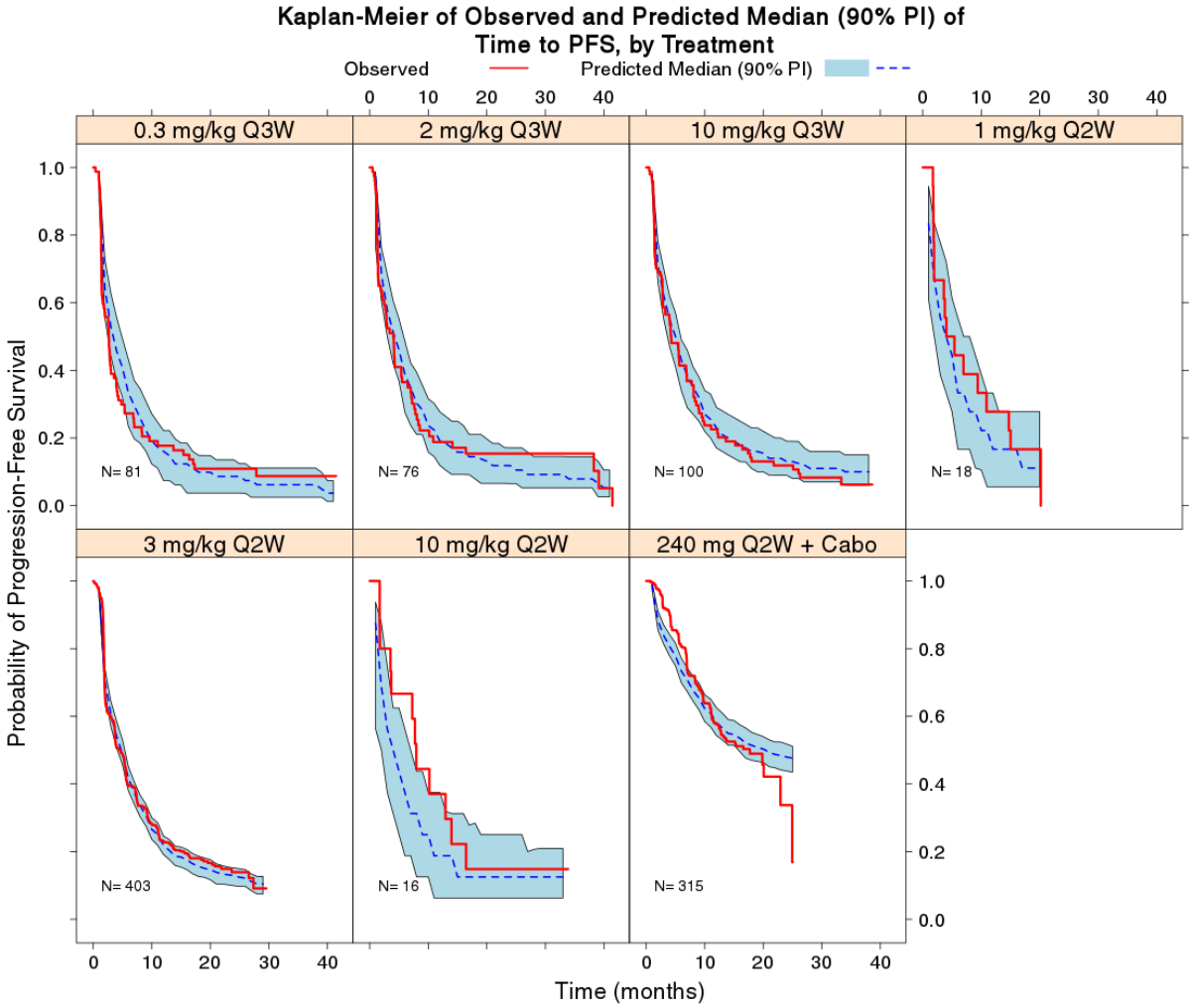
Figure 3 Estimated covariate effects on the hazard ratio of Progression-Free Survival (Full Model)



Note: Reference values: Performance Status = 0, IMDC Score = favorable, Sex = female, PD-L1 Status = negative, Region = US/Canada, and cabozantinib co-treatment = no.
Abbreviations: ALB = albumin; Cavg1 = time-averaged concentration over the first dosing interval; CI = confidence interval; EU = Europe; IMDC = International Metastatic RCC Database Consortium; PDL1 = programmed death ligand-1; PFS = progression-free survival; US = United States.

The final model predictions of the probability of PFS by treatment are shown in Figure 5. In general, the model-predicted median (90% PI) probability of PFS was consistent with the observed KM of PFS in most nivolumab treatment arms across time.

Figure 4 Exposure-response analysis: model evaluation of progression-free survival final model, by treatment



Abbreviations: N = number of subjects; PFS = progression-free survival; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks.

The final exposure-response PFS model was used to predict the HR for nivolumab 240 mg Q2W + cabozantinib 40 mg QD (N = 315) compared with nivolumab monotherapy 3 mg/kg Q2W (N = 403) as the reference. The hazard ratio was 0.385 (90%CI 0.325-0.385) and independent of nivolumab exposure: hazard ratio at 5% and 95% Cave (21.5 and 42.8 ng/ml) was 0.380 and 0.390, respectively.

Nivolumab exposure-response analyses for safety in RCC

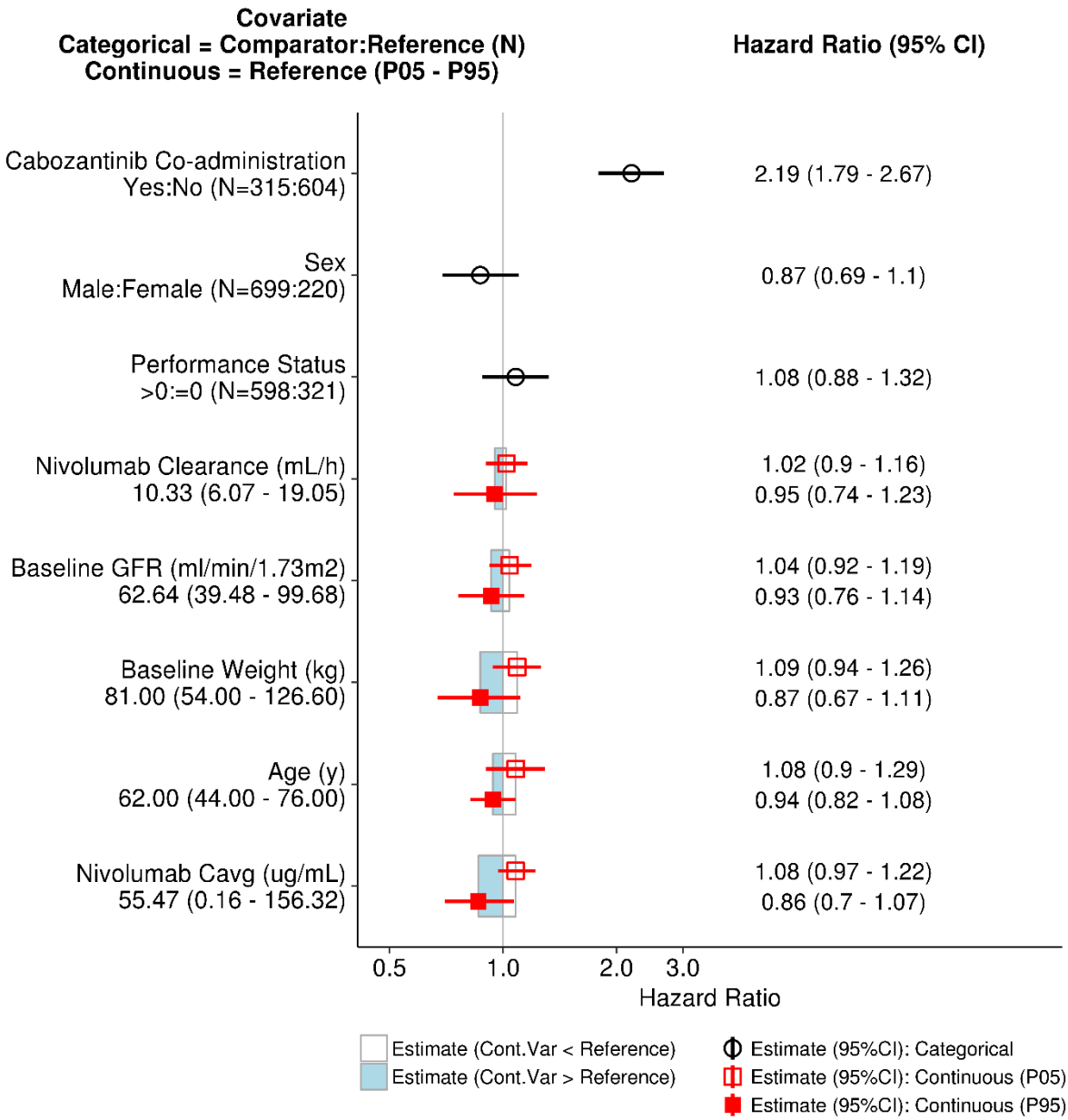
Gr2+ IMAEs were selected as the response endpoint for the exposure-response safety analysis, given the nature of immunotherapy, such that Gr2+ IMAEs are likely attributable to the treatment. The

exposure-response analysis of safety included 919 subjects with RCC from studies CA209003, CA209010, CA209025, and CA2099ER, including 315 subjects with mRCC treated with nivo+cabo in study CA2099ER and for whom estimates of nivolumab exposure (time-varying daily Cavg) were available from the popPK analysis. Study CA209009 is not included for safety analysis since IMAEs were not collected in this study.

The relationship between nivolumab (time-varying daily Cavg) and time to first occurrence of Gr2+ IMAEs was described by a semi-parametric CPH model and included assessments of the modulatory effect of covariates on the exposure-response relationship with data from study CA2099ER Arm A and previous nivolumab monotherapy studies. Among the evaluated functional forms of exposure effect (i.e., linear, and log-linear), the model with a linear function of nivolumab time-varying daily Cavg had the lowest BIC value and was therefore selected for the full model for Gr2+ IMAEs. Interaction between exposure of nivolumab time-varying daily Cavg and cabozantinib addition were assessed; however, no interaction term was found to have significant impact on Gr2+ IMAEs.

Figure 6 is a graphical presentation of all the estimated effects in the full Gr2+ IMAE model, showing the HRs across the predictor ranges and the associated 95% CIs. The effect of nivolumab exposure (daily Cavg) on the risk of Gr2+ IMAEs was not statistically significant since the 95% CI for the HR included 1 across nivolumab monotherapy and nivo+cabo studies. Only cabozantinib coadministration was identified as significant predictor of Gr2+ IMAEs in the full model. Subjects administered combination treatment of nivo+cabo had higher risk of Gr2+ IMAEs compared with nivolumab monotherapy.

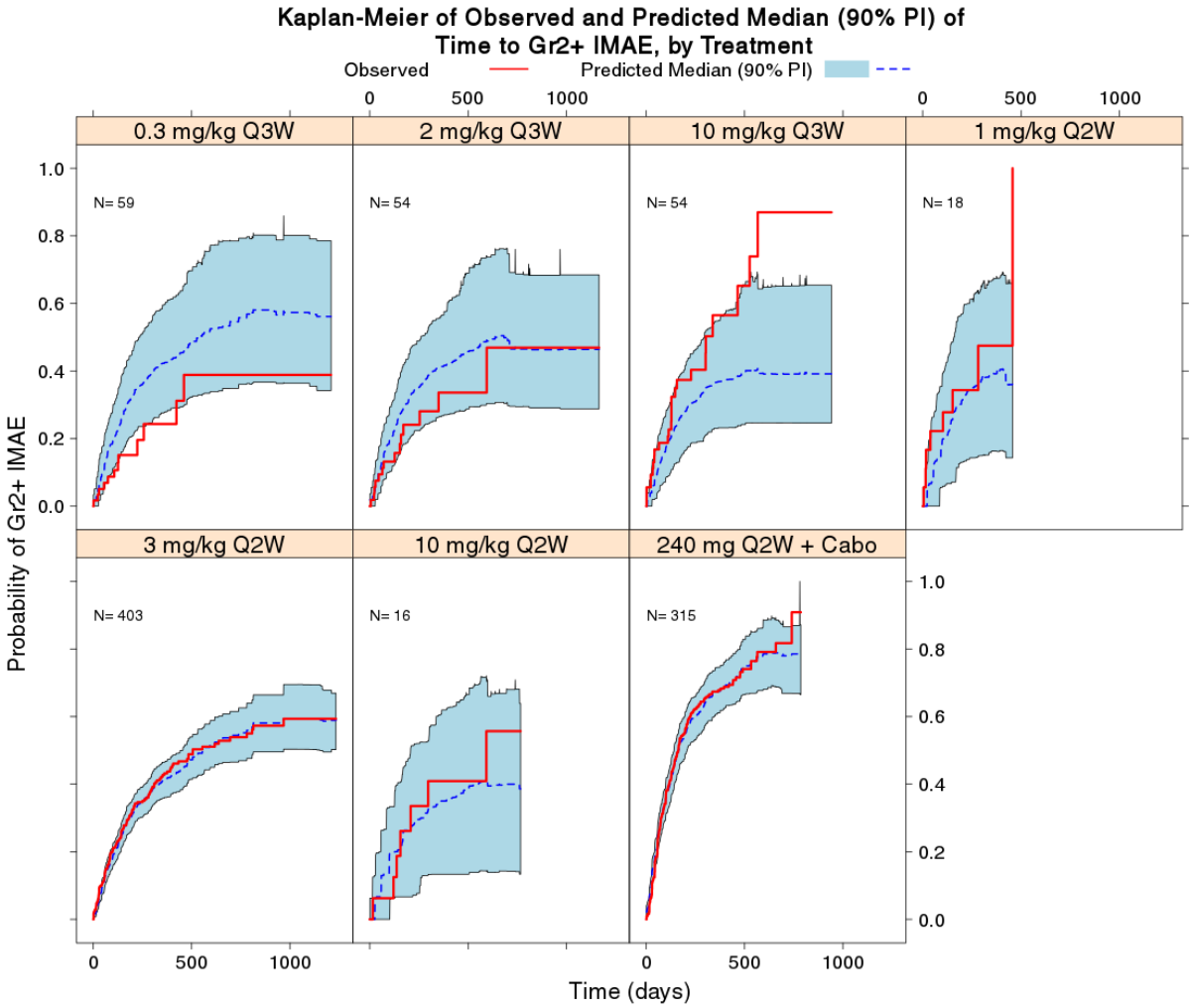
Figure 5 Exposure-safety analysis nivolumab + cabozantinib: estimated covariate effects on the hazard ratio of Grade 2+ IMAEs (Full Model)



Note: Reference values: Performance Status = 0, Sex = female, cabozantinib co-treatment = no.
Abbreviations: Cavg = time-averaged serum concentration; CI = confidence interval; GFR = glomerular filtration rate; IMAEs = immune mediated adverse events.

The final model predictions of the probability of Gr2+ IMAE by treatment are shown in Figure 7. In general, the model-predicted median (90% PI) probability of Gr2+ IMAE was consistent with the observed KM of Gr2+ IMAE in most nivolumab treatment arms across time. Gr2+ IMAE occurred already early in treatment for the combination of nivolumab and cabozantinib.

Figure 6 Exposure-safety analysis: model evaluation of Grade 2+ IMAE final model, by treatment



Abbreviations: Gr2+ = Grade 2+; IMAE = immune mediated adverse event; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks.

Extrapolation of nivolumab exposure-response model predictions for 240 mg Q2W+ Cabozantinib to 480 mg Q4W + Cabozantinib

Nivolumab exposures at 240 mg Q2W and 480 mg Q4W were predicted for subjects with RCC who received nivolumab and cabozantinib combination therapy (N = 315). The predicted concentration-time profiles were used to calculate the following 8 key summary measures of exposure: Cmin1, Cmax1, Cavg1, Cmind28, Cavgd28, Cminss, Cmaxss, and Cavgss. Comparison of these exposures between nivolumab 240 mg Q2W and 480 mg Q4W are presented in Table 3.

Table 3 Predicted nivolumab exposures at 240 mg every 2 weeks and 480 mg every 4 weeks for renal cell carcinoma subjects with cabozantinib combination therapy

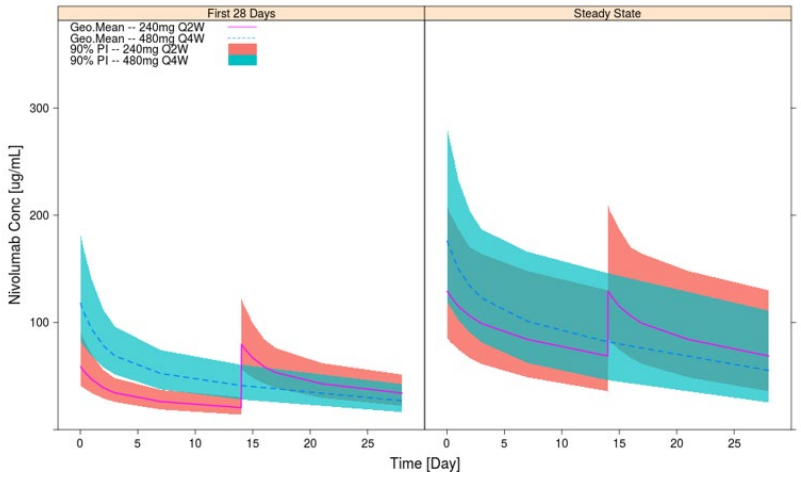
Exposure (µg/mL)	Nivo 240 mg Q2W Geo. Mean (CV%) N = 315	Nivo 480 mg Q4W Geo. Mean (CV%) N = 315	% Diff GM[a]
Cmin1	20.6 (23.0)	27.0 (27.6)	31.1
Cmax1	58.9 (38.9)	118 (38.9)	100
Cavg1	29.4 (21.6)	46.3 (22.4)	57.5
Cmind28	34.1 (24.6)	27.0 (27.6)	-20.8
Cavgd28	37.8 (22.0)	46.3 (22.4)	22.5

Exposure (µg/mL)	Nivo 240 mg Q2W Geo. Mean (CV%) N = 315	Nivo 480 mg Q4W Geo. Mean (CV%) N = 315	% Diff GM[a]
Cminss	68.7 (37.2)	55.3 (41.8)	-19.5
Cmaxss	129 (31.6)	176 (33.4)	36.4
Cavgss	87.9 (32.4)	87.9 (32.4)	0.00

[a] Percent difference in geometric mean of Nivo 480 mg Q4W relative to Nivo 240 mg Q2W.

The geometric means of nivolumab exposure were higher with 480 mg Q4W dosing relative to 240 mg Q2W dosing for 5 of the 8 summary measures of exposure, namely: Cmin1, Cmax1, Cavg1, Cavgd28, and Cmaxss, with the greatest difference noted with Cmax1 (100% higher with 480 mg Q4W). The exposures were lower by approximately 20% for Cmind28 and Cminss with nivolumab 480 mg Q4W relative to 240 mg Q2W. As expected, there was no exposure difference in Cavgss. The geometric mean (with 90% PI) of nivolumab concentration-time profiles for the 240 mg Q2W and 480 mg Q4W dosing regimens over the course of the first 28 days of treatment and at steady-state are presented in Figure 8.

Figure 7 Extrapolation 480 mg Q4W: Predicted geometric mean (with 90% CI) nivolumab concentration-time profiles (first 28 days and steady-state), by dosing regimen (240 mg Q2W and 480 mg Q4W) with cabozantinib combination therapy in subjects with RCC



Abbreviations: Conc =concentration; Geo. = geometric; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Table 4 shows the model-predicted mean PFS values for subjects in study CA2099ER based on Cavg1 for nivolumab 240 mg Q2W + cabozantinib 40 mg QD and extrapolated nivolumab 480 mg Q4W + cabozantinib 40 mg QD compared with the observed PFS over time in the sunitinib treatment arm. Predicted 6-month, 9-month, 1-year, and 2-year probabilities of PFS for the nivolumab 240 mg Q2W + cabozantinib 40 mg QD and 480 mg Q4W + cabozantinib 40 mg QD regimens were similar (i.e., ≤ 1% different between the regimens) and were all greater than the PFS probabilities for the sunitinib comparator arm in study CA2099ER.

Table 4 Extrapolation 480 mg Q4W: Predicted mean probability of PFS at select times for nivolumab 240 mg Q2W + cabozantinib and nivolumab 480 mg Q4W + cabozantinib relative to the observed incidence of PFS from the sunitinib comparator arm in study CA2099ER

Time	Nivolumab 240 mg Q2W + Cabozantinib 40 mg QD	Nivolumab 480 mg Q4W + Cabozantinib 40 mg QD	Sunitinib
6 Months	0.736 (0.637, 0.787)	0.739 (0.639, 0.79)	0.605
9 Months	0.66 (0.541, 0.722)	0.663 (0.544, 0.725)	0.487
1 Year	0.584 (0.45, 0.656)	0.587 (0.454, 0.659)	0.37
2 Years	0.48 (0.336, 0.562)	0.485 (0.34, 0.566)	0.106

Abbreviations: PFS = progression-free survival; Q2W = every 2 weeks; Q4W = every 4 weeks.

The model-predicted mean probabilities of Gr2+ IMAE for subjects in study CA2099ER based on daily Cavg for nivolumab 240 mg Q2W + cabozantinib 40 mg QD and extrapolated nivolumab 480 mg Q4W + cabozantinib 40 mg QD were similar over time between the regimens. Table 5 shows that the predicted 6 month, 9 month, 1 year, and 2 year probabilities of Gr2+ IMAE for the nivolumab 240 mg Q2W + cabozantinib 40 mg QD and 480 mg Q4W + cabozantinib 40 mg QD regimens were similar between the regimens (ie, ≤ 2.5% different).

Table 5 Extrapolation 480 mg Q4W: Predicted mean probability of Grade 2+ IMAEs at select times for nivolumab 240 mg Q2W + cabozantinib and nivolumab 480 mg Q4W + cabozantinib

Time	Nivolumab 240 mg Q2W + Cabozantinib 40 mg QD	Nivolumab 480 mg Q4W + Cabozantinib 40 mg QD
6 Months	0.526 (0.509, 0.539)	0.513 (0.527, 0.488)
9 Months	0.614 (0.595, 0.627)	0.602 (0.617, 0.576)
1 Year	0.677 (0.657, 0.691)	0.666 (0.68, 0.639)
2 Years	0.813 (0.812, 0.814)	0.801 (0.814, 0.778)

Source: Refer to Table 5.2.3-1 in the CA2099ER E-R Report.
Abbreviations: IMAE = immune mediated adverse event; Q2W = every 2 weeks; Q4W = every 4 weeks.

2.3.4. Discussion on clinical pharmacology

The pharmacology for nivolumab in combination with cabozantinib for the treatment of subjects with advanced RCC has been supported by pharmacokinetic and exposure-response data. Nivolumab and cabozantinib pharmacokinetics from study CA2099ER were analysed and compared with historical pharmacokinetic and exposure-response monotherapy data of nivolumab and cabozantinib in treatment of RCC. In this report the pharmacokinetics and exposure-response analyses of nivolumab from the pivotal study CA2099ER have been discussed with cabozantinib as covariate while in procedure **EMEA/H/C/004163/II/0017** the pharmacokinetics and exposure-response analyses of cabozantinib with nivolumab as covariate are discussed. Immunogenicity of nivolumab was assessed in study CA2099ER and this is discussed in the clinical safety section.

Bioanalytical methods

The same validated bioanalytical methods to analyse nivolumab or (neutralizing) antibodies against nivolumab have been used as evaluated in previous applications.

Pharmacokinetics

The nivolumab and cabozantinib pharmacokinetic assessment support lack of clinically relevant pharmacokinetic interaction between nivolumab and cabozantinib in study CA2099ER. Nivolumab popPK analysis showed that coadministration with cabozantinib 40 mg QD had a statistically significant impact on nivolumab baseline CL following the first dose, i.e. a lower baseline clearance of nivolumab. This may be partly due to different disease/health status of the patients population considering the

different line of treatment for nivolumab + cabozantinib vs nivolumab monotherapy. Even so, at steady-state nivolumab exposures were similar between nivolumab monotherapy and combination of nivolumab with cabozantinib and the magnitude of the difference following the first dose is considered not to be clinically relevant.

Exposure-response analyses

The exposure-efficacy (ORR, OS) relationships for nivolumab monotherapy for treatment of RCC (studies CA209003, CA209009, CA209010, and CA209025) have already been evaluated in procedures EMEA/H/C/003985/II/0005 and EMEA/H/C/003985/II/0036/G. Nivolumab clearance but not Cavg,ss was shown to be predictive of efficacy and a flat exposure-response over the dose range 1-10 mg/kg was concluded.

In this procedure exposure-PFS relationship has been explored since PFS was primary endpoint of study CA2099ER. It should be noted that for PD-1/PD-L1 antibodies PFS is not always predictive for OS and is therefore not the preferred efficacy parameter for exposure-response analysis but PFS is in case of first line RCC considered an acceptable parameter (see efficacy discussion). In general, the model-predicted median (90% PI) probability of PFS was consistent with the observed KM of PFS in most nivolumab monotherapy treatment arms across time (Figure 5). Since there was no significant interaction between cabozantinib administration and nivolumab Cavg1, a similar nivolumab flat exposure-efficacy correlation is expected for the combination of nivolumab + cabozantinib. The exposure-PFS model, however, cannot be used to elucidate the contribution of cabozantinib to the efficacy of the combination treatment because it is confounded by different line of therapies. The line of therapies were different for patients treated in study CA2099ER with the combination of nivolumab and cabozantinib (first-line) and patients treated with nivolumab monotherapy in studies CA209003, CA209009, CA209010, and CA209025 (second-line and later treatment). The respective contributions of cabozantinib and nivolumab to efficacy for the combination are discussed in the clinical efficacy section.

Subjects administered combination treatment of nivolumab + cabozantinib had higher risk of Gr2+ IMAEs compared with nivolumab monotherapy, and Gr2+ IMAEs occurred already early in treatment (Figure 7). This is not unexpected given the overlapping safety profiles of nivolumab and cabozantinib e.g. hepatic events, diarrhoea, rash and hypothyroidism, which may also classify as IMAEs. The nivolumab exposure-Gr2+ IMAEs analyses showed that nivolumab exposure was not a significant predictor of Gr2+ IMAEs, the incidence of Gr2+ IMAEs and the probability across time was independent of the nivolumab concentrations over the dose range 0.3-10 mg/kg.

Extrapolation to nivolumab 480 mg Q4W + cabozantinib 40 mg QD

Besides the studied dosing in study CA2099ER of nivolumab 240 mg Q2W + cabozantinib 40 mg QD, the applicant also applies for a 4 weekly administration of nivolumab i.e. nivolumab 480 mg Q4W + cabozantinib 40 mg QD. Nivolumab 480 mg Q4W has already been approved for nivolumab monotherapy in second-line (and later) treatment of RCC based on the flat exposure-response efficacy and safety analyses for nivolumab monotherapy (EMEA/H/C/003985/II/0036/G). Modelling and simulations demonstrated that the alterations in nivolumab pharmacokinetics between 240 mg Q2W and 480 Q4W i.e. higher Cmax and lower Cmin and comparable Cavg for 480 mg Q4W compared to 240 mg Q2W (see also Table 3) did not result in an altered benefit or safety profile.

The flat dose-responses and flat exposure-responses of nivolumab have been demonstrated in second-line treatment of RCC and because binding of nivolumab to PD-1 receptor is independent of line of therapy, the flat exposure-response demonstrated in second-line treatment of RCC is also applicable to first-line treatment of RCC. This is further supported by the currently presented exposure-response analyses. There was no interaction between cabozantinib administration and nivolumab Cavg1 in the

exposure-efficacy analysis, hence a similar nivolumab flat exposure-efficacy correlation is expected for the combination of nivolumab + cabozantinib. Therefore, the additional dosing option of nivolumab 480 mg Q4W + cabozantinib 40 mg QD is considered acceptable.

2.3.5. Conclusions on clinical pharmacology

Pharmacokinetics and exposure response relationships of nivolumab have been sufficiently investigated for the extension of the indication of nivolumab 240 mg Q2W+ cabozantinib 40 mg QD or nivolumab 480 mg Q4W + cabozantinib 40 mg QD for 1L treatment of patients with advanced renal cell carcinoma.

2.4. Clinical efficacy

2.4.1. Dose response study

Dose selection for nivolumab combined with cabozantinib was based on an investigator-sponsored phase 1 trial (CTEP-9681; Apolo et al. J Clin Oncol. 2020), supported by the National Cancer Institute NCI/NIH evaluating the combination of cabozantinib with nivolumab (doublet) or cabozantinib with nivolumab and ipilimumab (triplet) in patients with previously treated advanced genitourinary cancers, including urothelial carcinoma (UC) and RCC. Among the primary objectives of CTEP-9681 was determining the dose limiting toxicity (DLT) and the recommended phase 2 dose (RP2D) of the nivo+cabo doublet in patients with genitourinary tumours.

In the Part 1 dose escalation stage of CTEP-9681, 24 patients (6 per Level) were treated with the doublet regimen in 4 dose levels (Level 1: cabozantinib at 40 mg by mouth [PO], daily and nivolumab at 1 mg/kg Q2W; Level 2: cabozantinib at 40 mg PO, daily and nivolumab at 3 mg/kg Q2W; Level 3: cabozantinib at 60 mg PO, daily and nivolumab at 1 mg/kg Q2W; Level 4: cabozantinib at 60 mg PO, daily and nivolumab at 3 mg/kg Q2W) with 6 patients treated in each dose level. In the dose escalation stage of the study, no DLTs were reported for the doublet combination. However, a trend towards fewer treatment-related adverse events (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 (Apolo et al. J Clin Oncol. 2020).

