15 November 2018
EMA/902855/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

YERVOY

International non-proprietary name: ipilimumab

Procedure No. EMEA/H/C/WS1278

Note

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
ADA	anti-drug antibody (antibodies to nivolumab or ipilimumab)
ADR	adverse drug reaction
AE	adverse event
AE-DC/D	adverse events leading to death or discontinuation
ALB	albumin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUCss	area-under the steady-state concentration-time curve
BALB	baseline albumin
BBWT	baseline body weight
BIC	Bayesian information criterion
BLDH	baseline lactate dehydrogenase
BMS	Bristol-Myers Squibb
BOR	best overall response
BORR	best overall response rate
BTSIZE	baseline tumour size
BW	body weight
Cavg	time-averaged concentration
Cavg1	time-averaged concentration during the first dosing interval
Cavgss	time-averaged concentration at steady state
CR	complete response
CI	confidence interval
CL	clearance
Cmax	maximum observed concentration
Cmaxss	maximum concentration at steady-state
Cmin	trough concentration
Cminss	theoretical steady-state trough concentration obtained by the nominal (initially assigned) nivolumab dosing regimen
CMV	cytomegalovirus
CPH	cox proportional hazard
CRC	colorectal cancer
CSR	clinical study report
CTC	common terminology criteria
CTLA-4	cytotoxic T cell Lymphocyte antigen 4
CV	coefficient of variation
CV%	coefficient of variation in percentage
CXR	chest X-ray
DBL	database lock
DC	discontinuation
DOR	duration of response
DILI	drug-induced liver injury
ECOG	Eastern Cooperative Oncology Group
ECL	Electrochemilumunescence
EU	European Union
E-R	exposure-response
Emax	maximum effect

FDA	Food and Drug Administration
GC	gastric cancer
Geo.Mean	geometric mean
GEJ	gastroesophageal junction
GI	gastrointestinal
Gr. 2+ IMAE	Immune-mediated adverse events grade 2 or higher
G-CSF	granulocyte-colony stimulating factor
HR	hazard ratio
HLGT	High-level Group Term
IL	interleukin
IMAE	immune-mediated adverse event
IRRC	Independent Radiology Review Committee
ICH	International Conference on Harmonisation
I-O	immune-oncology
IV	intravenous/intravenously
IRRC	independent radiological review committee
IV	intravenous
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LLN	lower limit of normal
mAb	monoclonal antibody
MAP	Maximum a posteriori
MDSCs	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
mOS	median OS
mPFS	median PFS
MSKCC	Memorial Sloan Kettering Cancer Center
NAb	neutralizing antibody
NC	not calculated
ND	not determined
NCA	non-compartmental analysis
NSCLC	non-small cell lung carcinoma
OESI	other events of special interest
OR	objective response
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD	Progressive disease
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	partial response
Pr(OR)	probability of objective response
PS	performance status
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks

Q	inter-compartmental clearance
QC	quality control
QD	once daily
Q2W	every two weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
R^2	coefficient of determination
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RSE	relative standard error
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized Medical Dictionary for Regulatory Activities query
SQ	squamous
SOC	system organ class
T-HALF	terminal elimination half-life
Tmax	time to reach peak concentration (Cmax)
TS-W12	tumour shrinkage at week 12
TTR	time to response
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VC	volume of distribution of central compartment
VEGF	vascular endothelial growth factor
VSS	volume of distribution at steady state

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 7 November 2017 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

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 the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs were proposed to be updated. The Package Leaflet and the Risk Management Plan (version 19.0 for Yervoy and version 13.0 for Opdivo) were proposed to be updated in accordance. In addition, the Worksharing applicant (WSA) would take the opportunity to correct some typos throughout the Yervoy and Opdivo product information.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0003/2017 for Yervoy and P/0064/2014 and P/0004/2017 for Opdivo on the agreement of a paediatric investigation plan (PIP) and CW/1/2011 on the granting of a class waiver.

At the time of submission of the application, the PIP P/0003/2017 for Yervoy was completed and the PIP P/0064/2014 and P/0004/2017 for Opdivo 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 application included a critical report addressing the possible similarity with authorised orphan medicinal products. However no similarity assessment was conducted as the market exclusivity for Torisel (temsirolimus) expired on 19/11/2017 before the start of this worksharing procedure.

Scientific advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Jorge Camarero Jiménez Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	7 November 2017
Start of procedure	25 November 2017
CHMP Co-Rapporteur Assessment Report	30 January 2018
CHMP Rapporteur Assessment Report	19 January 2018
PRAC Rapporteur Assessment Report	26 January 2018
PRAC members comments	31 January 2018
PRAC Outcome	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteurs Joint Assessment Report	15 February 2018
Request for supplementary information (RSI)	22 February 2018
Submission of responses	27 March 2018
Re-start	2 April 2018
CHMP Rapporteurs Joint Assessment Report	3 May 2018
PRAC Rapporteur Assessment Report	3 May 2018
PRAC members comments	4 May 2018
Updated PRAC Rapporteur Assessment Report	8 May 2018
PRAC Outcome	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteurs Joint Assessment Report	24 May 2018
2nd Request for supplementary information (RSI)	31 May 2018
Submission of responses	26 June 2018
Re-start	27 June 2018
PRAC Rapporteur Assessment Report	2 July 2018
PRAC members comments	4 July 2018
Updated PRAC Rapporteur Assessment Report	5 July 2018
CHMP Rapporteurs Joint Assessment Report	12 July 2018
PRAC Outcome	12 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur Assessment Report	20 July 2018

Timetable	Actual dates
An Oral explanation took place	25 July 2018
Start of written procedure	2 August 2018
CHMP opinion adopted by written procedure	3 August 2018

1.3. Steps taken for the re-examination procedure

Appointed re-examination (Co-)Rapporteurs for the WS procedure:

Bjorg Bolstad Filip Jospehson

Timetable	Actual dates
Detailed grounds for the Re-examination submitted on	17 September 2018
Start of procedure	18 September 2018
Re-examination CHMP Co-Rapporteur Assessment Report	15 October 2018
Re-examination CHMP Rapporteur Assessment Report	15 october 2018
PRAC Rapporteur Assessment Report	19 October 2018
CHMP and PRAC members comments	24 October 2018
PRAC endorsed relevant sections of the assessment report	31 October 2018
Updated Joint Assessment Report	2 November 2018
SAG experts meeting to address questions raised by the CHMP	8 November 2018
An Oral explanation on the detailed grounds for re-examination took place on	13 November 2018
CHMP Opinion	15 November 2018
CHMP assessment report adopted via written procedure	7 December 2018

2. Scientific discussion

2.1. Introduction

This application concerns an extension of indication to include the first-line combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

OPDIVO (nivolumab)

Nivolumab, a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), binds to the programmed death-1 (PD-1) receptor and blocks the interaction with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (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. Interaction between the PD-1 receptor and PD-L1/ PD-L2 results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab blocks the binding of the PD-1 receptor to PD-L1/PD-L2 and potentiates T-cell responses, including anti-tumour responses. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth. Nivolumab is currently approved as OPDIVO® in the United States (US), European Union (EU), Japan, and several other countries. Initial and subsequent approvals have resulted in indications for advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, classical Hodgkin's lymphoma (cHL), and hepatocellular carcinoma (HCC) (US only).

YERVOY (ipilimumab)

Ipilimumab, a fully human monoclonal antibody (IgG1κ), is a cytotoxic T-lymphocyte antigen 4 CTLA-4 immune checkpoint inhibitor. CTLA-4 is a regulator of T-cell activity. Ipilimumab blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoural T-effector/ T-regulatory cell ratio which drives tumour cell death. YERVOY® is indicated for the treatment of unresectable or metastatic melanoma and, in the US only, for adjuvant treatment after complete resection of high-risk stage III melanoma.

Combination therapy with nivolumab + ipilimumab

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity. The combination of nivolumab + ipilimumab is approved for the treatment of unresectable or metastatic melanoma.

Renal cell carcinoma

Renal cell carcinoma overall accounts for 2% of all adult malignancies. Worldwide, about 270,000 new cases are diagnosed and about 116,000 patients die each year. Metastatic disease is found in ~ 30% of subjects at diagnosis, and close to 90-95% is of clear-cell histology. A couple of risk models have been developed to predict the prognosis of patients with mRRC, for example the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (Noe, A. *et al.* World J Uro. 2016;34:1067-72). The IMDC developed a prognostic model that classifies advanced RCC based on six risk factors: Karnofsky Performance Status (KPS)<80%, <1 year from diagnosis to treatment, haemoglobin concentration <lower limit of normal, Calcium concentration > upper limit of normal, neutrophil count >upper limit of normal, platelet count > upper limit of normal (Heng *et al.*Lancet Oncology. 2013;14:141-48). Based on prognostic factors, three risk groups are identified: favourable risk (0 factors), intermediate risk (1-2 factors) or poor-risk (3-6 factors).

The median OS is estimated to be around 7.8 months in the poor-risk group, 22.5 months in the intermediate risk group and 43.2 months in the favourable risk group.

Standard treatments for previously untreated advanced RCC

Cytokine therapy, such as IL-2 and IFN, can achieve objective responses in 5% to 20% of patients, including durable complete responses in some patients, but these treatments are associated with significant toxicity. Currently, available targeted therapies for previously untreated advanced RCC can be divided into two classes, namely anti-angiogenic agents and mTOR inhibitors. The anti-angiogenic agents are sorafenib, sunitinib, pazopanib, axitinib, tivozanib (VEGF-binding tyrosine kinase inhibitors), and bevacizumab (VEGF-binding monoclonal antibody). Everolimus and temsirolimus target the mTOR pathway.

Table 1 provides a summary of available agents in the US and EU for previously untreated RCC and Table 2 shows the results of clinical trials of approved agents for the treatment of first-line advanced RCC.

Table 1 Preferred Agents Approved in US and EU for the Treatment of Previously Untreated Advanced Renal Cell Carcinoma

Agent	Date of Approval	Indication
Aldesleukin	US approval: May-1992	Treatment of adults with metastatic RCC
Sorafenib	US approval: Dec-2005	Treatment of patients with advanced RCC
	EU approval: Jul-2006	Treatment of patients with advanced RCC who have failed prior interferon-alpha or IL-2 based therapy or are considered unsuitable for such therapy
Sunitinib	US approval: Jan-2006	Treatment of advanced RCC
	EU approval:	
	Jul-2006 (initial)	Treatment of advanced and/or metastatic RCC after failure of interferon alfa or interleukin-2 therapy
	Oct-2006 (expanded)	Treatment of advanced and/or metastatic RCC
Temsirolimus	US approval: May-2007	Treatment of advanced RCC
	EU approval: Nov-2011	Treatment of adult patients with advanced RCC who have at least 3 of 6 prognostic risk factors
Bevacizumab	US approval: Jul-2009	Treatment of metastatic RCC in combination with interferon alfa
	EU approval: Dec-2007	Treatment of adult patients with advanced and/or metastatic RCC in combination with interferon alfa-2a
Pazopanib	US approval: Oct-2009	Treatment of patients with advanced RCC
	EU approval: Jun-2010	First-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease
Tivozanib	EU approval: Aug-2017	First-line treatment of adult patients with advanced RCC and for patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after 1 prior treatment with cytokine therapy for advanced RCC

Abbreviations: EU: European Union; RCC: renal cell carcinoma; US: United States.
Source: current approved product labels

According to the 2016 ESMO guideline, sunitinib, bevacizumab plus interferon alpha, and pazopanib are all standard treatment options for favourable-risk and intermediate-risk patients, but sunitinib is an alternative to temsirolimus for the treatment of poor-risk patients in first-line RCC. According to NCCN guidelines, sunitinib, temsirolimus (poor-risk only), bevacizumab plus interferon alpha, and pazopanib are category 1 recommendations for first-line therapy of RCC.

Table 2 Results of Clinical Trials of Approved Agents for the Treatment of First-line Advanced RCC

Agents[a]	Comparator	Study year for OS results	ORR (%)	Median PFS (months)	Median OS (months)
Tivozanib[3]	sorafenib	2017	11.9 vs 9.1	12.7 vs 9.1[b]	28.2 vs 30.8
Pazopanib[4,5]	Placebo	2013	33 vs 4[b]	11.1 vs 2.8[c]	22.9 vs 20.5
Bev + IFN-α [6,7]	IFN-α	2010	31 vs 13[b]	10.2 vs 5.4[c]	23.3 vs 21.3
Sorafenib[8]	IFN-α	2009	9.8 vs 1.8[b]	5.5 vs 2.8[c]	Not reported
Sunitinib[9]	IFN-α	2009	47 vs 12[b]	11 vs 5[c]	26.4 vs 21.8
Temsirolimus[10,d]	IFN-α	2007	8.6 vs 4.8	5.5 vs 3.1[c]	10.9 vs 7.3[b]

[a] None of the trials reported results specifically in intermediate and poor-risk patients.

[b] No prior treatment for 'metastatic RCC subgroup.' The study included patients who had all undergone prior nephrectomy, and who had received either no prior therapy or no more than one prior systemic therapy in the metastatic setting (immunotherapy/chemotherapy); prior treatment with VEGF or mechanistic target of rapamycin (mTOR) targeted therapy was not allowed.

[c] Statistically significant. Based on independent radiology review.

[d] Poor prognosis patients only, defined as at least 3 of the following 6 risk factors: serum LDH > 1.5 X ULN; hemoglobin < LLN; corrected serum calcium > 10 mg/dL; time from initial diagnosis to randomization < 1 year; Karnofsky performance status 60% or 70%; metastases in multiple organs.

Nivolumab in advanced second line renal cell carcinoma

Study CA209025 was the registrational Phase 3 study conducted in advanced RCC subjects previously treated with anti-angiogenic therapy. Nivolumab monotherapy demonstrated statistically significant and superior OS compared with everolimus (HR: 0.73 [98.52% CI: 0.57, 0.93]; stratified log-rank test p-value = 0.0018). Median OS was 25.00 months (95% CI: 21.75, NA) in the nivolumab group and 19.55 months (95% CI: 17.64, 23.06) in the everolimus group.

Ipilimumab in RCC

Study MDX010-11 was a Phase 2 study of ipilimumab monotherapy in metastatic RCC. A total of 61 subjects received a single dose of ipilimumab 3 mg/kg followed by either 1 mg/kg (21 subjects; 3-to-1 mg/kg group) or 3 mg/kg (40 subjects; 3-to-3 mg/kg group) Q3W. All subjects were treated IV Q3W with 1 of 2 dosing regimens in sequential cohorts: in Cohort A, IL-2 experienced subjects received a loading dose of 3 mg/kg ipilimumab with all subsequent doses of ipilimumab given at 1 mg/kg; and in Cohort B, subjects received all doses of ipilimumab at 3 mg/kg only.
Among the 21 subjects in Cohort A, 1 (5%) subject experienced PR (partial response) to ipilimumab treatment with response duration lasting 18 months. 5 of 40 (12.5%) subjects in Cohort B achieved a PR with response durations of 7, 8, 12, 17, and 21 months; of these, 3 (25%) were treatment-naive and experienced the longest response durations (12, 17, and 21 months). In Cohort B, 25 subjects (63%) had Grade 3/4 AEs, including 6 subjects (15%) with Grade 4 AEs. Seventeen subjects (43%) had AEs that led to treatment discontinuation. Four subjects in Cohort B reported Grade ≥ 3 colitis leading to bowel perforation or colectomy, ultimately resulting in death in 2 subjects. Based on these safety results, development of ipilimumab monotherapy for the treatment of advanced RCC was stopped.

Nivolumab + ipilimumab in RCC

Treatment with a combination of nivolumab + ipilimumab, recognising the potential for incremental toxicity associated with the addition of ipilimumab, was considered by the applicant for several reasons. The non-redundant and complementary pathways of PD-1 and CTLA-4 inhibitors suggest the potential for synergy when used in combination. This is consistent with preclinical data from in vitro studies and syngeneic mouse models which indicate that the combination of PD-1 and CTLA-4 receptor blockade may have synergistic anti-tumour activity. In advanced melanoma, nivolumab in combination with ipilimumab resulted in an improved PFS and OS compared to ipilimumab monotherapy, and a numerically but not statistically significantly longer OS when compared to nivolumab monotherapy (HR 0.85, 95% CI, 0.68 to 1.07) (Wolchok, J.D. *et al.* N Engl J Med. 2017;377:1345-56).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The applicant claimed that the clinical trials were performed in accordance with GCP.

The MAH has provided a statement that clinical trials conducted outside the European community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Two studies were submitted to support this new indication, one phase III trial (CA209214) and one supportive phase I trial (see table below).

- **Tabular overview of clinical studies**

Study Number	Primary Objectives Reported in CSR	Study Design	Randomization Dosage, Route, and Duration of Treatment	No. of Treated Subjects	Subject Population	Study Status
CA209214	OS; ORR, and PFS based on IRRC assessments	Phase 3 randomized, open-label	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks OR Sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off, every cycle	1082 (nivolumab + ipilimumab: 547, sunitinib: 535)	Favorable, intermediate, and poor-risk subjects with previously untreated advanced RCC	Completed
CA209016	Safety, maximum tolerated dose, recommended Phase 2 dose	Phase 1 open-label	Nivolumab 2 mg/kg or 5 mg/kg + sunitinib (Arm S) Nivolumab 2 mg/kg + pazopanib (Arm P) Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (Arm I-1) Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (Arm I-3) Nivolumab 3 mg/kg + ipilimumab 3 mg/kg (Arm IN-3)	153 (Arm S: 33, Arm P: 20, Arm I-1: 47, Arm I-3: 47, Arm IN-3: 6)	Subjects with advanced RCC	Ongoing

Abbreviations: CSR = clinical study report; IRRC = independent radiology review committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma

2.3.2. Pharmacokinetics

For this application, the clinical pharmacology program of nivolumab in combination with ipilimumab was based on data from two studies: one phase 1 study CA209016 in prior treated and treatment-naïve subjects with metastatic Renal Cell Carcinoma (mRCC) to evaluate nivolumab in combination with ipilimumab, and a phase 3, randomised, open-label study of nivolumab combined with ipilimumab versus sunitinib in subjects with previously untreated advanced or mRCC (study CA209214).