Based on the overall tolerability, RP2D for the doublet regimen was cabozantinib 40 mg administered orally with nivolumab 3 mg/kg administered IV. Additionally, 25 patients were treated at the RP2D level in an expansion cohort and the data confirmed initial safety findings and further supported the RP2D safety and tolerability (Nadal et al. J Clin Oncol. 2018). Preliminary anti-tumour activities were also observed and reported among patients treated with cabozantinib 40 mg PO daily in combination of nivolumab 3 mg/kg Q2W (Apolo et al. J Clin Oncol. 2020; Nadal et al. J Clin Oncol. 2018).

The lower 40 mg dose of cabozantinib in combination with nivolumab is further supported by an exposure-response analysis of safety and efficacy endpoints from cabozantinib monotherapy data in the METEOR trial in previously treated, advanced RCC evaluating 60 mg cabozantinib vs everolimus (Lacy et al. Cancer Chemotherapy and Pharmacology. 2018). Dose reductions to 40 mg and then 20 mg were allowed and occurred in 60% of patients in the cabozantinib group. From the exposure-response analyses, there was a higher risk for selected AEs fatigue/asthenia (Grade ≥ 3), palmar-plantar erythrodysaesthesia (PPE) syndrome [Grade ≥ 1], diarrhoea (Grade ≥ 3) and hypertension (HTN) with predicted HRs of 1.42, 1.49, 1.33, 1.36, respectively, based on the predicted steady-state average cabozantinib concentration for the 60 mg dose relative to a 40 mg starting dose. Given the

efficacy was predicted to be somewhat lower with a 40 mg monotherapy dose compared with the 60 mg dose (higher risk of disease progression/death [HR 1.1], lower maximal median reduction in tumour size [-9.1% vs -11.9%] and lower ORR [15.6 % vs 19.1%]), the benefit-risk assessment was favourable for 60 mg cabozantinib single agent to maximize tumour response with safety management using dose modifications. However, the 60 mg dose, when given in combination with nivolumab, was expected to have combination effects of both efficacy and safety and, thereby, as a conservative measure, the 40 mg dose was chosen to increase tolerability, with the theory that any potential decreased efficacy would be supported by the effect of the combination.

In study CA2099ER, a flat dose of nivolumab 240 mg Q2W was administered in combination with cabozantinib 40 mg/day (Arm A) in patients with previously untreated advanced RCC, because at the time of the study CA2099ER protocol initiation, only the nivolumab 240 mg Q2W dose was approved. It is noted that the doses of nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W have been accepted to have a similar benefit-risk (B/R) balance for treatment of melanoma and RCC (EMEA/H/C/003985/II/0036/G).

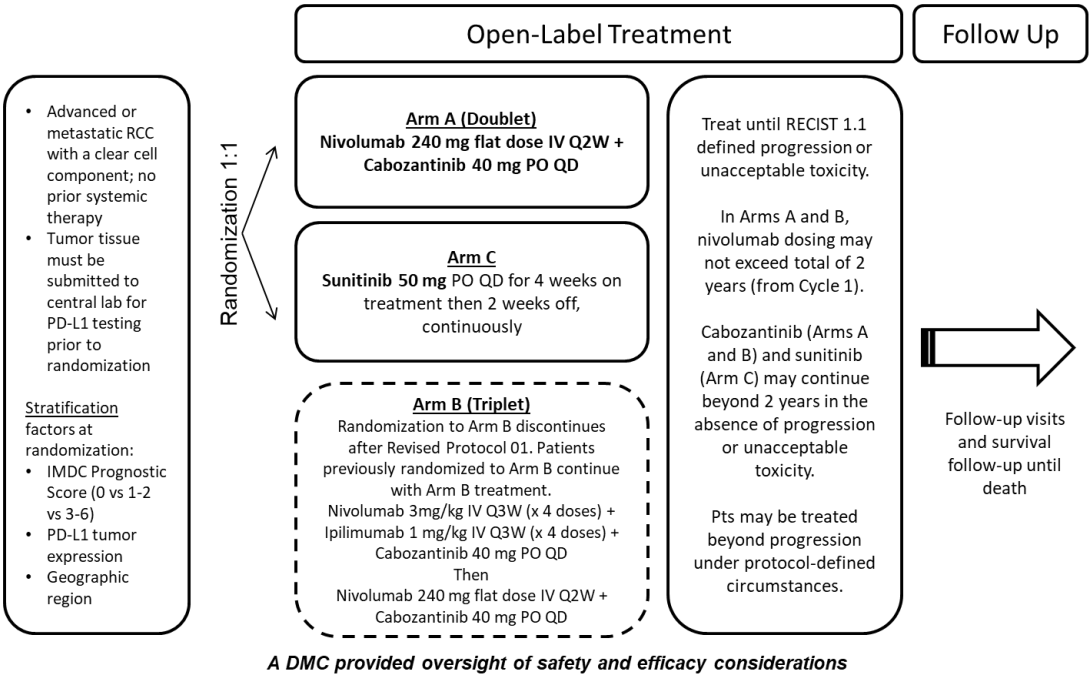
2.4.2. Main study

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

Study CA2099ER (NCT03141177) is a phase 3, open-label, randomized trial of nivolumab combined with cabozantinib (nivo+cabo, doublet regimen, Arm A) vs sunitinib (Arm C) in patients with previously untreated (first-line; 1L) advanced RCC. Per protocol, no crossover was allowed. The CA2099ER study design schematic is presented in Figure 9.

Figure 8 CA2099ER Study design schematic



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.

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

First tumour assessment post-baseline was performed at 12 weeks (± 7 days) following randomisation using the same imaging method as was used at baseline (i.e. computerized tomography [CT]/ magnetic resonance imaging [MRI] of the chest, abdomen, pelvis, and all known sites of disease). Subsequent tumour assessments occurred at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, assessed by the investigator (using RECIST v1.1) and confirmed by the BICR.

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 tumor 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

Study treatment began within 3 days (72 hours) of randomization. Patients were randomly assigned to 1 of the 2 treatment arms as noted in Figure 9.

- **Arm A** (nivo+cabo doublet): 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

- **Arm C** (sunitinib): 50 mg sunitinib PO QD for 4 weeks, followed by 2 weeks off, per cycle. Cycles were to be continued until progression or unacceptable toxicity

Rationale for nivolumab and cabozantinib dosing in Arm A

See above **Error! Reference source not found.**

Rationale for sunitinib dosing in Arm C

As stated above, sunitinib was SoC at the start of study CA2099ER. The used standard dosing schedule of 4 weeks on treatment followed by 2 weeks off is consistent with the sunitinib prescribing information as approved in the EU (Sutent SmPC).

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 (though nivolumab treatment was maximized at 2 years, see above).

Objectives and outcomes/endpoints

The **research hypothesis** of study CA2099ER was that treatment with nivolumab combined with cabozantinib (doublet regimen) would demonstrate an improvement in PFS per BICR compared to sunitinib monotherapy in patients with previously untreated mRCC.

The objectives and endpoints of study CA2099ER are shown in Table 6.

Table 6 Study CA2099ER objectives and endpoints

Objectives		
Primary:		
To compare progression-free survival (PFS) per BICR of Arm A with Arm C in all randomized patients.	**PFS**	The primary endpoint is **to compare PFS per BICR of nivolumab combined with cabozantinib (Arm A: doublet) with sunitinib (Arm C) in all randomized patients**. The primary definition of PFS (PFS censored at subsequent therapy, which includes anti-cancer therapy, tumour directed radiotherapy, or tumour directed surgery) is defined as the time between the date of randomization and the date of first documented tumour progression, based on BICR assessments (per RECIST v1.1), or death due to any cause, whichever occurs first.
Secondary:		
To compare overall survival (OS) of Arm A with Arm C.	**OS**	The first secondary endpoint is **to compare OS of Arm A vs Arm C** in all randomized patients. OS is defined as the time between the date of randomization and the date of death due to any cause. A patient who has not died will be censored at the last known alive date.
To compare the objective response rate (ORR) per BICR	**ORR** per BICR	The second secondary endpoint is **to compare ORR per BICR of Arm A vs Arm C** in all randomized patients. ORR is defined as the proportion of randomized patients who achieve a best response of complete response (CR) or partial response (PR) using RECIST v1.1. Best overall response (BOR) is defined as the best response designation recorded between the date of

of Arm A with Arm C.		randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. For patients without document progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Duration of response (DoR) is defined as the time between the date of first confirmed documented response (CR or PR) to the date of first documented tumour progression (per RECIST v1.1) or death due to any cause, whichever occurs first. Patients who neither progress nor die will be censored on the date of their last tumour assessment. Responders who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumour assessment prior to the initiation of first subsequent anti-cancer therapy. Time to response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by BICR. DoR and TTR will be evaluated for responders (CR or PR) only.
To assess overall safety and tolerability in all treated patients.		
Exploratory:		
To explore potential predictive biomarkers of clinical response to nivolumab and cabozantinib combination.	Biomarkers	Analysis of tumour specimens and blood samples for proteins and genes involved in regulating immune response (e.g., PD-1, PD-L1, PD-L2). Other exploratory endpoints for biomarkers, pharmacogenomics, and immunogenicity are described in Section 9.8 of the protocol (Appendix 1.1).
To evaluate health related quality of life (HRQoL).	HRQoL	Assessed by the NCCN Functional Assessment of Cancer Therapy- Kidney Symptom Index (FKSI-19) and the EuroQoL Group's EQ-5D (3L version).
To characterize the PK of nivolumab and cabozantinib and explore exposure response relationships, if applicable.	PK	Population PK parameters, E-R relationship between select PK measures of exposure and safety and efficacy endpoints, if applicable.
To characterize the	Immunogenicity	Incidence of anti-nivolumab antibodies and their potential relationship with safety and efficacy endpoints

immunogenicity of nivolumab		
To assess PFS after next line of treatment (PFS2) in each arm.	PFS2	PFS2 is defined as the time from randomization to the date of investigator-defined documented second objective disease progression on second-line therapy or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A patient who neither progresses nor dies will be censored on the date of his/her last adequate tumour assessment or last follow-up for progression/subsequent therapy. A patient who does not have any post-baseline tumour assessments and who has not died will be censored on the date at which he/she was randomized.

Abbreviations: AEs: adverse events; BICR: blinded independent central review; BOR: best overall response; CR: complete response: DoR: duration of response; E-R: exposure-response; FKSI-19: Functional Assessment of Cancer Therapy - Kidney Symptom Index; HRQoL: health related quality of life; MedDRA: Medical Dictionary for Regulatory Activities; NCCN: National Comprehensive Cancer Network; ORR: objective response rate; OS: overall survival; PD-L1 (or 2): programmed death ligand 1 (or 2); PFS: progression-free survival: PFS2: PFS after next line of treatment; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SAEs: serious adverse events; SAP: statistical analysis plan; TTR - time to response.

Exploratory objective to evaluate health related quality of life (HRQoL)

Patient-reported outcomes (PROs) were captured through the use of two validated self-reported questionnaires: the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19), and the EuroQoL Group's EQ-5D-3L. Analysis of the FKSI-19 and EQ-5D-3L was restricted to randomized patients in Arm A and Arm C who had an assessment at baseline and at least one post-baseline assessment.

The NCCN **FKSI-19** (@ FACIT.org website; actual measure) is a 19-item scale that measures tumour specific HRQoL in RCC patients. The FKSI-19 uses 5 Likert-type response categories that range from "not at all" to "very much." Patients are asked to circle the response category that best characterizes their response over the last 7 days on 19 items that include symptoms such as lack of energy, fatigue, appetite, coughing, shortness of breath, pain, nausea, and ability to work. The instrument yields a total score and three subscale scores: Disease Related Symptoms (DRS), Treatment Side Effects (TSE), and Functional Well Being (FWB). A higher score indicates fewer symptoms.

The 3-level version of the EQ-5D (**EQ-5D-3L**) will be used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations. The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety) and depression (see EQ-5D-3L User Guide). Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions [11111] to severe/extreme problems on all 5 dimensions [33333]. Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility index representing the societal desirability of his/her own health. In addition, the EQ-5D includes a VAS allowing a respondent to rate his/her health on a scale 0–100, with 0 being the worst health state and 100 being the best health state imaginable.

Sample size

Sample size justification for primary PFS endpoint

The primary endpoint of PFS per BICR of Arm A vs Arm C analysis was conducted on all randomized patients. The PFS analysis was to occur after approximately 9-10 months minimum follow-up on all randomized patients by which approximately 350 events from Arm A and Arm C were observed. The 350 PFS events were to provide at least 95% power to detect a hazard ratio (HR) of 0.68 for PFS of Arm A vs Arm C with a type I error of 0.05 (two-sided). The HR of 0.68 corresponded to a 47% increase in the median PFS, assuming a median PFS of 18.2 months for Arm A and 12.4 months for Arm C. It was projected that an observed HR of 0.811 or less, which corresponded to a 2.89 months or greater improvement in median PFS (12.4 vs 15.3 months), would result in a statistically significant improvement in PFS for the Arm A vs Arm C comparison.

Assuming a 25% screen failure rate, it was expected that approximately 850 patients were needed in order to randomize 638 patients (319 per arm) in a 1:1 ratio. This number of patients was chosen to achieve the 350 events in the projected time frames. To represent the normal frequency of favourable risk in mRCC, the favourable risk patient group was capped at approximate 25%.

Sample size computation for secondary OS endpoint

The secondary endpoint of OS in all randomized patients was for the comparison of Arm A vs Arm C. Among all randomized patients, approximately 254 events (i.e., deaths) in Arm A and Arm C was to provide at least 80% power to detect a HR of 0.70 for OS of Arm A and Arm C with an overall type 1 error of 0.05 (two-sided). The HR of 0.70 corresponded to a 43% increase in the median OS, assuming a median OS of 47.1 months for Arm A and 33 months for Arm C.

Two formal IAs of OS were planned for this study.

- The first IA was planned at the time of final PFS and expected to observe 165 OS events (65% of the targeted OS events for final analysis). With 165 OS events, observed HR of 0.673 or less, which corresponded to a 16.0 months or greater improvement in median OS (33 vs 49 months), would result in a statistically significant improvement in OS for the Arm A vs Arm C comparison.
- In the event a first IA for OS was not statistically significant, the second IA was planned to occur after observing approximately 211 events (83% of targeted OS events needed for final analysis). With 211 deaths, an observed HR of 0.734 or less, which corresponded to a 12.0 months or greater improvement in median OS (33 vs 45 months), would result in a statistically significant improvement in OS for the Arm A vs Arm C comparison.

Note that, at the time of final OS analysis with 254 deaths, an observed HR of 0.774 or less, which corresponded to a 9.6 months or greater improvement in median OS (33 vs 42.6 months), would result in a statistically significant improvement in OS for the Arm A vs Arm C comparison.

O'Brien and Fleming α spending function is used to determine the stopping boundaries at interim and final analyses. For the above specified number of events in Arms A and C, the respective stopping boundaries would be α=0.011 (two-sided), α=0.025 (two-sided), and α=0.041 (two-sided) for the first interim, second interim, and final analyses, respectively.

Assuming a constant accrual rate (an average rate of 3 patients/month in the first 4 months, afterwards an average rate of 42 patients/month), the accrual would take approximately 19 months. The final PFS analysis was not to occur prior to these conditions being met:

- at least 8 months minimum follow-up on all randomized patients;

- at least 283 PFS events, which would provide at least 90% power to detect a HR of 0.68 for PFS of Arm A vs Arm C; and
- at least 149 OS events, which would provide 66% power if the target HR for OS was 0.60. (Note that if the analysis of first IA OS was to take place with 149 OS events, the alpha spending for the OS comparison would be 0.007 with a critical HR=0.643.)

This expected PFS analysis was to occur at approximately 29 months from FPFV.

Secondary endpoints (including both efficacy endpoints OS and ORR) were analysed at the time of the final analysis of PFS based on a **hierarchical testing strategy**: 1. the primary endpoint PFS (per BICR); 2. the secondary endpoint OS; 3. the secondary endpoint ORR (per BICR). In the event that the IA for superiority of OS is positive, final analyses were to be performed prior to achieving 254 deaths.

Randomisation

Patients were randomized between Arm A and Arm C in a 1:1 ratio and stratified at the time of randomization by:

- IMDC prognostic score (0 [favourable risk] vs 1-2 [intermediate risk] vs 3-6 [poor risk]);
- Tumour PD-L1 expression (≥1% vs <1% or indeterminate); and
- region (US/Canada/Western Europe/Northern Europe vs rest of the world [ROW]).

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 by the Interactive Response Technology (IRT) system. Randomization was carried out via permuted blocks within each stratum. Randomization to IMDC favourable risk patients was capped at approximately 25% to represent the typical frequency of favourable risk patients among mRCC.

Blinding (masking)

Not applicable, as study CA2099ER has an open-label study design.

Statistical methods

Description of analysis populations

All analyses were performed using the treatment arm as randomized (intent to treat [ITT]), with the exception of dosing and safety, for which the treatment arm as received was used. All populations for analyses refer to patients in Arm A and Arm C. Patients randomized to Arm B prior to Revised Protocol 01 were considered as part of the population of interest only for descriptive summary of efficacy and safety analyses.

Statistical analyses

Analyses were conducted according to the Statistical Analysis Plan (SAP) that was developed and finalized before DBL (SAP v1 finalized in Jun-2019; SAP v2 finalized in Dec-2019; DBL: 30-Mar-2020), and described the selection of patients to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

Efficacy analyses

See Table 6 for the definitions of the endpoints.

Primary endpoint PFS (per BICR):

The primary objective/endpoint of the study was to compare PFS per BICR using RECIST v1.1 of Arm A to Arm C in all randomized patients. For the **primary analysis** PFS per BICR were compared between the treatment groups via stratified log-rank test among all randomized patients at a two-sided α = 0.05 level. The estimate of the PFS HR between treatment groups was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties were to be handled using the exact method. A two-sided 95% CI for the HR is presented.

The **primary definition** of PFS was used in this analysis, i.e. PFS censored at subsequent therapy, including anti-cancer therapy, tumour directed radiotherapy, or tumour directed surgery. The censoring scheme for this primary definition of PFS is shown in Table 7.

Table 7 Censoring scheme for primary definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments*	Date of randomization	Censored
No on study tumor assessments and no death*	Date of randomization	Censored
Subsequent anti-cancer therapy started without death or progression per RECIST v1.1 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer started before	Date of the first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed
No progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1 and no new anti-cancer started before	Date of death	Progressed

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.

The censoring scheme for the **secondary definition** of PFS (only used as a supportive analysis) is shown in Table 8.

Table 8 Censoring scheme for secondary definition of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression per RECIST v1.1	Date of first documented progression per RECIST v1.1 criteria (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1	Date of death	Progressed

The following **sensitivity analyses** of PFS were also conducted:

- Investigator-assessed PFS.
- PFS using an unstratified log rank test. The HR associated with treatment was presented along with the associated two-sided 95% CIs.
- A stratified multivariate Cox regression model was used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors.

The influence of baseline and demographic characteristics on the treatment effect among all randomized patients will be explored via exploratory **subgroup analyses**. The median PFS based on KM product-limit method along with two-sided 95% CIs will be produced for amongst others the following subgroups: age categorization, sex, race, region, baseline IMDC prognostic score, and baseline PD-L1+ status based on a 1% cut-off. A forest plot of the unstratified PFS HRs (along with the 95% CIs) will be produced for each level of the subgroups listed above. The analysis comparing treatment (i.e., HR) will be conducted if the number of patients in the subgroup category is more than 10.

Secondary endpoint OS:

A secondary objective of the study was to compare the OS of Arm A to Arm C in all randomized patients. If the formal analysis of PFS was statistically significant, the formal IA of OS was to be tested, as per hierarchical testing procedure.

OS was planned to be compared between the treatment groups at the first and possibly second interim, and the final analysis using a stratified log-rank test. The stratification factors were those used in the analysis of PFS. An O'Brien and Fleming α-spending function was employed to determine the nominal significance levels for the interim and final analysis. The stratified HR between the treatment groups was presented along with 100*(1- α)% CI (adjusted for interim). In addition, two-sided p-value was reported for the analysis of OS.

OS was estimated using the KM techniques. A two-sided 95% CI for median OS in each treatment group was computed via the log-log transformation method. OS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) were presented along with their associated 95% CIs.

Minimum follow-up of OS for all randomized patients, defined as the time from last patient's randomization date to the cut-off date for OS, was summarized in months.

Subgroup analyses were performed for OS, for the same subgroups as used for PFS and by the same method, see above.

Secondary endpoint ORR (per BICR):

If the formal analysis of OS was statistically significant, the formal analysis of ORR would be tested, as per hierarchical testing procedure.

The number and percentage of patients in each category of BOR per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) were presented, by treatment group. Estimates of ORR, along with its exact two-sided 95% CI by Clopper and Pearson were presented, by treatment group.

Similar analyses were repeated based on the investigator's assessment of ORR. A cross tabulation of BICR best response vs the investigator best response was presented, by treatment group and by response categories.

DoR and TTR were also evaluated for patients who achieved confirmed PR or CR. The DoR for each treatment group was estimated using the KM product limit method and displayed graphically.

Subgroup analyses were also performed for ORR.

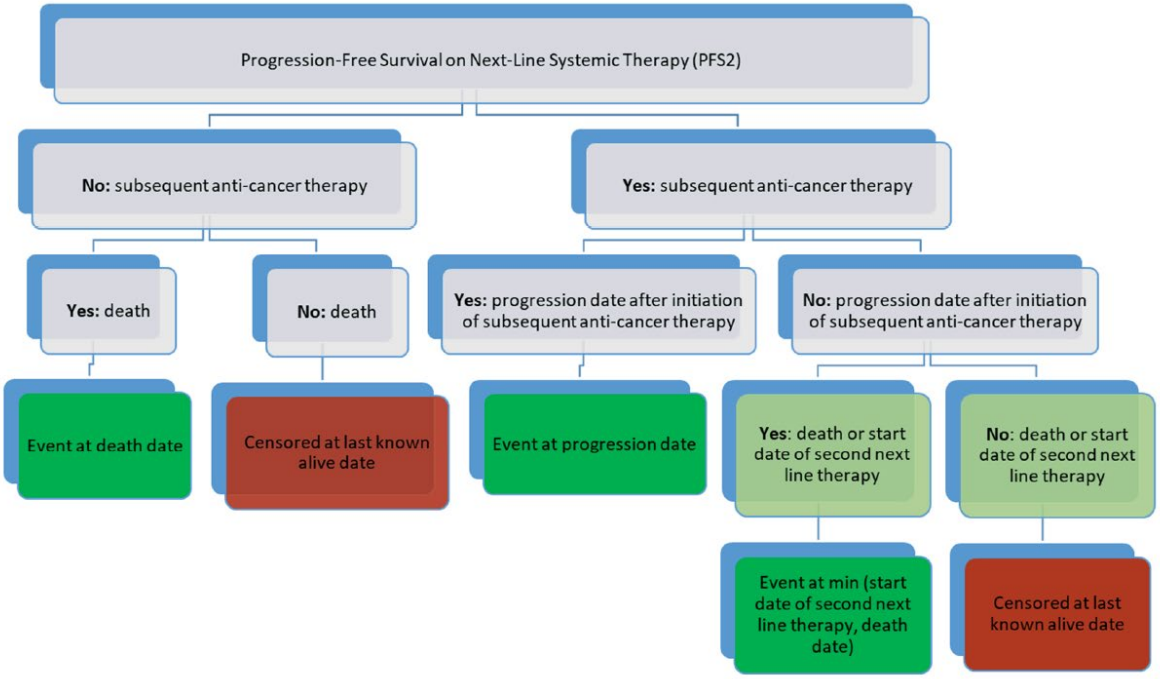
Exploratory endpoint HRQoL:

The analysis of FKSI-19 and EQ-5D-3L was restricted to randomized patients in Arm A and Arm C who had an assessment at baseline and at least one post-baseline assessment.

Planned analyses include: questionnaire completion rate; mean score and mean change from baseline (for both total and subscale scores) at each assessment time point; the number and percentage of patients endorsing each response at each assessment time point (for categorical data); figures summarizing the mean change from baseline (including 95% CI); and by patient listings of PRO responses at each assessment time point.

Exploratory endpoint PFS2:

The following censoring rules will be applied for PFS2:



Results

Participant flow

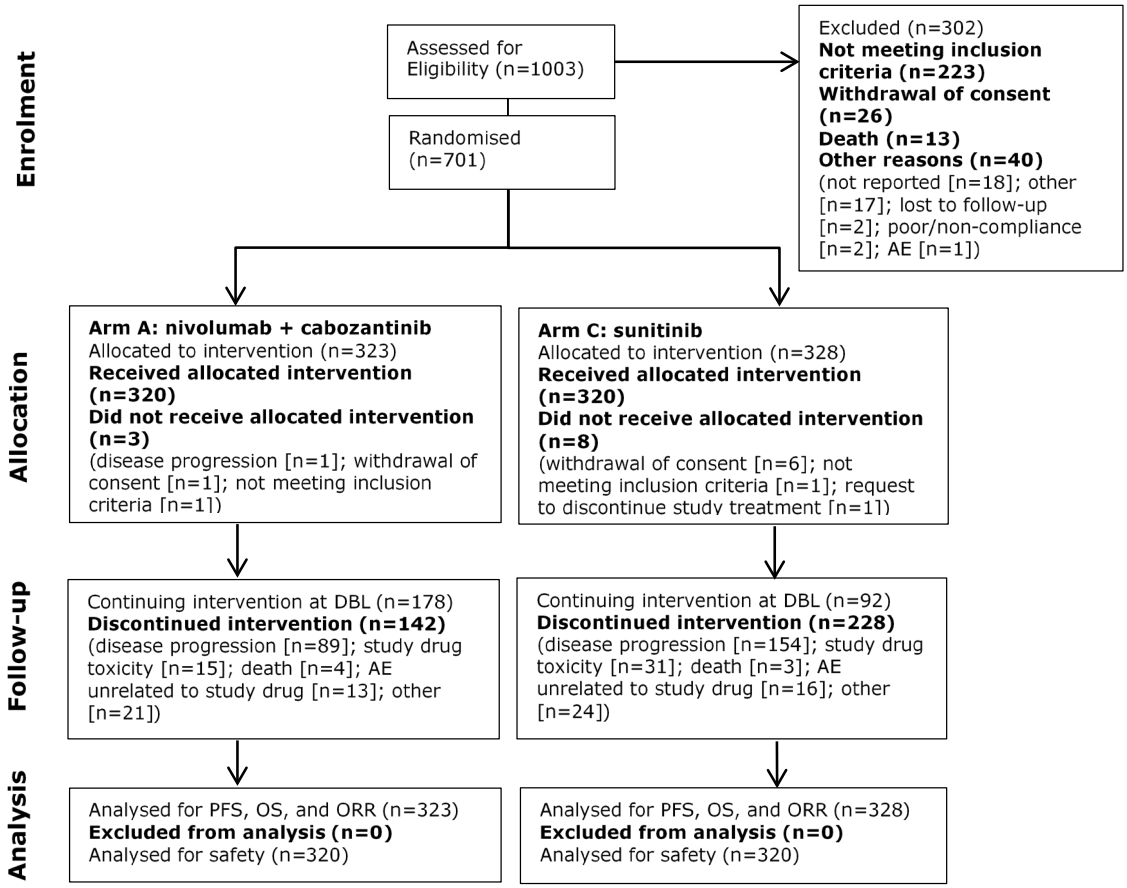
The participant flow in study CA2099ER is shown in Figure 10. Overall, 1003 patients were enrolled and 701 were randomized, including 323 to the nivo+cabo arm and 328 to the sunitinib arm (and 50 to Arm B, see below at **Conduct of the study** - Protocol amendments). Of these, **640 patients were treated in Arm A and Arm C: 320 with nivo+cabo and 320 with sunitinib**.

Of the 223/1003 enrolled patients (22.2%) who were not randomized, for 74/223 (33.2%), 116/223 (52.0%), and 33/223 (14.8%) this was due to not meeting inclusion criteria, meeting exclusion criteria, or for other reasons, respectively.

The most common reasons for patients who were randomized but not treated was withdrawal of consent (1 for nivo+cabo, 6 for sunitinib). 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).

Figure 9 Study CA2099ER participant flow



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.

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 protocol for study CA2099ER was dated 08-Mar-2017. There were two global revisions to the protocol, see Table 9. The rationales for the changes in these two global revisions are summarized below the table.

Table 9 Global revisions to protocol of study CA2099ER

Document	Date of Issue	Primary Revisions
Original Protocol (Global)	08-Mar-2017	Not applicable
Revised Protocol 01 (Global)	18-Dec-2017	(i) to stop enrolment into Arm B (nivolumab + ipilimumab + cabozantinib triplet); and (ii) to include favourable risk patients (capped at 25%) in study to allow for potential meaningful differences in efficacy to be detected in a broader population that includes favourable-risk patients.
Revised Protocol 02 (Global)	03-May-2019	(i) to adjust timing of PFS and OS interim analyses with modified hypothesized OS hazard ratio (HR). Number of randomized patients increased from 290 to 319 per arm; and (ii) to remove interim analysis for ORR resulting in revised overall alpha for PFS and OS endpoints.

- CA2099ER Global Revised Protocol 01 (Dated 18-Dec-2017)

Rationale for (i) to stop enrolment into Arm B: CA2099ER was revised to discontinue enrolment into Arm B since Study CA209214 (nivo+ipi vs sunitinib) demonstrated superior OS with nivo+ipi compared to sunitinib in patients with previously untreated, IMDC intermediate and poor risk mRCC (07-Sep-2017 BMS press release). In light of this, the CA2099ER trial design was no longer sufficient for the Arm B triplet regimen to demonstrate superiority over sunitinib, since the nivo+ipi combination within the triplet regimen had already been shown to be superior to sunitinib in CA209214. In the original protocol, the overall alpha for CA2099ER was 0.05 (two sided), split for each of two comparisons (Arm A vs Arm C, and Arm B vs Arm C) to evaluate PFS as the primary endpoint. The statistical plan was updated to reflect Arm B being removed in revised protocol 01, with the entire alpha allocated to Arm A vs Arm C comparison. The primary endpoint remained PFS (Arm A vs Arm C comparison).

As of 18-Dec-2017, at the time this amendment was finalized, 15 patients had been randomized to CA2099ER (5, 4, and 6 patients to Arms A, B, and C, respectively). Implementation of CA2099ER Revised Protocol 01 (stopping enrolment to Arm B) was done at the site level when the revised protocol was approved at the site; thus, 50 patients had been randomized to Arm B as of the time of revised protocol implementation at the last site (Sep-2018). These patients previously randomized to Arm B continued with Arm B treatment and planned clinical evaluation, per protocol. Data collected for patients in Arm B were included in the submitted datasets and in the appendices of the CA2099ER clinical study report (CSR). However, results from Arm B are not included (or discussed) in this AR.

Rationale for (ii) to include favourable risk patients (capped at 25%): given that in CA209214, nivo+ipi did not demonstrate a similar clinical benefit in favourable risk patients as was shown in intermediate and poor risk patients (Motzer et al. N Engl J Med 2018; Opdivo + Yervoy 1L RCC EPAR), a decision was made to broaden the 1L mRCC analysis population that may benefit from nivo+cabo in combination in CA2099ER to include all IMDC risk groups, including favourable risk.

- CA2099ER Global Revised Protocol 02 (Dated 03-May-2019)

Rationale for (i) to adjust the timing of the PFS and OS IAs with modified hypothesized OS HR, to increase the number of randomized patients: This protocol revision was based on the fact that both the CA209214 (nivo+ipi vs sunitinib; Motzer et al. N Engl J Med. 2018) and KEYNOTE-426 (pembrolizumab + axitinib vs sunitinib, published Mar-2019; Rini et al. N Engl J Med. 2019) studies had shown clinically and statistically significant improvements in OS with immunotherapy-containing combinations compared with single agent sunitinib in previously untreated advanced RCC, with an OS HR of 0.63 (for intermediate/poor risk patients) and 0.53, respectively. To be more consistent with these emerging data (particularly, as KEYNOTE-426 data became available in addition to CA209214 results), the hypothesized OS HR for CA2099ER was updated from 0.76 to a more clinically meaningful 0.70, and the sample size was increased by 10% from 580 to 638, thereby increasing the power to detect a difference in OS from 75% to 80%, with less required overall clinical follow-up time. The statistical plan was updated to reflect a longer overall enrolment and accrual period.

Rationale for (ii) to remove the IA for ORR resulting in revised overall alpha for PFS and OS endpoints: Based on results of the phase 3 studies mentioned above, the planned IA for ORR was removed, with the corresponding 0.001 alpha reallocated to the primary PFS analysis.

These changes were based on emerging external data only, as Company personnel continued to be blinded to CA2099ER. No changes in eligibility or study procedures were made. As of 03-May-2019, at the time the amendment was finalized, 647 patients had been randomized to CA2099ER (321 and 326 to Arms A and C, respectively).

Protocol deviations

Significant protocol deviations were defined as study conduct that differed significantly from the protocol, including GCP noncompliance. A complete summary of significant protocol deviations is provided in Table 10.

Table 10 Summary of significant protocol deviations

	Arm A	Arm C	Total of Arms A and C
Failure to obtain written consent prior to each patient's participation in the study#	**31**	**30**	**61**
Failure to report all SAEs in accordance with the time period required by GCP, the protocol, BMS and applicable regulations	**17**	**20**	**37**
Implementation of protocol changes prior to review by IRB/IEC or failure to implement an IRB/IEC approved amendment	**6**	**5**	**11**
Inclusion or exclusion	**58**	**50**	**108**

	Arm A	Arm C	Total of Arms A and C
Baseline labs collected not within 14 days of randomization	23	15	38
Lab Values at baseline are assessed and not meeting protocol required criteria	0	2	2
Exclusionary Medical History, Concurrent Disease, Physical Laboratory Test Findings, Allergies or Adverse Drug Reactions as outlined in the Exclusion Criteria section of the protocol.	4	7	11
Baseline procedure not performed within 28 days prior to randomization (per protocol)	11	10	21
Baseline procedure (PD-L1 test) not performed prior to randomization (per protocol)[##]	6	2	8
Baseline Tumour Assessments not performed within 28 days prior to randomization	12	14	26
No sites of measurable disease	2	0	2
Incorrect dosing or study treatment assignment	**14**	**8**	**22**
Nivolumab dosing not within correct window: Minimum - <12 days from previous dose for Q2W	11	0	11
Sunitinib dosing: Sunitinib 50 mg PO QD treatment for 4 weeks then 2 weeks off each cycle	0	8	8
Flat dose: Administration error of <75% or >125% of the planned dosage	3	0	3
Other	**22**	**12**	**34**
Two consecutive Tumour Assessments were not performed per protocol schedule	7	4	11
Patient not treated within protocol required time frame from Randomization	1	1	2
Required labs not performed prior to dosing	5	2	7
Pregnancy Tests not performed as per protocol specified schedule	0	1	1
Unspecified[###]	9	4	13
Patients not withdrawn from treatment and/or study despite having met specified criteria for withdrawal	**1**	**1**	**2**
Patient not discontinued from study drug treatment per protocol specified criteria	1	0	1
Dosing continued after Informed Consent Withdrawn	0	1	1
Use of prohibited concomitant medications	0	0	0

	Arm A	Arm C	Total of Arms A and C
Grand Total	**149**	**126**	**275**

All randomized patients signed an initial informed consent form (ICF). 2 patients had clinical study procedures conducted prior to signing initial ICF (signed prior to randomization). 3 patients had incorrect ICF process: date of signatures were pre-populated, signature of illiterate patient was not done in accordance to site's SOP, and PI's signature was signed retrospectively. The remaining 56 protocol deviations were related to delays in getting updated versions signed.
The deviations in the 'Baseline procedure (PD-L1 test) not performed prior to randomization (per protocol)' were mostly related to tests being performed out of window or tumour tissue did not meet requirements.
Unspecified PDs: Protocol Deviations sub-classified as unspecified were due to stratification errors and some missing protocol procedures.

Relevant protocol deviations are those that are related to inclusion or exclusion criteria, study conduct, study management, or patient assessment that were programmable and could potentially affect the interpretability of study results. Relevant protocol deviations are predefined in the SAP, whereas significant protocol deviations were captured during monitoring.

Overall, a single relevant protocol deviation was reported for one patient (0.3%) in the nivo+cabo arm. This patient had received prior anti-cancer treatment with pazopanib in the adjuvant disease setting (from 10-Jan-2012 to 12-Jan-2013).

No patients were excluded from the ITT analysis.

Baseline data

Only three patients (0.5%) were documented to have non-clear cell components (besides the mandatory clear-cell component); of these, one patient (randomized to sunitinib) was documented as having translocation RCC and the other two (one randomized to nivo+cabo; one randomized to sunitinib) as having mixed histology with papillary RCC.

A summary of key demographic and baseline characteristics are shown in Table 11.

Table 11 Key demographic and baseline characteristics in CA2099ER - All randomized patients

	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 (%)			

	Nivo+Cabo N = 323	Sunitinib N = 328	Total N = 651
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)
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 (%)			
Favourable 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)
PD-L1+ Status Based On A 1% Cut Off, n (%)			
≥ 1%	81 (25.1)	81 (24.7)	162 (24.9)
< 1%	232 (71.8)	240 (73.2)	472 (72.5)
Indeterminate	0 (0%)	0 (0%)	0 (0%)
Not reported	10 (%)	7 (%)	17 (%)
Prior Nephrectomy, n (%)			
Yes	222 (68.7)	233 (71.0)	455 (69.9)
No	101 (31.3)	95 (29.0)	196 (30.1)
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)

	Nivo+Cabo N = 323	Sunitinib N = 328	Total N = 651
Stage at Initial Diagnosis, n (%)			
Stage IV	167 (51.7)	173 (52.7)	340 (52.2)
Non-stage IV	150 (46.4)	148 (45.1)	298 (45.8)
Not reported	6 (1.9)	7 (2.1)	13 (2.0)
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)

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

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

Prior anti-cancer treatment

In Table 11 it is shown that 69.9% of patients had prior nephrectomy. Also, 14.0% had prior radiotherapy (14.2% in the nivo+cabo arm and 13.7% in the sunitinib arm).

No prior systemic therapy for RCC was permitted with the following exception (see **Study participants**): "*One prior adjuvant or neoadjuvant therapy was allowed 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.*". Three patients (0.9%) in the nivo+cabo arm and 2 (0.6%) in the sunitinib arm received one prior systemic anticancer therapy, all of which were in the adjuvant therapy setting. These therapies were pazopanib (n=1), gemcitabine (n=1), interleukin-2 (n=1) and placebo (n=1) in the nivo+cabo arm, and placebo (n=1) and everolimus (n=1) in the sunitinib arm. It was considered a relevant protocol deviation that the one patient in the nivo+cabo arm received prior treatment with pazopanib (see Protocol deviations).

Concomitant medications

Most patients (98.1%) received concomitant medication(s) during the treatment period. However, the use of any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents) was prohibited during the study per protocol and there was no use of prohibited concomitant medications (Table 10).

For information on concomitant immune-modulating medications (IMMs) for the treatment of certain AEs, see the safety section.

Subsequent anti-cancer treatment

Subsequent anti-cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 61 patients (18.9%) in the nivo+cabo arm compared to 108 patients (32.9%) in the sunitinib arm.

Subsequent systemic anti-cancer therapy was received by 36 patients (11.1%) in the nivo+cabo arm and 91 patients (27.7%) 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 14 patients (4.3%) in the nivo+cabo arm compared with 81 (24.7%) for the sunitinib arm. This included subsequent anti-PD1/anti-PD-L1 therapy in 9 patients (2.8%) in the nivo+cabo arm compared with 67 (20.4%) for the sunitinib arm. Subsequent antiangiogenic drugs were received by 31 patients (9.6%) in the nivo+cabo arm and 35 patients (10.7%) sunitinib arm.

Numbers analysed

Overall, 323 patients were randomized to the nivo+cabo arm and 328 to the sunitinib arm. Of these, 320 patients in each arm received at least one dose of study medication, see also Figure 10.

All analyses were performed using the treatment arm as randomized (ITT; i.e. 323 nivo+cabo vs 328 sunitinib), with the exception of dosing and safety, for which the treatment arm as received was used (i.e. 320 vs 320).

Outcomes and estimation

The median follow-up (date of randomization to the last known date alive or death) was 15.70 months (range 0.0 – 27.8) for the nivo+cabo arm and 14.59 months (range 0.0 – 27.4) for the sunitinib arm. As of the 30-Mar-2020 DBL, the minimum and median follow-up for OS was approximately 10.6 and 18.1 months, respectively.

Primary endpoint PFS

Primary analytical method

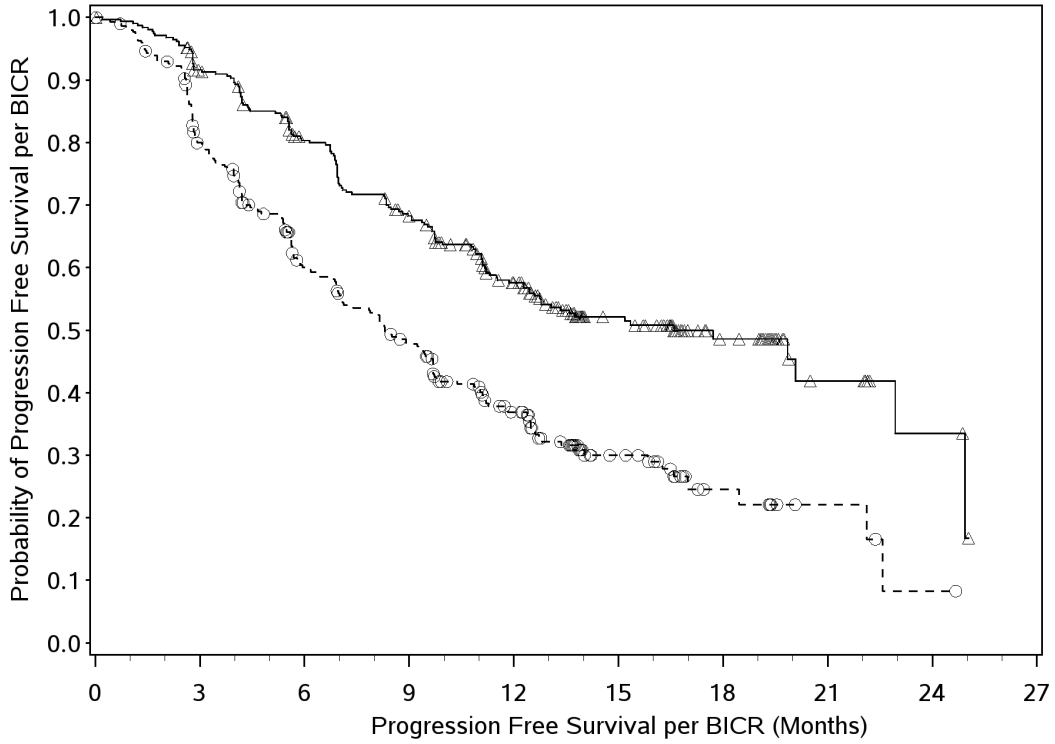
Study CA2099ER met its primary endpoint at a pre-planned final analysis for PFS.

In all randomized patients, nivo+cabo demonstrated a statistically significant improvement in PFS per BICR (primary definition) compared with sunitinib (Figure 11): 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 (an increase of 8.28 months).

At both 6 and 9 months, PFS rates were higher with nivo+cabo compared with sunitinib: 80.3% (95% CI: 75.4, 84.3) vs 60.1% (95% CI: 54.1, 65.5), and 68.3% (95% CI: 62.6, 73.2) vs 47.8% (95% CI: 41.7, 53.6), respectively.

At 30-Mar-2020 DBL, there had been 144 PFS events (44.6%) in the nivo+cabo arm and 191 PFS events (58.2%) in the sunitinib arm (Table 12). The number of patients censored for PFS was 179 (55.4%) and 137 (41.8%), respectively, with "still on treatment" being the most common reason for censoring.

Figure 10 *Kaplan-Meier plot of progression-free survival per BICR (primary definition) - All randomized patients*



Number of Subjects at Risk

Nivolumab + Cabozantinib

323	279	234	196	144	77	35	11	4	0

Sunitinib

328	228	159	122	79	31	10	4	1	0

Nivolumab + Cabozantinib (events : 144/323), median and 95% CI : 16.59 (12.45, 24.94)

Sunitinib (events : 191/328), median and 95% CI : 8.31 (6.97, 9.69)

Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.51 (0.41, 0.64), P-value: <0.0001

Symbols represent censored observations.

Table 12 Summary of reason for censoring, PFS per BICR (primary definition) - All randomized patients

	Nivo+Cabo N = 323	Sun N = 328
NUMBER OF EVENTS (%)	144 (44.6)	191 (58.2)
TYPE OF EVENTS (%)		
PROGRESSION (1)	121 (37.5)	151 (46.0)
DEATH	23 (7.1)	40 (12.2)
NUMBER OF PATIENTS CENSORED (%)	179 (55.4)	137 (41.8)
CENSORED ON RANDOMIZATION DATE	7 (2.2)	19 (5.8)
CENSORED ON DATE OF LAST TUMOUR ASSESSMENT ON-STUDY	172 (53.3)	118 (36.0)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (2)	23 (7.1)	43 (13.1)
STILL ON-TREATMENT	133 (41.2)	61 (18.6)
IN FOLLOW-UP	13 (4.0)	10 (3.0)
OFF STUDY	3 (0.9)	4 (1.2)

(1) RECIST v1.1.
(2) Includes patients, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those patients were censored at the

last evaluable tumour assessment prior to/on start date of subsequent anti-cancer therapy.

Sensitivity analyses

Investigator-assessed PFS results using the primary definition were generally consistent with the BICR assessed results. Median PFS by primary definition was 19.38 months and 9.20 months for nivo+cabo and sunitinib respectively, HR = 0.46 (95%CI: 0.36, 0.57) for nivo+cabo vs sunitinib, p < 0.0001. Concordance between BICR and investigator PFS assessments was 83.9% and 82.9% for nivo+cabo and sunitinib arms, respectively.

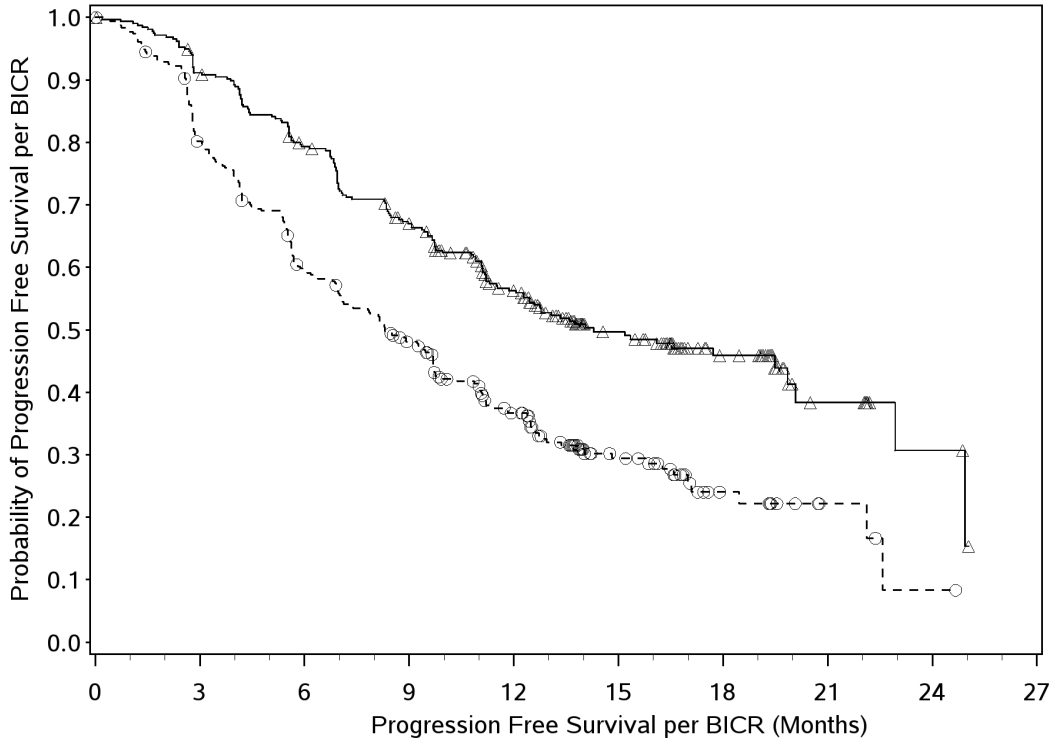
Results for the sensitivity analyses of PFS by an **unstratified analysis** and by an **analysis using stratification factors as covariates** were consistent with the primary PFS analysis as well.

Also in a **multivariate analysis**, the treatment effect of nivo+cabo vs sunitinib when adjusted for the following baseline factors: 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 consistent (HR = 0.51; 95% CI: 0.41, 0.64; p <0.0001) with the primary PFS analysis.

Secondary analytical method

An analysis of PFS per BICR using the secondary PFS definition was consistent with the analysis for the primary PFS definition (Figure 12): nivo+cabo vs sunitinib: HR = 0.54; 95% CI: 0.44, 0.67. Median PFS was longer with nivo+cabo compared with sunitinib: 14.29 (95% CI: 12.29, 19.84) vs 8.31 (95% CI: 7.00, 9.69) months, respectively (an increase of 5.98 months).

Figure 11 Kaplan-Meier plot of progression-free survival per BICR (secondary definition) - All randomized patients



Number of Subjects at Risk

Nivolumab + Cabozantinib	323	287	246	204	151	81	38	12	4	0
Sunitinib	328	245	179	140	90	38	13	4	1	0

Nivolumab + Cabozantinib (events : 159/323), median and 95% CI : 14.29 (12.29, 19.84)
Sunitinib (events : 211/328), median and 95% CI : 8.31 (7.00, 9.69)
Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.54 (0.44, 0.67), P-value: <0.0001

Symbols represent censored observations.

Subgroup analysis

In a subgroup analysis for all randomized patients (Figure 13), PFS HRs by primary definition for almost all subgroups favoured nivo+cabo vs sunitinib (HR <1) with the exception of patients ≥85 years of age and Asian patients.

PFS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status:

- Baseline IMDC prognostic score (CRF):
  - 0 (favourable 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)
- Tumour PD-L1 expression status (≥1%, <1%) (CRF):
  - 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)

Figure 12 Forest plot of progression-free survival per BICR (primary definition) in pre-defined subgroups - All randomized patients

	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
Overall	651	144 (323)	16.59 (12.45, 24.94)	191 (328)	8.31 (6.97, 9.69)	0.51 (0.41, 0.64)
Age categorization						
< 65	401	84 (191)	16.59 (12.58, 24.94)	131 (210)	7.85 (5.62, 9.26)	0.44 (0.33, 0.58)
>= 65 and < 75	188	46 (103)	19.84 (11.17, N.A.)	49 (85)	9.69 (6.90, 15.84)	0.64 (0.43, 0.96)
>= 75 and < 85	56	13 (27)	13.08 (6.14, 22.93)	10 (29)	11.20 (5.82, N.A.)	0.84 (0.35, 1.98)
>= 85	6	1 (2)	N.A. (2.04, N.A.)	1 (4)	9.69 (N.A., N.A.)	1.22 (0.08, 19.86)
>= 75	62	14 (29)	13.08 (6.14, 22.93)	11 (33)	9.69 (5.95, N.A.)	0.88 (0.39, 2.00)
>= 65	250	60 (132)	19.84 (11.17, 22.93)	60 (118)	9.69 (7.10, 13.37)	0.68 (0.48, 0.98)
Region (IRT)						
US/Canada/W.Europe/N.Europe	319	61 (158)	20.07 (13.60, N.A.)	85 (161)	9.56 (7.89, 11.76)	0.46 (0.33, 0.64)
ROW	332	83 (165)	12.29 (9.07, 24.94)	106 (167)	7.03 (5.65, 9.46)	0.57 (0.42, 0.76)
Race						
White	533	119 (267)	17.71 (12.75, 22.93)	160 (266)	8.15 (6.80, 9.46)	0.48 (0.38, 0.61)
Black or African American	5	0 (1)	N.A.	3 (4)	12.45 (5.78, 16.26)	<0.01 (<0.01, N.A.)
Asian	51	11 (26)	12.45 (6.97, N.A.)	6 (25)	N.A. (6.93, N.A.)	1.29 (0.47, 3.54)
Other	61	14 (29)	10.41 (6.90, N.A.)	21 (32)	8.31 (4.21, 12.62)	0.65 (0.33, 1.30)
Not Reported	1	0 (0)	N.A.	1 (1)	11.04 (N.A., N.A.)	N.A.
Ethnicity						
Hispanic or Latino	77	19 (38)	11.53 (8.31, N.A.)	34 (39)	5.62 (4.14, 8.15)	0.38 (0.21, 0.67)
Not Hispanic or Latino	300	62 (149)	22.93 (13.34, N.A.)	83 (151)	8.18 (6.87, 9.76)	0.43 (0.31, 0.61)
Not Reported	274	63 (136)	19.84 (9.72, N.A.)	74 (138)	9.76 (7.03, 12.71)	0.68 (0.49, 0.95)
Sex						
Male	481	108 (249)	17.71 (12.75, N.A.)	136 (232)	8.38 (6.97, 9.72)	0.48 (0.37, 0.62)
Female	170	36 (74)	12.45 (8.97, 24.94)	55 (96)	7.13 (5.88, 11.17)	0.61 (0.40, 0.94)
Karnofsky performance status						
100-90	498	109 (257)	17.71 (12.78, N.A.)	129 (241)	9.69 (8.15, 11.20)	0.55 (0.43, 0.71)
< 90	151	35 (66)	11.07 (6.93, 20.07)	62 (85)	5.62 (4.11, 7.89)	0.44 (0.29, 0.68)
Not Reported	2	0 (0)	N.A.	0 (2)	N.A.	
Baseline IMDC prognostic score (IRT)						
0	146	30 (74)	N.A. (12.75, N.A.)	35 (72)	12.81 (9.56, 16.99)	0.62 (0.38, 1.01)
1-2	376	82 (188)	17.71 (11.20, 24.94)	108 (188)	8.51 (7.00, 10.38)	0.54 (0.40, 0.72)
3-6	129	32 (61)	12.29 (6.87, 20.07)	48 (68)	4.21 (2.92, 5.62)	0.37 (0.23, 0.58)
Baseline IMDC prognostic score (CRF)						
0	147	30 (74)	N.A. (12.75, N.A.)	35 (73)	12.81 (9.56, 16.99)	0.60 (0.37, 0.98)
1-2	375	83 (189)	17.71 (11.20, 24.94)	108 (186)	8.38 (6.93, 10.38)	0.54 (0.41, 0.73)
3-6	128	31 (60)	12.29 (6.87, 20.07)	48 (68)	4.21 (2.92, 5.62)	0.36 (0.23, 0.58)
Not Reported	1	0 (0)	N.A.	0 (1)	N.A.	
Time from initial disease diagnosis to randomization						
< 1 Year	424	102 (210)	12.58 (10.91, 24.94)	137 (214)	6.90 (5.59, 8.18)	0.48 (0.37, 0.62)
>= 1 Year	223	42 (112)	20.07 (13.60, N.A.)	53 (111)	12.48 (9.43, 18.46)	0.60 (0.40, 0.89)
Not Reported	4	0 (1)	N.A.	1 (3)	6.08 (N.A., N.A.)	
Baseline LDH level						
<= 1.5*ULN	596	134 (301)	17.71 (12.58, 24.94)	169 (295)	9.40 (7.85, 11.04)	0.53 (0.43, 0.67)
> 1.5*ULN	38	8 (15)	6.14 (2.56, N.A.)	21 (23)	2.45 (1.18, 3.71)	0.34 (0.15, 0.78)
Not Reported	17	2 (7)	9.36 (0.20, N.A.)	1 (10)	N.A. (8.15, N.A.)	
Hemoglobin						
< LLN	290	74 (150)	13.08 (9.76, 20.07)	94 (140)	5.68 (4.21, 8.31)	0.49 (0.36, 0.67)
>= LLN	348	67 (168)	N.A. (12.75, N.A.)	97 (180)	9.76 (8.28, 12.39)	0.51 (0.37, 0.69)
Not Reported	13	3 (5)	2.23 (0.20, 9.36)	0 (8)	N.A.	

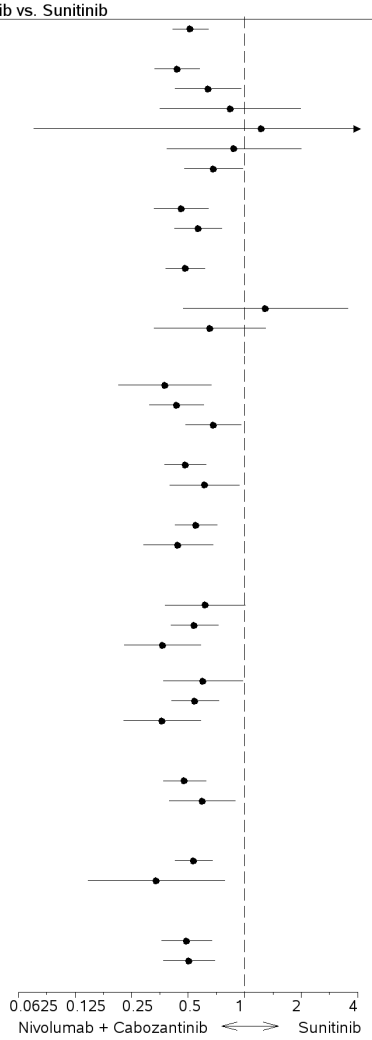
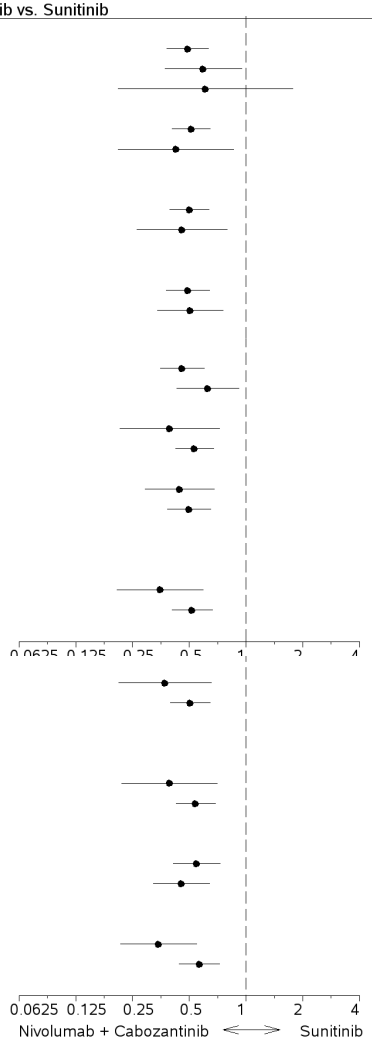


Figure 13 Forest plot of progression-free survival per BICR (primary definition) in pre-defined subgroups - All randomized patients (continued)

	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)



HR is not computed for subset (except age, race, region, and gender) category with less than 10 patients per treatment group.