Population PK (popPK) of the nivolumab+ipilimumab combination was performed by combining data from these studies with data from selected nivolumab and ipilimumab studies, which supported previous monotherapy and combination therapy submissions of nivolumab and ipilimumab. The nivolumab and ipilimumab exposures determined by popPK analyses were used to characterise the E-R relationships of efficacy and safety. The immunogenicity of nivolumab and ipilimumab was also assessed in each of the above studies.

Pharmacokinetic characteristics of nivolumab and ipilimumab as previously described by a time-independent clearance (CL) model for their respective melanoma monotherapy MAAs is summarised in Table 3. Pharmacokinetics of nivolumab was similar in subjects with melanoma as with mRCC.

Table 3 Summary of pharmacokinetic parameters for nivolumab and ipilimumab monotherapies 3 mg/kg.

	Nivolumab	Ipilimumab
Cl (ml/h)	9.5 (49.7%)	15.3 (38.5%)
Vss (L)	8.0 (30.4%)	7.2 (10.5%)
$T_{1/2}$ (days)	27 (101%)	15 (30.6%)
$C_{trough,ss}$ (µg/ml)	66 (26%)	21.8 (51%)
Cmax,ss (µg/ml)	129 (84%)	82
Cave,ss (µg/ml)	84 (28%)	36

Combination therapy in RCC, nivolumab and ipilimumab pharmacokinetics

Analytical methods

Bioanalytical methods used for quantifying nivolumab serum concentrations in the development program were cross-validated and evaluated for interference with ipilimumab, hence allowed merging of the exposure data for popPK analysis.

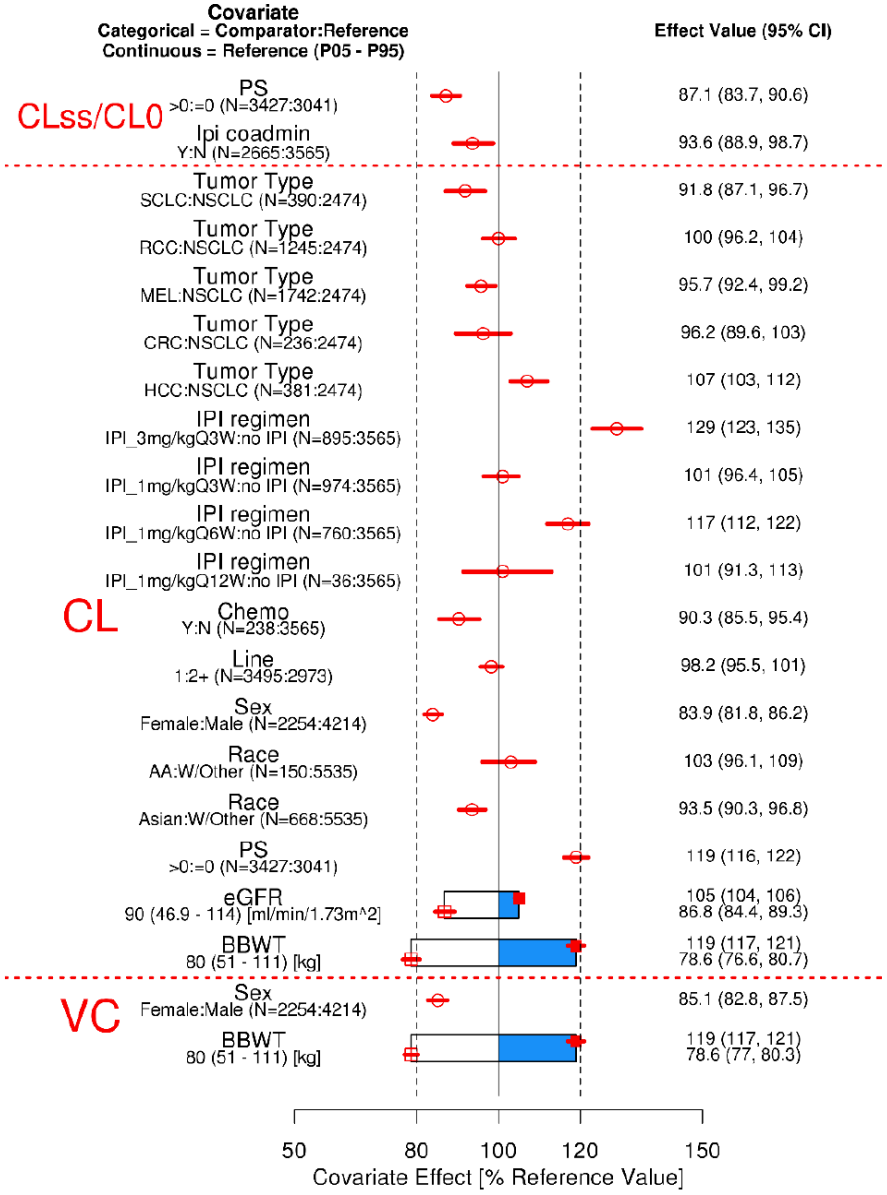
Nivolumab PopPK analyses

For the current analyses, the nivolumab popPK analysis dataset included 32843 nivolumab concentration values from 6468 subjects with melanoma, NSCLC, SCLC, CRC, HCC or mRCC who received nivolumab monotherapy or combination therapy (with ipilimumab or chemotherapy). The covariates assessed included administration with ipilimumab 3 mg/kg (Q3W) or 1 mg/kg (Q3W, Q6W, or Q12W), sex, race, baseline body weight (BBWT), baseline eGFR, baseline PS, and tumour type on nivolumab clearance; and sex and BBWT on Volume of distribution. The predictive performance of the full popPK model was determined using prediction corrected visual predictive check (pcVPC) with stratification by the selected nivolumab dosing regimen in different solid tumours. The popPK model was adequately re-evaluated.

Nivolumab pharmacokinetics was described by a linear 2-compartment model with time-varying clearance, such that nivolumab clearance decreases by ~33% at steady-state compared to initial clearance. Compared to nivolumab therapy, the clearance of nivolumab administered with ipilimumab increased somewhat: 1 mg/kg Q3W (the proposed regimen for metastatic mRCC subjects) or Q12W was not different than that of nivolumab monotherapy, whereas administration with ipilimumab 1 mg/kg Q6W resulted in a 17% increase in nivolumab clearance, and ipilimumab 3 mg/kg Q3W resulted in a 29% increase in nivolumab clearance (compared to monotherapy). Nivolumab clearance was higher in subjects with higher baseline body weight and eGFR, and lower in female subjects, but the magnitude of the differences was not considered to be clinically relevant. Sensitivity analyses found that nivolumab clearance was higher in subjects with higher baseline LDH (up to 44%) and with lower baseline albumin (< 20%), and higher (~20%) in the presence of nivolumab anti-drug antibody (ADA). Nivolumab volume of distribution was higher in subjects with higher baseline body weight. Sex, ethnicity, PS, and eGFR did not have clinically relevant effect on nivolumab clearance; sex did not have a clinically relevant effect on nivolumab volume of distribution.

Graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters of clearance and volume of distribution are presented in Figure 1.

Figure 1 Covariate Effects on Nivolumab PK Model Parameters (Full Nivolumab popPK Model)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/cov-eff-plot-full.r
Source: Analysis-Directory/R/plots/k-full-3-ppk-cov-eff-plot.png
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.

The individual parameter estimates for nivolumab 3 mg/kg in combination with 1 mg/kg ipilimumab obtained from the full popPK model and the exposure estimates are summarized in Table 4 and Table 5. Keeping in mind the time-dependent and time-independent clearance models, clearance, volume of distribution at steady-state and terminal elimination half-life are similar to those determined previously for nivolumab monotherapy (compare with Table 3). The steady-state exposure estimates for nivolmab in subject with RCC in combination with ipilimumab were slightly higher than estimated for nivolumab monotherapy (compare with Table 3), but the variability in the estimations is very high for the combination (52-244%, Table 5). This was caused by a single outlier, for which the

dose was recorded 1 mg nivolumab rather than the nominal dose amount of 187 mg. Without the single outlier (Table 5 lower part), the intersubject variability was in line with previous data.

Table 4 Summary Statistics of Nivolumab Parameters for Nivo: 3 mg/kg Q3W, Ipi: 1 mg/kg Q3W x 4 followed by Nivolumab Monotherapy in Subjects with mRCC

Parameters	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CL0 [mL/h]	497	11.2	10.4	10.5(0.185,40.1)	4.27	38.3
CLSS [mL/h]	497	7.86	7.37	7.32(0.436,28.6)	3.08	39.2
VC [L]	497	4.05	3.92	3.99(0.0275,9.53)	0.944	23.3
VSS [L]	497	6.7	6.55	6.65(0.112,12.8)	1.23	18.4
PEMAX[%]	497	71.8	70.5	70.2(34.7,236)	15.6	21.7
T-HALFα [h]	497	29.6	29.4	29.8(3.05,39.4)	3.24	10.9
T-HALFα-SS [h]	497	30.1	29.9	30.3(2.95,40.3)	3.37	11.2
T-HALFβ -SS[d]	497	19.6	19.1	19.6(5.25,35.3)	4.51	22.9
T-HALFβ [d]	497	27.6	26.6	27.8(7.54,50.5)	6.86	24.9

Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/parameter-summary.r
Source: Analysis-Directory/R/plots/ para.regN3I1.rcc.csv
VSS was calculated using formula: VSS=VC+VP.
PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.

Table 5 Summary Statistics of Individual Measures of Nivolumab Exposures with Nivo: 3 mg/kg Q3W, Ipi: 1 mg/kg Q3W x 4 doses followed by Nivolumab Monotherapy in Subjects with mRCC. Lower part of the table without single outlier.

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	497	17.2	15.3	15.7(1.78,701)	31.1	180
CMAX1	497	75.8	62	62.2(27.7,6230)	277	366
CAVG1	497	28.2	25.7	25.9(9.47,1130)	49.8	176
CMINSS	497	83.6	76.7	78.7(12.5,785)	43.8	52.4
CMAXSS	497	162	140	139(52.6,8770)	389	241
CAVGSS	497	105	96.9	97.6(25,1640)	76.4	72.9

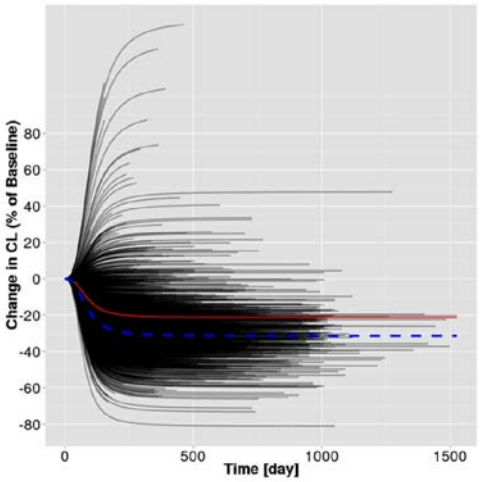
Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/process-nm-output.r
Source: Analysis-Directory/R/plots/ expo.regN3I1.rcc.csv

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	496	15.8	15.1	15.7(1.78,32.9)	4.46	28.2
CMAX1	496	63.4	61.4	62.2(27.7,303)	20.8	32.8
CAVG1	496	26	25.5	25.9(9.47,46.4)	5.32	20.5
CMINSS	496	82.2	76.3	78.7(12.5,192)	30.5	37.1
CMAXSS	496	144	139	139(52.6,352)	42.1	29.1
CAVGSS	496	102	96.4	97.5(25,222)	33.2	32.6

Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/process-nm-output-new.r
Source: Analysis-Directory/R/export/new.expo.regN3I1.rcc.csv

Figure 2 demonstrates the change in nivolumab clearance over time. The maximal model predicted decrease in clearance is ~21% in subjects with PS of 0, and ~31% in subjects with PS > 0. The time for half maximal reduction is ~92 days (2200 hours). The variability around Emax predicted by the model is ~29%. The maximal change in clearance (Emax) was similar across dose regimens and tumour types.

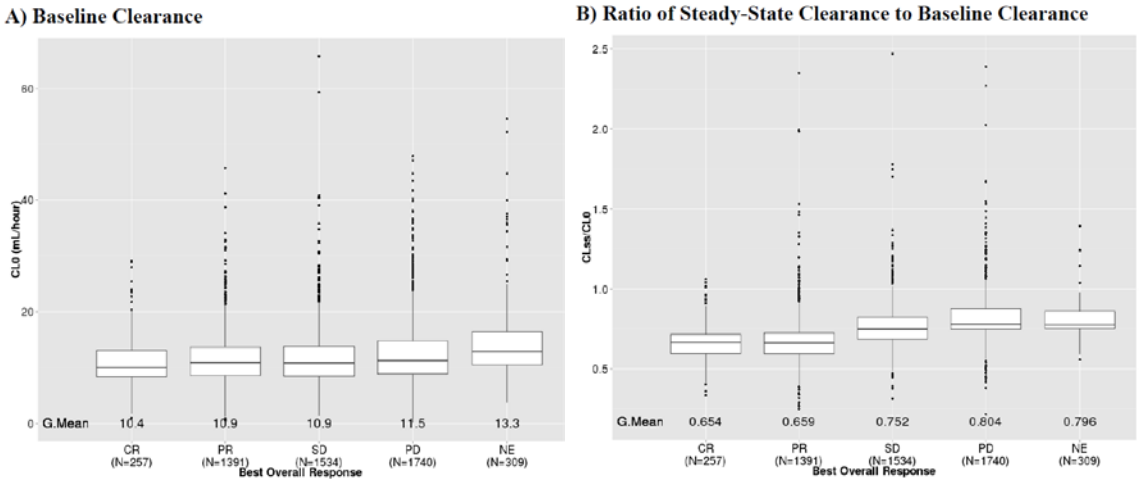
Figure 2 Model-Estimated Change in Nivolumab Clearance versus Time from the Final Model



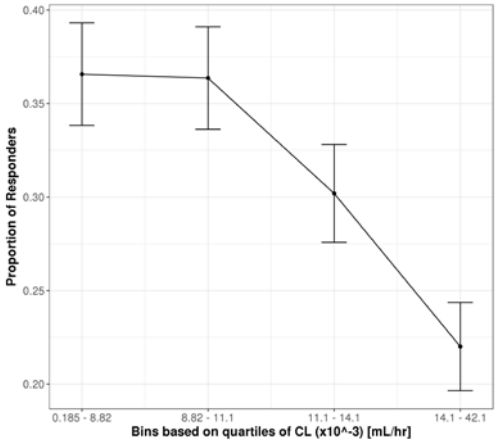
Note: % change in CL was calculated using formula below:
%Difference in CL = 100 * ((CLt-CLt=0)/CLt=0)
Note: The red line represents the CL-Time profile for a typical subject with PS = 0, the blue dashed line represents the CL-Time profile for a typical subject with PS > 0.
Analysis -Directory: /global/pkms/data/CA/209/C20/prd/nivoppk-combo2016/final/
R-Program Source: Analysis-Directory/R/scripts/plot-cl-time.r
Source: Analysis-Directory/R/plots/changeCL-vs-time-oppk.png

Relation between nivolumab clearance and best overall response is shown in Figure 3. Mean baseline clearance of nivolumab was lowest in subjects with complete remission (CR), however, there is a full overlap in clearance between subjects with complete remission and other responses. Nivolumab clearance decreased more in subjects with a complete or partial remission (PR) than subjects with Stable Disease, and clearance decreased less in subjects with progressive disease (PD) than subjects with stable disease (SD).