Secondary endpoint OS

Primary analytical method

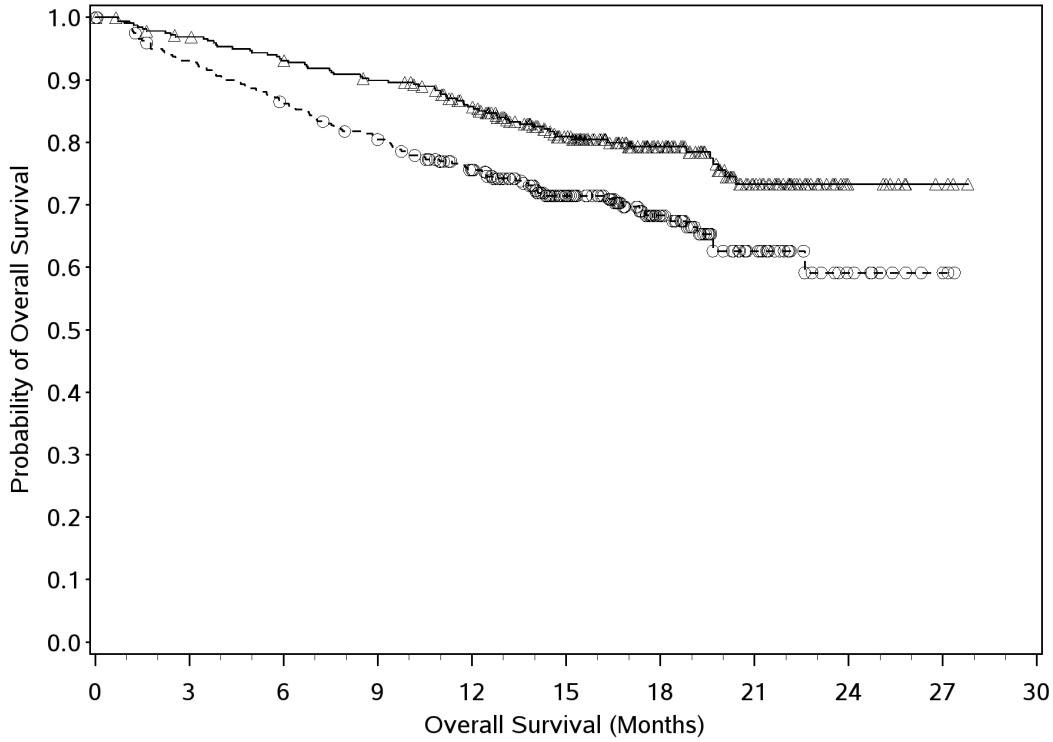
As the formal analysis of PFS was statistically significant, the formal (first planned) IA of OS was tested, as per hierarchical testing procedure. As this IA of OS crossed the pre-specified boundary for statistical significance (nominal significance level $p < 0.0111$), it is considered the final analysis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

In all randomized patients, nivo+cabo demonstrated a statistically significant improvement in OS compared with sunitinib (Figure 14): HR = 0.60 (98.89% CI: 0.40, 0.89); stratified log-rank test p value = 0.0010. Median OS was not reached in either treatment group.

At both 6 and 9 months, OS rates were higher with nivo+cabo compared with sunitinib: 93.1% (95% CI: 89.7, 95.4) vs 86.2% (95% CI: 81.9, 89.5), and 89.9% (95% CI: 86.0, 92.8) vs 80.5% (95% CI: 75.7, 84.4), respectively.

At 30-Mar-2020 DBL, there had been 67 deaths (20.7%) in the nivo+cabo arm and 99 deaths (30.2%) in the sunitinib arm. The number of patients censored for OS was 256 (79.3%) and 229 (69.8%), respectively. Most patients who were censored in the nivo+cabo arm were "still on treatment" (178 patients [55.1%]) and most censored patients in the sunitinib arm were "in follow-up" (118 patients [36.0%]). Of these patients "still on treatment", there were patients who had already progressed (either radiographically or clinically) and these patients were thus being treated beyond progression: 30 patients (9.3%) in the nivo+cabo arm and 16 patients (4.9%) in the sunitinib arm.

Figure 13 Kaplan-Meier plot of overall survival - All randomized patients



Number of Subjects at Risk

Nivolumab + Cabozantinib	323	308	295	283	259	184	106	55	11	3	0
Sunitinib	328	296	273	253	223	154	83	36	10	3	0

Nivolumab + Cabozantinib (events : 67/323), median and 95% CI : N.A.
Sunitinib (events : 99/328), median and 95% CI : N.A. (22.60, N.A.)
Nivolumab + Cabozantinib vs. Sunitinib - HR and 98.89% CI: 0.60 (0.40, 0.89), P-value: 0.0010

Symbols represent censored observations.

Subgroup analysis

In a subgroup analysis for all randomized patients (Figure 15), OS HRs for most subgroups favoured nivo+cabo vs sunitinib (HR <1) with the exception of patients ≥75 years of age and Asian patients.

OS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status:

- Baseline IMDC prognostic score (CRF):
  - 0 (favourable risk): HR = 0.84 (95% CI: 0.36, 1.99), median OS was not reached in both arms
  - 1-2 (intermediate risk): HR = 0.68 (95% CI: 0.45, 1.03), median OS was not reached in both arms
  - 3-6 (poor risk): HR = 0.40 (95% CI: 0.22, 0.70), median OS was not reached for nivo+cabo, and was 10.51 months for sunitinib
- Tumour PD-L1 expression status (≥1%, <1%) (CRF):
  - PD-L1 ≥1%: HR = 0.72 (95% CI: 0.42, 1.23), median OS was not reached in both arms
  - PD-L1 <1%: HR = 0.51 (95% CI: 0.34, 0.76), median OS was not reached in both arms

Figure 14 Forest plot of overall survival in pre-defined subgroups - All randomized patients

	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
Overall	651	67 (323)	N.A.	99 (328)	N.A. (22.60, N.A.)	0.60 (0.44, 0.82)
Age categorization						
< 65	401	31 (191)	N.A.	66 (210)	N.A. (22.60, N.A.)	0.44 (0.29, 0.67)
>= 65 and < 75	188	26 (103)	N.A.	25 (85)	N.A.	0.84 (0.48, 1.45)
>= 75 and < 85	56	9 (27)	N.A. (18.83, N.A.)	8 (29)	N.A. (12.32, N.A.)	0.85 (0.32, 2.22)
>= 85	6	1 (2)	15.21 (N.A., N.A.)	0 (4)	N.A.	>99.99 (<0.01, N.A.)
>= 75	62	10 (29)	N.A. (15.21, N.A.)	8 (33)	N.A. (17.51, N.A.)	1.05 (0.41, 2.67)
>= 65	250	36 (132)	N.A.	33 (118)	N.A.	0.90 (0.56, 1.44)
Region (IRT)						
US/Canada/W.Europe/N.Europe	319	26 (158)	N.A.	45 (161)	N.A.	0.48 (0.30, 0.79)
ROW	332	41 (165)	N.A.	54 (167)	N.A. (19.68, N.A.)	0.71 (0.48, 1.07)
Race						
White	533	55 (267)	N.A.	84 (266)	N.A. (22.60, N.A.)	0.57 (0.41, 0.80)
Black or African American	5	0 (1)	N.A.	0 (4)	N.A.	1.00 (1.00, 1.00)
Asian	51	4 (26)	N.A.	1 (25)	N.A.	3.83 (0.43, 34.27)
Other	61	8 (29)	N.A. (18.83, N.A.)	14 (32)	19.19 (9.46, N.A.)	0.51 (0.22, 1.23)
Not Reported	1	0 (0)	N.A.	0 (1)	N.A.	N.A.
Ethnicity						
Hispanic or Latino	77	7 (38)	N.A.	21 (39)	16.56 (7.59, N.A.)	0.26 (0.11, 0.62)
Not Hispanic or Latino	300	23 (149)	N.A.	40 (151)	N.A.	0.49 (0.29, 0.82)
Not Reported	274	37 (136)	N.A.	38 (138)	N.A. (19.68, N.A.)	0.93 (0.59, 1.46)
Sex						
Male	481	47 (249)	N.A.	66 (232)	N.A. (22.60, N.A.)	0.59 (0.40, 0.85)
Female	170	20 (74)	N.A. (19.68, N.A.)	33 (96)	N.A. (16.56, N.A.)	0.68 (0.39, 1.18)
Karnofsky performance status						
100-90	498	45 (257)	N.A.	56 (241)	N.A.	0.69 (0.47, 1.03)
< 90	151	22 (66)	N.A. (19.58, N.A.)	43 (85)	14.36 (9.23, N.A.)	0.52 (0.31, 0.86)
Not Reported	2	0 (0)	N.A.	0 (2)	N.A.	
Baseline IMDC prognostic score (IRT)						
0	146	10 (74)	N.A.	11 (72)	N.A. (22.60, N.A.)	0.84 (0.35, 1.97)
1-2	376	40 (188)	N.A.	51 (188)	N.A.	0.70 (0.46, 1.07)
3-6	129	17 (61)	N.A. (19.84, N.A.)	37 (68)	10.51 (6.83, N.A.)	0.37 (0.21, 0.66)
Baseline IMDC prognostic score (CRF)						
0	147	10 (74)	N.A.	11 (73)	N.A. (22.60, N.A.)	0.84 (0.36, 1.99)
1-2	375	39 (189)	N.A.	51 (186)	N.A.	0.68 (0.45, 1.03)
3-6	128	18 (60)	N.A. (19.84, N.A.)	37 (68)	10.51 (6.83, N.A.)	0.40 (0.22, 0.70)
Not Reported	1	0 (0)	N.A.	0 (1)	N.A.	
Time from initial disease diagnosis to randomization						
< 1 Year	424	53 (210)	N.A.	77 (214)	N.A. (18.83, N.A.)	0.60 (0.42, 0.85)
>= 1 Year	223	14 (112)	N.A.	22 (111)	N.A. (22.60, N.A.)	0.57 (0.29, 1.11)
Not Reported	4	0 (1)	N.A.	0 (3)	N.A.	
Baseline LDH level						
<= 1.5*ULN	596	59 (301)	N.A.	78 (295)	N.A.	0.68 (0.48, 0.95)
> 1.5*ULN	38	8 (15)	14.65 (2.56, N.A.)	21 (23)	4.63 (1.31, 6.37)	0.31 (0.13, 0.72)
Not Reported	17	0 (7)	N.A.	0 (10)	N.A.	
Hemoglobin						
< LLN	290	43 (150)	N.A. (20.07, N.A.)	58 (140)	N.A. (17.35, N.A.)	0.59 (0.40, 0.87)
>= LLN	348	23 (168)	N.A.	41 (180)	N.A.	0.54 (0.32, 0.90)
Not Reported	13	1 (5)	N.A. (2.23, N.A.)	0 (8)	N.A.	

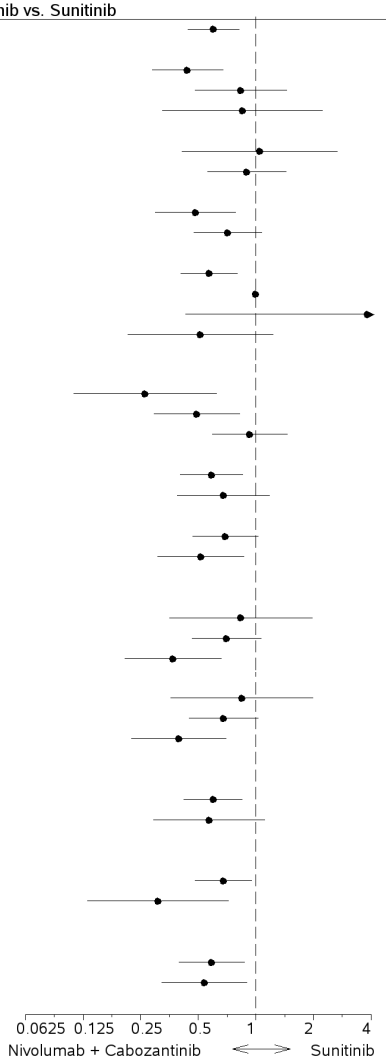
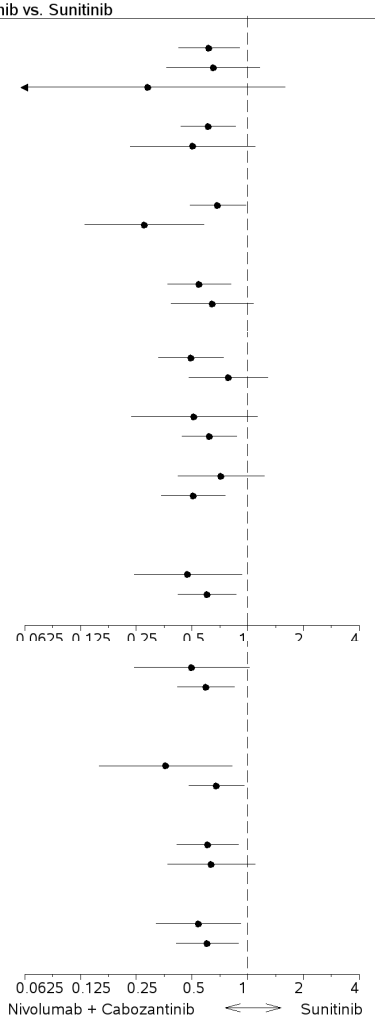


Figure 15 Forest plot of overall survival in pre-defined subgroups - All randomized patients (continued)

	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)



HR is not computed for subset (except age, race, region, and gender) category with less than 10 patients per treatment group.

Secondary endpoint ORR

Primary analytical method

As the formal interim analysis of OS was statistically significant, the formal analysis of ORR was tested, as per hierarchical testing procedure.

BICR-assessed confirmed ORR 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); stratified CMH test p value <0.0001 (Table 13).

In the nivo+cabo arm compared with the sunitinib arm, a numerically higher proportion of patients had a best overall response (BOR) of CR (8.0% vs 4.6%) or PR (47.7% vs 22.6%), and a numerically lower proportion of patients had a BOR of PD (5.6% vs 13.7%) or unable to determine (UTD) (6.5% vs 16.8%) due to various reasons including most commonly death prior to disease assessment (10 patients [3.1%] vs 20 patients [6.1%]).

Table 13 Confirmed best overall response per BICR and investigator - All randomized patients

	Number of Patients (%)	
	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)
OBJECTIVE RESPONSE RATE (1)	192/323 (59.4%)	105/328 (32.0%)
(95% CI)	(53.9, 64.8)	(27.0, 37.4)

Per RECIST v1.1, 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), tumour PD-L1 expression (≥ 1% vs < 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.

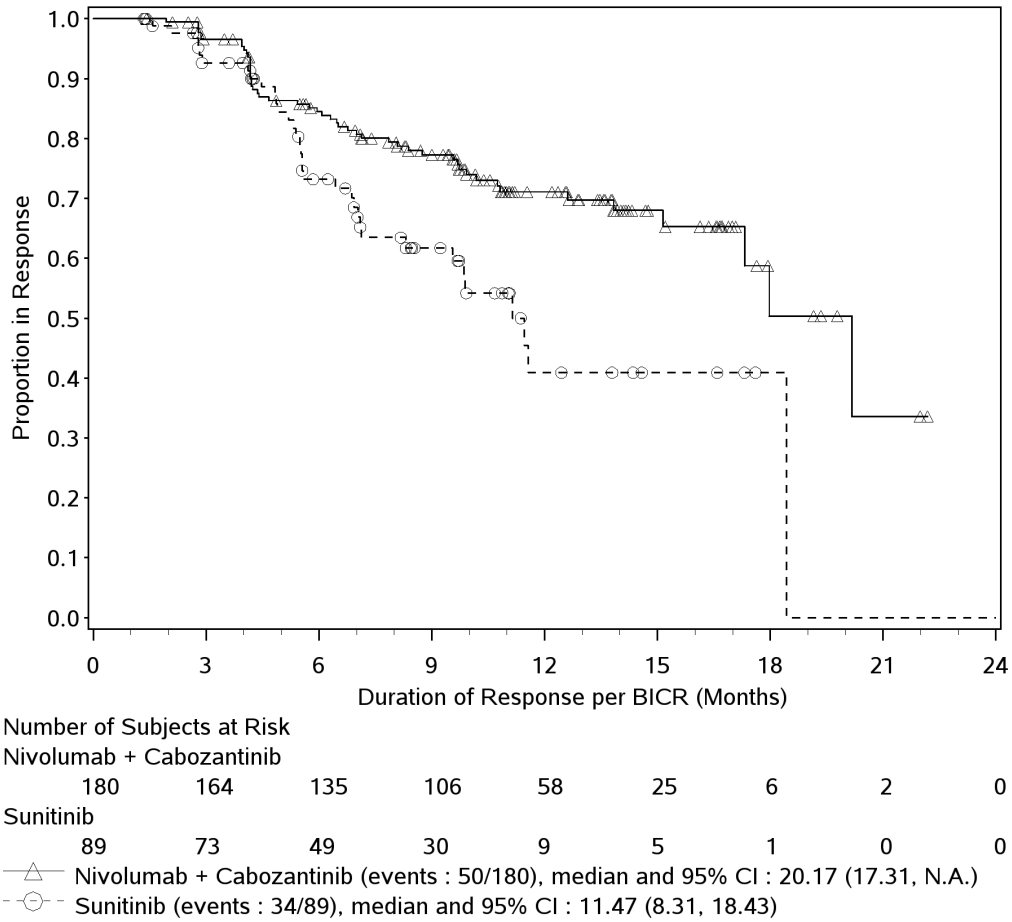
Sensitivity analysis

Investigator-assessed ORR was 59.4% vs 32.0% for nivo+cabo and sunitinib respectively. Concordance between BICR and investigator ORR assessments in the nivo+cabo arm was 80.8% for responders and non-responders and 69.0% for each response category vs in the sunitinib arm 80.4% for responders and non-responders and 65.7% for each response category.

Duration of response

Figure 16 shows a Kaplan-Meier plot of duration of response (DoR) per BICR.

Figure 15 Kaplan-Meier plot of duration of response per BICR (responders only) - All randomized patients



Symbols represent censored observations.

Time to response

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.

Subgroup analysis

In a subgroup analysis for all randomized patients, the difference in unweighted ORRs per BICR (ORR difference >0%) favoured nivo+cabo vs sunitinib in all subgroups including patients of all age subgroups (e.g. patients ≥75 years of age: 44.8% vs 9.1%) and Asian patients (42.3% vs 28.0%).

ORR benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status:

- Baseline IMDC prognostic score (CRF):
  - 0 (favourable risk): unweighted ORR difference = 25.1% (95% CI: 9.0, 39.4)
  - 1-2 (intermediate risk): unweighted ORR difference = 28.7% (95% CI: 18.8, 37.7)
  - 3-6 (poor risk): unweighted ORR difference = 29.5% (95% CI: 15.0, 43.0)
- Tumour PD-L1 expression status (≥1%, <1%) (CRF):
  - PD-L1 ≥1%: unweighted ORR difference = 33.3% (95% CI: 18.4, 46.3)
  - PD-L1 <1%: unweighted ORR difference = 27.3% (95% CI: 18.5, 35.5)

Exploratory endpoint biomarkers

Tumour PD-L1 expression

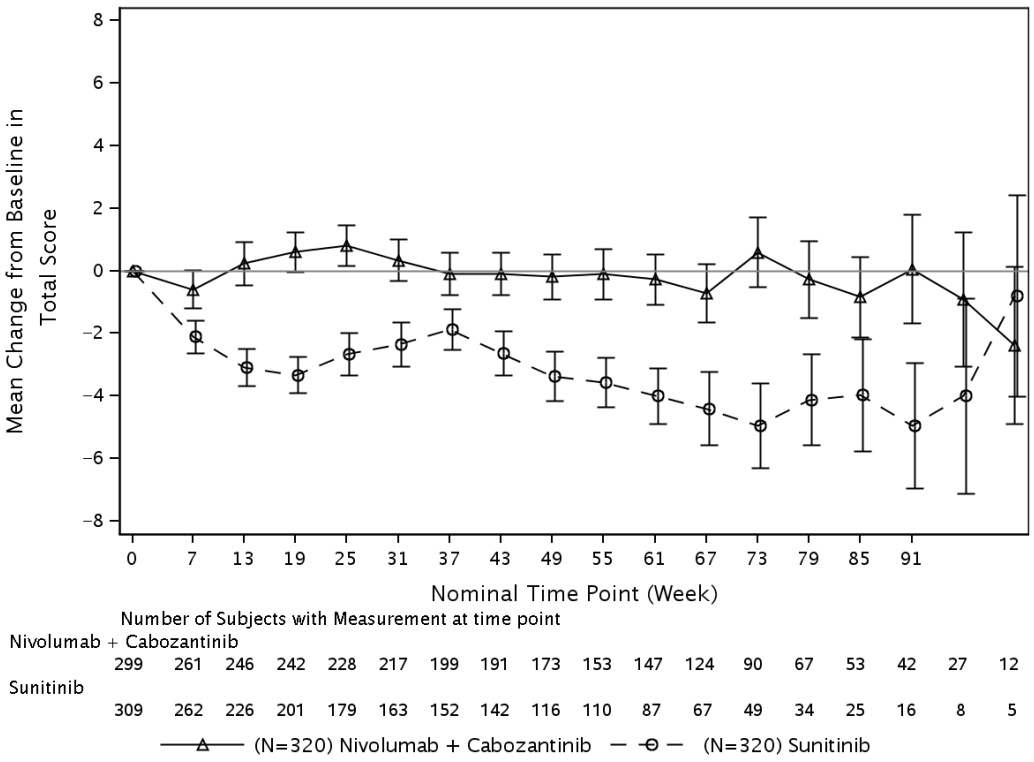
Across all efficacy endpoints (PFS, OS, and ORR), an efficacy benefit of nivo+cabo vs sunitinib was observed regardless of tumour cell PD-L1 expression status (<1%, ≥1%), see above.

Efficacy results with PD-L1 at 5% and 10% cut-off are consistent with the 1% cut off, see Figure 13 and Figure 15.

Exploratory endpoint health related quality of life (HRQoL)

At baseline, 93.4% of patients completed the **FKSI-19** in the nivo+cabo arm, while 97.2% of patients in the sunitinib arm had a baseline assessment. Completion rates were ≥80% in both treatment arms at all subsequent on-treatment assessments with sufficient data (≥10 patients), through Week 105 for the nivo+cabo arm and Week 97 for the sunitinib arm. 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 patients in the sunitinib arm had a trend toward decreased scores (Figure 17).

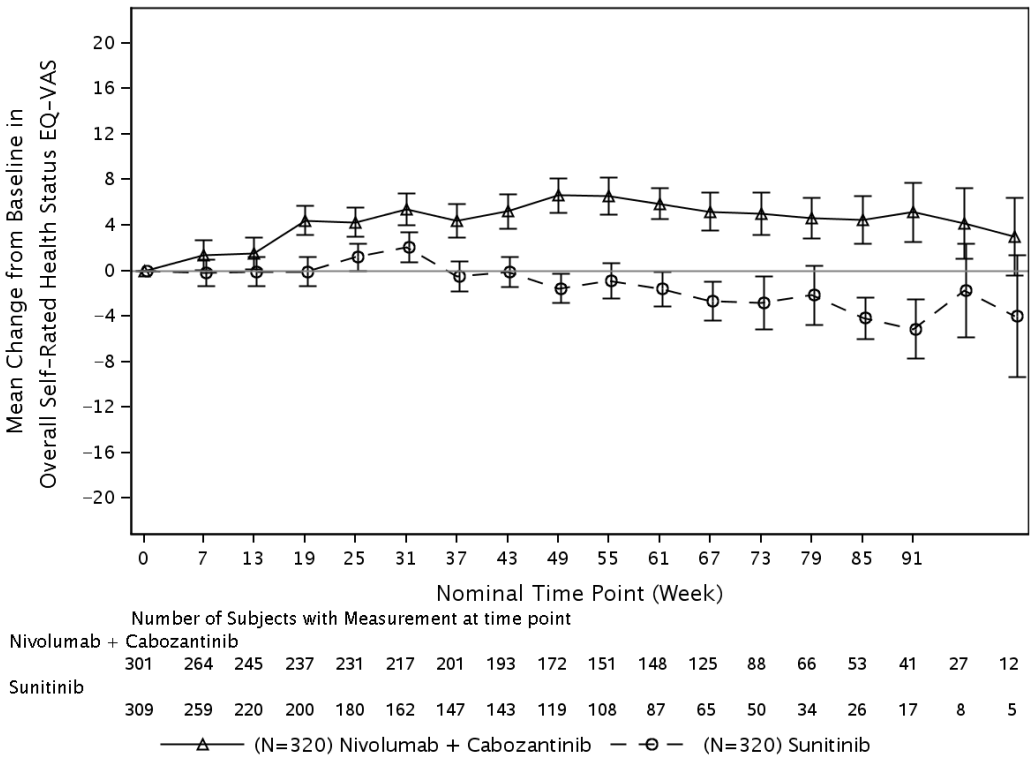
Figure 16 Mean changes from baseline in overall self-rated health status FKSI-19



Error bars represent standard error for the mean.
Only time points where data available for ≥ 5 patients in each treatment group are plotted.
Figure reports common time points for nivo+cabo and sunitinib arm (Q6W).

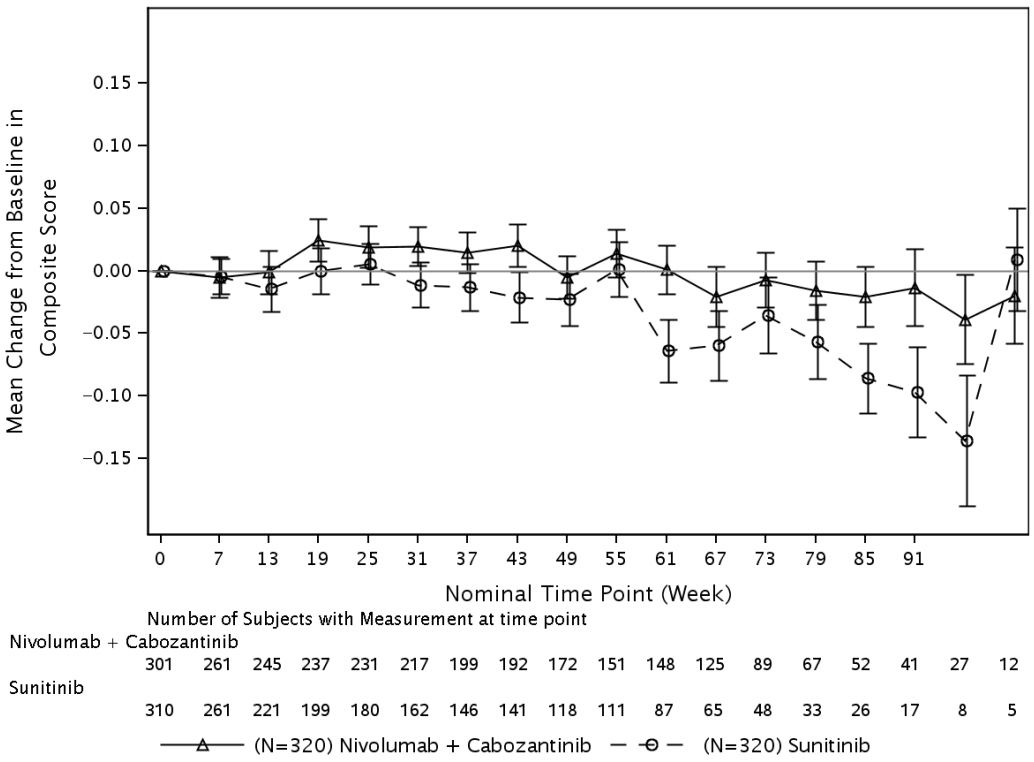
At baseline, 94.1% of patients completed the **EQ-5D-3L** in the nivo+cabo arm, while 97.5% of the sunitinib patients had a baseline assessment. Completion rates were ≥80% in both treatment arms at all subsequent on-treatment assessments with sufficient data (≥10 patients, through Week 105 for nivo+cabo and Week 97 for sunitinib), with the exception of the nivo+cabo arm at Week 93 (76.6%). Mean 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. Generic QoL measured by the EQ-5D VAS shows trends for improvement in patients treated with nivolumab in combination with cabozantinib. The mean EQ-5D VAS scores increased over time in the nivo+cabo arm, while in the sunitinib arm, mean EQ-5D VAS scores varied with a trend toward decline observed from Weeks 37-91 (Figure 18). For EQ-5D utility index (based on the UK value set), at baseline, the scores were 0.73 (0.29) in the sunitinib treatment arm and 0.77 (0.25) in the nivo+cabo arm. Patients in the nivo+cabo arm remained relatively stable, while patients in the sunitinib arm had a trend toward decline (Figure 19).

Figure 17 Mean changes from baseline in overall self-rated health status EQ-VAS



Error bars represent standard error for the mean.
Only time points where data available for ≥ 5 patients in each treatment group are plotted.
Figure reports common time points for nivo+cabo and sunitinib arm (Q6W).

Figure 18 Mean changes from baseline in EQ-5D utility index



Error bars represent standard error for the mean.
Only time points where data available for ≥ 5 patients in each treatment group are plotted.

Figure reports common time points for nivo+cabo and sunitinib arm (Q6W).

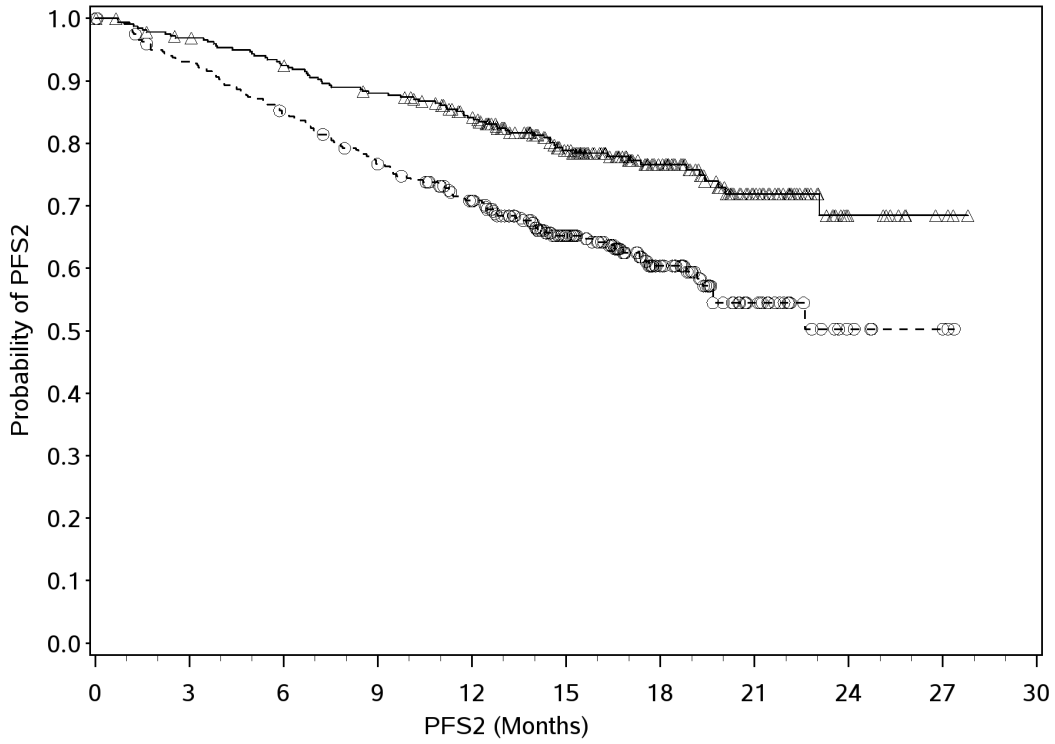
Exploratory endpoint PFS2

For the definition of PFS after next line of treatment (PFS2), see Table 6.

Median PFS2 per investigator was not reached in either treatment groups. The HR favoured the nivo+cabo arm over the sunitinib arm: 0.52 (95% CI: 0.39, 0.70).

At 30-Mar-2020 DBL, there had been 74 PFS2 events (22.9%) in the nivo+cabo arm and 121 PFS2 events (36.9%) events in the sunitinib arm.

Figure 19 Kaplan-Meier plot of progression-free survival after next line of treatment (PFS2) - All randomized patients



Number of Subjects at Risk

Nivolumab + Cabozantinib	323	308	293	277	254	180	103	53	11	3	0
Sunitinib	328	296	268	241	210	144	75	30	6	3	0

Nivolumab + Cabozantinib (events : 74/323), median and 95% CI : N.A.
Sunitinib (events : 121/328), median and 95% CI : N.A. (19.68, N.A.)
Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.52 (0.39, 0.70)

Symbols represent censored observations.

Ancillary analyses

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, see below. In addition, updated ORR and DoR analysis results were described.

A summary of the provided updated efficacy data is presented in Table 14, 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 21, Figure 22, and Figure 23.

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 24. For tumour PD-L1 expression status (≥1%, <1%) the updated results were (refer to pages 57-58 and/or Figure 13 for the 30-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 25. For tumour PD-L1 expression status (≥1%, <1%) the updated results were (refer to page 62 and/or 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 14 CA2099ER summary of efficacy – All randomized 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)
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 (%)				

	Mar-2020 DBL		Sep-2020 DBL	
	Nivo+Cabo N = 323	**Sunitinib N = 328**	**Nivo+Cabo N = 323**	**Sunitinib N = 328**
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.

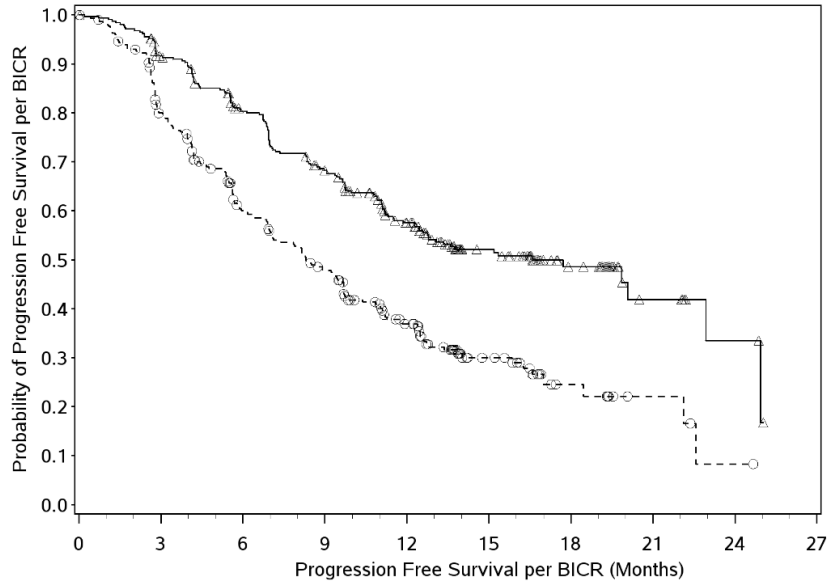
[i] 2-sided p value from stratified Cochran-Mantel-Haenszel test.

[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.

Figure 20: Kaplan-Meier plot of progression-free survival per BICR (primary definition) - All randomized patients - Mar-2020 DBL vs Sep-2020 DBL

Mar-2020 DBL



Number of Subjects at Risk

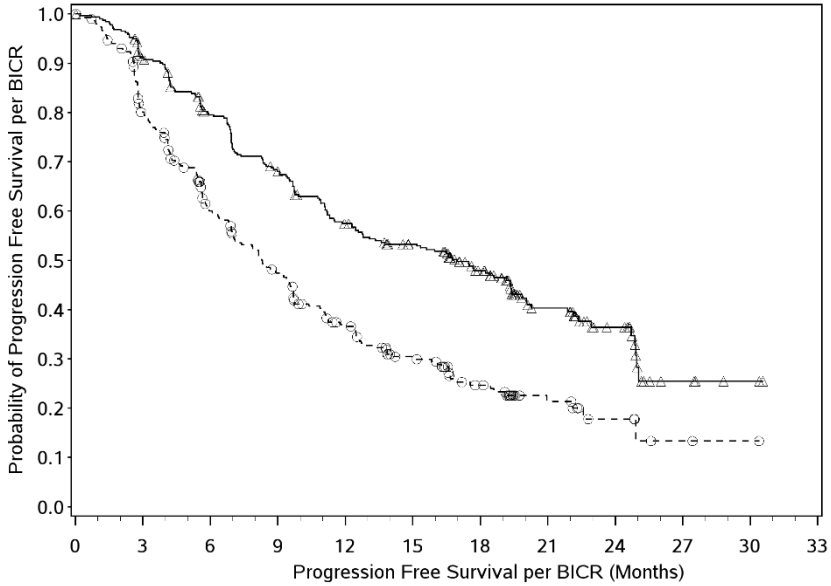
Nivolumab + Cabozantinib										
323	279	234	196	144	77	35	11	4	0	
Sunitinib										
328	228	159	122	79	31	10	4	1	0	

Nivolumab + Cabozantinib (events : 144/323), median and 95% CI : 16.59 (12.45, 24.94)

Sunitinib (events : 191/328), median and 95% CI : 8.31 (6.97, 9.69)

Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.51 (0.41, 0.64), P-value: <0.0001

Sep-2020 DBL



Number of Subjects at Risk

Nivolumab + Cabozantinib												
323	280	236	201	166	145	102	56	26	5	2	0	
Sunitinib												
328	230	160	122	87	61	37	17	7	2	1	0	

Nivolumab + Cabozantinib (events : 175/323), median and 95% CI : 16.95 (12.58, 19.38)

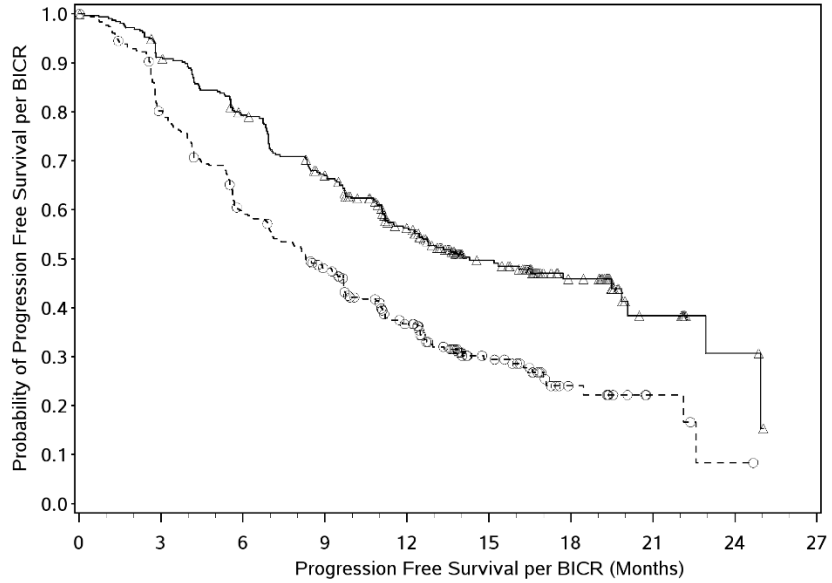
Sunitinib (events : 206/328), median and 95% CI : 8.31 (6.93, 9.69)

Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.52 (0.43, 0.64)

Symbols represent censored observations.

Figure 21: Kaplan-Meier plot of progression-free survival per BICR (secondary definition) - All randomized patients - Mar-2020 DBL vs Sep-2020 DBL

Mar-2020 DBL



Number of Subjects at Risk

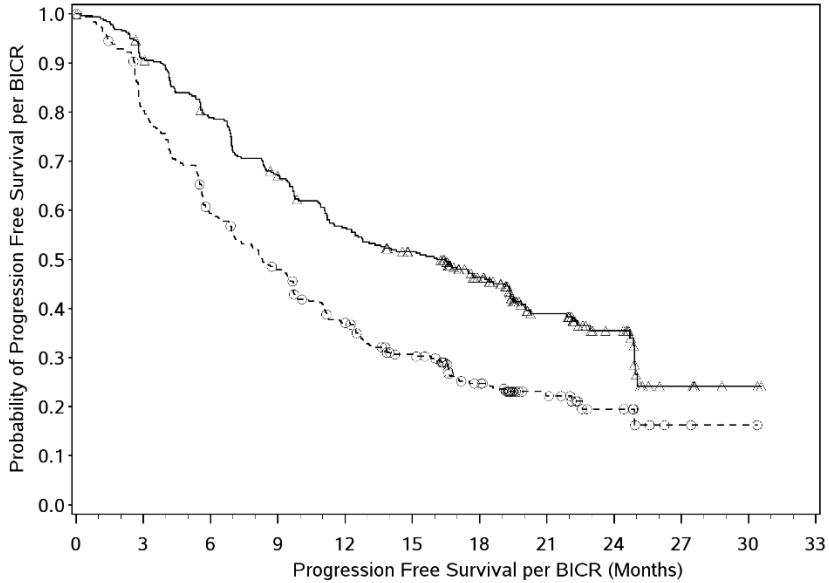
Nivolumab + Cabozantinib									
323	287	246	204	151	81	38	12	4	0
Sunitinib									
328	245	179	140	90	38	13	4	1	0

Nivolumab + Cabozantinib (events : 159/323), median and 95% CI : 14.29 (12.29, 19.84)

Sunitinib (events : 211/328), median and 95% CI : 8.31 (7.00, 9.69)

Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.54 (0.44, 0.67), P-value: <0.0001

Sep-2020 DBL



Number of Subjects at Risk

Nivolumab + Cabozantinib												
323	288	248	210	175	153	108	60	29	6	2	0	
Sunitinib												
328	247	181	144	108	78	48	24	10	2	1	0	

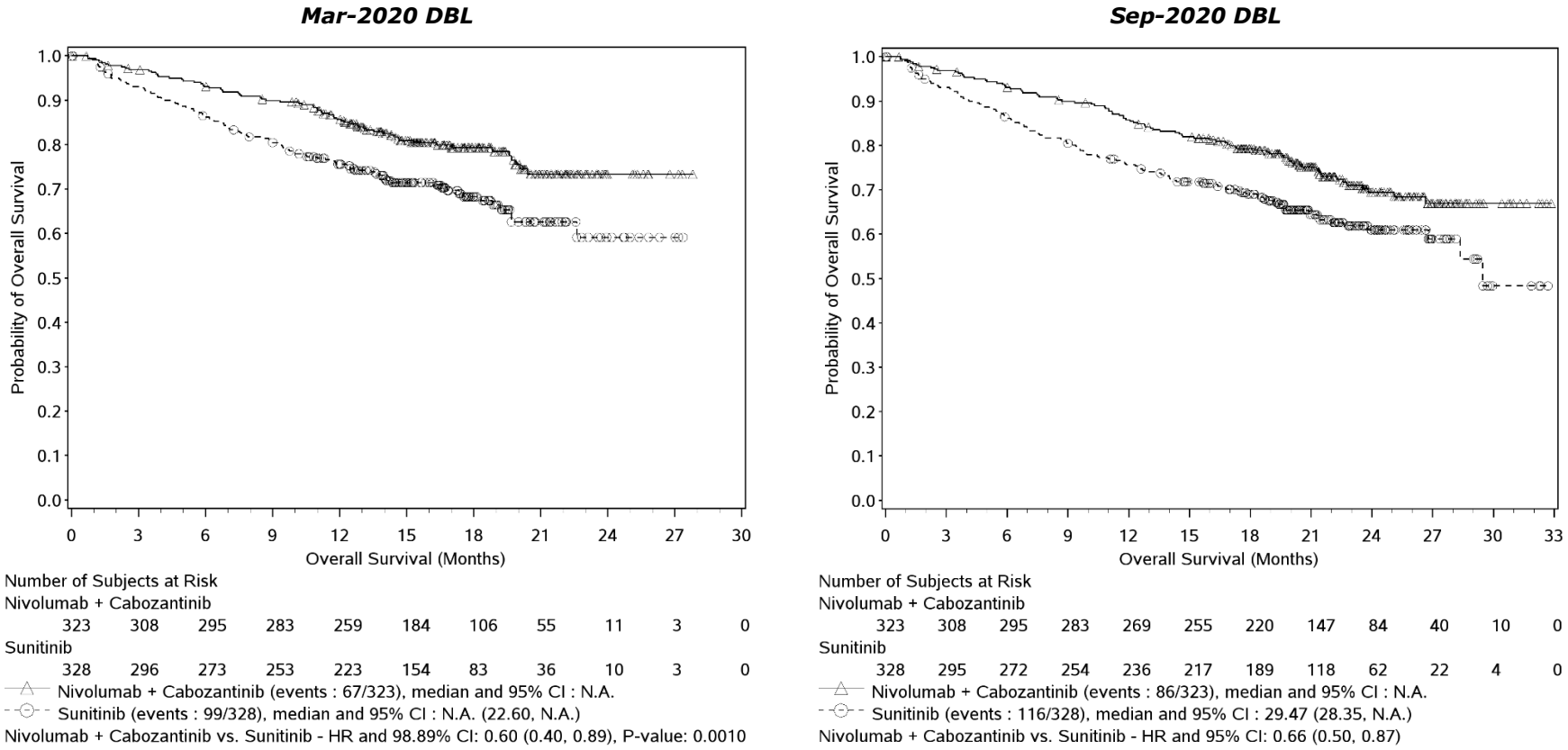
Nivolumab + Cabozantinib (events : 190/323), median and 95% CI : 16.10 (12.29, 19.32)

Sunitinib (events : 230/328), median and 95% CI : 8.31 (6.97, 9.69)

Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.57 (0.47, 0.69)

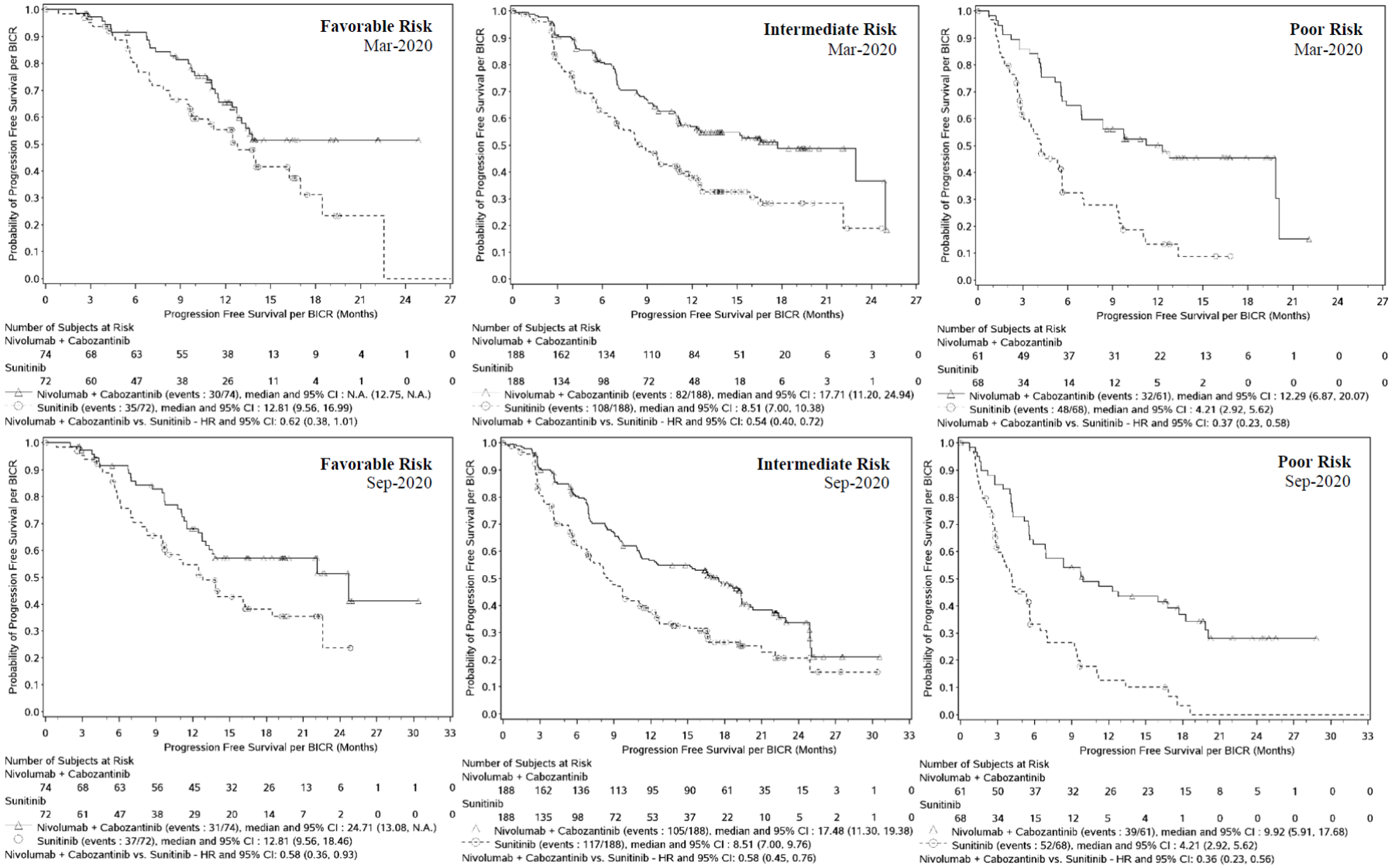
Symbols represent censored observations.

Figure 22: Kaplan-Meier plot of overall survival - All randomized patients - Mar-2020 DBL vs Sep-2020 DBL



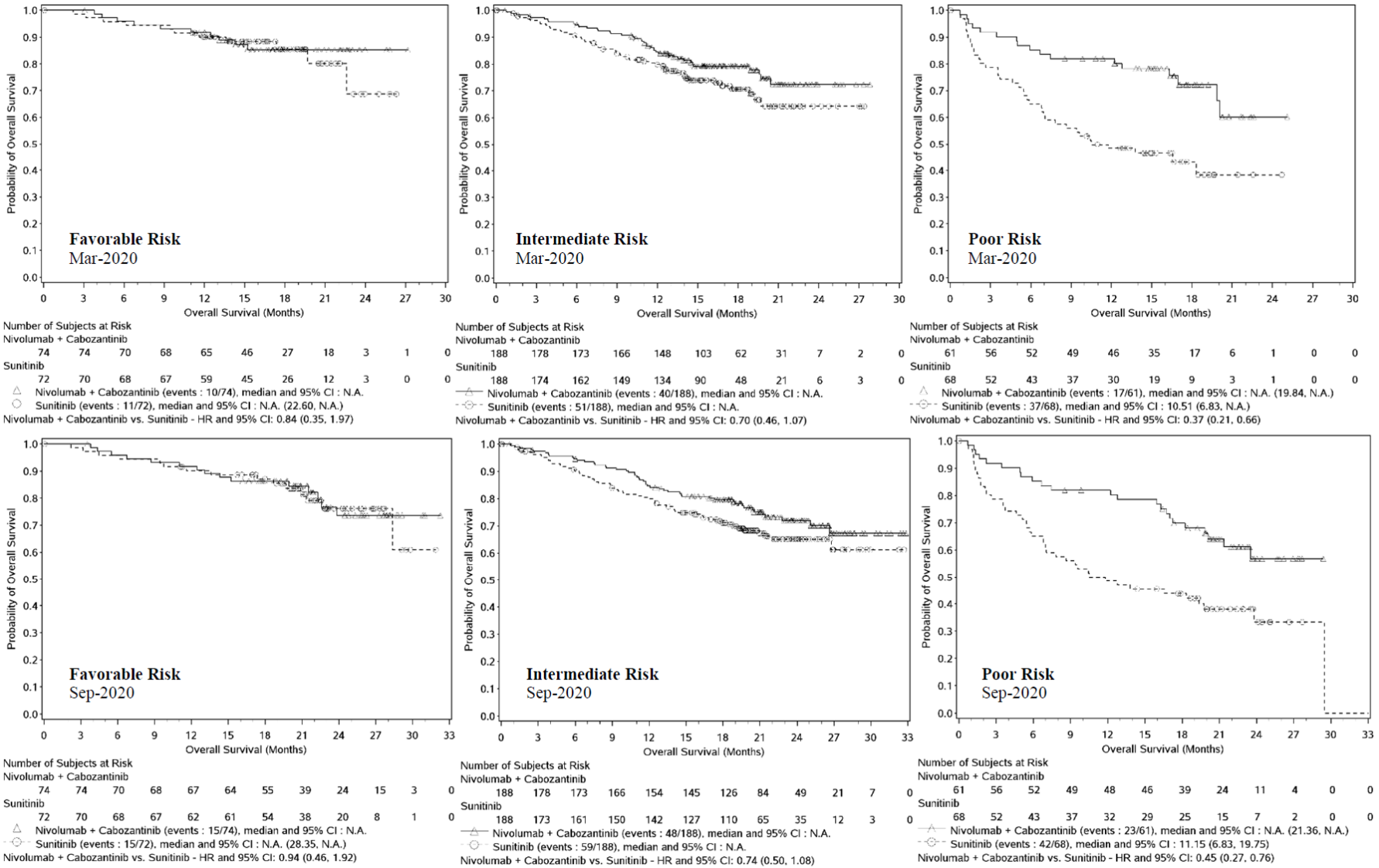
Symbols represent censored observations.

Figure 23: Kaplan-Meier plot of progression-free survival per BICR (primary definition) - All randomized patients by IMDC risk category (favourable/intermediate/poor) - Mar-2020 DBL vs Sep-2020 DBL



Symbols represent censored observations.

Figure 24: Kaplan-Meier plot of overall survival - All randomized patients by IMDC risk category (favourable/intermediate/poor) - Mar-2020 DBL vs Sep-2020 DBL



Symbols represent censored observations.

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

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15 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 13).

	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

To establish the contribution of the individual components nivolumab and cabozantinib to the nivo+cabo regimen in 1L advanced RCC, CA2099ER results were assessed relative to cabozantinib monotherapy data from the 1L CABOSUN trial and nivolumab monotherapy data from study CA209669 in 1L advanced RCC, respectively. As, however, CABOSUN included only I/P-risk patients, data from METEOR, a phase 3 trial in 2L advanced RCC, are described to compare the efficacy of the favourable risk patients to those of the I/P-risk population to support the contribution of nivolumab in a favourable

risk population. Key details of the study design, primary and secondary objectives of CA2099ER, CABOSUN, CA209669, and METEOR are summarized in Table 1 Key aspects of studies investigating nivolumab and cabozantinib in advanced RCC.

Contribution of nivolumab

Primary assessment (CA2099ER and CABOSUN)

The contribution of nivolumab to the nivo+cabo combination in CA2099ER is supported by comparison with cabozantinib monotherapy data from the CABOSUN trial (Choueiri et al. Eur J Cancer 2018; Cabometyx 1L RCC EPAR). Given that the same control (sunitinib) was tested in CA2099ER and CABOSUN, and nivolumab may be considered as 'add-on' to cabozantinib in intermediate/poor risk patients, it is possible to cross compare using both relative (i.e., hazard ratios) and absolute differences. The relative comparisons are important given that the absolute results in the overall CABOSUN population were different than most other studies of targeted therapy (i.e., TKIs) in the first-line setting. As CABOSUN included only I/P-risk patients, the comparison herein focuses only on the I/P-risk patients in study CA2099ER.

A summary of key **demographic and baseline characteristics** for patients in the two studies is provided in Table 16. Baseline characteristics were similar, indicating comparable populations; however, it can be noted that the CABOSUN study included a relatively high proportion of patients with poor prognostic features not explicitly included in the IMDC criteria, including the presence of bone metastases (39% vs 22.9%). This is one of the possible explanations for the relatively short PFS in both groups in CABOSUN.

The contribution of nivolumab efficacy in the nivo+cabo combination was based upon consideration of the totality of the data. Given the potential limitations of cross-trial comparisons, since ORR directly reflects drug activity by indicating tumour shrinkage, the results for the cross-trial comparison are provided below with ORR described first, and PFS and OS comparisons provide some context. Key efficacy results for CA2099ER and CABOSUN are presented in Table 17. There was a large 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. In addition, in CA2099ER, the CR rate was 8.4% with nivo+cabo and 3.5% with sunitinib, compared to 0% with cabozantinib monotherapy and sunitinib in CABOSUN. The best overall response of PD was 6.4% with nivo+cabo and 16.8% with sunitinib in CA2099ER compared to 18% with cabozantinib monotherapy and 29% with sunitinib in CABOSUN.

For **PFS** in both studies, the HRs (based here on BICR) were the same = 0.48. However, the increase in median PFS of 9.5 months in CA2099ER compared favourably to the 3.3 month increase in CABOSUN.

Although median **OS** has not yet been reached in CA2099ER and the OS assessment in CABOSUN was not fully powered, having the same comparator (sunitinib) enables cross-study comparisons. The OS HR with nivo+cabo in CA2099ER was 0.56 vs 0.80 for cabozantinib monotherapy in CABOSUN. The upper bound of the 95% CI for nivo+cabo was 0.79, which was lower than the point estimate of the OS HR for cabozantinib monotherapy. In addition, the OS KM curves in CA2099ER show clear early and sustained separation (see Figure 14), whereas this was not the case in CABOSUN (see Choueiri et al. Eur J Cancer 2018).

Table 16 Summary of demographics and baseline characteristics in CA2099ER and CABOSUN - Intermediate or poor risk population only

Study ID	CA2099ER (N=505)		CABOSUN (N=157)	
Treatment(s) (n)	**Nivo+Cabo (n=249)**	**Sunitinib (n=256)**	**Cabozantinib (n=79)**	**Sunitinib (n=78)**
Gender, n (%)				
Male	193 (77.5)	183 (71.5)	66 (84)	57 (73)
Female	56 (22.5)	73 (28.5)	13 (16)	21 (27)
Age, years				
Median (range)	62.0 (29-90)	61.0 (28-86)	63 (56-69)	64 (57-71)
Ethnic origin, n (%)				
White	202 (81.1)	205 (80.1)	70 (89)	75 (96)
Black or African	0 (0)	3 (1.2)	3 (4)	2 (3)
Other	47 (18.9)	48 (18.8)	7 (9)	1 (1)
ECOG performance status, n (%)				
0	NA	NA	36 (46)	36 (46)
1	NA	NA	33 (42)	32 (41)
2	NA	NA	10 (13)	10 (13)
Karnofsky Performance Status, n (%)				
90-100	190 (76.3)	183 (71.5)	NA	NA
70-80	59 (23.7)	72 (28.1)	NA	NA
Not reported	0 (0)	1 (0.4)	NA	NA
Baseline IMDC Prognostic Score (CRF), n (%)				
Intermediate	189 (75.9)[a]	186 (72.7)[a]	64 (81)	63 (81)
Poor	60 (24.1)[a]	68 (26.6)[a]	15 (19)	15 (19)
Prior nephrectomy, n (%)				
Yes	159 (63.9)	174 (68.0)	57 (72)	60 (77)
No	90 (36.1)	82 (32.0)	22 (28)	18 (23)
Site of metastatic disease, n (%)				
Lung	182 (73.1)	200 (78.1)	55 (70)	54 (69)
Lymph Node	104 (41.8)	103 (40.2)	45 (57)	42 (54)
Bone	57 (22.9)	65 (25.4)	31 (39)	30 (38)
Liver	62 (24.9)	45 (17.6)	15 (19)	20 (26)
CNS/brain	--	--	3 (4)	2 (3)
Adrenal gland	24 (9.6)	28 (10.9)	--	--

[a] Percentages based on number of I/P-risk patients in each group.
Abbreviations: cc = clear cell; PO = by mouth; QD = once daily; QxW = every x weeks; RCC = Renal cell carcinoma.

Table 17 Summary of efficacy in CA2099ER and CABOSUN - Intermediate or poor risk population only

Study	**CA2099ER**		**CABOSUN**	
	Enrolment: Aug-2017 to May-2019		**Enrolment: 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)	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; mono = monotherapy; nivo = nivolumab; NA = Not applicable; NR = Not reached; ORR = Objective response rate; PFS = Progression-free survival; RCC = Renal cell carcinoma; OS = overall survival; QxW = every x weeks.

Supportive evidence in favourable risk population (METEOR)

It is acknowledged that the above primary assessment was limited to I/P-risk patients, as CABOSUN did not include favourable risk patients. To establish that the contribution of components demonstrated can be extrapolated to 1L favourable risk patients, additional supportive data from the METEOR study are provided to compare the effect of cabozantinib monotherapy in the favourable population to the intermediate or poor risk populations. METEOR was a randomized, 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. The primary endpoint was PFS as assessed by BICR and secondary endpoints were OS and ORR (Choueiri et al. N Engl. J Med. 2015; Choueiri et al. Lancet Oncol. 2016; Cabometyx 2L RCC EPAR).