Figure 3 Distribution of Nivolumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance by Best Overall Response



C) Proportion of responders in RCC subjects across studies included in E-R dataset with respect to nivolumab baseline clearance



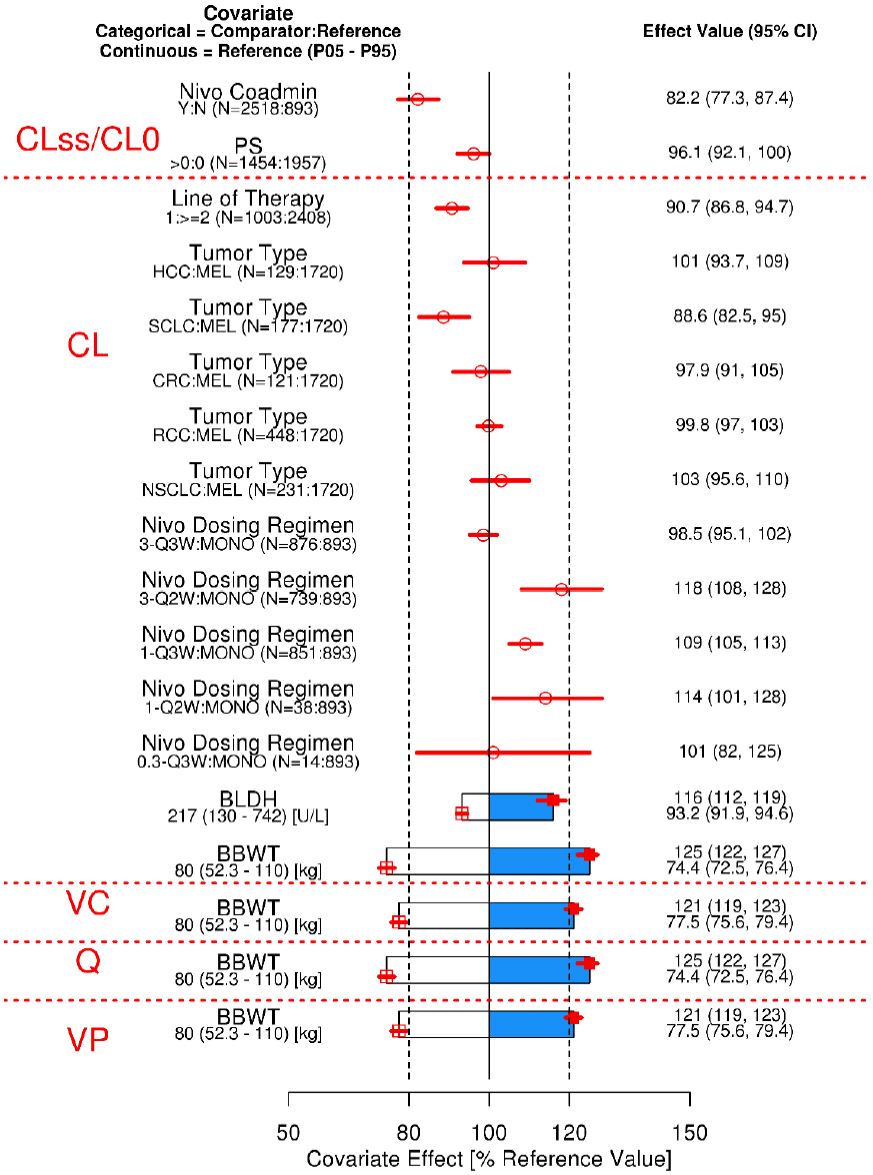
Ipilimumab popPK analyses

The current ipilimumab integrated popPK analysis used data from 3411 subjects from 16 studies conducted in subjects with solid tumours, specifically, melanoma, NSCLC, SCLC, CRC, HCC, and mRCC who received ipilimumab either as monotherapy or in combination with nivolumab. The covariates assessed included administration with nivolumab (various regimens), baseline body weight, baseline LDH, line of therapy, and tumour type on ipilimumab clearance, and baseline body weight on ipilimumab volume of distribution.

The pharmacokinetics of ipilimumab was described by a linear 2-compartment model with time-varying clearance, such that ipilimumab clearance decreases by ~22% over time when administered with nivolumab. Nivolumab 3 mg/kg Q2W, 1 mg/kg Q2W, and 1 mg/kg Q3W had a statistically significant effect on ipilimumab clearance increasing by ~18% (95% CI 8%-28%), 14% (95% CI 1%-28%), and 9% (95% CI 5%-13%); however, the magnitude of these effects were < 20% and as such not considered clinically relevant. Nivolumab 3 mg/kg Q3W (the proposed regimen for mRCC) did not have a significant effect on ipilimumab clearance. The magnitude of the effect of baseline body weight on clearance and volume of distribution was outside the ± 20% boundaries, which is consistent with results from the previous analysis describing ipilimumab monotherapy pharmacokinetics, and thus baseline body weight was found to be a statistically significant covariate. The magnitude of the effect of baseline LDH was statistically significant (95% CI of estimated effect does not include 0); however, the magnitude of the effect was <20%, which is unlikely to be clinically relevant. Additionally, ipilimumab clearance was significantly lower (-9.3%; 95 CI -13.2% to -5.3%) in subjects who received first-line treatment compared to second-line treatment. There was no statistically significant difference in ipilimumab clearance in mRCC subjects compared to that in melanoma subjects. Sensitivity analyses found that ipilimumab clearance was higher in subjects with larger baseline tumour size and with lower baseline ALB, however, the magnitude of these differences was not considered to be clinically relevant. Ipilimumab clearance was not significantly different in the presence of anti-ipilimumab ADA.

Graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters of clearance and volume of distribution are presented in Figure 4.

Figure 4 Covariate Effects on Ipilimumab PK Model Parameters (Full Ipilimumab Population Pharmacokinetic Model)



Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final

PsN Program Source: Analysis Directory/psn/run4_5.dir3/NM_run1/sdtab4_1

Program Source: Analysis Directory/R/scripts/coveff-plot-full_nregi.r

Figure Source: Analysis Directory/R/plots/full-nivoregi-ppk-coveff-plot-new.png

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 with melanoma as tumor type, receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: Covariate effects on CL apply to both CL0 and CLss.

The individual parameter estimates for ipilimumab 1 mg/kg in combination with 3 mg/kg nivolumab obtained from the full popPK model and the exposure estimates are summarized in Table 6 and Table 7. The estimated pharmacokinetic parameters are similar to those determined previously for 3 mg/kg ipilimumab monotherapy (compare with Table 3).

Table 6 Summary Statistics of Individual Measures of Ipilimumab Parameters in Nivolumab Combination Therapy (Nivo: 3 mg/kg Q3W, Ipi: 1 mg/kg Q3W x 4 Doses) in Subjects with Renal Cell Carcinoma

Parameters	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CL0 [mL/h]	448	13.6	12.9	13(3.88,31)	4.4	32.3
CLSS [mL/h]	448	10.4	9.9	9.99(3,23.8)	3.38	32.4
VC [L]	448	4.23	4.09	4.12(1.21,10.8)	1.11	26.3
VSS [L]	448	7.46	7.35	7.37(4.16,14.4)	1.35	18
PEMAX[%]	448	76.7	76.7	76.6(67.3,85.3)	1.54	2
T-HALFα [h]	448	40.2	40	40(14.9,56.5)	4.57	11.3
T-HALFα-SS [h]	448	41.2	40.9	40.9(15.7,57.2)	4.57	11.1
T-HALFβ -SS[d]	448	18.6	18.1	18(9.59,47.8)	5	26.8
T-HALFβ [d]	448	23.8	23.1	22.9(11.8,61.5)	6.53	27.4

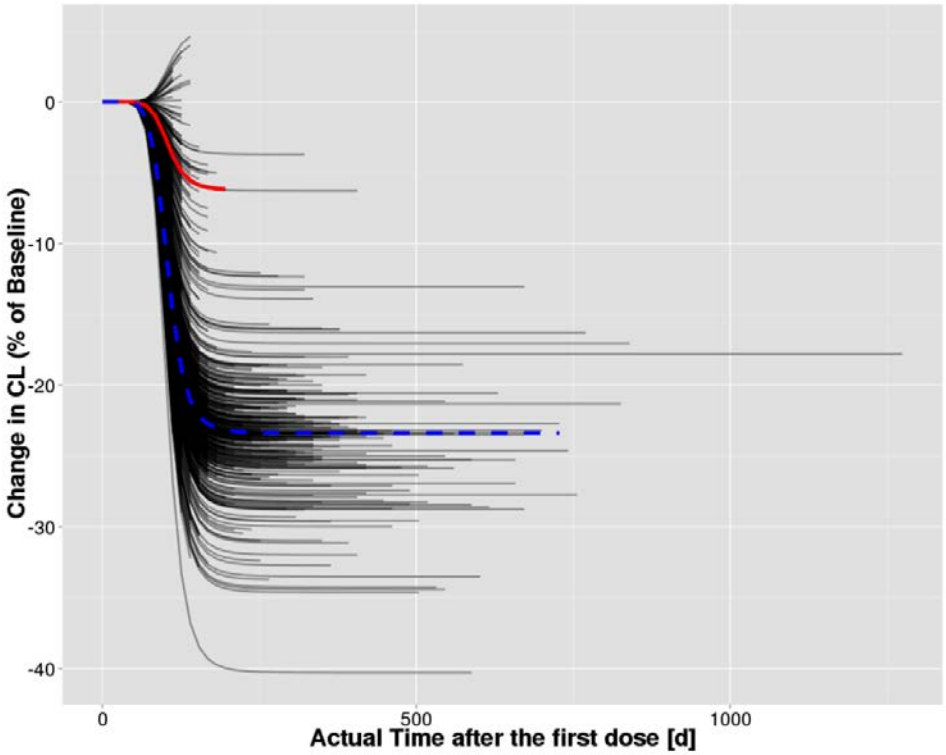
Table 7 Summary Statistics of Individual Measures of Ipilimumab Exposures in Combination Therapy (Nivo: 3 mg/kg Q3W, Ipi: 1 mg/kg Q3W x 4 Doses) in Subjects with Renal Cell Carcinoma (study CA209214)

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	448	4.1	3.93	3.96(1.49,9.32)	1.22	29.6
CMAX1	448	20.4	19.7	20(8.35,83.4)	5.75	28.2
CAVG1	448	7.5	7.35	7.41(3.98,12.8)	1.51	20.1
CMIN4	448	8.57	7.94	7.91(2.36,27.7)	3.65	42.6
CMAX4	448	28	27.1	27.5(12.3,88.6)	7.58	27.1
CAVG4	448	13.5	13	12.9(6.12,34.1)	4.17	30.9

Source: Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final/
Program Source: Analysis Directory/R/scripts/exposure-summary.R
Source: Analysis Directory/R/export/expo.ipi1.nivo3_rcc.csv

Figure 5 demonstrates the overall change in ipilimumab clearance over time. The maximal model predicted decrease in clearance was ~5% and 22% for ipilimumab monotherapy and ipilimumab in combination in nivolumab respectively. The time to half maximal reduction was ~106 days (2550 hours). The variability around Emax predicted by the model is ~38.5%. The maximal change in clearance (Emax) is similar across dose regimens and tumour types.

Figure 5 Model Estimated Change in Ipilimumab Clearance versus Time from the Final Model.



The red line and blue dashed line are typical change in clearance over time in ipilimumab monotherapy and in combination with nivolumab, respectively.

2.3.3. Pharmacodynamics

Mechanism of action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation.

PD-L1 has high affinity for PD-1 but can also bind to CD80 on T-cells and CD80 expression might contribute to PD-L1-induced inactivation of CD8+ T-cells (Rollins 2017). Combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) may thus result in enhanced T-cell function that is greater than the effects of either antibody alone. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity supporting the rationale for the combination of both products.

Primary and secondary pharmacology

Dose selection

The dose of nivolumab 3 mg/kg and ipilimumab 1 mg/kg for treatment of first line RCC was based on results from study CA209016, which included both prior treated and treatment-naïve subjects with mRCC. The study is described in detail in the dose response section 4.4.1. The decision was based on anti-tumour activity and safety data. Response rate in 1 mg/kg nivolumab + 3 mg/kg ipilimumab (cohort I-3) and 3 mg/kg nivolumab + 1 mg/kg ipilimumab (cohort I-1) was comparable 40.4% (see Table 8 and Table 9), but the safety profile of 3 mg/kg nivolumab + 1 mg/kg ipilimumab appeared to be more favourable: less subjects discontinued the study due to AEs and a lower incidence of Grade 3-4 drug-related AEs in the 3 mg/kg nivolumab + 1 mg/kg ipilimumab (see Table 8 and Table 10 in dose response section 4.4.1). Treatment with 3 mg/kg nivolumab and 3 mg/kg ipilimumab in Cohort IN-3 resulted in 3 of 6 subjects experiencing dose-limiting toxicities that exceeded the MTD.

Table 8 Summary of efficacy and safety results of dose finding study CA209016

treatment	Subject (N)	Overall response rate	Drug-related AEs grade 3-4	Drug related SAE grade 3-4	Drug-related AEs leading to discontinuation
Nivolumab 3 mg/kg + ipililumab 1 mg/kg	47	40.4%	38.3%	19.1%	10.6%
Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	47	40.4%	61.7%	34%	27.7%
Nivolumab 3 mg/kg + ipilimumab 3 mg/kg	6	0%	83.3%	50%	33.3%

2.3.1. Exposure-effect analyses

The exposure-response analyses performed by the applicant included data from studies with advanced or metastatic renal cell carcinoma (RCC). Phase I CA209016 study included both previously treated and previously untreated subjects with mRCC, and a Phase III CA209214 study included previously untreated advanced/metastatic RCC subjects. Subjects in these two studies were treated with nivolumab in combination with ipilimumab. In addition to study CA209214 and CA209016, other phase I/III studies, nivolumab monotherapy evaluated in metastatic RCC (CA209003, CA209009, CA209010, and CA209025), were also included as these dataset included information on nivolumab monotherapy at different dose levels (0.3–10 mg/kg).

The relationship between nivolumab exposure and objective response (OR) was characterised using a logistic regression model that incorporated the effects of covariates that may modulate the exposure-response relationship. The exposure-OR analysis characterised the probability of achieving an OR of investigator assessed complete or partial tumour response as defined by RECIST criteria, termed Pr(OR), as a function of nivolumab exposure and selected covariates that may modulate the exposure-response. Ipilimumab concentrations were not available for all studies, and therefore, ipilimumab dose was used as categorical predictor in exposure-response efficacy analyses.

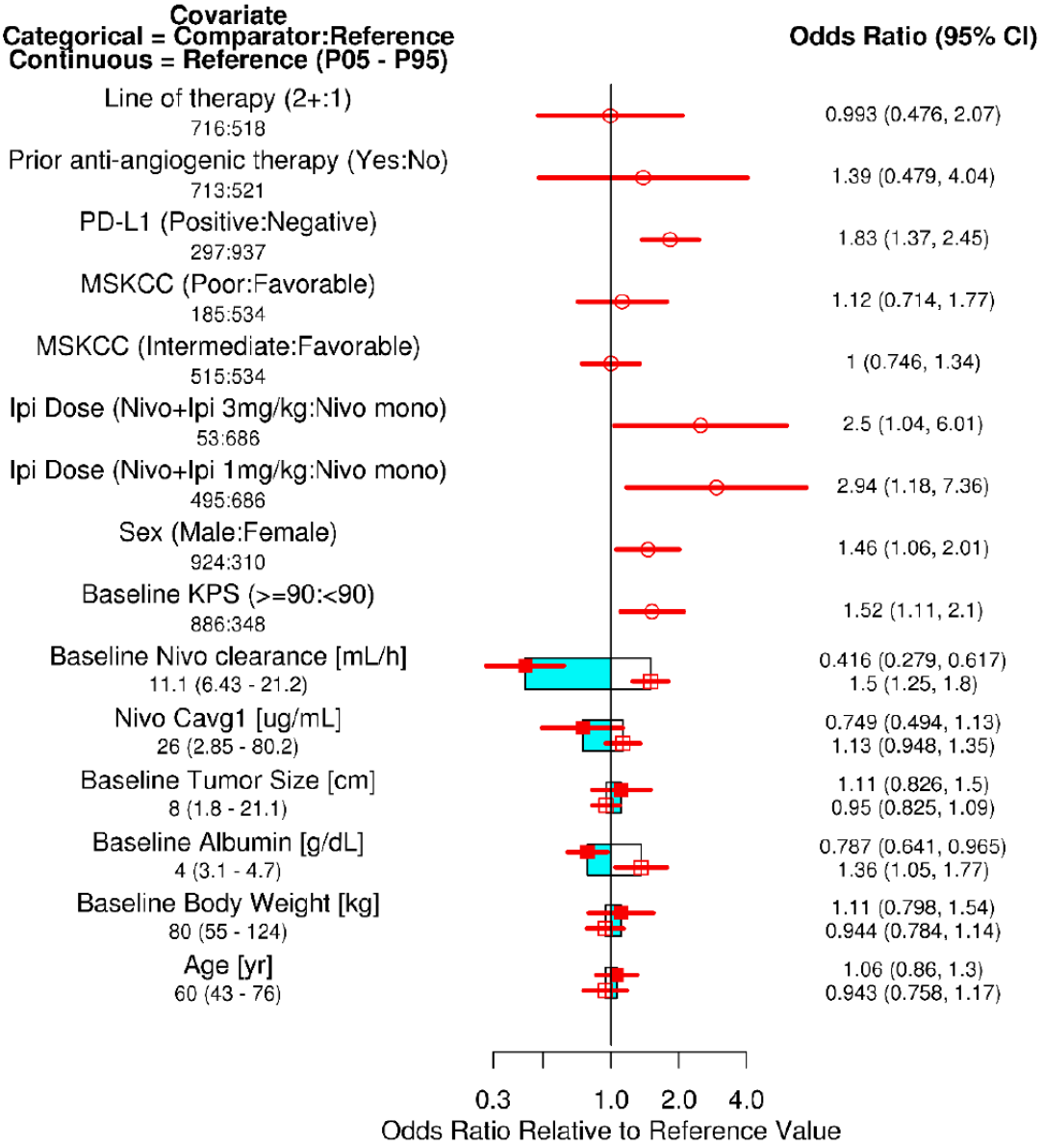
A full model was developed to quantify covariate effects, and this model was also used to establish the functional form of a relationship between Pr(OR) and exposure of nivolumab (Cavg1) and ipilimumab dose (as a categorical variable). Baseline covariates tested for E-R relationships of efficacy included: body weight (WT), age, sex, nivolumab clearance, albumin, Karnofsky Performance Scale (KPS) index, Memorial Sloan-Kettering Cancer Center (MSKCC) score, PD-L1 status, tumour size, prior anti-angiogenic therapy, and line of therapy.

A total of 1234 subjects were included in the analyses dataset for exposure-OR analyses.

Nivolumab Cavg1 was not a significant predictor of Pr(OR), given that the estimated odds ratio and 95% CI included 1. Ipilimumab treatment was a significant predictor of Pr(OR) (Figure 6), suggesting that odds ratio was higher for subjects treated with nivolumab in combination with ipilimumab 1 mg/kg (odds ratio=2.94) or ipilimumab 3 mg/kg (odds ratio=2.5), when compared to nivolumab monotherapy.

Covariates that had significant effect on the odds of OR in the model include: PD-L1, sex, baseline KPS, baseline albumin and baseline nivolumab clearance. Male subjects were associated with higher Pr(OR) compared to female subjects (odds ratio=1.46), subjects with higher PD-L1 expression were associated with higher Pr(OR) compared to subjects with no PD-L1 expression (odds ratio=1.83), subjects with higher base line KPS (≥ 90) were associated with higher Pr(OR) compared to subjects with lower baseline KPS (<90) (odds ratio=1.52), and subjects with lower nivolumab clearance were associated with higher Pr(OR) compared to subjects with higher nivolumab clearance. Age, MSKCC, baseline body-weight, and baseline tumour size were not significant predictors of OR.

Figure 6 Exposure-Effect: Predictors on Odds of OR (Full Model)



Exposure-response Analysis: OS

The relationship between nivolumab exposure and OS was described by a semi-parametric Cox Proportional-Hazards (CPH) model and included assessments of the modulatory effect of covariates on this exposure-response relationship.

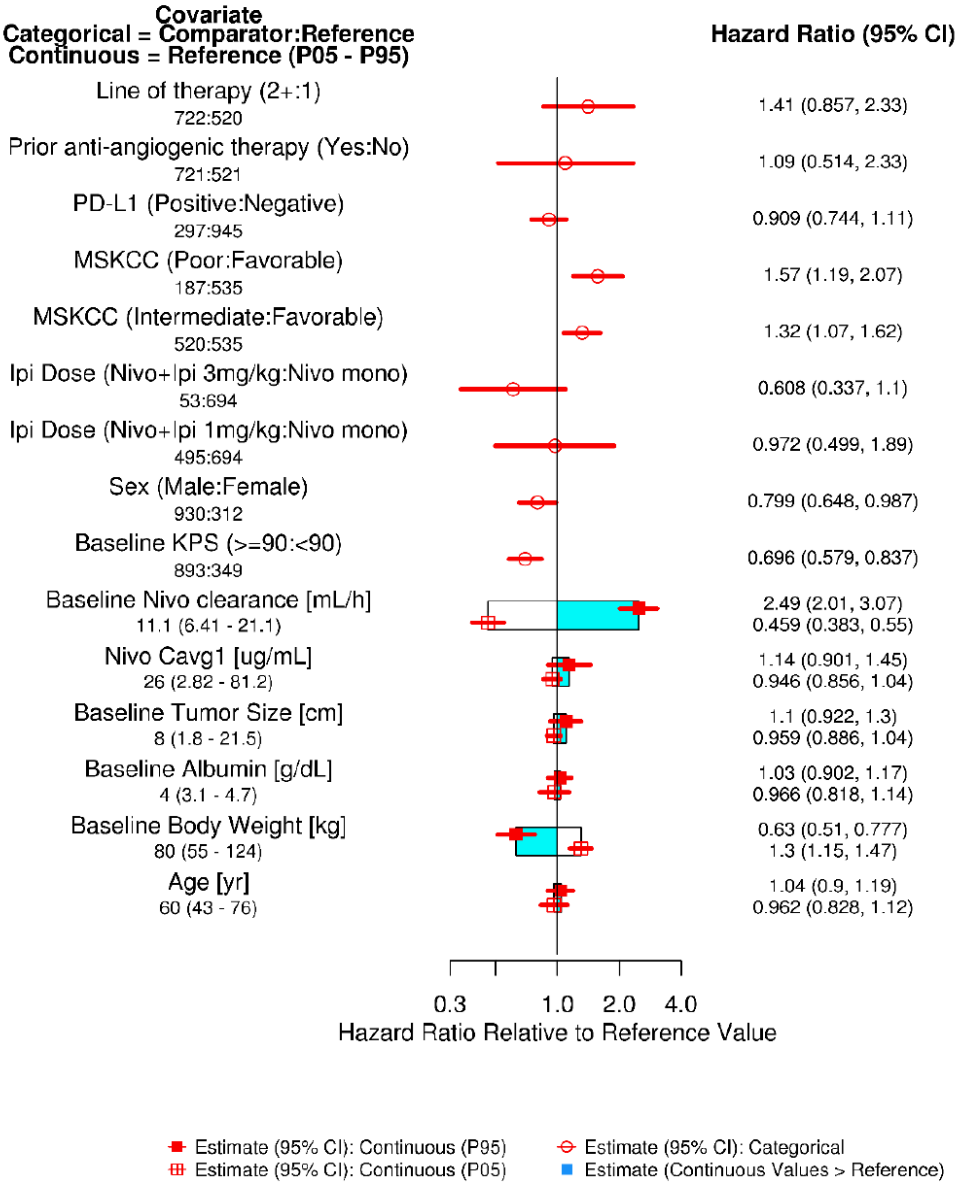
A full covariate model was developed to quantify covariate effects, and this model was also used to establish the functional form of a relationship between hazard of death and exposure of nivolumab (Cavg1) and ipilimumab dose (as a categorical variable). Baseline covariates tested for exposure-response relationships of efficacy included: body weight, age, sex, nivolumab clearance, albumin, KPS index, MSKCC score, PD-L1 status, tumour size, prior anti-angiogenic therapy, and line of therapy.

A total of 1242 subjects were included in exposure-OS analyses.

The predictor variables with a significant effect on OS were sex, MSKCC score, baseline KPS, PD-L1 status, baseline nivolumab clearance, body weight (95% CI of effect did not include 1)(Figure 7). The exposure-response analysis in the full model showed that there was not a significant relationship between nivolumab Cavg1 and OS hazard ratio (95% CI of effect included 1), after accounting for the effect of other potential predictors. Ipilimumab treatment was not a significant predictor of OS and the 95% CI of effect for subjects who received ipilimumab 1 mg/kg or 3 mg/kg in combination with nivolumab included 1. The 95% CI of all the other predictor variables (line of therapy, prior anti-angiogenic therapy, PD-L1, age and baseline tumour size) evaluated included unity, indicating a lack of evidence for the effect of these variables on OS.

The potential confounding of the effects of clearance and Cavg1 were assessed by examining the correlation between these estimated effects. The correlation between the estimated effects was not high, indicating that the full model containing these effects is not over-parameterized and both of these effects can be estimated simultaneously in the same model.

Figure 7 Effect of Predictors on OS (Full Model) for mRCC



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.
Analysis-Directory: /global/pkms/data/CA/209/C20/prd/er-os/final/
Program Source: Analysis-Directory/R/scripts/os-plot-coveff-full-2.r
Source: Analysis-Directory/R/export/os-coveff-full2.png

Exposure-response safety: Gr. 2+ immune mediated AE

Nivolumab daily Cavg was not a significant predictor of the risk of Gr. 2+ immune mediated AE. The risk of Gr. 2+ immune mediated AE was higher in subjects who received nivolumab + ipilimumab than in subjects who received nivolumab monotherapy, and the risk increased with increasing ipilimumab daily Cavg (see Figure 8). However, this did not increase the risk of discontinuation (Figure 9). The risk of Gr. 2+ immune mediated AE was higher in subjects who received 2+ lines of therapy relative to subjects who received one line of therapy.

Figure 8 Model Application Showing Hazard Ratio of Gr. 2+ IMAE in Subjects Who Receive Nivolumab as Monotherapy or in Combination with Ipilimumab

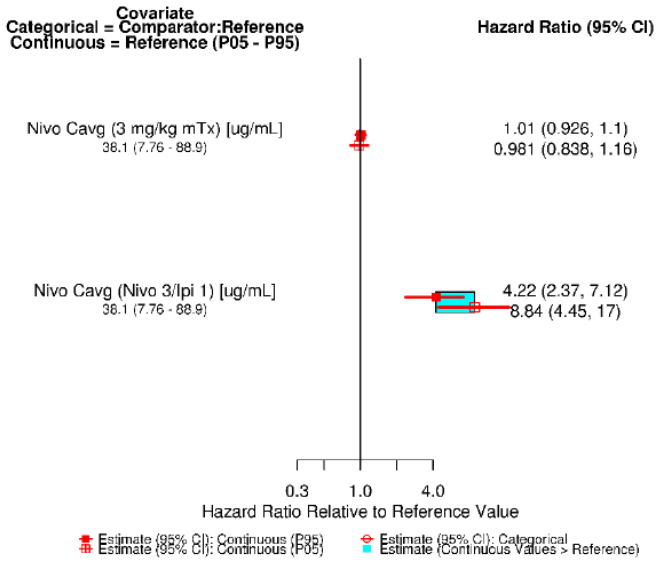
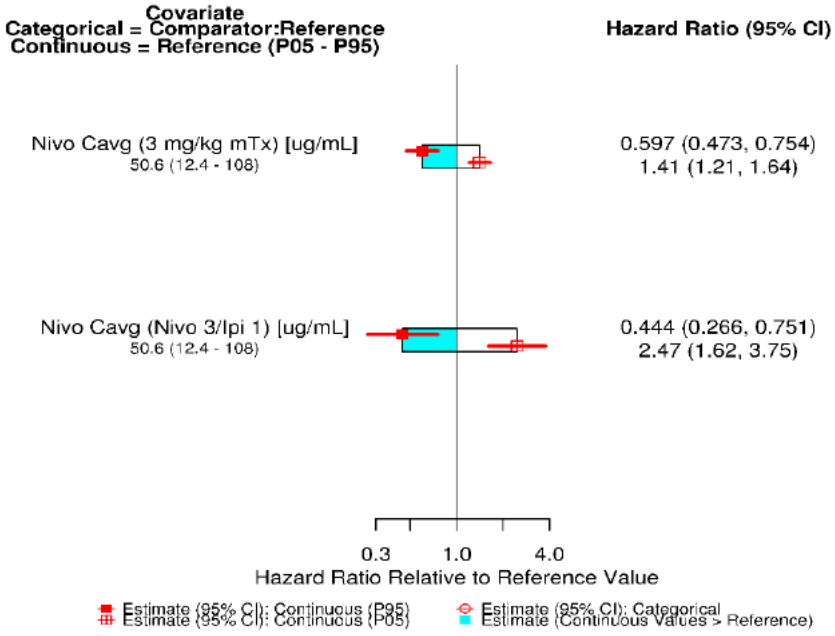


Figure 9 Model Application Showing Hazard Ratio of AE-DC/D in Subjects Who Receive Nivolumab as Monotherapy or in Combination with Ipilimumab



The following variables were not significant predictors of the risk of Gr. 2+ immune mediated AE: Body weight, age, sex, baseline KPS, baseline PD-L1, baseline tumour size, baseline albumin, and baseline nivolumab clearance.

Immunogenicity

In study CA209214, the incidence of nivolumab ADA was 26.0% (107/411 subjects) when nivolumab 3 mg/kg was administered with ipilimumab 1 mg/kg. Only 2 subjects were neutralising (NAb) ADA positive and 9 subjects (2.2%) were considered persistent positive. The incidence of ipilimumab ADA was 6.3% (26/415 subjects). No subject was neutralising ADA positive (to ipilimumab) or considered persistent positive.

Of the 107 subjects who were nivolumab ADA positive, 7 (6.5%) subjects had a best overall response (BOR) of CR and 39 (36.4%) had a BOR of PR, with an objective response rate of 42.9%. Similarly, of the 304 subjects who were nivolumab ADA negative, 31 (10.2%) had a BOR of CR and 82 (27.0%) had a BOR of PR, with an ORR of 37.2%. The 2 NAb positive subjects had BOR of PR and unable to determine (UTD).

The sample size for the ipilimumab ADA positive group was small and there were no ipilimumab neutralizing ADA positive subjects in the group to make any meaningful assessment of the ipilimumab immunogenicity effect on efficacy.

Out of all the subjects treated with ipilimumab + nivolumab combination therapy in Study CA209214 and who were evaluable for ADA, 5/107 (4.7%) nivolumab ADA positive subjects experienced AEs in the hypersensitivity/infusion reaction category. In comparison, 14/304 (4.6%) nivolumab ADA negative subjects experienced AEs in the hypersensitivity/infusion reaction category. No ipilimumab ADA positive subjects experienced hypersensitivity/infusion reactions AEs, whereas 19 (4.9%) ipilimumab ADA negative subjects experienced AEs in the hypersensitivity/infusion reaction category.

2.3.2. Discussion on clinical pharmacology

For this application an extension of indication to include the first-line combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma, the clinical pharmacology program of nivolumab in combination with ipilimumab was based on data from two studies: one phase 1 study CA209016 in previously treated or untreated advanced or mRCC evaluating the dose of nivolumab and ipilimumab when administered together, and a Phase 3, randomised, open-label study CA209214 of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg versus sunitinib in subjects with previously untreated advanced or mRCC.

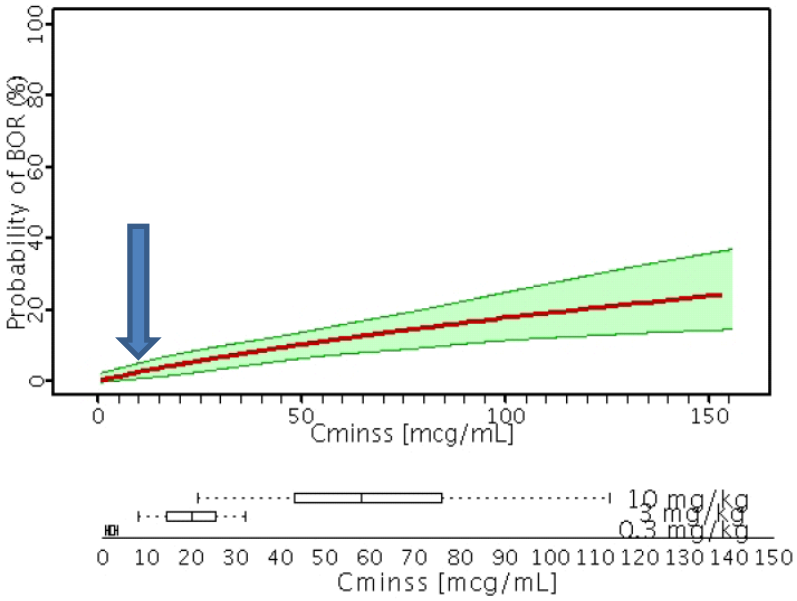
For the combination of nivolumab and ipilimumab, a dose finding study was conducted to select the dose of the combination in patients with advanced RCC. Three nivolumab/ipilimumab combinations, i.e. 1/3, 3/1 and 3/3 mg/kg, respectively, were included in this dose finding study. No nivolumab or ipilimumab monotherapy arms were included in this study, hence the contribution of both components to the efficacy and safety of the combination is not clear. Treatment with a combination of 3 mg/kg nivolumab and 3 mg/kg ipilimumab, the doses approved for monotherapy, resulted in dose-limiting toxicities that exceeded the MTD, although this was based on a low number of patients. More subjects discontinued treatment due to drug-related AEs in the 1 mg/kg nivolumab + 3 mg/kg ipilimumab cohort compared to the 3 mg/kg nivolumab + 1 mg/kg ipilimumab cohort, 27.7% vs. 10.6%, respectively (Table 8). Efficacy based on objective response rate seemed comparable in both cohorts (Table 8). Based on the difference in safety profile between 1 mg/kg nivolumab + 3 mg/kg ipilimumab and 3 mg/kg nivolumab + 1 mg/kg ipilimumab in study CA209016, 3 mg/kg nivolumab + 1 mg/kg ipilimumab was selected by the Applicant for treatment of untreated subjects with RCC in the phase 3 study CA209214. However, it is noted that patient characteristics with regard to prognostic/predictive factors for response to the combination differed to a relevant extent between the cohorts of patients treated with 1 mg/kg or 3 mg/kg (also refer to discussion on clinical efficacy). Therefore it is difficult to draw conclusions regarding dose-response for the combination therapy in RCC based on the current data.

Of note, in study CA209216, the safety profile of the combination 3 mg/kg nivolumab + ipilimumab 1 mg/kg appeared to be more favourable than in phase 3 study CA209214, where 21.6% of the subjects discontinued treatment due to drug-related adverse events.

For the monotherapy MAA, dose and exposure response evaluations suggested that increasing doses of nivolumab above 1 mg/kg did not change the likelihood of response in RCC. For ipilimumab no data are available in RCC for 1 mg/kg and limited data for 3 mg/kg ipilimumab followed by either 3 mg/kg or 1 mg/kg (MDX010-11). Therefore, knowledge regarding dose-response of ipilimumab in RCC is very limited.

Referring to dose response of ipilimumab monotherapy in melanoma, increasing doses of ipilimumab (0.3 mg/kg vs. 3 mg/kg vs. 10 mg/kg) increased the likelihood of clinical response in melanoma (Figure 10 below; ipilimumab 1 mg/kg mean Cminss is 8.5 µg/ml study CA209014, indicated by the arrow). For the combination nivolumab+ipilimumab no difference in response rate was observed for 1 mg/kg ipilimumab and 3 mg/kg ipilimumab, suggesting that ipilimumab dose-response for the combination therapy might be different from monotherapy. Furthermore, PD-L1 has high affinity for PD-1 but can also bind to CD80 on T-cells and CD80 expression might contribute to PD-L1-induced inactivation of CD8+ T-cells (Rollins 2017). In murine tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity. While in melanoma, it was shown that ipilimumab contributed to efficacy of the combination therapy in subjects with no PD-L1 expression (PD-L1 <1%) but not in subjects with PD-L1 >1% expression compared to the monotherapy nivolumab. Hence, it is unfortunate that no nivolumab monotherapy arm was included in studies CA209016 and CA209014 to evaluate the contribution of ipilimumab to the efficacy in mRCC.

Figure 10 Exposure-effect relationship of ipilimumab monotherapy in melanoma MAA Yervoy.



Note: Solid line and shaded area represent E-R model predicted Pr(BOR) and 95% bootstrap confidence interval (N=500). The horizontal box plots represent the distributions of Cminss at each dose group as follows: boxes (25th, 50th, and 75th percentiles) and whiskers (5th and 95th percentiles).