As presented in Table 18, cabozantinib monotherapy demonstrated improvement compared to everolimus in PFS, OS, and ORR across all IMDC risk categories. The **ORR** from cabozantinib monotherapy in METEOR was similar between the favourable risk subgroup and the intermediate and poor risk subgroups.

Table 18 Summary of efficacy in METEOR across IMDC risk categories

	IMDC Risk Categories						**Overall**	
	Favourable		**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 (%)	**16.7**	3.2	**19.0**	2.8	**11.1**	5.8	17.3	3.4

Abbreviations: CI = confidence interval; HR = hazard ratio; ORR = Objective response rate; OS = overall survival; PFS = Progression-free survival

Contribution of cabozantinib

Primary assessment (CA2099ER and CA209669)

The contribution of cabozantinib to the nivo+cabo combination in CA2099ER is supported by comparison with nivolumab monotherapy data from Study CA209669 (Atkins et al. J Clin Oncol. 2020). Again, given the potential limitations of cross-trial comparisons, since ORR directly reflects drug activity by indicating tumour shrinkage, the results for the cross trial comparison are provided below with ORR described first, and PFS and OS comparisons to provide some context, as the study populations appear reasonably comparable.

A summary of key **demographic and baseline characteristics** for the CA2099ER and CA209669 (ITT population = all IMDC risk groups) is provided in Table 19 and key efficacy results are presented in Table 20. Baseline characteristics were similar among studies, except for the higher proportion of poor risk patients enrolled in CA2099ER compared with CA209669 (18.6% vs 9.8%).

There was a large cross-study difference in **ORR** between nivo+cabo (55.7%) and nivolumab monotherapy (31.7%), with non-overlapping 95% CIs. In addition, in CA2099ER, the CR and PR rates were 8.0% and 47.7% with nivo+cabo compared to 5.7% and 26.0% with nivolumab monotherapy in CA209669, respectively.

The median **PFS** of 16.59 (95% CI: 12.45, 24.94) months in CA2099ER was 2 fold longer than that of 8.3 (95% CI: 5.5, 10.9) months in CA209669, with a difference of approximately 8 months and non-overlapping 95% CIs, despite the higher proportion of poor risk patients in CA2099ER. Additionally, the PFS rate at 9 months with nivo+cabo therapy was higher than that of nivolumab monotherapy (68.3% vs 46.7%).

In both CA2099ER and CA209669, given the current length of follow-up, the number of deaths relative to the population sizes remain relatively low and thus the **OS** medians have not yet been reached. It is in this setting, without the ability to compare HRs, that the 9-month survival rates are similar in CA2099ER and CA209669, at 89.9% and 87.9%, respectively. However, fewer early deaths were expected in the CA209669 study since there are proportionally half the number of IMDC poor risk patients compared to CA2099ER.

Table 19 Summary of demographics and baseline characteristics in CA2099ER and CA209669

Study ID	**CA2099ER (N=651)**[a]		**CA209669 (N=123)**[b]
Treatment(s) (n)	**Nivo+Cabo (n=323)**	**Sunitinib (n=328)**	**Nivolumab (n=123)**
Gender, n (%)			
Male	249 (77.1)	232 (70.7)	89 (72)
Female	74 (22.9)	96 (29.3)	34 (28)
Age, years			
Median (range)	62.0 (29-90)	61.0 (28-86)	65 (32-86)
Ethnic origin, n (%)			
White	267 (82.7)	266 (81.1)	104 (84)
Black or African American	1 (0.3)	4 (1.2)	11 (9)
Other	55 (17)	58 (18)	8 (7)

Study ID	CA2099ER (N=651)[a]		CA209669 (N=123)[b]
Treatment(s) (n)	**Nivo+Cabo (n=323)**	**Sunitinib (n=328)**	**Nivolumab (n=123)**
ECOG performance status, n (%)			
0	NA	NA	79 (64)
1	NA	NA	43 (35)
2	NA	NA	1 (1)
Karnofsky Performance Status, n (%)			NA
90-100	257 (79.6)	241 (73.5)	NA
70-80	66 (20.4)	85 (25.9)	NA
Not reported	0	2 (0.6)	NA
Baseline IMDC Prognostic Score (CRF), n (%)			
Favourable risk (0)	74 (2.9)	73 (22.3)	30 (24.3)
Intermediate risk (1-2)	189 (58.5)	186 (56.7)	80 (65.0)
Poor risk (3-6)	60 (18.6)	68 (20.7)	12 (9.8)
Not reported	0	1 (0.3)	1 (0.8)
Site of metastatic Disease, n (%)	238 (73.7)	249 (75.9)	--
Lung	130 (40.2)	131 (39.9)	--
Lymph node	73 (22.6)	53 (16.2)	28 (23)
Liver	78 (24.1)	72 (22.0)	--
Bone	36 (11.1)	36 (11.0)	--
Adrenal gland			

Abbreviations: cc = clear cell; PO = by mouth; QD = once daily; QxW = every x weeks; RCC = Renal cell carcinoma.

Table 20 Summary of efficacy in CA2099ER and CA209669

Study	CA2099ER		CA209669[a]
	Enrolment: Aug-2017 to May-2019		**Enrolment: May-2017 to Dec-2019**
	Nivo+Cabo (n=323)	**Sunitinib (n=328)**	**Nivolumab (n = 123)**
Follow-up (months)			
Median	18.1		15.9
ORR, (%) (95% CI)[b]	**55.7** (50.1, 61.2)	27.1 (22.4, 32.3)	**31.7** (23.6, 40.7)
CR (%)	8.0	4.6	5.7
PR (%)	47.7	22.6	26.0

Study	CA2099ER		CA209669[a]
	Enrolment: Aug-2017 to May-2019		Enrolment: May-2017 to Dec-2019
	Nivo+Cabo (n=323)	Sunitinib (n=328)	Nivolumab (n = 123)
PFS (months)[b]			
Median (95% CI)	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)	8.3 (5.5, 10.9)
HR (95% CI), p-value	0.51 (0.41, 0.64); p < 0.0001		NA
PFS Rate, 9 months (95% CI)[c]	68.3 (62.6, 73.2)	47.8 (41.7, 53.6)	46.7
OS (months)			
Median (95% CI),	NR	NR (22.60, N.A)	NR (27.3, NA)
HR (95% CI)[d], p-value HR (98.89% CI)[c]	0.60 (0.44, 0.81) 0.60 (0.40, 0.89); p = 0.0010		NA
OS rate, 6 mo, % (95% CI)	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)	90.8
OS rate, 9 mo, % (95% CI)	89.9 (86.0, 92.8)	80.5 (75.7, 84.4)	87.9

[a] Atkins et al. J Clin Oncol 2020
[b] ORR and PFS per BICR in CA2099ER and per investigator in CA209669. In CA2099ER, investigator-assessed PFS and ORR results were consistent with the BICR assessed-results.
Abbreviations: CI = confidence interval; DOR = duration of response; HR = hazard ratio; mono = monotherapy; nivo = nivolumab; NA = Not applicable; NR = Not reached; ORR = Objective response rate; PFS = Progression-free survival; RCC = Renal cell carcinoma; OS = overall survival; QxW = every x weeks.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design. The randomised, open-label, sunitinib-controlled study design that was used in CA2099ER is considered adequate to evaluate the benefits and risks of nivo+cabo as 1L treatment in advanced RCC. The study was open-label which is acceptable given that the administration route and schedule of administration of nivo+cabo and sunitinib differ, and that the primary endpoint PFS was BICR-assessed and OS was a key secondary endpoint.

Patient population. The inclusion and exclusion criteria for CA2099ER appear overall acceptable and it is noted that patients were enrolled regardless of baseline IMDC prognostic score and tumour PD-L1 expression status. It is, however, 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 were excluded (nivolumab specific); and patients receiving concomitant treatment with anticoagulants were excluded (cabozantinib specific). Additionally, patients with any active brain metastases were excluded. In the absence of data, nivolumab in combination with cabozantinib should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis (See SmPC section 4.4).

Only patients with RCC with a clear-cell component were eligible for CA2099ER and only few (three) patients were documented to also have non-clear cell components. 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, since nivolumab has shown efficacy in non-clear cell RCC in the prospective study CA209374 (Vogelzang et al. Clin Genitourin Cancer. 2020; Opdivo SmPC), and cabozantinib has shown efficacy in non-clear cell RCC in a retrospective study (Martinez Chanzá et al. Lancet Oncol. 2019). In addition, the efficacy (and safety) of the nivo+cabo combination is being investigated in a prospective phase 2 study in patients with non-clear cell RCC (NCT03635892).

Comparator. At the start of CA2099ER, i.e. in 2017, sunitinib was SoC for the treatment of advanced RCC across IMDC prognostic groups (Escudier et al. An Oncol. 2016). Therefore, this comparator is acceptable.

Endpoints. PFS as primary endpoint of the pivotal study is acceptable. Prolonged PFS as such is considered to be of benefit to the patient, with OS reported as key secondary endpoint (EMA/CHMP/205/95 Rev.5). Secondly, several prior approvals in 1L RCC were based on pivotal studies with PFS (superiority) as primary endpoint (e.g. Sutent 1L RCC EPAR; Bavencio + Inlyta 1L RCC EPAR). OS and ORR as secondary endpoints are acceptable. However, the primary definition of PFS censors for subsequent therapy, which is not in line with EMA recommended PFS definition (EMA/CHMP/27994/2008/Rev.1) Hence the secondary definition of PFS used in the study is considered more appropriate) (Table 8). Subsequent therapy is handled for ORR via the while-not-subsequent therapy, so targets the activity under the randomised treatment only, which is acceptable.

The exploratory endpoint PFS2 could be of value, in case OS results are inconclusive or immature. However, it is noted that the start of third-line therapy is counted as an event as well.

The fact that the pivotal study was open label could limit the value of the results of the exploratory endpoint HRQoL for the benefit-risk (B/R) assessment.

Statistical analysis. The hierarchical hypothesis testing order was as follows: PFS - OS - ORR. The used stratification factors (i.e. IMDC prognostic score, tumour PD-L1 expression, and region) are

acceptable and were also used in other recent pivotal studies in 1L RCC (Opdivo + Yervoy 1L RCC EPAR; Rini et al. Lancet. 2019; Keytruda + Inlyta 1L RCC EPAR). The number of strata (3x2x2=12) is rather large, but can still be acceptable given the sample size (n=651).

Other analyses as outlined in the SAP were appropriate given the type of endpoints.

Study conduct. In a first revision of the protocol, the enrolment was stopped in Arm B (nivolumab + ipilimumab + cabozantinib) of CA2099ER and the study design was thus changed from three arms to two. Also, the type I error for the comparison of arm A (nivolumab + cabozantinib) vs arm C (sunitinib), was increased from 0.025 (two-sided) to 0.05 (two-sided). These changes were not pre-planned according to e.g. an adaptive design. Although it cannot be excluded that major design changes in an open-label trial are informed by results of the trial, the impact of this is likely limited for the following reasons. This revision occurred quite early in the study. Therefore, the likelihood that these changes were (partly) informed by results from within the trial is small and leaving out these patients from the analysis would not change the results for PFS and OS. The rationale for this revision (i.e. nivo+ipi had demonstrated superior OS vs sunitinib in 1L I/P-risk RCC) is considered acceptable. Moreover, it can be understood that 50 patients had been randomized to Arm B by the time the revised protocol was implemented at the site level (Sep-2018; 9 months later). According to the MAH, the delay of inclusion in Arm B after the revised protocol was presented, was mainly due to dependence on the national approval process before implementation.

In a second revision of the protocol, the timing of the PFS and OS IAs were adjusted (and the OS HR modified) and the IA for ORR was removed (Table 9). Compared to the original protocol one interim analysis for OS was added (at 83%) which suggests a more aggressive testing approach. This revision occurred very late in the study. The impact of this is likely limited for this trial for the following reasons. If the originally planned interim analysis (original protocol) was followed, the first (and only) interim analysis was at 65% of planned events (192 events) and in the changed protocol, the actual first interim analysis was conducted again on 65% of planned events (which were now 165 events). As the 165-events interim analysis became already statistically significant, the originally planned interim analysis would likely be statistically significant as well given the shape of the survival curves. Therefore, this design change is not considered to impact the study being positive, based on PFS and OS.

Even though the number of 'significant' protocol deviations (275; Table 10) was large, this number was quite evenly distributed across both arms (149 vs 126) and, more importantly, the potential impact of these 'significant' deviations on the CA2099ER results is most likely very minor. Therefore, it is agreed that there was no impact of the reported protocol deviations on the interpretability of study results, i.e. it does not hamper the B/R assessment.

Efficacy data and additional analyses

Demographics and other baseline characteristics. Regarding the randomized (ITT) patient population (Arm A and Arm C; n=651), there were no meaningful imbalances in patients' demographic and baseline characteristics among treatment arms. The population enrolled is considered representative of the EU target population. The percentage of enrolled patients across IMDC prognostic score categories (i.e. 22.6% favourable; 57.6 intermediate; and 19.7% poor risk) is acceptable.

At the original 30-Mar-2020 DBL, a relatively low percentage of patients had received subsequent systemic anti-cancer therapy (11.1% vs 27.7%), whereas considerably more patients in both arms had progressed (not died; 37.5% vs 46.0%). As the short duration of clinical follow-up (18.1 months) may be among the reasons for the majority of patients not yet having received subsequent systemic anti-cancer therapy, the MAH provided updated data on subsequent systemic anti-cancer therapy. The MAH

provided data from 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). At this DBL, the percentages of patients who had received subsequent systemic anti-cancer therapy had increased only slightly to 17.3% vs 34.1%.

The MAH elaborated that using the number of patients that had discontinued as the denominator (Figure 10), 25.4% (36/142) in the nivo+cabo arm and 39.9% (91/228) in the sunitinib arm received subsequent systemic therapies. In addition, the MAH stated that the reason for the majority of patients not yet having received subsequent systemic anti-cancer therapy may, in part, be the current amount of clinical follow-up as well as the geographic enrolment distribution (with lower rates of therapy in ROW vs in EU/US; data not shown).

Primary endpoint - PFS. At the original 30-Mar-2020 DBL, reasonably mature PFS results (event rate nivo+cabo: 44.6%; sunitinib: 58.2%) showed a statistically significant improvement in PFS per BICR (primary definition) for nivo+cabo compared with sunitinib. There was a clear, early separation of the PFS KM curves that widened over time (Figure 11). The results of all sensitivity analyses (including e.g. PFS as assessed by the investigator) were consistent with the primary analytical method. This PFS benefit (HR = 0.51; gain in median PFS 8.28 months) could be regarded as being clinically relevant. As is stated above, the MAH provided updated data from a 10-Sep-2020 DBL. The updated PFS data were consistent with the primary data and thus confirmed the PFS benefit of nivo+cabo over sunitinib (Figure 21).

In a subgroup analysis, PFS HRs for almost all subgroups favoured nivo+cabo vs sunitinib (HR <1). For example, PFS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status (Figure 13). Plus, PFS benefit was observed in the subgroup of patients with tumours that had sarcomatoid features (11.5% of ITT), a subgroup with limited treatment options and poor prognosis. Only in the small subgroup of Asian patients (n=51; 7.8% of ITT) and the very small subgroup of patients ≥85 years of age (n=6; 0.9% of ITT) did the point estimate of the PFS HR (numerically) favour sunitinib (i.e. 1.29 and 1.22, respectively). The 95% CI for PFS HR was, however, wide for both these subgroups and, importantly, did encompass unity ('1'). Further discussion on the very limited number of patients aged ≥85 (with only 1 PFS event in each arm) does not seem warranted. It is also considered that the subgroup of Asian patients is too small and the number of PFS events is too limited to draw any firm conclusions questioning 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).

Whereas the censoring rules of the primary definition of PFS are not in accordance with the EMA preferred analysis (see above), the provided sensitivity analysis using the secondary definition of PFS *is* the EMA preferred analysis. Therefore, the results of this sensitivity analysis using the secondary definition of PFS could be regarded as the most important for regulatory decision-making. The results of this sensitivity analysis were consistent with the analysis using the primary PFS definition (Figure 12; HR = 0.54; gain in median PFS 5.98 months). Updated PFS results per BICR using the secondary definition were also consistent. Plus, 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 (Figure 22).

Secondary endpoint - OS. At the original 30-Mar-2020 DBL, rather immature OS results (death rate nivo+cabo: 20.7%; sunitinib: 30.2%; median OS not reached in either arm) did already show a statistically significant improvement in OS for nivo+cabo compared with sunitinib. There was a clear, early separation of the OS KM curves that persisted over time (Figure 14). This OS benefit (HR = 0.60) provides support for the primary endpoint PFS and the combination of PFS and OS benefit could

certainly be regarded as being clinically relevant to patients. Also for OS, updated data from 10-Sep-2020 DBL were provided (death rate nivo+cabo: 26.6%; sunitinib: 35.4%; median OS not reached in nivo+cabo arm) and these were consistent with the primary data confirming the OS benefit of nivo+cabo over sunitinib (Figure 23).

In a subgroup analysis, OS HRs for almost all subgroups favoured nivo+cabo vs sunitinib (HR <1). OS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status (Figure 15). 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'). Further discussion on the only borderline unfavourable OS HR in patients aged ≥75 does not seem warranted considering the small size of the subgroup. 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, also acknowledging the fact that ORR results *did* favour nivo+cabo in this subgroup (see below).

Secondary endpoints - ORR. At the original 30-Mar-2020 DBL, ORR per BICR was also statistically significantly higher with nivo+cabo than with sunitinib: 55.7% vs 27.1% (Table 13), plus in the nivo+cabo arm a numerically higher proportion of patients had a BOR of CR compared with the sunitinib arm: 8.0% vs 4.6%. The investigator-assessed ORR results were confirmatory. The median duration of response (**DoR**) also favoured nivo+cabo over sunitinib: 20.17 vs 11.47 months (Figure 16). These ORR and DoR results provide further support for the primary endpoint PFS.

In a subgroup analysis, ORR benefit was observed in all subgroups, e.g. regardless of baseline IMDC prognostic score and tumour PD-L1 expression status, and thus also in the subgroup of Asian patients (42.3% vs 28.0%, respectively). Though it is noted that this ORR in Asian patients in the nivo+cabo arm is still relatively low .

The updated ORR and DoR results from 10-Sep-2020 DBL were consistent with the original data (Table 14).

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%). For these subgroups also, the updated efficacy data confirmed the original results.

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).

Exploratory endpoint – 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 (see above). 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.

Exploratory endpoint – PFS2. Rather immature PFS2 results could nonetheless be regarded as providing some support for the primary endpoint PFS. Updated data from 10-Sep-2020 DBL were consistent with the primary PFS2 data (data not shown).

Proposed posology. The proposed posology, i.e. nivolumab 240 mg IV Q2W or 480 mg IV Q4W in combination with cabozantinib 40 mg PO QD is acceptable. Nivolumab is to be used up to 24 months in patients without disease progression in line with study CA2099ER, instead of indefinitely. The MAH has provided sufficient justification for the nivolumab posology and it is thus acceptable (refer **Error! Reference source not found.** and 2.4.1. Dose response study). For further information and discussion on the cabozantinib posology, see procedure **EMEA/H/C/004163/II/0017**.

Contribution of individual components

The ideal study design for two medicinal products A and B to be used in combination and a control arm C would be A vs B vs AB vs C (EMA/CHMP/205/95 Rev.5). However, studies powered for so many comparisons are often prohibitively large. Thus, if there is sufficient evidence to show efficacy for any of the individual components of the combination used as monotherapies, sometimes these can be omitted from the study design. This type of study does not include one or more monotherapy groups, but this should be justified based on available clinical and/or non-clinical data (Moscetti et al. ESMO Open. 2020). The pivotal study CA2099ER was conducted testing a new AB combination (nivo+cabo) against the standard of care C (sunitinib). This approach is similar to the pivotal studies of the three recently approved ICI combination treatments in the 1L RCC setting (Opdivo + Yervoy 1L RCC EPAR; Keytruda + Inlyta 1L RCC EPAR; Bavencio + Inlyta 1L RCC EPAR).

Contribution of nivolumab. For substantiating the individual contribution of nivolumab, the MAH provided a cross-study comparison between CA2099ER and CABOSUN (Table 17). It is agreed that this indirect comparison provides sufficient evidence for the contribution of nivolumab to the nivo+cabo combination in 1L RCC in I/P-risk patients. The higher ORR (and/or larger increase in ORR) in CA2099ER vs CABOSUN is regarded as primary evidence. It can also be agreed that the consistent efficacy results of cabozantinib across all IMDC subgroups in the 2L METEOR study (Table 18; i.e. primarily ORR, with support from PFS and OS) suggest that favourable-risk patients in the 1L setting could have outcomes similar in magnitude to that observed for the I/P-risk populations. Despite the lack of cabozantinib efficacy data on favourable-risk patients in the 1L setting, it can be agreed that the overall evidence supports the contribution of nivolumab to the nivo+cabo combination for the (entire) patient population targeted by the proposed indication.

Contribution of cabozantinib. The individual contribution of cabozantinib could be inferred from the fact that it is already approved for the 1L treatment of advanced RCC, albeit for I/P-risk patients only (Cabometyx SmPC). However, this approval is for a (recommended) dose of 60 mg cabozantinib QD, instead of the 40 mg QD used in CA2099ER. Thus, for substantiating the individual contribution of cabozantinib, the MAH provided a cross-study comparison between CA2099ER and CA209669 (Table 20). It can be agreed that this comparison provides sufficient evidence for the contribution of cabozantinib to the nivo+cabo combination. Again, the higher ORR in CA2099ER vs CA20996 is regarded as primary evidence.

Conclusion regarding contribution of individual components. The lack of monotherapy experimental arms in CA2099ER prevents a precise quantitative assessment of the contribution of each component of the nivo+cabo combination. Nevertheless, the additive efficacy of both individual components has sufficiently been shown in a qualitative sense based primarily on a substantial increase in ORR over the individual agents, even though based on cross-study comparisons only.

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 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

Summary of existing safety profiles

The existing safety profile of nivolumab monotherapy (240mg Q2W or 480 mg Q4W) has been established across several tumour types which includes previously treated RCC patients. In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types the most frequent adverse events (AEs) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%). Nivolumab is also associated with immune-related AEs. These include rash (26.4%), gastrointestinal AEs (13.1%) endocrine AEs, of which most within the thyroid disorder subcategory (9.6%), hepatic AEs (6.7%), hypersensitivity/infusion reactions (4.7%), pulmonary AEs (2.8%), and renal AEs (2.8%).

The existing safety profile of cabozantinib (60 mg QD) is derived from patients in the treatment-naïve and previously treated advanced RCC and previously treated HCC setting. The most frequent AEs of any Grade in the RCC population included diarrhoea, hypertension, fatigue, AST increased, ALT increased, nausea, decreased appetite, PPES, dysgeusia, platelet count decreased, stomatitis and anaemia. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%). Grade 3/4 AEs were observed with an incidence of 59%-68% in RCC patients. The most common serious adverse drug reactions in the RCC population are diarrhoea, hypertension, dehydration, hyponatraemia, nausea, decreased appetite, embolism, fatigue, hypomagnesaemia, palmar-plantar erythrodysaesthesia syndrome (PPES).

Other relevant AEs which have been observed with cabozantinib are GI perforation, GI fistula, thromboembolic events, haemorrhage, wound complications, osteonecrosis, reversible posterior leukoencephalopathy syndrome (RPLS), hypothyroidism and proteinuria.

Clinical safety for new indication

The safety data for this extension of indication in advanced RCC treatment-naïve patients is based on study CA2099ER (NCT03141177)

No separate or integrated safety data was provided for the dose response study.

Patient exposure

The DBL occurred on 30-Mar-2020. The subject disposition is reported in the efficacy section (see 2.4.2. Main study **- Results**). Median follow-up (between randomization date and last known date alive or death date) was 15.70 months for the nivo+cabo arm and 14.59 months for the sunitinib arm.

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 30-Mar-2020 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. An end of treatment period summary is provided in Table 21.

Table 21 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)

The number of doses, cumulative dose, dose intensity and average daily dose are reported in Table 21. The median duration of treatment (defined as last dose date - start dose date + 1 day) of nivo+cabo was 14.26 months (range 0.2-27.3 months; 13.31 months for nivolumab, 13.78 months for cabozantinib), and 9.23 months for sunitinib (range 0.8-27.6 months). In total 60.3% of the patients had a treatment duration of >12 months in the nivo+cabo arm (nivolumab 53.8% and cabozantinib 56.9%) and in the sunitinib arm this percentage was 40.3%. Excluding dose holds the median duration of therapy was 12.62 (range 0.2 - 26.9) months for cabozantinib and 6.05 (0.8 - 17.3) months for sunitinib.

The median exposure time (range) using 30 days safety window was 14.31 (0.7, 27.3) months in the nivo+cabo arm and 9.76 (0.7, 27.3) months in the sunitinib arm. The median exposure time (range) using the 100 days safety window was 14.72 (0.7, 27.7) months in the nivo+cabo arm and 11.09 (0.7, 27.3) months in the sunitinib arm.

Table 22 Cumulative Dose and Relative Dose Intensity - All Treated Patients

	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.

Dose delays for the 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 to be related to only nivolumab, and vice versa. A dose was considered as actually delayed if the delay exceeded 3 days for nivolumab. For cabozantinib, daily dose of 0 mg entered with CRF reason "Adverse Event" was considered as a delay if cabozantinib was given daily. For sunitinib, a dose was considered delayed if subjects had 0 mg with a CRF reason "Adverse Event".

- Nivo+cabo arm: in total 71.9% of patients had delays for nivolumab only (50.4% of the nivolumab only delays were due to AEs for nivolumab), 68.1% for cabozantinib only delays, 83.4% for either nivolumab or cabozantinib (all dose delays for cabozantinib and sunitinib were due to AEs by definition).
- Sunitinib arm: in addition to the planned 2 weeks off treatment, 51.9% of patients had dose delays.

A summary of dose delays is provided in Table 23.

Table 23 Dose Delay Summary - All Treated Patients

	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]

Dose reductions were not permitted with nivolumab treatment, but they were permitted with cabozantinib and sunitinib. Dose reductions (patients with at least 1 dose reduction) were reported as follows:

- Nivo+cabo arm: 56.3% of patients had dose reductions for cabozantinib
- Sunitinib arm: 51.6% of patients had dose reductions for sunitinib

The most common reason for dose reduction for cabozantinib and sunitinib was also AEs.

Dose reductions are summarized in Table 24 and Table 25.

Table 24 Oral Study Drugs Dose Reduction Summary - All Treated Patients

	Nivo + Cabo N = 320	Sun N = 320
	Cabo N = 320	Sun N = 320
SUBJECTS WITH AT LEAST ONE DOSE REDUCTION (%)	180 (56.3)	165 (51.6)
NUMBER OF DOSE REDUCTIONS PER SUBJECT (%)		
0	140 (43.8)	155 (48.4)
1	130 (40.6)	94 (29.4)
2	38 (11.9)	68 (21.3)
3	8 (2.5)	3 (0.9)
>= 4	4 (1.3)	0
TOTAL NUMBER OF DOSE REDUCTIONS / TOTAL NUMBER OF DOSES RECEIVED (%) (A)	249/108833 (0.2)	239/59888 (0.4)
REASON FOR DOSE REDUCTION (%) (B)		
ADVERSE EVENT	190 (76.3)	191 (79.9)
OTHER	8 (3.2)	6 (2.5)
NOT REPORTED	51 (20.5)	42 (17.6)

(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.
(B) Percentages are computed out of the total number of dose reductions.
A dose reduction is defined as at least one day with a non zero dose smaller than 50mg for Sunitinib and smaller than previous non zero dose with a CRF reason different from "Dosing Error".
Dose reduction for subjects treated with Cabozantinib is defined as at least one day with 20 mg or 20 mg every other day dosing and smaller than previous non zero dose with a CRF reason different from "Dosing Error".

Source: Refer to Table 6.3-4 of the CA2099ER Final CSR[2]

Table 25 Dose Reduction Summary for Cabozantinib - All Treated Patients

	Nivo + Cabo N = 320
	Cabo N = 320
PATIENTS 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 patient actually received the specified dose level; in each row, include all and only patients who received treatment at that level, regardless of reason (exclude patients who never received treatment at that level)
[2] Only patients who had dose reduction due to AE were considered.
[3] Only patients 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.

Adverse events

A summary of safety in all treated patients in shown in

Table 26

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)

Adverse Events (All-causality)

Any-Grade all-causality AEs were reported in 319 patients (99.7%) in the nivo+cabo arm, and 317 patients (99.1%) in the sunitinib arm (Table 27).

Table 27 Adverse Events by Worst CTC Grade in ≥ 10% of Patients within Either Arm - All Treated Patients

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320 Any Grade	Nivo + Cabo N = 320 Grade 3-4	Nivo + Cabo N = 320 Grade 5	Sun N = 320 Any Grade	Sun N = 320 Grade 3-4	Sun N = 320 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

System Organ Class (%) Preferred Term (%)	Nivo + Cabo N = 320 Any Grade	Nivo + Cabo N = 320 Grade 3-4	Nivo + Cabo N = 320 Grade 5	Sun N = 320 Any Grade	Sun N = 320 Grade 3-4	Sun N = 320 Grade 5
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: Table 6.1.3.1

Treatment-related Adverse Events

Any-Grade drug-related AEs were reported in 309 patients (96.6%) in the nivo+cabo arm, and 298 patients (93.1%) in the sunitinib arm (

Table 28).

Table 28 *Drug-Related Adverse Events by Worst CTC Grade in ≥ 5% of Patients within Either Arm - All Treated Patients*

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

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
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: Table 6.1.3.2

Exposure-adjusted AE summary

An exposure-adjusted unique AE summary was provided by the Applicant as supplementary information. In general, this resulted in relative increases in the number of events 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 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.