Source: Population Pharmacokinetic and Exposure-Response Report[9]

Model Predicted Probability (95% Confidence Interval) of BOR (CR or PR) versus Ipilimumab Steady-State Trough Concentration in subjects with advanced melanoma (studies CA184007, CA184008, CA184022); arrow indicates mean Cminss for ipilimumab 1 mg/kg for the combination 3 mg/kg nivolumab + 1 mg/kg ipilimumab in RCC study CA209014.

Exposure-effect relationships, comparing the efficacy parameters (ORR and OS) for nivolumab monotherapy with the combination nivolumab + ipilimumab, were provided by the applicant to support the combination therapy in mRCC. The exposure-effect models show no difference between first line vs. second line, which at first sight suggests that the positive effect of adding ipilimumab to nivolumab holds for both first and second line treatment. It should be noted, however, that there are few patients in the studies that have had nivolumab monotherapy in the first line and that there are no data for ipilimumab monotherapy as data from study MDX010-11 were not included in the model because of the different dosing regimen applying a 3 mg/kg loading dose of ipilimumab. Hence, prior anti-angiogenic therapy and line of therapy highly overlapped with ipilimumab administration. Actually, both type of models (Cox proportional hazard model and logistic regression) assume (i.e. 'force') that the covariates have an additive effect. This would mean that the model effect of first vs. second line is estimated from patients in first line on combination therapy and patients in second line on monotherapy; and also that the effect of ipilimumab on top of nivolumab is estimated from second line patients. If true, the model assumes by definition that the effect of nivolumab monotherapy and ipilimumab monotherapy is in the first line the same as in second line. To empirically justify this, the interaction term for line and nivolumab and line and ipilimumab should be estimated, but this can only be done when such patients are available in reasonable numbers, which is not the case. It was confirmed by the additional analyses of the same data provided by applicant at D90 that the numbers were too low to estimate the interaction term reliably. Therefore, the finding of 'no effect for first line vs. second line' in the model would rather be an assumption than a conclusion. A further point is that the differences between included patients are adjusted for, and also for this additivity of effects is used in addition to the assumption of 'no unmeasured confounders'. Overall, the exposure-effect relationships do not discern the contribution to efficacy of each component of the combination while this needs to be elucidated considering the safety risks associated with ipilimumab.

The risk of Gr. 2+ immune mediated AE was higher in subjects who received nivolumab + ipilimumab than in subjects who received nivolumab monotherapy, and the risk increased with increasing ipilimumab daily Cavg (Figure 8). According to the applicant this did not increase the risk of discontinuation (Figure 9). Subjects with low nivolumab exposure had an increased risk of discontinuation. Subjects with poor health condition have in general low nivolumab exposure and the risk of discontinuation increased for the combination therapy.

In conclusion, as no nivolumab monotherapy arm was included in studies CA209016 and CA209214, the contribution of ipilimumab to the efficacy of the combination is not known and needs further substantiation because ipilimumab increases the toxicity compared to monotherapy nivolumab (see also clinical efficacy & safety discussion).

Due to the different dosing recommendations for the combination of nivolumab and ipilimumab for melanoma and RCC and a different dose for ipilimumab compared to monotherapy, there might be a risk of medication errors. The combination of nivolumab and ipilimumab at recommended monotherapy doses was not well tolerated.

The incidence of nivolumab ADA was 26.0% (107/411 subjects) when nivolumab 3 mg/kg was administered with ipilimumab 1 mg/kg. This is higher than the incidence of nivolumab ADA for nivolumab monotherapy (~12%), but lower than for the combination 1 mg/kg nivolumab + 3 mg/kg ipilimumab in treatment of melanoma 37.8%. Neutralising antibodies were observed in 0.5% of subjects treated with the combination. Nivolumab clearance increased by ~20% in the presence of nivolumab antibodies. However, the response in ADA positive subjects was consistent with the overall response observed in CA209214. The immunogenicity of ipilimumab when given in combination with nivolumab was low (approximately 6.6% antibody positive), and had no impact on ipilimumab pharmacokinetics. Incidence of hypersensitivity/infusion reactions appeared not to be increased in subjects positive for either nivolumab or ipilimumab antibodies.

Based on assessment of the presence of ADA and neutralizing antibodies (NAbs) vs BOR, subjects with nivolumab and ipilimumab ADA did not show a reduction in efficacy. According to the applicant, the above conclusion is also valid for the relation between the presence of ADA and NAbs vs PFS and OS.

Pharmacokinetics

The pharmacokinetics of nivolumab and ipilimumab are in agreement with previous analyses for the combination (advanced melanoma EMEA/H/C/003985/II/0003). However, the intersubject variability in pharmacokinetic parameters of nivolumab in combination with ipilimumab in study CA209214 is very high 52-366% (Table 5), much higher than previously shown for nivolumab 3 mg/kg monotherapy in subjects with RCC (typically 30-40%). The maximal values reported e.g. for Cmax1 of 6230 µg/ml, are not realistic values for 3 mg/kg nivolumab treatment with an estimated Cmax1 of 60-90 µg/ml. The intersubject variability of ipilimumab pharmacokinetic parameters of 20-40% is in line with previous variability data. The high intersubject variability and unrealistic high estimated maximal PK values of nivolumab were due to a single outlier subject, which was recorded to have received 1 mg nivolumab rather than the nominal dose amount of 187 mg. When this subject was excluded, the intersubject variability in parameters was reduced to 20.5% to 37.1% of %CV, which is in line with previously reported variability data.

Co-administration of ipilimumab 1 mg/kg resulted in a modest <20% increase in nivolumab clearance, relative to the nivolumab clearance when given as monotherapy. Ipilimumab pharmacokinetics was similar when administered in combination with 3 mg/kg nivolumab or as monotherapy. The clearance of ipilimumab in RCC subjects was not significantly different than that of melanoma subjects treated with monotherapy. Baseline nivolumab clearance was a predictor for overall response and overall survival in line with previous mono- and combination therapy exposure-response analyses.

In an earlier analysis across multiple tumour types, nivolumab and ipilimumab pharmacokinetics were described by a time-dependent clearance model where nivolumab clearance decreased by a maximum of 33% and ipilimumab by ~5% monotherapy and by 22% in combination with nivolumab. In general, subjects with CR and PR were observed to have greater decrease in clearance compared to non-responders with SD and PD. This observation is consistent with that found for ipilimumab. Nivolumab baseline clearance was higher in subjects with PS > 0 subjects than subjects with PS = 0 by ~19%; however, the decrease in clearance with time was greater in subjects with PS > 0 than subjects with PS = 0 (31% vs. 21%). The hypothetical reason for this observation is that higher clearance is associated with greater disease severity. Thus, in subjects when disease condition is improved over time in responders, a decrease in clearance was observed. The underlying mechanism is not exactly clear, but may be related to decreases in cachexia in subjects who respond to therapy.

2.3.3. Conclusions on clinical pharmacology

The nivolumab and ipilimumab combination dose regimen (nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks) was selected for treatment of previously untreated subjects with RCC in the phase 3 study CA209214. The relative contribution of low dose ipilimumab to the efficacy of the combination is not clear, while exposure-response data indicate that ipilimumab increases toxicity (see also clinical efficacy & safety discussion). Therefore, the contribution of ipilimumab to the efficacy of the combination lacks sufficient substantiation.

2.4. Clinical efficacy

The pivotal trial for the nivolumab combined with ipilimumab clinical development programme in advanced renal cell carcinoma (RCC) is the phase 3 study, CA209214. The current application for

advanced RCC is based primarily on data from nivolumab combined with ipilimumab in CA209214 and supporting data from CA209016.

2.4.1. Dose response study

The dose-response study CA209016 is described briefly below and in more detail in section 4.4.2 under the heading: 'supportive study'. Study CA209016 was a phase 1 open-label study of nivolumab plus sunitinib or pazopanib, or nivolumab plus ipilimumab in subjects with metastatic renal cell carcinoma (mRCC).

Objectives

Primary:

- To assess the overall safety and tolerability of nivolumab plus sunitinib or pazopanib or ipilimumab, in order to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of nivolumab plus sunitinib or pazopanib or ipilimumab in subjects with metastatic renal cell carcinoma (mRCC).

Secondary:

- To assess preliminary anti-tumour activity of nivolumab plus sunitinib or pazopanib or ipilimumab in subjects with mRCC.

Exploratory:

- To evaluate pharmacodynamic and predictive biomarkers of nivolumab plus sunitinib or pazopanib or ipilimumab in subjects with mRCC. To characterize the pharmacokinetics of nivolumab in subjects with mRCC and to explore exposure-response with respect to safety, efficacy, and biomarkers. To assess the immunogenicity of nivolumab. To assess the overall survival (OS) in mRCC subjects receiving nivolumab in combination with sunitinib or pazopanib or ipilimumab.

Methodology

5 treatment arms were explored:

- Nivolumab 2mg/kg or 5 mg/kg plus sunitinib (Arm S)
- Nivolumab 2 mg/kg plus pazopanib (Arm P)
- nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (Arm I-1)
- nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (Arm I-3)
- nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (Arm IN-3)

Number of subjects

A total of 194 subjects were enrolled; 153 were treated, 33 in arm S, 20 in arm P, 47 in arm I-1, 47 in arm I-3, and 6 in arm IN-3.

Diagnosis and main criteria for inclusion

The study population included adults (≥ 18 years) with advanced or metastatic measurable RCC as defined by RECIST 1.1 criteria, with Karnofsky Performance Status (KPS) ≥ 80%, and histological confirmation of a clear-cell component (dose escalation or dose expansion of arms S and P, arms I-1 and I-3 and IN-3), or non-clear-cell limited to papillary, chromophobe or unclassified histology (dose escalation of arms S and P only). Subjects with prior systemic therapy and no prior systemic therapy in the advanced/metastatic setting and favourable or intermediate-risk MSKCC prognostic score were eligible to enrol for the initial cohorts of arm I-1 and I-3. Subjects with no prior systemic therapy, but the following exceptions of minimal treatment with any MSKCC prognostic score were eligible to enrol in the I-1 and I-3 expansion arms, and the IN-3 arm:

- One prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC with recurrence occurred ≥ 6 months after the last dose of the adjuvant or neoadjuvant therapy
- Only prior cytokine based treatment for metastatic RCC (e.g., IFN-α or IL-2)

Baseline demographics and disease characteristics

Among all treated subjects, the majority of subjects were under the age of 65, white and male. At baseline, the majority of subjects were diagnosed with clear-cell RCC with KPS of 90 or 100, had favourable or intermediate-risk MSKCC prognostic scores and PD-L1 level ≤ 5%. The lung, lymph node and liver were the most common site of disease reported outside of the kidney.

Efficacy results

Objective response rate

Nivolumab plus ipilimumab

The investigator-assessed confirmed ORR was 40.4% in arm I-1 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg), 40.4% in arm I-3 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) (Table 9). Five (10.6%) subjects in arm I-1 obtained a complete response. No confirmed ORR is observed in arm IN-3 (nivolumab 3 mg/kg + ipilimumab 3 mg/kg).

Table 9. Best Overall Response per Investigator Assessed by RECIST 1.1 – Efficacy Population

	IPI1 + NIV3 N = 47	IPI3 + NIV1 N = 47	IPI3 + NIV3 N = 6
BEST OVERALL RESPONSE (%)			
COMPLETE RESPONSE	5 (10.6)	0	0
PARTIAL RESPONSE	14 (29.8)	19 (40.4)	0
STABLE DISEASE	19 (40.4)	17 (36.2)	5 (83.3)
PROGRESSIVE DISEASE	8 (17.0)	8 (17.0)	1 (16.7)
UNABLE TO DETERMINE	1 (2.1)	3 (6.4)	0
CONFIRMED ORR (A) (%)	19 (40.4)	19 (40.4)	0
95% CONFIDENCE LIMIT	(26.4, 55.7)	(26.4, 55.7)	

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIV=Nivolumab
(A) Confirmed Response Only.
Source: Table S.5.1A.1

Safety Results

A summary of the safety results can be found in Table 10. No new safety concerns were identified with nivolumab combination therapies. No deaths by study drug toxicity were observed. Disease progression was the most common cause of death for all the groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose. Drug-related SAE (any grade) observed in arm I-1 and arm I-3 were 23.4% and 34%, respectively. Of these SAEs, 19.1% (arm I-1) and 34% (arm I-3) were grade 3-4 (Table 10). In arm I-1, diarrhoea was observed in more than two subjects, whereas colitis, diarrhoea, alanine aminotransferase increased, aspartate aminotransferase increase and dehydration was observed in more than two patients in arm I-3. Most observed AEs (any grade) in arm I-1 were fatigue (51.1%), rash (31.9%), pruritus (31.9%), nausea (27.7%) and arthralgia (25.5%). Observed treatment-related AEs were 91.5% for arm I-1 and 97.1% for arm I-3. 38.3% and 61.7% of the treatment-related AEs observed in arm I-1 and arm I-3 are grade 3-4, respectively. Most observed AEs (any grade) in arm I-3 were fatigue (68.1%), diarrhoea (44.7%), nausea (44.7%), pruritus (36.2%), lipase increased (34.0%), AST increased (31.9%), ALT increased (29.8%), decreased appetite (29.8%), hypothyroidism (27.7%) and rash (25.5%). Frequently reported grade 3-4 drug-related AEs were Lipase increased (14.9%) for arm I-1 and lipase increased (27.7%), ALT increased (21.3%), Diarrhoea (14.9%), colitis (14.9%) and AST increased (12.8%) for arm I-3.

Table 10 Summary of Safety Results Study CA209016 – All Treated Subjects

	Arm S N = 33				Arm P PAZ + NIV2 N = 20		Arm I-1 IPI1 + NIV3 N = 47		Arm I-3 IPI3 + NIV1 N = 47		Arm IN-3 IPI3 + NIV3 N = 6	
	SUN + NIV2 N = 7		SUN + NIV5 N = 26									
Death, n (%)	3 (42.9)		9 (34.6)		13 (65.0)		16 (34.0)		18 (38.3)		0	
Within 30 Days of Last Dose	0		0		1 (5.0)		0		1 (2.1)		0	
Within 100 Days of Last Dose	0		1 (3.8)		2 (10.0)		3 (6.4)		4 (8.5)		0	
Due to Study Drug Toxicity	0		0		0		0		0		0	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs, n (%)	3 (42.9)	1 (14.3)	16 (61.5)	14 (53.8)	13 (65.0)	10 (50.0)	29 (61.7)	20 (42.6)	30 (63.8)	24 (51.0)	4 (66.7)	4 (66.7)
Drug-related SAEs, n (%)	2 (28.6)	0	12 (46.2)	10 (38.5)	2 (10.0)	2 (10.0)	11 (23.4)	9 (19.1)	16 (34.0)	16 (34.0)	3 (50.0)	3 (50.0)
All-causality AEs Leading to Discontinuation, n (%)	3 (42.9)	2 (28.6)	10 (38.5)	9 (34.6)	5 (25.0)	4 (20.0)	5 (10.6)	3 (6.4)	15 (31.9)	11 (23.4)	2 (33.3)	0
Drug-related AEs Leading to Discontinuation, n (%)	3 (42.9)	2 (28.6)	10 (38.5)	9 (34.6)	5 (25.0)	4 (20.0)	5 (10.6)	3 (6.4)	13 (27.7)	9 (19.1)	2 (33.3)	0
All-causality AEs, n (%)	7 (100.0)	6 (85.7)	26 (100.0)	24 (92.3)	20 (100.0)	16 (80.0)	47 (100.0)	33 (70.2)	47 (100.0)	34 (72.3)	6 (100.0)	6 (100.0)
Drug-related AEs, n (%)	7 (100.0)	5 (71.4)	26 (100.0)	22 (84.6)	20 (100.0)	14 (70.0)	43 (91.5)	18 (38.3)	45 (95.7)	29 (61.7)	6 (100.0)	5 (83.3)
All-causality Select AEs, within 30 Days of Last Dose, by Category, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Endocrine	3 (42.9)	0	9 (34.6)	0	5 (25.0)	2 (10.0)	14 (29.8)	3 (6.4)	19 (40.4)	0	6 (100.0)	0
Gastrointestinal	6 (85.7)	0	15 (57.7)	3 (11.5)	14 (70.0)	5 (25.0)	16 (34.0)	3 (6.4)	25 (53.2)	12 (25.5)	5 (83.3)	2 (33.3)
Hepatic	3 (42.9)	2 (28.6)	13 (50.0)	7 (26.9)	7 (35.0)	4 (20.0)	11 (23.4)	3 (6.4)	15 (31.9)	8 (17.0)	3 (50.0)	1 (16.7)
Pulmonary	0	0	2 (7.7)	1 (3.8)	1 (5.0)	0	3 (6.4)	0	5 (10.6)	0	0	0
Renal	2 (28.6)	1 (14.3)	11 (42.3)	2 (7.7)	3 (15.0)	1 (5.0)	11 (23.4)	2 (4.3)	10 (21.3)	2 (4.3)	2 (33.3)	0
Skin	7 (100.0)	1 (14.3)	19 (73.1)	3 (11.5)	13 (65.0)	0	29 (61.7)	1 (2.1)	33 (70.2)	1 (2.1)	5 (83.3)	0
Hypersensitivity/Infusion Reactions	0	0	1 (3.8)	0	2 (10.0)	1 (5.0)	5 (10.6)	0	3 (6.4)	0	1 (16.7)	0

	Arm S N = 33				Arm P PAZ + NIV2 N = 20		Arm I-1 IPI1 + NIV3 N = 47		Arm I-3 IPI3 + NIV1 N = 47		Arm IN-3 IPI3 + NIV3 N = 6	
	SUN + NIV2 N = 7		SUN + NIV5 N = 26									
Drug-related Select AEs, within 30 Days of Last Dose, by Category, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Endocrine	3 (42.9)	0	8 (30.8)	0	5 (25.0)	2 (10.0)	13 (27.7)	2 (4.3)	19 (40.4)	0	6 (100.0)	0
Gastrointestinal	6 (85.7)	0	15 (57.7)	3 (11.5)	12 (60.0)	4 (20.0)	12 (25.5)	2 (4.3)	21 (44.7)	11 (23.4)	3 (50.0)	2 (33.3)
Hepatic	3 (42.9)	2 (28.6)	12 (46.2)	6 (23.1)	7 (35.0)	4 (20.0)	9 (19.1)	3 (6.4)	13 (27.7)	8 (17.0)	3 (50.0)	1 (16.7)
Pulmonary	0	0	1 (3.8)	1 (3.8)	1 (5.0)	0	3 (6.4)	0	5 (10.6)	0	0	0
Renal	2 (28.6)	1 (14.3)	10 (38.5)	2 (7.7)	1 (5.0)	0	9 (19.1)	2 (4.3)	6 (12.8)	1 (2.1)	2 (33.3)	0
Skin	7 (100.0)	1 (14.3)	19 (73.1)	1 (3.8)	11 (55.0)	0	23 (48.9)	0	28 (59.6)	1 (2.1)	3(50.0)	0
Hypersensitivity/Infusion Reactions	0	0	0	0	1 (5.0)	0	5 (10.6)	0	3 (6.4)	0	1 (16.7)	0
All-causality Immune-mediated AEs, by Category												
Immune-mediated AEs Treated with Immune-modulating medication	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Diarrhea/Colitis	0	0	0	0	1 (5.0)	1 (5.0)	3 (6.4)	2 (4.3)	12 (25.5)	10 (21.3)	2 (33.3)	2 (33.3)
Hepatitis	0	0	4 (15.4)	3 (11.5)	4 (20.0)	3 (15.0)	5 (10.6)	2 (4.3)	11 (23.4)	8 (17.0)	0	0
Pneumonitis	0	0	2 (7.7)	1 (3.8)	1 (5.0)	0	1 (2.1)	0	5 (10.6)	0	0	0
Nephritis and Renal Dysfunction	1 (14.3)	1 (14.3)	1 (3.8)	0	0	0	2 (4.3)	1 (2.1)	1 (2.1)	0	0	0
Rash	2 (28.6)	0	4 (15.4)	2 (7.7)	2 (10.0)	0	8 (17.0)	1 (2.1)	9 (19.1)	1 (2.1)	1 (16.7)	0
Hypersensitivity	0	0	0	0	1 (5.0)	1 (5.0)	0	0	0	0	0	0
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Adrenal Insufficiency	0	0	0	0	0	0	3 (6.4)	1 (2.1)	6 (12.8)	0	2 (33.3)	0
Hypophysitis	0	0	0	0	0	0	1 (2.1)	1 (2.1)	2 (4.3)	0	1 (16.7)	0
Hypothyroidism/Thyroiditis	2 (28.6)	0	8 (30.8)	0	4 (20.0)	1 (5.0)	10 (21.3)	0	14 (29.8)	0	6 (100.0)	0
Hyperthyroidism	1 (14.3)	0	4 (15.4)	0	0	0	4 (8.5)	1 (2.1)	8 (17.0)	0	3 (50.0)	0
Diabetes Mellitus	0	0	0	0	1 (5.0)	1 (5.0)	0	0	0	0	0	0

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIV=Nivolumab
MedDRA version 18.1; CTC version 4.0. All events are within 100 days of the last dose of study drug, unless otherwise indicated.

Serious adverse events

SAEs were reported in 61.7%, 63.8%, and 66.7% of subjects in arms I-1, I-3 and IN-3, whereas 51.1%, and 66.7% of subjects experienced grade 3-4 SAEs. Drug-related SAEs were reported in 23.4%, 34%, and 50% of subjects in arms I-1, I-3 and IN-3, whereas 19.1%, 34%, and 50% of subjects experienced grade 3-4 drug-related SAEs (Table 11).

Table 11 Drug-related SAEs by Worst CTC Grade Reported in at Least 2 Subjects with Extended Follow-up – All Treated Subjects in Arms I-1, I-3 and IN-3

System Organ Class (%) Preferred Term (%)	Arm I-1 (IPI1 + NIV3) N = 47			Arm I-3 (IPI3 + NIV1) N = 47			Arm IN-3 (IPI3 + NIV3) N = 6		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade-5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	11 (23.4)	9 (19.1)	0	16 (34.0)	16 (34.0)	0	3 (50.0)	3 (50.0)	0
RENAL AND URINARY DISORDERS	1 (2.1)	1 (2.1)	0	1 (2.1)	1 (2.1)	0	0	0	0
ACUTE KIDNEY INJURY	1 (2.1)	1 (2.1)	0	1 (2.1)	1 (2.1)	0	0	0	0
GASTROINTESTINAL DISORDERS	5 (10.6)	5 (10.6)	0	10 (21.3)	10 (21.3)	0	2 (33.3)	2 (33.3)	0
COLITIS	0	0	0	6 (12.8)	6 (12.8)	0	0	0	0
DIARRHOEA	3 (6.4)	2 (4.3)	0	5 (10.6)	4 (8.5)	0	1 (16.7)	1 (16.7)	0
GENERAL DISORDERS AND ADMINISTRATION SITE	3 (6.4)	2 (4.3)	0	1 (2.1)	0	0	2 (33.3)	1 (16.7)	0
PYREXIA	3 (6.4)	1 (2.1)	0	1 (2.1)	0	0	2 (33.3)	0	0
INVESTIGATIONS	1 (2.1)	0	0	5 (10.6)	5 (10.6)	0	0	0	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	4 (8.5)	4 (8.5)	0	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	0	4 (8.5)	4 (8.5)	0	0	0	0
TRANSAMINASES INCREASED	0	0	0	2 (4.3)	2 (4.3)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	3 (6.4)	3 (6.4)	0	0	0	0
DEHYDRATION	0	0	0	2 (4.3)	2 (4.3)	0	0	0	0
HYPONATRAEMIA	0	0	0	1 (2.1)	1 (2.1)	0	0	0	0

Treatment: IPI=Ipilimumab; NIV=Nivolumab
MedDRA Version: 18.1; CTC Version 4.0; Includes events reported between first dose and 100 days after last dose of study therapy.
Source: Table S.6.3B

AEs leading to discontinuation

AEs leading to discontinuation were reported in 5 (10.6%), 15 (31.9%) and 2 (33.3%) subjects in Arms I-1, I-3, and IN-3, respectively. Grade 3-4 AEs leading to discontinuation were reported in 3 (6.4%), 11 (23.4%), and 0% of the subjects in these arms, respectively.

Drug-related AEs leading to discontinuation were reported in 5 (10.6%), 13 (27.7%) and 2 (33.3%) subjects in arms I-1, I-3, and IN-3, respectively. Grade 3-4 drug-related AEs leading to discontinuation were reported in 3 (6.4%), 9 (19.1%), and 0% of the subjects in these arms (Table 10).

2.4.2. Main study

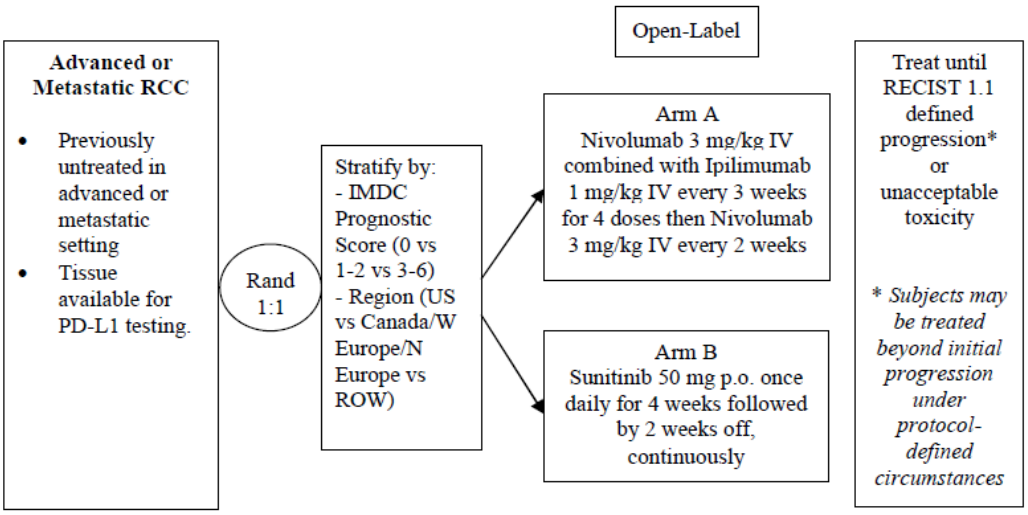
CA209214

CA209214 is a phase 3, randomised, open-label study of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks vs. sunitinib monotherapy using the approved dose and schedule (50 mg orally once daily for 4 weeks followed by 2 weeks off, every cycle) in adult (≥ 18 years) subjects with previously untreated advanced RCC (either not amenable to curative surgery or radiation, or American Joint Committee on Cancer [AJCC] Stage IV). A final clinical study report (CSR) was completed based on a database lock date of 07-Aug-2017. These data form the basis of this application, and include efficacy and safety data with a median follow-up of 25.2 months (minimum follow-up of 17.5 months).

CA209214 consisted of 3 phases: screening, treatment, and follow-up (Figure 11). At the time of randomisation, subjects were stratified according to IMDC prognostic score into one of 3 risk groups:

favourable risk, intermediate risk or poor risk. Subjects were also stratified by region. Subjects were assessed for response (Response Evaluation Criteria in Solid Tumours [RECIST] v1.1) by computed tomography or magnetic resonance imaging beginning 12 weeks (± 1 week) from randomisation and continuing every 6 weeks (± 1 week) for the first 13 months and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Subjects were allowed to continue study therapy after initial investigator-assessed RECIST v1.1-defined progression if the subject had an investigator-assessed clinical benefit and was tolerating study drug(s). After discontinuation of study therapy and completion of 2 follow-up visits to assess safety and collect pharmacokinetic/immunogenicity samples, subjects were followed every 3 months for survival.

Figure 11 CA209214 Study Design



Abbreviations: PD-L1: programmed death ligand 1; IMDC: International Metastatic RCC Database Consortium; IV: intravenous(ly); ROW: rest of world; US: United States

Study participants

The study included adults (≥ 18 years of age) with advanced (either not amenable to curative surgery or radiation, or AJCC Stage IV) histologically confirmed RCC with a clear-cell component. Prior systemic therapy for RCC was not permitted except for one prior adjuvant or neoadjuvant therapy provided such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. Subjects were to have a Karnofsky Performance Status (KPS) of at least 70%. To be eligible for the intermediate/poor-risk cohort, at least 1 of the 6 following prognostic factors as per IMDC criteria had to be present: 1) KPS equal to 70%; 2) less than 1 year from diagnosis to randomisation; 3) haemoglobin < lower limit of normal; 4) corrected calcium concentration > 10 mg/dL; 5) absolute neutrophil count > upper limit of normal (ULN); 6) platelet count > ULN.

A total of 174 sites in 28 countries randomised subjects (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Poland, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom, and United States). Of the 1096 randomised subjects, 1082 were treated. The first patient first visit date was 16-Oct-2014 and the last patient randomisation date was 04-Mar-2016. The last patient last visit date (clinical cut-off date) was 26-Jun-2017.

Key Inclusion Criteria were:

- Histological confirmation of RCC with a clear-cell component

- Advanced (not amenable 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) of at least 70%

- Measurable disease as per RECIST 1.1

- Tumour tissue (formalin-fixed paraffin-embedded (FFPE) archival or recent acquisition) must be received by the central vendor (block or unstained slides) in order to randomise a subject to study treatment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).

- Patients with favourable, intermediate and poor risk categories were eligible for the study. Patients must be categorised according to favourable versus intermediate/poor risk status at registration. To be eligible for the Intermediate and Poor-Risk cohort, at least one of the following prognostic factors as per International Metastatic RCC Database Consortium (IMDC) must be present:

a) KPS equal to 70
b) Less than 1 year from diagnosis to randomisation
c) Haemoglobin less than the LLN
d) Corrected calcium concentration greater than 10 mg/dL
e) Absolute neutrophil count greater than the ULN
f) Platelet count greater than the ULN

If none of the above factors were present, subjects were only eligible for the favourable-risk cohort. The favourable-risk cohort may close to enrolment earlier than the intermediate- or poor-risk cohort.

Key Exclusion Criteria were:

- Any history of or current CNS metastases. Baseline imaging of the brain was required within 28 days prior to randomisation.

- Prior systemic treatment with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab).

- 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.

- Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement were permitted to enrol.

- Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease.

Treatments

In subjects randomised to the nivolumab + ipilimumab group (arm A), nivolumab at 3 mg/kg was administered IV over approximately 60 minutes followed by ipilimumab at 1 mg/kg administered IV over approximately 30 minutes. Separate infusion bags and filters were used for each infusion and the second infusion (ipilimumab) was started at least 30 minutes after the completion of the nivolumab infusion. Infusions were administered every 3 weeks for 4 cycles. Thereafter, nivolumab 3 mg/kg was administered IV over approximately 60 minutes every other week until treatment discontinuation.

In subjects randomised to the sunitinib group (arm B), sunitinib was administered using the approved dose and schedule of 50 mg p.o. once daily for 4 weeks followed by 2 weeks off, continuously. No dose increases or reductions were allowed for nivolumab.

Dose modifications were not permitted for nivolumab or ipilimumab but were permitted for sunitinib as per the approved product label. A maximum of 2 sunitinib dose reductions in 12.5 mg decrements was allowed. Dose escalations of sunitinib were permitted as per the approved product label when a concomitant CYP3A4 inducer was needed.

Objectives

The hypothesis of the study was:

Treatment with nivolumab combined with ipilimumab will improve ORR, PFS or OS compared to sunitinib monotherapy in subjects with previously untreated, advanced or metastatic RCC.

Primary objectives of study CA209214:

- To describe the ORR of nivolumab + ipilimumab and sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC, based on IRRC assessments.
- To compare the PFS of nivolumab + ipilimimab to sunitinib in intermediate and poor-risk subjects with previously untreated mRCC, based on IRRC assessments
- To compare the OS of nivolumab + ipilimimab to sunitinib in intermediate and poor-risk subjects with previously untreated mRCC

Secondary objectives of study CA209214:

- To estimate the ORR of nivolumab + ipilimumab and sunitinib monotherapy in subjects with previously untreated mRCC (any-risk), based on IRRC assessments
- To compare the PFS of nivolumab + ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC, based on IRRC assessments
- To compare the OS of nivolumab + ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC
- To estimate the incidence of AEs of nivolumab + ipilimumab and sunitinib monotherapy in all treated subjects with previously untreated mRCC

Exploratory objectives of study CA209214:

- To assess the overall safety and tolerability of nivolumab combined with ipilimumab vs. sunitinib monotherapy
- To estimate the PFS based on IRRC assessments and OS of nivolumab combined with ipilimumab vs. sunitinib monotherapy in favourable risk subjects with previously untreated mRCC
- To characterise the pharmacokinetics (PK) of nivolumab and ipilimumab when coadministered

- To evaluate immunogenicity of nivolumab and ipilimumab administered as combination therapy
- To explore potential predictive biomarkers of clinical response to nivolumab-ipilimumab combination by analysing tumour specimens and blood samples for proteins and genes involved in regulating immune responses (e.g., PD-1, PD-L1, PD-L2, CXCL10)
- To assess the effects of single nucleotide polymorphisms (SNPs) in select genes (e.g., PD-1, PD-L1, PD-L2, CTLA-4) on clinical endpoints and/or on the occurrence of adverse events
- To explore associations between baseline measures of Myeloid Derived Suppressor Cells (MDSCs) and clinical outcomes
- To evaluate health related quality of life (HRQoL) as assessed by the Functional Assessment of Cancer Therapy-General (FACT-G)
- To assess disease related symptoms in each arm based on the NCCN Functional Assessment of Cancer Therapy- Kidney Symptom Index (FKSI-19)
- To assess changes in global health status in each treatment arm based on EuroQol's EQ-5D
- To assess healthcare resource utilization in each treatment arm

Endpoints

The study had three co-primary efficacy endpoints (Table 12).

Table 12 CA209214 - Primary, Secondary and Exploratory endpoints

Endpoints and Definitions			
Objective	**Endpoint**	**Endpoint Description**	**Analysis**
PRIMARY			
To describe the ORR of nivolumab + ipilimumab and sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC, based on IRRC assessments	ORR	ORR was defined as the proportion of randomized subjects who achieved a best response of complete response (CR) or partial response (PR) using the RECIST v1.1 criteria based on IRRC assessment. BOR was defined as the best response designation, as determined by the IRRC, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations contributed to the BOR assessment. Confirmation of response was required at least 4 weeks after the initial response.	See Section 4.1.1 of the SAP (Appendix 1.11A)
	DOR	DOR was defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented progression as determined by the IRRC (per RECIST v1.1), or death due to any cause, whichever occurs first. The duration of response for a subject who neither progresses nor dies was censored at the same time as for the primary definition of PFS. DOR was evaluated for responders only.	
	TTR	TTR was defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the IRRC. TTR was evaluated for responders only.	