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 10-Sept-2020 DBL

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 10-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 10-Sep-2020 DBL, 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 Table 29 a summary of safety data from the March 2020 and September 2020 cut-off is shown.

Table 29 CA2099ER Summary of Safety - All Treated Subjects - Mar-2020 and Sep-2020

	No. of Subjects (%)							
	Mar-2020				Sep-2020			
Safety Parameters	**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)

Safety Parameters	No. of Subjects (%)							
	Mar-2020				Sep-2020			
	Nivo+Cabo (N =320)		Sunitinib (N =320)		Nivo+Cabo (N =320)		Sunitinib (N =320)	
	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
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.

Serious adverse event/deaths/other significant events

Serious adverse events

Any-Grade all-causality SAEs (within 30 days of last dose) were reported in 148 (46.3%) patients in the nivo+cabo arm vs 127 (39.7%) patients in the sunitinib arm (

Table 30).

Table 30 Serious Adverse Events Reported in ≥ 1% of All Treated Patients

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

Table 31 Drug-Related Serious Adverse Events Reported in ≥ 1% of All Treated Patients

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 32 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) (95% CI)	2.00 (1.57, 2.57)	2.00 (1.43, 2.29)	1.57 (1.14, 2.43)	1.71 (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

As of the 30-Mar-2020 DBL, 67 (20.9%) patients in the nivo+cabo arm and 99 (30.9%) of patients in the sunitinib arm had died during the study. Disease progression was the most common cause of death in both arms (respectively 15.9% and 23.1%).

Treatment related deaths

Death in 1 (0.3%) patient due to small intestine perforation in the nivo+cabo arm, and 2 (0.6%) patients (due to respiratory distress and pneumonia/acute respiratory failure) in the sunitinib arm were considered as related to study drug toxicity by the investigator.

Deaths attributed to other reasons

Deaths attributed to other reasons were reported in 12 (3.8%) of patients in the nivo+cabo arm and 17 (5.3%) of patients in the sunitinib arm. The verbatim terms and PT terms with relationship reported for the 'other' reasons for death in treated patients are provided in Table 33. For one patient who died from a GI bleeding and two patients who died from intestinal perforation a causal role of study therapy cannot be excluded or ascertained due to limited available information.

Table 33 Deaths Attributed to "Other" Reasons - All Treated Patients

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

Verbatim Term for cause of Death	PT (Relationship)	Days since last dose
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 patient 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 patients 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.

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 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.

Below a specification is given for dose delays and dose reductions.

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

All-causality AEs leading to dose reductions**:**

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

Select Adverse Events

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab and/or ipilimumab, the MAH identified select AEs based on the following four guiding principles: AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies; AEs that may require immunosuppression (e.g., corticosteroids) as part of their management; AEs whose early recognition and management may mitigate severe toxicity and 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.

The total number patients with select AEs was 164 (57.5%) in the nivo+cabo arm and 136 (42.5%) in the sunitinib arm. The most frequently reported drug-related select AE categories (any Grade) were as follows in each treatment arm:

- Nivo+cabo: skin (62.2%), gastrointestinal (57.5%), endocrine (42.8%), and hepatic (40.0%)
- Sunitinib: skin (47.2%), gastrointestinal (42.5%), and hepatic (21.9%).

Refer to Table 34 for further information on drug-related select AEs in the nivo+cabo arm. In the sunitinib arm the frequencies of the other reported drug-related select AE categories (any Grade) were as follows: endocrine (33.1%), renal (8.1%), pulmonary (0.3%) and hypersensitivity (0.3%).

The most frequently reported drug-related select AEs by preferred term (any Grade) were as follows in each treatment arm:

- Nivo+cabo: diarrhoea (56.9%), PPES (38.1%), and hypothyroidism (33.4%)
- Sunitinib: diarrhoea (42.5%), PPES (40.3%), and hypothyroidism (28.1%)

The majority of Select AEs were Grade 1-2 and most were considered drug-related by the investigator. The most frequently reported drug-related serious select AEs by preferred term (any Grade) were as follows in each treatment arm

- Nivo+cabo: diarrhoea (3.4%), pneumonitis (2.8%), and adrenal insufficiency (1.9%)
- Sunitinib: acute kidney injury (0.6%)

For all causality related Select AE categories, 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.

Across the select AE categories established immune-related management algorithms were used to manage IMAEs (e.g. dose interruptions and immune-modulating medication, mainly systemic corticosteroids). Except for endocrine events, most drug-related select AEs with nivo+cabo had resolved (ranging from 65.8% to 100.0% across categories) at the time of 30-Mar-2020 DBL. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Data regarding Onset, Management, and Resolution of Drug-Related Select AEs are shown in Table 34. Note that some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 34 Onset, Management, and Resolution of Drug-Related Select AEs - Nivolumab + Cabozantinib Treated Patients (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 patients who experienced the event

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

[d] Patients 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. - patients, wks - weeks

Immune-mediated Adverse Events

IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (i.e., with extended follow-up). These analyses occurred on patients who received immune-modulating medication for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate aetiology and an immune mediated component.

The most frequently reported IMAEs (any Grade) were as follows in each treatment arm:

- Nivo+cabo: hypothyroidism/thyroiditis (25.3%), hepatitis (10.0%), and rash (10.0%)
- Sunitinib: hypothyroidism/thyroiditis (9.7%) and hepatitis (2.2%)

The frequencies of the remaining reported IMAEs (any-Grade) in the sunitinib arm were as follows: Adrenal insufficiency (0%), DM (0%), Hyperthyroidism (0.3%), Hypophysitis (0%), pneumonitis (0%), Diarrhoea/colitis (0.3%), Nephritis/Renal Dysfunction (0.6%), rash (0.6%) and hypersensitivity (0%). For more information on IMAEs in the nivo+cabo arm refer to Table 35.

Across IMAE categories, established immune-related management algorithms were used to manage IMAEs (e.g. dose interruptions and immune-modulating medication, mainly systemic corticosteroids). Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. Non-endocrine IMAEs occurred infrequent in the sunitinib arm.

Table 35 Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - Nivolumab + Cabozantinib Treated Patients (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[g] or Dose Reduction	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks
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)
Diarrhoea/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)
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)
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)
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)
Hypersensitivity	0.6 / 0	2.14 (0.1 - 4.1)	0 / 0	100.0 / 50.0	2.07 (0.1 - 4.0)
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)
Hypophysitis	0.6 / 0.3	47.93 (18.1 - 77.7)	0 / 0.6	50.0 / 50.0	58.00 (58.0 - 58.0)

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)
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)
Diabetes Mellitus	0 / 0	N.A.	0 / 0		

IMAE Category	% Subj. with Resolution of IMAE[d,e]	Median[b] Time to Resolution (range), wks[c,d,e]	% Subj. with Recurrence after Reinitiation[f]
Pneumonitis	70.0	11.93 (2.9 - 32.6)	25.0 (1/4)
Diarrhoea/Colitis	82.4	6.14 (0.6 - 62.3+)	33.3 (1/3)
Hepatitis	96.9	4.07 (0.9 - 37.4)	58.8 (10/17)
Nephritis/Renal Dysfunction	80.0	1.14 (0.9 - 8.0+)	0 (0/3)
Rash	78.1	8.14 (0.1 - 55.0+)	0 (0/2)
Hypersensitivity	100.0	3.07 (0.1 - 6.0)	N.A. (0/0)
Endocrine IMAEs			
Adrenal Insufficiency	27.3	N.A. (0.9 - 82.1+)	66.7 (2/3)
Hypophysitis	50.0	N.A. (1.3 - 59.1+)	N.A. (0/0)
Hypothyroidism/Thyroiditis	37.0	N.A. (0.4 - 95.4+)	33.3 (1/3)
Hyperthyroidism	86.7	7.71 (0.3 - 70.0+)	0 (0/4)
Diabetes Mellitus	N.A.	N.A.	N.A. (0/0)

[a] Denominator is based on the number of patients who experienced the event.
[b] From Kaplan-Meier estimation.
[c] Symbol + indicates a censored value.
[d] Patients who experienced IMAE 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.
[f] Percentages are based on patients who were re-challenged. Numerator is the number of patients who had a recurrence (or a positive re-challenge) and the denominator is the number of patients 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.
[g] For oral drugs, dose delays include delays and interruptions.

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

Other Events of Special Interest

Other Events of Special Interest are defined as events that do not fulfil all criteria to qualify as IMAEs or select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Overall, OESIs were reported in 8/320 (2.5%) patients (14 OESIs) in the nivo+cabo arm and 1/320 (0.3%) patient in the sunitinib arm (see Table 36).

In the nivo+cabo arm, 11 of the 14 OESIs were resolved at the time of DBL, whereas three events were not (acute pancreatitis, pancreatitis, and myocarditis). Of the 11 resolved events, 8 resolved with IMM treatment. In the sunitinib arm, a single patient reported uveitis; there were no events in any other OESI categories. The single event of uveitis resolved with IMM treatment.

Table 36 Treatment, Onset, and Resolution Information for Other Events of Special Interest by Patient -All Treated Patients

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, PID - patient identification number, SAE - serious adverse event
Source: Appendix 6.83 (by-patient listing, OESIs, immune-modulating medication) and Appendix 6.1.1 (seriousness, duration of event).

Events to Monitor for Cabozantinib

A set of events to monitor (ETMs) has been defined for cabozantinib to track events known to be associated with tyrosine kinase inhibitors (TKIs) or vascular endothelial growth factor (VEGF) pathway inhibition, that may have potentially serious consequences, or that were determined to warrant ongoing routine surveillance. Refer to

Table 37 for a summary of these events.. Data on time to resolution of ETMs and on recurrence after reinititating therapy for ETMs is provided in Table 38 and

Table 39.

ETMs Grade≥3

The most frequently observed ETMs with Grade 3 or higher (>5% in any treatment arm) events in the study population were PPES, hypertension, and venous and mixed thrombotic events. ETMs with Grade 3 or higher events occurring at rates between 2 and 5% (in any treatment arm) were hepatotoxicity, proteinuria and haemorrhage. The remaining Grade 3 or higher ETMs included events at a rate of less than 2%.

Grade 3 or higher ETM rates for nivo+cabo which were higher to those in the sunitinib treatment arm are venous and mixed thrombotic events (7.2% for nivo+cabo vs 2.5% for sunitinib) and hepatotoxicity (4.4% for nivo+cabo vs 1.3% for sunitinib).

Serious ETMs

The serious events in the venous and mixed thrombotic ETM showed an event onset range from 29 to 430 days (approximately 40% of the events occurred beyond study day 100) and the highest severity was Grade 4. Approximately two thirds of these events were pulmonary embolism, which were generally successfully treated with low molecular weight heparins, as demonstrated by the short time (within 10 days) to event resolution. Although venous and mixed thromboembolic events are a well-characterized risk for cabozantinib, some of the observed events included alternative aetiologies.

Hepatotoxicity

In order to monitor for more severe hepatic events, the hepatotoxicity ETM was established. The serious events in the hepatotoxicity ETM showed an event onset ranging from 44 to 70 days and the highest severity was Grade 4. They were short-lasting and generally resolved with the use of steroids for these events. The study drug actions with regard to cabozantinib and nivolumab (i.e. interruptions, delays or discontinuations) were variable across these events.

Grade 5 ETMs

Grade 5 ETMs had low and similar rates across treatment arms and consisted of different isolated events within each treatment arm. In the nivo+cabo treatment arm, the 5 reported events were all assessed as not related to study drug by the investigator. A GI perforation occurred on study day 20 following an intestinal obstruction after having received only 1 nivolumab infusion and 5 days of cabozantinib therapy. An upper GI haemorrhage, leading to a hypovolemic shock, was observed on study day 264 and the last nivolumab and cabozantinib administration occurred 26 and 22 days, respectively, prior to the event. In the 3 remaining patients the observed causes for the fatal outcome were not specified: sudden death (patient was found dead on day 33), cardiorespiratory arrest (event occurred on day 21, 20 and 6 days, respectively after study drugs were discontinued for increased blood creatinine levels) and cardiac arrest (event occurred on day 180 in a patient who started sulfamethoxazole/trimethoprim on day 170 for an unknown indication whilst being treated with a statin, ACE inhibitor and a tricyclic antidepressant). In addition, the patient with Grade 4 AE of small intestinal perforation died 51 days after the last dose of nivolumab and 46 days after the last dose of cabozantinib. The event was considered by the investigator to be related to study drug toxicity, and the narrative for this event is provided in the section on treatment related deaths.

Table 37 *Summary of Adverse Events to Monitor by Grade Sorted in Descending Difference in Percentages in Any Grade - All Treatment-Emergent Adverse Events to Monitor - All Treated Patients*

Group 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
HYPERTENSION	115 (35.9)	44 (13.8)	1 (0.3)	0	125 (39.1)	46 (14.4)	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)
PROTEINURIA	36 (11.3)	10 (3.1)	0	0	25 (7.8)	7 (2.2)	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
HEPATOTOXICITY	29 (9.1)	14 (4.4)	1 (0.3)	0	15 (4.7)	4 (1.3)	1 (0.3)	0
RENAL FAILURE	22 (6.9)	3 (0.9)	0	0	21 (6.6)	4 (1.3)	2 (0.6)	0
OSTEONECROSIS	18 (5.6)	2 (0.6)	0	0	12 (3.8)	1 (0.3)	0	0
ABSCESS	13 (4.1)	3 (0.9)	0	0	4 (1.3)	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)
WOUND COMPLICATION	9 (2.8)	1 (0.3)	0	0	4 (1.3)	1 (0.3)	0	0
ARTERIAL THROMBOTIC EVENTS	7 (2.2)	3 (0.9)	0	0	3 (0.9)	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
FISTULA	3 (0.9)	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 38 *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

	Nivo + Cabo Number of subjects with an Event (N = 250)	Sunitinib Number of subjects with an Event (N = 233)
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)
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%)

	Nivo + Cabo Number of subjects with an Event (N = 250)	Sunitinib Number of subjects with an Event (N = 233)
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.

Table 39 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)

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.

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 are presented below for all patients treated with nivo+cabo or sunitinib in CA2099ER.

A summary of clinical laboratory parameters that worsened relative to baseline is presented in

Table 40 and Table 41.

Table 40 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 41 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)**

Haematology

For on-treatment worsening of haematology parameters relative to baseline refer to

Table 40.

Haematologic abnormalities were mostly grade 1-2. Grade 3 or 4 hematologic abnormalities reported in ≥ 5% of patients in either arm were as follows:

- Nivo+cabo: decreased absolute lymphocytes (6.9% Grade 3)
- Sunitinib: 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)

Liver function tests

On-treatment liver function parameters that worsened relative to baseline are summarized in

Table 40. 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).

Of the 83 (26.2%) patients with ALT/AST of > 3X ULN in the nivo+cabo arm, the median (range) time to onset was 10.14 (2.0-88.3) weeks; 23 (27.7%) were treated with systemic corticosteroids. The abnormalities of AST/ALT > 3X ULN resolved in 74 (89.2%) patients, with the median (range) time to resolution of 2.14 (0.4, 83.6+) weeks. Of 32 patients who were re challenged with either nivolumab and/or cabozantinib (8 re-challenged with nivolumab only; 6 re-challenged with cabozantinib only, and 18 re-challenged with both nivolumab and cabozantinib), 22 (62.9%) patients had no recurrence of ALT/AST > 3X ULN. There were 9 subjects who had no ALT/AST lab values indicating resolution to ≤ 3 xULN. Four out of these had died due to disease progression. In four other patients the adverse events eventually resolved, while nivo+cabo or nivolumab was discontinued in these patients. One patient withdrew consent.

Of the 35 (11.0%) patients with AST or ALT > 5X ULN (CTCAE Grade 3+) in the nivo+cabo arm, the median (range) time to onset was 8.29 (2.1 - 53.9) weeks, 14 (40.0%) were treated with systemic corticosteroids. The abnormalities of AST/ALT > 5X ULN resolved in 29 (82.9%) patients, with the median (range) time to resolution was 3.00 (0.4 - 81.6+) weeks. Of 14 patients who were re challenged with either nivolumab and/or cabozantinib (4 re-challenged with nivolumab only; 4 with cabozantinib only, and 6 re challenged with both nivolumab and cabozantinib treatment), 9 (60.0%) patients had no recurrence of ALT/AST > 5X ULN.

A total of 4/317 (1.3%) patients in the nivo+cabo arm had concurrent ALT or AST elevation > 3X ULN with total bilirubin (TBili) > 2X ULN within 1 day and within 30 days of last dose of study. One additional patient in the nivo+cabo arm reported concurrent ALT or AST elevation > 3X ULN with total bilirubin > 2X ULN more than 30 days after last dose of either nivolumab or cabozantinib, and therefore not included in Table 42.

A summary of patients with liver function abnormalities is provided in Table 42 and a summary of patients with concurrent ALT/AST > 3XULN and Bilirubin > 2 X ULN in Nivo+Cabo Group is provided in Table 43.

Table 42 On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Patients

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 patients with at least one on-treatment measurement of the corresponding laboratory parameter

Details of these 5 patients in the nivo+cabo arm who had concurrent ALT or AST > 3X ULN with TBili > 2X ULN are provided in Table 43.

Table 43 Summary of Patients with Concurrent ALT/AST > 3XULN and Bilirubin > 2 X ULN in Nivo+Cabo Group

Patient ID	Event Description	Relevant Medical History	Treatment	Resolution (Yes/No)
CA2099ER-xxxx	Concurrent ALT or AST > 3X ULN and T.Bili > 2X ULN (Day 50); hepatotoxicity (Grade 3, related, Day 50); hepatotoxicity (Grade 3, related, Day 78); hepatotoxicity (Grade 2, related, Day 85); hepatotoxicity (Grade 1, related, Day 92)	Hepatobiliary: Gilbert Syndrome	Corticosteroid	Yes
CA2099ER-xxxx	Concurrent ALT or AST > 3X ULN and T.Bili > 2X ULN (Day 35, 146, 188, and 196); alanine aminotransferase increased (Grade 3, related, Day 28); blood bilirubin increased (Grade 2, related, Day 35); hypothyroidism (Grade 2, related, Day 80); hypothyroidism (Grade 1, related, Day 90); malignant neoplasm progression (Grade 5, not related, Day 206)	Hepatobiliary: cholecystectomy	Corticosteroid	Yes
CA2099ER-xxxx	Concurrent ALT or AST > 3X ULN and T.Bili > 2X ULN (Day 44);hepatotoxicity (Grade 4, related, Day 46); renal failure (Grade 3, related, Day 151); renal failure (Grade 2, related, Day 170); hepatic failure (Grade 3, related, Day 171); general physical health deterioration (Grade 3, not related, Day 198)	Hypertension, renal failure, chronic kidney disease	Corticosteroid	Yes
CA2099ER-xxxx	Concurrent ALT or AST > 3X ULN and T.Bili > 2X ULN (Day 148) and hepatotoxicity (Grade 3, related, Day 57)	Respiratory: asthma	Corticosteroid	No
CA2099ER-xxxx	Concurrent ALT or AST > 3X ULN and T.Bili > 2X ULN (Day 169); blood bilirubin increased (Grade 2, related, Day 155); aspartate aminotransferase increased (Grade 2, related, Day 167); alanine aminotransferase increased (Grade 2, related, Day 169); blood bilirubin increased (Grade 2, related, Day 169)	Alcohol use: 1990 to current	Corticosteroid	Yes

Kidney Function Tests

In the nivo+cabo and sunitinib arms, 31.2% of patients with at least 1 on treatment measurement had normal (Grade 0) creatinine values during the treatment reporting period.

In both treatment arms, a similar amount of kidney function abnormalities was seen (Table 44). 4 (1.3%) patients in the nivo+cabo arm and 2 (0.6%) of patients in the sunitinib arm had a Grade 3-4 increased creatinine level.

Table 44 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

Thyroid Function Tests

Thyroid stimulating hormone (TSH) increases (> ULN) from baseline (≥ ULN) were reported in 201/317 (63.4%) patients in the nivo+cabo arm, and 159/306 (52.0%) patients in the sunitinib arm. Decreases (< lower limit of normal [LLN]) from baseline (≥LLN) were reported in 95/317 (30.0%) patients in the nivo+cabo arm, and 58/306 (19.0%) patients in the sunitinib arm.

Table 45 On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Patients 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 patients 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: Table 7.6.3 [SI units]

Electrolytes

On-treatment electrolyte laboratory parameters that worsened relative to baseline are summarized in

Table 40. Any-Grade hypocalcaemia, hypomagnesemia, and hypophosphatemia were reported more frequently with nivo+cabo (54.8%, 49.7%, and 68.4%, respectively) compared to sunitinib (23.9%, 28.9%, and 47.6% respectively). The following Grade 3 abnormalities in electrolytes were observed in ≥ 5% of treated patients in either arm with on-treatment laboratory results:

- Nivo+cabo: hyponatremia (11.7%), hypophosphatemia (20.6%)
- Sunitinib: hyponatremia (11.9%), hypophosphatemia (6.8%)

ECG abnormalities

ECG abnormalities at baseline and on-treatment are shown in *Table 46*. 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 46 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

The MAH analysed frequencies of all-causality and drug-related AEs in the nivo+cabo arm and sunitinib arm for subgroups of age, gender, and geographic region.

- 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.
- The frequencies of all-causality and drug-related AEs in the nivo+cabo arm and sunitinib arm for the subgroup of geographic region (US/Canada/West Europe/North Europe) were similar to the AE frequencies reported for the rest of the world by treatment.
- Subgroup analyses comparing favourable risk patients with 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.

  Subgroup analyses for safety per age are presented in Table 47, Table 48 and

  Table 49.

Table 47 Summary of Safety Results by Age Group - All Treated Patients in CA2099ER

MedDRA Terms (%)	Age Group (Years) < 65 N = 189	65–74 N = 102	75–84 N = 27	>= 85 N = 2	Total N = 320
Treatment Group: Nivolumab + Cabozantinb N = 320					
TOTAL SUBJECTS WITH AN EVENT	188 (99.5)	102 (100.0)	27 (100.0)	2 (100.0)	319 (99.7)
SERIOUS AE - TOTAL	80 (42.3)	51 (50.0)	15 (55.6)	2 (100.0)	148 (46.3)
FATAL (DEATH)	11 (5.8)	8 (7.8)	1 (3.7)	0	20 (6.3)
HOSPITALIZATION/PROLONGATION	76 (40.2)	47 (46.1)	14 (51.9)	2 (100.0)	139 (43.4)
LIFE THREATENING	10 (5.3)	5 (4.9)	2 (7.4)	0	17 (5.3)
CANCER	17 (9.0)	4 (3.9)	3 (11.1)	0	24 (7.5)
DISABILITY/INCAPACITY	4 (2.1)	1 (1.0)	3 (11.1)	0	8 (2.5)
AE LEADING TO DISCONTINUATION	27 (14.3)	26 (25.5)	9 (33.3)	1 (50.0)	63 (19.7)
PSYCHIATRIC DISORDERS	33 (17.5)	17 (16.7)	8 (29.6)	1 (50.0)	59 (18.4)
NERVOUS SYSTEM DISORDERS	88 (46.6)	54 (52.9)	19 (70.4)	2 (100.0)	163 (50.9)
ACCIDENT AND INJURIES	25 (13.2)	15 (14.7)	2 (7.4)	1 (50.0)	43 (13.4)
CARDIAC DISORDERS	9 (4.8)	10 (9.8)	4 (14.8)	0	23 (7.2)
VASCULAR DISORDERS	68 (36.0)	47 (46.1)	14 (51.9)	1 (50.0)	130 (40.6)
CEREBROVASCULAR DISORDERS	5 (2.6)	1 (1.0)	0	0	6 (1.9)
INFECTIONS AND INFESTATIONS	92 (48.7)	58 (56.9)	17 (63.0)	1 (50.0)	168 (52.5)
ANTICHOLINERGIC SYNDROME	59 (31.2)	36 (35.3)	8 (29.6)	2 (100.0)	105 (32.8)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	24 (12.7)	19 (18.6)	6 (22.2)	1 (50.0)	50 (15.6)

Table 48 Summary of Safety Results by Age Group - All Treated Patients in CA2099ER

MedDRA Terms (%)	Age Group (Years) < 65 N = 206	65–74 N = 85	75–84 N = 25	>= 85 N = 4	Total N = 320
Treatment Group: Sunitinib N = 320					
TOTAL SUBJECTS WITH AN EVENT	203 (98.5)	85 (100.0)	25 (100.0)	4 (100.0)	317 (99.1)
SERIOUS AE - TOTAL	72 (35.0)	40 (47.1)	12 (48.0)	3 (75.0)	127 (39.7)
FATAL (DEATH)	22 (10.7)	7 (8.2)	2 (8.0)	0	31 (9.7)
HOSPITALIZATION/PROLONGATION	65 (31.6)	39 (45.9)	11 (44.0)	3 (75.0)	118 (36.9)
LIFE THREATENING	11 (5.3)	6 (7.1)	2 (8.0)	0	19 (5.9)
CANCER	11 (5.3)	8 (9.4)	2 (8.0)	0	21 (6.6)
DISABILITY/INCAPACITY	3 (1.5)	3 (3.5)	0	0	6 (1.9)
AE LEADING TO DISCONTINUATION	26 (12.6)	22 (25.9)	5 (20.0)	1 (25.0)	54 (16.9)
PSYCHIATRIC DISORDERS	26 (12.6)	9 (10.6)	3 (12.0)	0	38 (11.9)
NERVOUS SYSTEM DISORDERS	95 (46.1)	41 (48.2)	8 (32.0)	2 (50.0)	146 (45.6)
ACCIDENT AND INJURIES	14 (6.8)	4 (4.7)	2 (8.0)	0	20 (6.3)
CARDIAC DISORDERS	9 (4.4)	8 (9.4)	0	0	17 (5.3)
VASCULAR DISORDERS	80 (38.8)	44 (51.8)	9 (36.0)	0	133 (41.6)
CEREBROVASCULAR DISORDERS	6 (2.9)	2 (2.4)	0	0	8 (2.5)
INFECTIONS AND INFESTATIONS	68 (33.0)	28 (32.9)	10 (40.0)	3 (75.0)	109 (34.1)
ANTICHOLINERGIC SYNDROME	43 (20.9)	20 (23.5)	8 (32.0)	2 (50.0)	73 (22.8)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	19 (9.2)	6 (7.1)	5 (20.0)	1 (25.0)	31 (9.7)

CTC Version 4.0; MedDRA Version: 22.1
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Appendix RCC.424-EUSCS

Table 49 Summary of On-treatment Adverse Events by Age Group - All Treated Subjects in CA2099ER

MedDRA Terms (%)	Age Group (Years)			
	Nivo+Cabo (N = 320)		Sunitinib (N = 320)	
	< 65 N = 189	≥ 65 N = 131	< 65 N = 206	≥ 65 N = 114
TOTAL SUBJECTS WITH AN EVENT	188 (99.5)	131 (100.0)	203 (98.5)	114 (100.0)
SERIOUS AE - TOTAL	80 (42.3)	68 (51.9)	72 (35.0)	55 (48.2)
FATAL (DEATH)	11 (5.8)	9 (6.9)	22 (10.7)	9 (7.9)
HOSPITALIZATION/PROLONGATION	76 (40.2)	63 (48.1)	65 (31.6)	53 (46.5)
LIFE THREATENING	10 (5.3)	7 (5.3)	11 (5.3)	8 (7.0)
CANCER	17 (9.0)	7 (5.3)	11 (5.3)	10 (8.8)
DISABILITY/INCAPACITY	4 (2.1)	4 (3.1)	3 (1.5)	3 (2.6)
AE LEADING TO DISCONTINUATION	27 (14.3)	36 (27.5)	26 (12.6)	28 (24.6)
PSYCHIATRIC DISORDERS	33 (17.5)	26 (19.8)	26 (12.6)	12 (10.5)
NERVOUS SYSTEM DISORDERS	88 (46.6)	75 (57.3)	95 (46.1)	51 (44.7)
ACCIDENT AND INJURIES	25 (13.2)	18 (13.7)	14 (6.8)	6 (5.3)
CARDIAC DISORDERS	9 (4.8)	14 (10.7)	9 (4.4)	8 (7.0)
VASCULAR DISORDERS	68 (36.0)	62 (47.3)	80 (38.8)	53 (46.5)
CEREBROVASCULAR DISORDERS	5 (2.6)	1 (0.76)	6 (2.9)	2 (1.8)
INFECTIONS AND INFESTATIONS	92 (48.7)	76 (58.0)	68 (33.0)	41 (36.0)
ANTICHOLINERGIC SYNDROME	59 (31.2)	46 (35.1)	43 (20.9)	30 (26.3)
QUALITY OF LIFE DECREASED	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	24 (12.7)	26 (19.8)	19 (9.2)	12 (10.5)

CTC Version 4.0; MedDRA Version: 22.1
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: refer to Table 6.1.5.3 in CA209 9ER Final CSR[1] and Appendix RCC.424-EUSCS in CA2099ER SCS[2]

Immunogenicity

Of the 263 nivolumab ADA evaluable patients in the nivo+cabo arm, 12 patients (4.6%) were nivolumab ADA positive at baseline, and 13 patients (4.9%) were nivolumab treatment-emergent ADA positive after the start of treatment. For baseline positive patients in order to be categorized as treatment-emergent ADA positive, the titer post-treatment had to increase by 4-fold after start of treatment (Table 50).

- 1 (0.4%) patient was considered persistent positive, and 1 (0.4%) patient was neutralizing ADA positive.
- Treatment-emergent ADA titers ranged from 2 to 16. The highest titer value observed in nivolumab ADA positive patients was 16, which occurred in 1 patient on Cycle 4 Day 1.