Endpoints and Definitions			
Objective	**Endpoint**	**Endpoint Description**	**Analysis**
To compare the PFS of nivolumab + ipilimumab to sunitinib in intermediate and poor-risk subjects with previously untreated mRCC, based on IRRC assessments	PFS	The primary definition of PFS (PFS truncated at subsequent therapy) was specified as the time between the date of randomization and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first. Subsequent therapy included anticancer therapy, tumor directed radiotherapy, or tumor directed surgery. Subjects who died without a reported progression were considered to have progressed on the date of their death. The secondary definition of PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first. Subjects who died without a reported progression were considered to have progressed on the date of their death. The following censoring rules were applied to both the primary and secondary definitions of PFS: Subjects who did not progress or died were censored on the date of the last evaluable tumor assessment. Subjects who did not have any on study tumor assessments or died were censored on the date of randomization. These additional censoring rules applied to only the primary definition of PFS: Subjects who received subsequent systemic anti-cancer therapy prior to documented progression were censored at the date of the last tumor assessment conducted on or prior to the initiation of the new therapy. Subjects who did not have a documented progression and received subsequent anti-cancer therapy were censored at the date of the last tumor assessment conducted on or prior to the initiation of the new therapy.	See Sections 4.1.2 and 4.1.3 of the SAP (Appendix 1.11A)
To compare the OS of nivolumab + ipilimumab to sunitinib in intermediate and poor-risk subjects with previously untreated mRCC	OS	OS was defined as the time from randomization to the date of death from any cause. Survival time was censored at the date of last contact ("last known alive date") for subjects who were alive. OS was censored for subjects, if randomized, at the date of randomization but had no follow-up. Survival follow-up was to be conducted every 3 months after the subject's off-treatment date.	See Section 4.1.4 of the SAP (Appendix 1.11A)

Endpoints and Definitions

Objective	Endpoint	Endpoint Description	Analysis
SECONDARY			
To estimate the ORR of nivolumab + ipilimumab and sunitinib monotherapy in subjects with previously untreated mRCC (any-risk), based on IRRC assessments	ORR	See above for the endpoint descriptions of ORR, DOR, and TTR.	See Section 4.1.1 of the SAP (Appendix 1.11A)
To compare the PFS of nivolumab + ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC, based on IRRC assessments	PFS	See above for the endpoint description of PFS	See Section 4.1.2 and 4.1.3 of the SAP (Appendix 1.11A)
To compare the OS of nivolumab + ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC	OS	See above for the endpoint description of OS	See Section 7.5.8 of the SAP (Appendix 1.11A)
To estimate the incidence of AEs of nivolumab + ipilimumab and sunitinib monotherapy in all treated subjects with previously untreated mRCC	AEs	This assessment of safety was based on frequency of AEs. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the MedDRA version 19.0. AEs and laboratory values were graded for severity according to the NCI CTCAE version 4.0.	See Section 7.6 of the Core Safety SAP (Appendix 1.11B)

Endpoints and Definitions

Objective	Endpoint	Endpoint Description	Analysis
EXPLORATORY			
To estimate the ORR and PFS based on IRRC-assessments and OS of nivolumab + ipilimumab vs sunitinib monotherapy in favorable-risk subjects with previously untreated mRCC	ORR, DOR, TTR, PFS, and OS	See above for the endpoint description of ORR, DOR, TTR, PFS, and OS	
To explore potential predictive biomarkers of clinical response to nivolumab + ipilimumab by analyzing PD-L1 tumor expression.	PD-L1 tumor expression	PD-L1 tumor expression was defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using an immunohistochemistry (IHC) assay. Tumor biopsy specimens without measurable PD-L1 tumor expression were classified as indeterminate if the staining was hampered for reasons attributed to the biology of the specimen and not because of improper specimen preparation or handling. Missing specimens, specimens that were not optimally collected, and all other specimens were classified as unknown.	Refer to SAP Section 4.3.4 for details
To assess the overall safety and tolerability of nivolumab + ipilimumab vs sunitinib monotherapy	Deaths, AEs, SAEs, AEs leading to DC & dose delay, vital signs, specific lab abnormalities	The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, and abnormalities in specific clinical laboratory assessments. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the MedDRA Version 19.0. AEs and laboratory values were graded for severity according to the NCI CTCAE version 4.0.	See Section 7.6 of the Core Safety SAP (Appendix 1.11B)

Endpoints and Definitions			
Objective	**Endpoint**	**Endpoint Description**	**Analysis**
To monitor immunogenicity of nivolumab and ipilimumab administered as combination therapy	Serum ADA and neutralizing ADA response to nivolumab and ipilimumab	Human serum samples from nivolumab + ipilimumab treated subjects were evaluated for the presence of nivolumab ADA at PPD Inc. (Richmond, VA) using a validated immunoassay method (Method ICDIM 140)[1] and neutralizing activity at BMS (Princeton NJ) using a validated functional cell-based assay (Method 15400).[2] See Appendix 8.3 and 8.5 for nivolumab immunogenicity bioanalytical study reports. Human serum samples from nivolumab + ipilimumab treated subjects also were evaluated for the presence of ipilimumab ADA at PPD Inc. (Richmond, VA) using a validated immunoassay method (Method ICDIM 14)[3] and neutralizing activity at BMS (Princeton NJ) using a validated functional cell-based assay (Method 15818).[4] See Appendix 8.4 and 8.6 for ipilimumab immunogenicity bioanalytical study reports. **Baseline ADA Positive**: an ADA-positive sample at baseline. **ADA Positive**: at least one ADA-positive sample relative to baseline at any time after initiation of treatment. ***Persistent Positive:*** ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart. ***Other Positive:*** not persistent positive with ADA-negative sample in the last sampling time point. ***Last Sample Positive:*** Not persistent positive with ADA-positive sample in the last sampling time point. ***Neutralizing Positive:*** At least 1 ADA positive sample with neutralizing antibodies detected. **ADA Negative:** no ADA positive sample after the initiation of treatment.	See Section 6.1 of the Immunogenicity SAP (Appendix 1.11C)
To evaluate health related quality of life (HRQoL) as assessed by the Functional Assessment of Cancer Therapy-General (FACT-G).	To evaluate HRQoL as assessed by the FACT-G	The FACT-G was a 27-item questionnaire that measured general cancer health related quality of life. The scale was a compilation of general questions divided into four primary HrQoL dimensions: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Summary scores were calculated for each domain in addition to a single overall summary score.	Refer to SAP Section 4.3.5 for details

Endpoints and Definitions			
Objective	**Endpoint**	**Endpoint Description**	**Analysis**
To assess disease related symptoms in each arm based on the NCCN Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19).	To assess disease related symptoms in each arm based on the NCCN FKSI-19	The NCCN FKSI-19 was a 19-item scale that measures tumor specific HrQoL in kidney cancer patients. The FKSI-19 uses five 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, and shortness of breath, pain, nausea and ability to work.	Refer to SAP Section 4.3.5 for details
To assess changes in global health status in each treatment arm based on EuroQol's EQ-5D.	To assess changes in global health status in each treatment arm based on EuroQol's EQ-5D.	Subjects' overall health status was assessed using the EuroQol Group's self-reported health status measure (EQ-5D-3L). EQ-5D had 2 components; the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension had 3 levels: no problems, some problems and severe problems. Once the data was collected and a database created, a scoring function was used to assign a value (ie, EQ-5D index score) to self-reported health states from a set of population-based preference weights. The EQ VAS recorded the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state)	Refer to SAP Section 4.3.6 for details

Note: Objectives not listed in the table are not included in the Clinical Study Report.

Sample size and schedule of analyses

The sample size of the study accounts for the 3 co-primary efficacy endpoints: ORR and PFS as per IRRC and OS evaluated in intermediate and poor-risk subjects with previously untreated mRCC. The overall alpha for this study is 0.05, which was split with 0.001 to evaluate ORR, 0.009 to evaluate PFS and 0.04 to evaluate OS.

ORR was analysed with an alpha of 0.001. PFS was evaluated for treatment effect at an alpha of 0.009 (two-sided, penalized 0.001 from a 0.01 allocation), with at least 80% power; no interim analysis of PFS was planned. OS was evaluated for treatment effect at an alpha level of 0.04 (two-sided) with 90% power, accounting for two formal interim analyses to assess efficacy (Table 13).

It was estimated that approximately 1070 previously untreated mRCC subjects would be randomised in a 1:1 ratio. Among them, 820 subjects (76.6%) with intermediate/poor-risk and approximately 250 (23.4%) subjects with favourable risk as per IMDC (IMDC prognostic score = 0) were to be randomised. Assuming a 21% screen failure rate, it was estimated that approximately 1355 subjects would be enrolled in order to have 820 intermediate/poor-risk subjects randomised. The hypothesized median PFS in the control group was 9 months, based on weightedly averaging 11 months in the intermediate risk and 4 months in the poor risk (Motzer et al, NEJM 2007). The hypothesized median OS in the control group was based on a weighted average of 26 months for intermediate risk and 8 months in the poor risk group (Motzer et al, NEJM, 2014).

Table 13 Summary of Sample Size Parameters and Schedule of Analyses

Co-Primary Endpoints	ORR	PFS	OS
Primary analysis population	Intermediate/poor risk subjects (IMDC score ≥ 1)		
Accrual rate per month	53[b]		
Power	N/A	~80%	90%
Alpha	Administrative 0.001	0.009 2-sided	0.04 2-sided (0.0024 at IA1, 0.0137 at IA2 , 0.0354 at FA)
Hypothesized Median Control vs. exp (months)	25% vs 40%	9 vs. 12.4	20 vs. 26.1
Hypothesized Hazard ratio	N/A	0.726	0.766
Critical Hazard ratio (Observed hazard ratio at which a statistically significant difference would be observed) / Difference in median (months) Corresponding to a minimal clinically significant effect size	N/A	0.785 / 2.5	0.846/ 3.6
Critical HR at interim analysis-1(IA1) /effect size	N/A	N/A	0.72/ 7.8
Expected number of event for IA1 (percentage of target events)	N/A	N/A	330 (52%)
Timing of IA1 from FPFV l(months)	N/A	N/A	35
Critical HR at interim analysis-2(IA2) /effect size	N/A	N/A	0.8 / 5.1
Target number of event for IA2 (percentage of target events)	N/A	N/A	479 (75%)
Timing of IA2 from FPFV (months)	N/A	N/A	46
Accrual Duration (months)	16	16	16
Timing of final analysis (FA) from FPFV (months)	22	35	65
Sample size[a]	820	820	820
Target number of events (Event Goal)	N/A	465	639

[a] East version 5.4 was used for sample size / power computation.

[b] Accrual rate adjusted to reflect observed accrual.

Randomisation

Subjects were randomised 1:1 and stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score (0 vs. 1-2 vs. 3-6) and region (US vs. Canada/Western Europe/Northern Europe vs. Rest of World).

Of the 1096 subjects randomised (550 to nivolumab + ipilimumab, 546 to sunitinib), 1082 (98.7%) were treated (547 with nivolumab + ipilimumab, 535 with sunitinib).

Blinding (masking)

CA209214 was an open-label study.

Statistical methods

ORR: For the intermediate/poor risk group, descriptive estimates of response rate, along with its exact two-sided 95% CI by Clopper-Pearson method, were computed within each treatment arm. A two sided 95% CI for difference of response rate between the treatment arms was also computed using Newcombe's method. If the exact 95%-CIs did not overlap for the intermediate/poor risk, then 95% exact CIs among intermediate/poor/favourable was calculated and a 2-sided, 95% confidence interval for the difference of ORR between treatment arms was computed for all randomised subjects by the method of DerSimonian and Laird, using a fixed effects model (setting the random effect to zero), adjusting for the stratification factors.

PFS: the primary (among intermediate/poor risk subjects) analysis of PFS (as determined by IRRC) was to compare the 2 treatment arms via two-sided 0.009 stratified log-rank test reporting a two-sided log-rank p-value. The estimate of the PFS hazard ratio, of nivolumab combined with ipilimumab to sunitinib monotherapy, was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties were handled using the Exact method. A two-sided, 99.1% CI for the hazard ratio was also presented. The method of Gail and Simon was used to test for a qualitative interaction between treatment and strata, IMDC prognostic risk score (1-2 vs. 3-6) and Region (US vs. Canada/W.Europe/N.Europe vs. ROW). This test was conducted at α= 0.10 level. The proportional hazards assumption was tested at 0.10 in a stratified Cox model by testing the a log(t) term. Sensitivity analyses included accounting for delayed effect by using a weighted log rank test (is primary if unstable than normal stratified test). The estimate of the PFS hazard ratio in the period following 6 months, of nivolumab combined with ipilimumab compared to sunitinib monotherapy, was calculated using a stratified time-dependent Cox model with effects for treatment and period-by-treatment interaction. In this model, period is a binary variable indicating pre- vs. post- 6 months. The second line phase 3 mRCC study (CA209-025) served as the basis for the 6 month delayed treatment effect in PFS. Ties were handled using the exact method. A two-sided 99.1% CI for the hazard ratio was presented. Additionally, unstratified log-rank tests and unstratified Cox models (but adjusted for stratification factors i.e. assuming a common, not stratified baseline hazard), multivariate Cox-model, PFS by investigator, with CRF instead of IVRS values of the covariates, PFS for those without relevant deviations were investigated.

The primary definition of PFS censors for new anti-cancer therapy, tumour-directed radiotherapy, or tumour-directed surgery without prior documented progression; the secondary definition of PFS does not.

OS: Overall survival was compared between the treatment arms at the interim and final analyses, using 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 (two interims: first at time of PFS analysis with around 58% of planned events, and second at 73% of planned events) and final analyses. The stratified hazard ratio between the treatment groups will be presented along with 100*(1- α)% CI (adjusted for interim). At the time of database lock, the actual number of deaths was 328 (51%) of the 639 total number of events. Similar methods were used to analyse OS except the O'Brien and Fleming adjusted α = 0.002 was applied. Therefore a two-sided, 99.8% CI for the hazard ratio was presented. In addition, two-sided p-value was also reported for the primary analysis of OS.

Results

Participant flow

A total of 1390 patients were enrolled in the study (Figure 12). Of the 1096 subjects randomised (550 to nivolumab + ipilimumab, 546 to sunitinib), 1082 (98.7%) were treated (547 with nivolumab + ipilimumab, 535 with sunitinib). Of the 1096 subjects randomised, 847 subjects were randomised in the intermediate/poor-risk group (425 nivolumab + ipilimumab, 422 sunitinib). Of these 847 subjects randomised in the intermediate/poor-risk group, 839 subjects were treated (423 with nivolumab + ipilimumab, 416 with sunitinib). The primary objective was to study efficacy in the intermediate/poor-risk subjects (Table 14).

Figure 12 Participant Flow

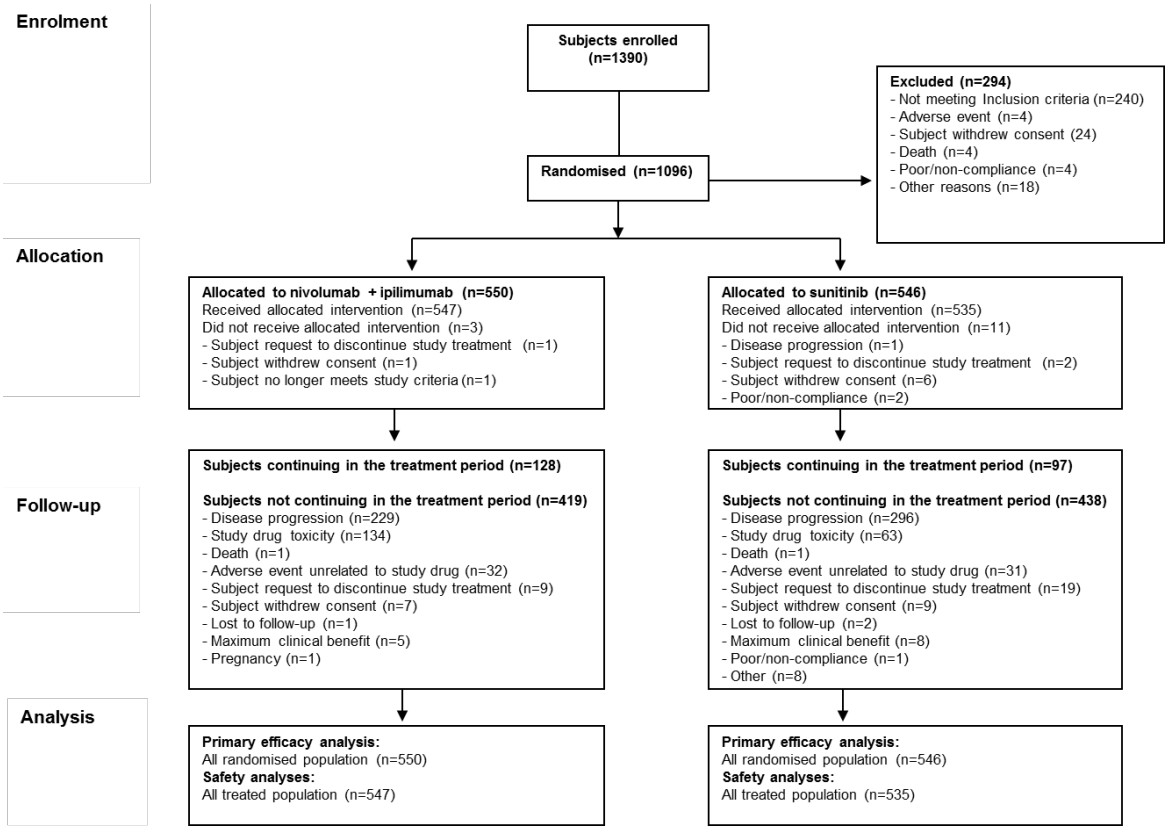


Table 14 Subject Status Summary – All Randomised and Treated Subjects

	Nivolumab + Ipilimmab	Sunitinib	Total
All Intermediate/Poor-risk Subjects (A)			
SUBJECTS RANDOMIZED	425	422	847
SUBJECTS TREATED (%)	423 (99.5)	416 (98.6)	839 (99.1)
SUBJECTS NOT TREATED (%)	2 (0.5)	6 (1.4)	8 (0.9)
REASON FOR NOT BEING TREATED (%)			
DISEASE PROGRESSION	0	1 (0.2)	1 (0.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	1 (0.2)	1 (0.1)
SUBJECT WITHDREW CONSENT	1 (0.2)	2 (0.5)	3 (0.4)
POOR/NON-COMPLIANCE	0	2 (0.5)	2 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.2)	0	1 (0.1)

(A) Percentages based on subjects randomized.
(B) Percentages based on subjects entering period.
Source: Table S.2.6A (randomized), Table S.2.6B (all intermediate/poor-risk subjects),Table S.2.7 (treated)

Recruitment

A total of 174 sites in 28 countries randomised subjects (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Poland, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom, and United States). Of the 1096 randomised subjects, 1082 were treated. The first patient first visit date was 16-Oct-2014 and the last patient randomisation date was 04-Mar-2016. The last patient last visit date (clinical cut-off date) was 26-Jun-2017. The cut-off date for the IRRC scans was 07-Jul-2017. The clinical database lock for this CSR occurred on 07-Aug-2017 for the planned final analysis of co-primary endpoints of IRRC-assessed ORR and PFS in intermediate and poor-risk subjects, and the planned interim analysis of the co-primary OS endpoint in intermediate and poor-risk subjects. The independent DMC reviewed the interim OS data on 06-Sep-2017 and confirmed that the pre-specified boundary for OS was crossed. The DMC recommended the study be stopped early.