Table 50 ADA Assessments Summary - All Nivolumab Treated Patients with Baseline and at Least One Post-Baseline Assessment

Patient ADA Status (%)	Nivolumab + Cabozantinib Nivolumab ADA N = 263
BASELINE ADA POSITIVE	12 (4.6)
ADA POSITIVE	13 (4.9)
PERSISTENT POSITIVE (PP)	1 (0.4)
NOT PP - LAST SAMPLE POSITIVE	4 (1.5)
OTHER POSITIVE	8 (3.0)
NEUTRALIZING POSITIVE	1 (0.4)

	Nivolumab + Cabozantinib
Patient ADA Status (%)	Nivolumab ADA N = 263
ADA NEGATIVE	250 (95.1)

Baseline ADA Positive: A patient with baseline ADA-positive sample;

ADA Positive: A patient with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [≥] than baseline positive titer) at any time after initiation of treatment;

Persistent Positive (PP): ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart;

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point;

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;

Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;

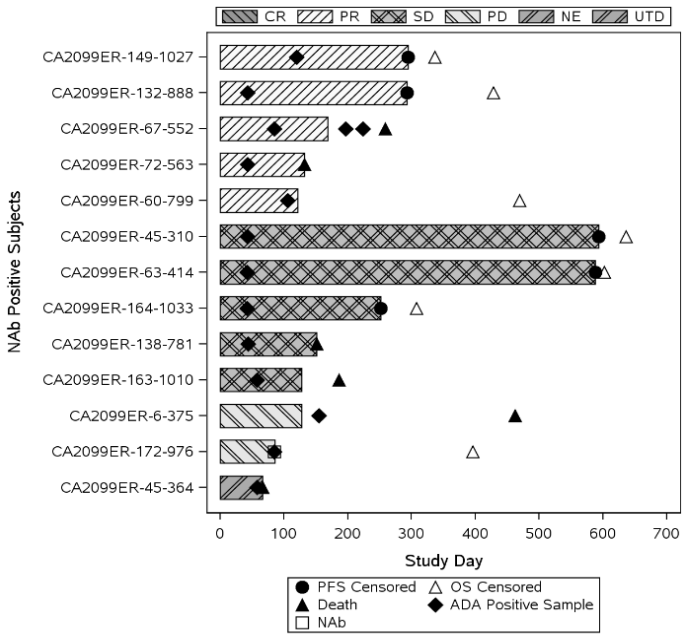
ADA Negative: A patient with no ADA-positive sample after initiation of treatment.

Post-baseline assessments are assessments reported after initiation of treatment.

Source: Table 7.10

Of the 13 nivolumab ADA positive patients, 5 patients had a BOR of PR, 5 patients had SD, 2 patients had PD (including the 1 patient that had neutralizing antibodies), and 1 patient was not evaluable due to unable to determine status (NE/UTD). The ADA titers in these patients ranged from 2 to 16; the highest titer was in a patient with NE/UTD.

Figure 25 ADA and NAb Occurrence in Relation to PFS, BOR per Investigator and OS -Treated Patients with ADA Positive Nivolumab in Combination with Cabozantinib



The effect of immunogenicity on safety was assessed in the nivo+cabo arm. Overall, the incidence of treatment-emergent nivolumab ADA was 4.9%. Of all the nivo+cabo-treated patients who were evaluable for ADA, hypersensitivity/infusion reaction select AEs were experienced by 10 (4.0%) nivolumab ADA-negative patients, and no nivolumab ADA-positive patients.

Table 51 Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All Treated Patients with ADA Positive or ADA Negative

	Nivolumab	
Preferred Term (%)	Nivolumab ADA Positive N = 13	Nivolumab ADA Negative N = 250
TOTAL PATIENTS WITH AN EVENT	0	10 (4.0)
Anaphylactic reaction	0	1 (0.4)
Bronchospasm	0	2 (0.8)
Hypersensitivity	0	4 (1.6)
Infusion related hypersensitivity reaction	0	1 (0.4)
Infusion related reaction	0	3 (1.2)

Comparison of safety data for nivo+cabo to safety data of monotherapy components

Nivolumab Monotherapy

In advanced RCC, nivolumab monotherapy safety data are available from two studies (CA209025 and study CA209669).

CA209025 - Previously Treated Advanced RCC

CA209025 was a phase 3 study of nivolumab (3 mg/kg Q2W) vs everolimus (10 mg PO QD) in patients with advanced or metastatic clear cell RCC who have received prior angiogenic therapy (n = 803 treated [406 with nivolumab and 397 with everolimus. In this study AEs were reported by the Investigator, and were based on a 18-Jun-2015 DBL, with a minimum follow-up of approximately 14 months (Table 52). All-causality AEs occurred in 97.8% of the patients in the nivolumab arm vs 97.2% of the patients in the everolimus arm. Severe all-causality AEs were observed in respectively 53.2% vs 56.4% of the patients, all-causality SAEs in respectively 47.8% vs 43.6% of the patients and deaths due to study drug toxicity respectively in 0 vs 0.5%(n=2) patients.

CA209669 - Previously Untreated Advanced RCC (unapproved indication)

CA209669 was a phase 2, investigator-sponsored research, single-arm study of nivolumab monotherapy (240 mg Q2W for 6 doses, then 360 mg Q3W for 4 doses, followed by 480 mg Q4W) in previously untreated advanced RCC (n = 123 treated with nivolumab). Safety data presented from Study CA209669 are based on a 27-Apr-2020 DBL, with a median follow-up of 15.9 months (Table 52). In CA209669, AEs were not reported according to select AE or IMAE criteria per standard nivolumab program definitions. Laboratory test abnormalities were not collected in CA209669. All-causality AEs occurred in 100% of the patients, severe all-causality AEs were observed in 56.9% of the patients, all-causality SAEs in 26.8% of the patients and deaths due to study drug toxicity was reported in 0.8% (n=1) patient.

Cabozantinib Monotherapy

In advanced RCC, cabozantinib monotherapy safety data are available the METEOR and CABOSUN studies.

METEOR - Previously Treated Advanced RCC

METEOR is a phase 3, randomized, controlled study of cabozantinib (60 mg PO QD) vs everolimus (10 mg PO QD) in patients with advanced RCC who had progressed after at least one prior VEGFR TKI therapy (n = 653 treated [331 with cabozantinib and 322 with everolimus]). Safety data from METEOR, presented in Table 52, comprise AEs as reported by Investigator, and are based on a 31 Dec-

2015 data cut-off date, with a median follow-up of 18.7 months. All-causality AEs occurred in 100% of the patients in the cabozantinib arm vs 99.7% of the patients in the everolimus arm. Severe all-causality AEs were observed in respectively 68% vs 58% of the patients, all-causality SAEs in respectively 40% vs 43% of the patients and deaths due to study drug toxicity respectively in 0.3% (n=1) vs 0.6%(n=2) of the patients.

CABOSUN - Previously Untreated Advanced RCC

CABOSUN was a phase 2, randomized study of cabozantinib (60 mg QD) vs sunitinib (50 mg PO QD [4 weeks on/ 2 weeks off]) in previously untreated advanced RCC (n = 150 treated [78 with cabozantinib and 72 with sunitinib]). Safety data presented from CABOSUN comprise AEs that are based on a 13-Jan-2017 data cut-off date, with a median follow-up of 25.0 months. ALT/AST increases were only collected as AEs in CABOSUN (laboratory test abnormalities were not collected in these studies). All-causality AEs occurred in 96% of the patients in the cabozantinib arm vs 99% of the patients in the sunitinib arm. Severe all-causality AEs were observed in respectively 68% vs 65% of the patients, all-causality SAEs in respectively 49% vs 51% of the patients and deaths due to study drug toxicity respectively in 2.6% (n=2) vs 5.6%(n=4) of the patients. See also Table 52.

Assessment of Nivo+Cabo Safety Relative to the Profiles of Monotherapy Components

In Table 52 a comparison is shown of most common all causality AEs between study CA2099ER and occurrence with monotherapies.

Table 52 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]

Hepatotoxicity

Nivolumab Monotherapy

In CA209025, all causality any Grade AEs of increased ALT and AST were reported in 6.4% (3.0% Grade 3-4) and 7.6% (2.7% Grade 3-4) of nivolumab-treated patients, respectively. Laboratory test abnormalities of increased ALT (21.7% any Grade; 3.2% Grade 3-4) and AST (32.8% any Grade; 2.8% Grade 3-4) were mostly Grade 1-2 in severity.

In CA209025, all causality hepatic select AEs were reported in 16% of nivolumab-treated patients (4.7% Grade 3-4),13 including the PTs ALT increased and AST increased (same frequencies and severities within 'select AE category' as using all-causality AE definition, above). The majority of hepatic select AEs were considered drug-related (11.3% any Grade; 2.7% Grade 3-4) by the investigator.

In CA209669, the majority of all causality AEs of increased ALT (17.1% any Grade; 2.4% Grade 3-4) and AST (15.4% any Grade; 2.4% Grade 3-4) were Grade 1-2 in severity.

Cabozantinib Monotherapy

In METEOR, all causality AEs of increased ALT (16% any Grade, 2.4% Grade 3-4) and AST (18% any Grade, 1.8% Grade 3-4; see Table 7.2.1-1) as well as laboratory test abnormalities of increased ALT (68% any Grade; 3.3% Grade 3-4) and AST (74% any Grade, 3.3% Grade 3-4) were mostly Grade 1-2 in severity.

In CABOSUN, most of the all causality AEs of increased ALT (55% any Grade, 5.1% Grade 3-4) and AST (60% any Grade, 2.6% Grade 3-4) reported were Grade 1-2.

Nivolumab + Cabozantinib

Any Grade laboratory abnormalities of increased ALT and AST were reported in 78.8% and 77.3%. When comparing the Grade 3-4 lab abnormalities of increased ALT and AST with nivolumab (3.2% ALT and 2.8% AST) and cabozantinib (3.3% ALT and 3.3% ALT) monotherapies, a higher incidence of Grade 3-4 lab abnormalities of increased ALT (9.8%) and AST (7.9%) were noted with nivo+cabo in CA2099ER.

Safety related to drug-drug interactions and other interactions

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

Any-Grade all-causality AEs leading to discontinuation of any study drugs were reported in 63 patients (19.7%) in the nivo+cabo arm, and 54 patients (16.9%) in the sunitinib arm (Table 53)

- 21 patients (6.6%) discontinued nivolumab only due to AEs
- 24 patients (7.5%) discontinued cabozantinib only due to AEs
- 18 patients (5.6%) discontinued both nivolumab and cabozantinib due to the same AE at the same time
- Sunitinib arm: 54 (16.9%) patients

There were no subjects that had AEs leading to sequential discontinuation (subject had an AE which led to discontinuation of only one drug followed by another incidence of AE which led to the discontinuation of the other drug only) as of the 30-Mar-2020 DBL.

The most common all-causality AEs leading to discontinuation of any study drugs were:

- Nivo+cabo: ALT increased (1.9%), AST increased (1.6%), proteinuria (1.6%), adrenal insufficiency (0.9%), malignant neoplasm progression (0.9%), and pneumonitis (0.9%)
- Sunitinib: malignant neoplasm progression (2.2%), proteinuria (1.9%), ALT increased (0.9%), AST increased (0.9%), blood bilirubin increased (0.9%), and PPES (0.9%)

Grade 3-4 AEs leading to discontinuation of any study drugs were reported in 34 (10.6%) patients in the nivo+cabo arm and 32 (10.0%) patients in the sunitinib arm.

Most AEs which lead to discontinuation were considered to be treatment related (Table 54).

Table 53 Adverse Events Leading to Discontinuation in ≥ 2 Patients - All Treated Patients

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: Table 6.4.2.1

Table 54 Drug-Related Adverse Events Leading to Discontinuation in ≥ 2 Patients - All Treated Patients

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: Table 6.4.2.2

Post marketing experience

Nivolumab:

- 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 European Union (EU), and for other indications as monotherapy.
- Based on pharmacovigilance activities conducted by BMS WorldWide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab.

Cabozantinib:

- Cabozantinib was first approved on 25-Apr-2016 in the US for the treatment of patients with advanced RCC and patients with HCC.
- Based on worldwide pharmacovigilance activities conducted by Exelixis Drug Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for cabozantinib.

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 and is based on the safety data from the open-label pivotal study CA2099ER which is an ongoing, phase 3, randomized, open-label, multicenter study vs. sunitinib (database lock date 30 March 2020). It should also be noted that the pivotal CE2099ER study was performed open-label, which is a potential source of bias.

Exposure

In total 320 patients received treatment with nivo+cabo. Median follow-up was 15.70 months for the nivo+cabo arm and 14.59 months for the sunitinib arm. The 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. Overall, 29.4% of patients discontinued the study (24.4% in the nivo+cabo treatment arm, 34.4% in the sunitinib arm). 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). 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.

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). 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 (refer to procedure **EMEA/H/C/004163/II/0017**).

Adverse events

Nearly all study patients reported any-Grade all-causality AEs; 99.7% in the nivo+cabo arm and 99.1% in the sunitinib arm. The most frequently reported any-Grade all-causality AEs in the nivo-carbo 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. There were no large difference between the two study arms in frequencies of all causality AEs occurring in ≥ 20% of patients with, however, the exception of more frequently reported AEs of diarrhoea (63.8% vs 47.2%), an increased ALT (28.1% vs 8.4%), an increased AST (25.3% vs 10.9%) and rash (21.6% vs 8.1%) in the nivo+cabo arm, while anaemia (26.6% vs 45.6%) occurred more frequently in the sunitinib arm.

Any-Grade treatment-related AEs occurring in ≥ 15% of patients were also reported in largely comparable frequencies between the two study arms, with the exceptions of the AEs listed in the previous paragraph plus pruritus (16.3% vs 4.1%) which occurred more frequently in the nivo+cabo arm compared to the sunitinib arm, whereas thrombocytopenia (5.9% vs 19.1%) and a decreased platelet count (5.3% vs 18.4%) occurred less frequently in the nivo+cabo arm.

Grade 3-4 all-causality AEs occurred slightly more frequently in the nivo+cabo arm (70.3%) compared to the sunitinib arm (65.3%), particularly when treatment-related AEs were considered (respectively 60.6% vs 50.6%). 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%). Differences between the two study arms were mostly observed in SOCs metabolism and nutrition disorders (22.5% vs 12.8%) and blood and lymphatic disorders (3.1% vs 12.5%), but cannot be attributed to large difference in AEs by preferred term (PT).

When AE incidence rates were exposure-adjusted, all-causality AE incidence rates (events per 100 person-years) were 1705.2 in the nivo+cabo arm and 1852.6 in the sunitinib arm. A relative increase of events was thus observed in the sunitinib arm compared to the nivo+cabo arm, since exposure was

shorter in the sunitinib arm. Nevertheless, 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.

Thus, the toxicity profile for nivo+cabo has similarities to the toxicity profile for sunitinib, mainly due to events known to be associated with TKIs or VEGF pathway inhibition. However, AEs with overlapping toxicities for nivolumab and cabozantinib such as hepatotoxicity, diarrhoea and rash are observed more frequently with nivo+cabo treatment, as are immune-related events (discussed below), while haematological toxicity is less frequently observed with nivo+cabo treatment compared to sunitinib.

No new safety concerns arise for nivo+cabo treatment compared to the established safety profile of monotherapy nivolumab and cabozantinib (60 mg QD) in RCC patients. Increases in ALT and AST (except in CABOSUN where these were solicited) and hypothyroidism appear to occur more frequently with nivo+cabo than with the both monotherapies. Diarrhoea with nivo+cabo was observed more frequent compared to nivolumab monotherapy, and rash with nivo+cabo was observed more frequent compared to cabozantinib monotherapy. These are overlapping toxicities for nivolumab and cabozantinib. The limitations of cross-trial comparison of different studies should be noted when comparing these numbers. The nivolumab SmPC has been updated with the safety profile for nivo+cabo and with warnings to reflect that higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported and liver enzymes should be monitored before initiation of and periodically throughout treatment. Dose modifications for elevated liver enzymes specify: if ALT or AST > 3 times ULN but ≤ 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, nivo and cabo should be withheld until these recover to Grades 0-1 (rechallenge with a single or both medicines may be considered); if ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both nivo and cabo should be permanently discontinued. In these situations, corticosteroid therapy may be considered. Hypothyroidism is already adequately reflected in the nivolumab SmPC.

The method for considering which ADRs to include in the tabulated list of Section 4.8 of the cabozantinib and nivolumab 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.

SAEs and deaths

The overall incidence of any-Grade all-causality SAEs was slightly higher in the nivo+cabo vs the sunitinib arm (respectively 46.3% vs 39.7%). The most frequently reported all-causality SAEs in ≥ 1% patients were diarrhoea (4.7%), malignant neoplasm progression (4.1%), pneumonitis (2.8%), pulmonary embolism (2.8%), pneumonia (2.2%) and hyponatraemia (2.2%) in the nivo+cabo arm. There were no large differences in frequencies of SAEs, except in SAEs of diarrhoea (4.7% in the nivo+cabo arm vs 0% in the sunitinib arm). All-causality SAEs resolved in 73.6% of the patients in the nivo+cabo arm and 65.4% of the patients in the sunitinib arm.

During the study less patients died in the nivo+cabo arm (20.9%) compared to the sunitinib arm (30.9%). Most deaths were attributed to disease progression (15.9% vs 23.1%). The frequency of death from drug toxicity was low in both treatment arms; in the nivo+cabo arm a single death (0.3%) patient due to small intestine perforation was considered related to the study drug by the investigator, which is a known ADR for cabozantinib. In the sunitinib arm two deaths (0.6%; patients due to respiratory distress and pneumonia/acute respiratory failure) were considered related to study drug toxicity. 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. This is somewhat unfortunate, however considering the small sample this uncertainty is not considered to influence the B/R balance. The cabozantinib SmPC already contains a warning/precautionary for serious GI perforations and fistulas (including fatal cases).

Dose modifications

In the nivo+cabo arm dose delays (83.4% for both nivo+cabo vs 51.9% for sunitinib) and dose reductions (respectively 56.3% [cabozantinib only] vs 51.6%) were more frequent compared to the sunitinib arm. Most dose delays (79.9% vs 100%) and reductions (76.3% vs 79.9%) were due to AEs. For respectively 20% and 18% of the patients the reason for dose reduction was not reported, thus it cannot be excluded that the actual number of dose reductions due to AEs is higher.

AEs leading to dose modifications (delays + reductions) were seen more often in patients in the nivo+cabo arm (83.4%) compared to the sunitinib arm (72.5%), indicating less tolerance in the nivo+cabo arm. In the nivo+cabo arm the most frequently reported all-causality AEs leading to dose delays or reductions of any study drug were diarrhoea (24.4%), PPES (19.1%), and hypertension (10.6%), ALT increased (10.0%). Any-grade all-causality AEs leading to dose delays (delays and interruptions) occurred in 78.8% of the patients in the nivo+cabo arm, versus 65.3% patients in the sunitinib arm. Any-grade all-causality AEs leading to dose reductions of cabozantinib occurred in 39.4% versus 28.1% of the patients in the sunitinib arm.

Discontinuation due to AEs

Any-grade all-causality AEs leading to discontinuation of any study drug occurred at a slightly higher rate for the nivo+cabo arm compared to the sunitinib arm; in total 19.7% of the patients discontinued any study drug due to an AE in the nivo+cabo arm (6.6% nivolumab only; 7.5% cabozantinib only; 5.6% both drugs [due to the same AE at the same time]) vs 16.9% of the patients in the sunitinib arm. There were no subjects that had AEs leading to sequential discontinuation in the nivo+cabo arm. Most of the AEs leading to discontinuation were Grade 3-4 AEs (10.6% vs 10.0%). In the nivo+cabo arm ALT increased (1.9%), AST increased (1.6%), proteinuria (1.6%), adrenal insufficiency (0.9%), malignant neoplasm progression (0.9%), and pneumonitis (0.9%) were the most frequent reasons for discontinuation.

AEs specific to nivolumab and cabozantinib

AEs with potential immune-related aetiology consistent with the mechanism of action of immunotherapies/nivolumab (select AEs (57.5% vs 42.5%), immune-mediate AEs (IMAEs; total number not provided), other AEs of special interest (OESIs; 2.5% vs 0.3%) were observed more frequently in the nivo+cabo arm compared to 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 most frequent IMAEs in the nivo+cabo arm (vs the sunitinib arm) were hypothyroidism/ thyroiditis (25.3% vs 9.7%), hepatitis (10.0% vs 2.2%), and rash (10.0% vs 0.6%). The majority of these AEs were low grade and most AEs resolved, except for endocrine AEs due to the continuing need for hormone replacement therapy. Management consisted amongst others of dose delays and immune modulating medications (the latter per definition for IMAEs). In the nivo+cabo arm 11 of the 14 OESIs (almost 80%) had resolved at the time of 30-Mar-2020 DBL, whereas three events did not resolve (acute pancreatitis, pancreatitis, and myocarditis) at the time of DBL. Information and warnings on these type of AEs and recommended management strategies are generally well reflected in the nivolumab SmPC. The MAH has stated in the nivolumab SmPC that the warnings (SmPC section 4.4) and recommended treatment modifications for these type

of AEs (SmPC section 4.2) also apply for nivolumab only when given in combination with cabozantinib, however there are separate instructions/warnings for the nivo+cabo combination with regard to liver enzyme elevations (as mentioned above).

Events to monitor (ETMs, i.e. events known to be associated with TKIs or VEGF pathway inhibition that may have serious consequences/ require surveillance) were observed at comparable rates in the nivo+cabo arm (78.1%) vs the sunitinib arm (72.8%). The majority of ETMs resolved prior to the database lock. However, considering the differences in time exposure between the treatment arms, the frequencies of ETMs 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 observed Grade ≥3 ETMs were PPES, hypertension, and venous and mixed thrombotic events. 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%). 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. According to the MAH, these events were generally successfully treated with low molecular weight heparins, and had a short time (within 10 days) to event resolution. Thrombotic events including pulmonary embolism are a commonly occurring event with cabozantinib, and are adequately reflected in the cabozantinib 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 not included in the hepatotoxicity ETM, but adequately reflected in the ADR tables as separate events of hepatitis (PTs hepatitis and autoimmune hepatitis) in the Hepatobiliary SOC, and by the ADRs increased ALT, increased AST, increased alkaline phosphatase, and increased total bilirubin in the Investigations SOC.

Laboratory findings

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 (hypocalcaemia, hypomagnesaemia, hypophosphataemia) occurred more frequently. Grade 3-4 electrolyte abnormalities were similar between the two study arms, except for Grade 3-4 hypophosphataemia (20.6% vs 6.8%) which occurred more frequently in the nivo+cabo arm. This has been adequately reflected in the nivolumab SmPC.

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). In the nivo+cabo arm, ALT or AST elevations > 3XULN, >5XULN, >10xULN and > 20XULN occurred for 26.2%, 11.0%, 3.8% and 0.6% of patients, respectively. In most patients with abnormalities > 3XULN these resolved, however for the remaining 10.8% (n=9) of patients with AST or ALT abnormalities these did not resolve; four had died due to disease progression, in four patients the adverse events eventually resolved, while nivo+cabo or nivolumab was discontinued in these patients. One patient withdrew consent. In the nivo+cabo arm five patients met Hy's law vs 6 in the sunitinib arm. In the nivo+cabo arm 4/5 patients recovered after corticosteroid treatment, dose delays or discontinuations.

As previously stated, the SmPC has been updated with information and warnings on liver function abnormalities. 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%).

Safety in special populations

When assessing patients younger and older than 65 years there are no large differences between the nivo+cabo and sunitinib arm. The subgroup of patients ≥75 years, patients appeared to have worse toxicity in the nivo+cabo arm compared to the sunitinib arm, however due to the small sample of patients ≥75 years and the non-randomized comparison (patients were not stratified according to age [categories]) a definite conclusions on the toxicity in these patients is not possible. Female patients also reported more AEs in the endocrine category than male patients for both treatment arms. There are no large differences in all-causality AEs, SAEs and AEs leading to discontinuation between subgroups with favourable risk versus intermediate/poor risk for the nivo+cabo arm.

Immunogenicity

Of the ADA-evaluable patients in the nivo+cabo arm (n=263) 13 patients (4.9%) were nivolumab treatment-emergent ADA positive after the start of treatment. One (0.4%) patient was considered persistent positive, and 1 (0.4%) patient was neutralizing ADA positive. The latter number corresponds to rates reported for nivolumab monotherapy. ADAs did not appear to have a negative impact on safety or efficacy, but the small numbers hinder definite conclusions.

Updated safety data

Updated safety data with a 10-Sep-2020 DBL indicate comparable safety data to the 30-March-2020 DBL, with the exception of 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.

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 frequent compared to nivolumab monotherapy, and rash was observed more frequent compared to cabozantinib monotherapy. This is likely due to that these are overlapping toxicities for nivolumab and cabozantinib. This 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 in terms of a slightly higher rate 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 MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 19.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 19.1 with the following content:

No changes are proposed to the list of safety concerns, pharmacovigilance plan and risk minimisations measures based on the data supporting the new indication for Opdivo.
Existing pharmacovigilance plans and risk minimisations measures remain sufficient to identify and address the risks of the medicinal product in the new indication.

Safety concerns

Summary of Safety Concerns

Important identified risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis and renal dysfunction
	Immune-related endocrinopathies
	Immune-related skin ARs
	Other immune-related ARs
	Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity
	Complications of allogeneic HSCT following nivolumab therapy in cHL
	Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06/2019 4Q2022

Risk minimisation measures

Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs	Additional risk minimization measures: Patient Alert Card	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

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:

- The general design and layout of the proposed PL have not changed compared to the tested one.
- The new proposed indication concerns the same route of administration.
- The safety profile remains similar to the currently approved indications.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is an extension of indication for Opdivo in combination with cabozantinib for the first-line treatment of adult patients with advanced renal cell carcinoma.

3.1.2. Available therapies and unmet medical need

The medicinal products and combinations of medicinal products that are currently recommended by ESMO for first-line (1L) systemic treatment in ccRCC are the following (see Figure 1 or eUpdate - ESMO RCC algorithm): pembrolizumab + axitinib, sunitinib, pazopanib, tivozanib, nivolumab + ipilimumab, and cabozantinib. All are approved by EMA.

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).

In spite of this (systemic) treatment armamentarium, both (median) progression-free survival (PFS) and OS for patients with advanced RCC are still rather limited, especially for patients in the intermediate and poor risk groups. There thus remains an unmet medical need.

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 (Figure 11): 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).

The results of all sensitivity analyses were consistent with the primary analytical method, and so were the results of the secondary analytical method of PFS per BICR (secondary definition) that is the EMA preferred analysis (Figure 12): 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 (Figure 14): 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 (Table 13). 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 (Figure 16). 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 (~5.5 months additional follow-up) were confirmative (Table 14).

3.3. Uncertainties and limitations about favourable effects

Notwithstanding the statistically significant improvement in PFS, OS, and ORR observed for nivo+cabo compared with sunitinib that were confirmed by the updated results, efficacy data in terms of OS remains overall somewhat immature. For example, 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), and a relatively low percentage of patients had received subsequent systemic anti-cancer therapy (17.3% vs 34.1%). There thus remains some uncertainty regarding an OS benefit, for example 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. Further, 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 noted 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-Sep-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.

The dose finding trial (CTEP-9681) did not explore lower initial dose levels than 40 mg of cabozantinib.

3.6. Effects Table

Table 55 Effects Table for Opdivo (nivolumab) in combination with Cabometyx (cabozantinib) for the 1L treatment of adult patients with advanced RCC (clinical data cut-off: 12-Feb-2020; database lock 30-Mar-2020)

Effect	Short description	Unit	Nivolumab + cabozantinib	Sunitinib	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression-free survival, i.e. time from randomization to first BICR-assessed tumour progression (per RECIST v1.1), or death due to any cause, whichever occurs first	Median in months (95% CI)	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)	**Strengths**: - Efficacy data derived from phase 3 RCT vs standard of care active comparator - Updated results confirmatory **Uncertainties**: - Median OS has not been reached in either of treatment arms; thus, long term benefit is uncertain. - Even updated	**2.4.2. Main study**, e.g. Figure 11 and Table 12
			Hazard ratio = 0.51 (95% CI: 0.41, 0.64) p <0.0001			
OS	Overall survival, i.e. time from randomization to	Median in months	Not reached (NA, NA)	Not reached (22.60, NA)		**2.4.2. Main study**, e.g. Figure 14

Effect	Short description	Unit	Nivolumab + cabozantinib	Sunitinib	Uncertainties / Strength of evidence	References
	death due to any cause	(98.89% CI)			results are somewhat immature regarding OS	
			Hazard ratio = 0.60 (0.40, 0.89) p = 0.0010			
ORR	Objective response rate, i.e. proportion of patients achieving a complete or partial response (per RECIST v1.1)	% (95% CI)	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)		**2.4.2. Main study**, e.g. Table 13
			Odds ratio = 3.52 (2.51, 4.95) p <0.0001			
Unfavourable Effects						
Drug-related AEs	Grade 3-4	%	60.6%	50.6%	**Strengths**: - Safety data derived from phase 3 RCT vs standard of care active comparator **Uncertainties**: - Long-term safety unknown - Safety reporting may be influenced by open-label study design - Real effect size difference uncertain due to longer treatment duration in nivo+cabo arm.	**2.5- Adverse events** Table 27
						2.5- Adverse events Table 27
Deaths	Treatment related deaths		0.3% (n=1)	0.6% (n=2)		**2.5- Deaths**
Discontinuations	Discontinuation of any study drug due to AEs		19.7%	16.9%		**2.5- Discontinuation due to AEs** Table 53

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 in the sense that the results of all sensitivity analyses and of the secondary analytical method of PFS (that is the EMA preferred analysis) were consistent with the primary analytical method. 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 at this time. There thus remains some uncertainty regarding an OS benefit, for example 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, even though based on cross-study comparisons (only).

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.

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 for Opdivo in combination with cabozantinib for the first-line treatment of adult patients with advanced RCC 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 cabozantinib for the first line treatment of advanced renal cell carcinoma for Opdivo; 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 19.1 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.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0092'