Conduct of the study

The original protocol for this study was dated 17-Jul-2014. As of 07-Aug-2017, three global amendments, 10 country-specific amendments and 1 administrative letter were issued for this study. Global amendments can be seen in Table 15.

Table 15 Global Changes to Protocol CA209214

Document (Sites)	Date	Summary of Change
Amendment 01 (All)	17-Jul-2014	This amendment permitted the collection and storage of blood samples for use in future exploratory pharmacogenetic research at all sites that permit pharmacogenetic studies to be conducted. Subjects must provide a signed Pharmacogenetic Blood DNA informed consent.
Amendment 04 (All)	05-Nov-2014	An additional secondary endpoint of incidence of AEs was added, which was previously encompassed in the exploratory objective of assessment of overall safety. One of the IMDC prognostic factor was changed because not all laboratories have an upper limit of normal for corrected calcium. Additional LFT testing for nivolumab subjects prior to each dose for cycle 3 onward was added along with various clarifications throughout the document in response to questions from the clinical sites.
Amendment 13 (All)	04-Aug-2016	A third primary endpoint was added. Objective Response Rate (ORR) was added as a co-Primary Endpoint to provide a descriptive analyses on randomized subjects who achieve a confirmed response (complete response [CR] or partial response [PR]) using the RECIST1.1 criteria and based on IRRC assessment among the intermediate and poor-risk subjects. In addition, modifications to the protocol were made based on required updates from Version 15 of the Nivolumab Investigator Brochure. Language allowing for the collection of additional survival data outside of the original protocol-specified visit windows was added.

Baseline data

Among intermediate/poor-risk subjects, the median age was 61.0 years and the majority of subjects were white and male. The majority of subjects had baseline KPS of 100 (Table 16, Table 17).

Between the 2 treatment groups, 79.4% of subjects had 2 or more disease sites. The most common site of disease (target) was the lung (54.6% and 56.4%), followed by lymph node (33.6% and 38.2%), and kidney (24.2% and 23.9%), in the nivolumab + ipilimumab and the sunitinib group, respectively.

Of the intermediate/poor-risk subjects who had a baseline tumour tissue sample tested for PD-L1, 100/422 (23.7%) in the nivolumab + ipilimumab group and 114/420 (27.1%) in the sunitinib group had tumours that were positive for PD-L1 expression (≥ 1%) at baseline.

Among intermediate/poor-risk subjects, consistent with the inclusion criteria, most (99.3% and 99.5%) subjects in the nivolumab + ipilimumab and sunitinib groups, respectively, had received no prior anticancer therapy. A total of 0.5% of subjects in the nivolumab + ipilimumab and sunitinib groups, respectively, received prior systemic therapy in the adjuvant setting and 0.2% of subjects in the nivolumab + ipilimumab and no sunitinib subjects received prior systemic therapy in the neoadjuvant setting. The most frequent prior systemic cancer therapies in the nivolumab + ipilimumab and sunitinib groups were interferon and interferon alpha (0.2%) for both treatment groups and interleukin 2 (0.2%) in the nivolumab + ipilimumab group.

Baseline demographics and disease characteristics for all randomised subjects are presented in table 17 and table 18.

Table 16 Baseline Demographic Characteristics - Intermediate/Poor-risk Subjects

	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	Total N = 847
AGE (YEARS)			
N	425	422	847
MEAN	60.9	60.1	60.5
MEDIAN	62.0	61.0	61.0
MIN , MAX	26 , 85	21 , 85	21 , 85
STANDARD DEVIATION	9.81	10.48	10.15
AGE CATEGORIZATION (%)			
< 65	265 (62.4)	259 (61.4)	524 (61.9)
>= 65 AND < 75	125 (29.4)	133 (31.5)	258 (30.5)
>= 75 AND < 85	33 (7.8)	29 (6.9)	62 (7.3)
>= 85	2 (0.5)	1 (0.2)	3 (0.4)
>= 75	35 (8.2)	30 (7.1)	65 (7.7)
>= 65	160 (37.6)	163 (38.6)	323 (38.1)
GENDER (%)			
MALE	314 (73.9)	301 (71.3)	615 (72.6)
FEMALE	111 (26.1)	121 (28.7)	232 (27.4)
RACE (%)			
WHITE	369 (86.8)	368 (87.2)	737 (87.0)
BLACK OR AFRICAN AMERICAN	7 (1.6)	6 (1.4)	13 (1.5)
ASIAN	38 (8.9)	39 (9.2)	77 (9.1)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
OTHER	10 (2.4)	9 (2.1)	19 (2.2)
NOT REPORTED	1 (0.2)	0	1 (0.1)
ETHNICITY (%)			
HISPANIC OR LATINO	9 (2.1)	17 (4.0)	26 (3.1)
NOT HISPANIC OR LATINO	201 (47.3)	180 (42.7)	381 (45.0)
NOT REPORTED	215 (50.6)	225 (53.3)	440 (51.9)

Reporting of Ethnicity is required in the US only.
Source: Table S.3.1B

Table 17 Baseline Disease Characteristics and Tumour Assessments – Intermediate/Poor-risk Subjects

	Number of Subjects (%)		
	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	Total N = 847
KARNOFSKY PERFORMANCE STATUS			
100	166 (39.1)	152 (36.0)	318 (37.5)
90	129 (30.4)	134 (31.8)	263 (31.1)
80	76 (17.9)	85 (20.1)	161 (19.0)
70	53 (12.5)	50 (11.8)	103 (12.2)
< 70	1 (0.2)	1 (0.2)	2 (0.2)
BASELINE IMDC PROGNOSTIC SCORE			
0	9 (2.1)	8 (1.9)	17 (2.0)
1-2	314 (73.9)	317 (75.1)	631 (74.5)
3-6	102 (24.0)	97 (23.0)	199 (23.5)
PRIOR NEPHRECTOMY STATUS			
YES	341 (80.2)	319 (75.6)	660 (77.9)
NO	84 (19.8)	103 (24.4)	187 (22.1)
PRIOR RADIOTHERAPY STATUS			
YES	52 (12.2)	52 (12.3)	104 (12.3)
NO	373 (87.8)	370 (87.7)	743 (87.7)
TIME FROM INITIAL DIAGNOSIS TO RANDOMIZATION			
< 1 YEAR	294 (69.2)	296 (70.1)	590 (69.7)
>= 1 YEAR	131 (30.8)	126 (29.9)	257 (30.3)
LDH LEVEL			
<= 1.5*ULN	393 (92.5)	394 (93.4)	787 (92.9)
> 1.5*ULN	25 (5.9)	20 (4.7)	45 (5.3)
NOT REPORTED	7 (1.6)	8 (1.9)	15 (1.8)
HEMOGLOBIN			
< LLN	223 (52.5)	242 (57.3)	465 (54.9)
>= LLN	199 (46.8)	172 (40.8)	371 (43.8)
NOT REPORTED	3 (0.7)	8 (1.9)	11 (1.3)
CORRECTED CALCIUM			
<= 10 MG/DL	63 (14.8)	61 (14.5)	124 (14.6)
> 10 MG/DL	9 (2.1)	18 (4.3)	27 (3.2)
NOT REPORTED	353 (83.1)	343 (81.3)	696 (82.2)
ALKALINE PHOSPHATASE			
< ULN	333 (78.4)	309 (73.2)	642 (75.8)
>= ULN	89 (20.9)	102 (24.2)	191 (22.6)
NOT REPORTED	3 (0.7)	11 (2.6)	14 (1.7)
REGION (PER IVRS)			
US	112 (26.4)	111 (26.3)	223 (26.3)
CANADA/W EUROPE/N EUROPE	148 (34.8)	146 (34.6)	294 (34.7)
REST OF WORLD	165 (38.8)	165 (39.1)	330 (39.0)
BASELINE PD-L1 + STATUS			
0 - < 1%	284 (66.8)	278 (65.9)	562 (66.4)
1 - < 5%	37 (8.7)	34 (8.1)	71 (8.4)
5 - < 10%	8 (1.9)	10 (2.4)	18 (2.1)
>= 10%	55 (12.9)	70 (16.6)	125 (14.8)
NOT REPORTED	41 (9.6)	30 (7.1)	71 (8.4)
SUBJECTS WITH AT LEAST ONE LESION (A) (%)	425 (100.0)	421 (99.8)	846 (99.9)
NUMBER OF SITES WITH AT LEAST ONE LESION (A) (%)			
1	90 (21.2)	84 (19.9)	174 (20.5)
2	135 (31.8)	141 (33.4)	276 (32.6)
3	108 (25.4)	106 (25.1)	214 (25.3)
4	65 (15.3)	55 (13.0)	120 (14.2)
>= 5	27 (6.4)	35 (8.3)	62 (7.3)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)			
N	425	420	845
MEDIAN (MIN - MAX)	72.0 (10 - 357)	68.0 (10 - 359)	70.0 (10 - 359)

(A) Includes both target and non-target lesions.
Source: Table S.3.2B (baseline characteristics), Table S.3.3B (pretreatment tumor assessments)

Numbers analysed

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC (425 with nivolumab + ipilimumab, 422 with sunitinib) (Table 18). 839 subjects were treated (423 with nivolumab + ipilimumab, 416 with sunitinib) in the intermediate/poor-risk group.

Table 18 Analysis Populations

Population	Nivolumab + ipilimumab group N	Sunitinib group N	Total N
All enrolled subjects: All subjects who signed an ICF and were registered into the IVRS. This is the population for pre-treatment disposition.	NA	NA	1390
All randomized subjects: All subjects who were randomized to any treatment arm in the study. This population was considered as the secondary efficacy analysis population. Analysis of demography, protocol deviations, baseline characteristics, and secondary efficacy analysis were performed for this population.	550	546	1096
Intermediate/poor-risk subjects: All randomized subjects with baseline IMDC prognostic score ≥ 1 at the time of randomization (IVRS). This was the primary efficacy analysis population. Analysis of demography, protocol deviations, baseline characteristics and primary efficacy analysis will be performed for this population	425	422	847
All treated subjects: All subjects who received any dose of study therapy. This was the primary dataset for drug exposure and safety analysis.	547	535	1082
All treated intermediate/poor-risk subjects: All intermediate/poor-risk subjects who received any dose of study therapy.	423	416	839
PD-L1 evaluable subjects All treated subjects with evaluable tumor tissue specimens tested at baseline	500	504	1004
Immunogenicity (ADA evaluable) subjects: All nivolumab + ipilimumab-treated subjects with baseline and at least 1 post-baseline assessment for ADA	411 nivolumab-treated subjects; 415 ipilimumab-treated subjects	NA	NA

Outcomes and estimation

In this study, 547 subjects received at least 1 infusion of nivolumab and ipilimumab, and 535 subjects received at least 1 dose of sunitinib (all treated subjects). In the nivolumab + ipilimumab group, 87.6% and 80.3% of subjects received 90% to ≥ 110% of the planned dose intensity of nivolumab and ipilimumab, respectively (Table 19). In the sunitinib group, 54.0% of subjects received 90% to ≥110% of the planned dose intensity of sunitinib. In the nivolumab + ipilimumab group (intermediate/poor-risk) 88.0% and 80.3% of subjects received 90% to ≥ 110% of the planned dose intensity of nivolumab and ipilimumab, respectively (Table 20). In the sunitinib group (intermediate/poor-risk), 58.5% of subjects received 90% to ≥110% of the planned dose intensity of sunitinib.

At the time of the final database lock (07-Aug-2017), the median duration of therapy was 7.85 months in the nivolumab + ipilimumab group, with a median of 14 nivolumab doses and 4 ipilimumab doses received, and 7.82 months in the sunitinib group, with a median daily dose of 31.33 mg/day (range 14.2-50.0) received.

Table 19 Cumulative Dose and Relative Dose Intensity Summary – All Treated Subjects

	Nivolumab + Ipilimumab N = 547		Sunitinib N = 535
	Nivolumab	Ipilimumab	Sunitinib
NUMBER OF DOSES RECEIVED			
MEAN (SD)	20.9 (18.69)	3.6 (0.81)	208.8 (163.92)
MEDIAN (MIN - MAX)	14.0 (1 - 63)	4.0 (1 - 4)	154.0 (1 - 838)
CUMULATIVE DOSE (1)			
MEAN (SD)	62.39 (55.779)	3.63 (0.817)	8702.83 (6743.477)
MEDIAN (MIN - MAX)	41.03 (2.9 - 188.3)	4.00 (1.0 - 6.0)	7000.00 (50.0 - 41900.0)
RELATIVE DOSE INTENSITY (%)			
>= 110%	2 (0.4)	2 (0.4)	108 (20.2)
90% TO < 110%	477 (87.2)	437 (79.9)	181 (33.8)
70% TO < 90%	64 (11.7)	81 (14.8)	149 (27.9)
50% TO < 70%	4 (0.7)	23 (4.2)	87 (16.3)
< 50%	0	4 (0.7)	10 (1.9)
MISSING	0	0	0
AVERAGE DAILY DOSE (MG/DAY) (2)			
MEAN (SD)			31.26 (8.611)
MEDIAN (MIN - MAX)			31.33 (14.2 - 50.0)

(1) Dose units are mg for Sunitinib and mg/kg for Nivolumab/Ipilimumab.
(2) Only for Sunitinib.
Source: Table S.4.1

Table 20 Cumulative Dose and Relative Dose Intensity Summary – Intermediate/poor-risk subjects

	Nivolumab + Ipilimumab N= 423		Sunitinib N= 416
	Nivolumab	Ipilimumab	Sunitinib
NUMBER OF DOSES RECEIVED			
MEAN (SD)	20.5 (18.62)	3.6 (0.83)	177.0 (147.25)
MEDIAN (MIN - MAX)	13.0 (1 - 61)	4.0 (1 - 4)	116.0 (1 - 838)
CUMULATIVE DOSE (1)			
MEAN (SD)	61.15 (55.393)	3.62 (0.840)	7497.51 (6086.151)
MEDIAN (MIN - MAX)	38.91 (2.9 - 185.0)	4.00 (1.0 - 6.0)	5600.00 (50.0 - 41900.0)
RELATIVE DOSE INTENSITY (%)			
>= 110%	2 (0.5)	2 (0.5)	102 (24.5)
90% TO < 110%	370 (87.5)	340 (80.4)	140 (33.7)
70% TO < 90%	49 (11.6)	63 (14.9)	103 (24.8)
50% TO < 70%	2 (0.5)	14 (3.3)	66 (15.9)
< 50%	0	4 (0.9)	5 (1.2)
MISSING	0	0	0
AVERAGE DAILY DOSE (MG/DAY) (2)			
MEAN (SD)			32.13 (8.787)
MEDIAN (MIN - MAX)			32.19 (14.2 - 50.0)

(1) Dose units are mg for Sunitinib and mg/kg for Nivolumab/Ipilimumab.
(2) Only for Sunitinib.
Program Source: /gbs/prod/clin/programs/ca/209/214/csrfa02/rpt/adhoc/20180124/rt-ex-rdi-ip-v01.sas 01-FEB-2018 18:19

Subsequent therapy

Subsequent therapy was received by 45.6% and 57.7% of subjects in the nivolumab + ipilimumab and sunitinib groups, respectively, including 39.5% and 54.0%, respectively, who received subsequent systemic cancer therapy (All treated subjects - Table 6.6-1 in CSR). In the nivolumab + ipilimumab group, 20.2% of subjects received subsequent treatment with sunitinib. In the sunitinib group, 28.2% of subjects received subsequent therapy with an anti-PD-1 pathway agent (nivolumab or pembrolizumab).

Protocol deviations

Relevant protocol deviations (significant protocol deviations that were programmable and could potentially affect the interpretability of the study) were reported in 2.4% of intermediate/poor-risk subjects (2.4 of subjects in eacht treatment group. Most common relevant protocol deviation at study entry was 'subjects with a baseline IMDC score of <1' (2.1% of intermediate/poor-risk subjects) (Table 21).

Table 21 Relevant Protocol Deviations – All Intermediate/Poor-risk Subjects

	Number of Subjects (%)		
	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	Total N = 847
SUBJECTS WITH AT LEAST ONE DEVIATION	10 (2.4)	10 (2.4)	20 (2.4)
AT ENTRANCE			
SUBJECT WITH BASELINE KPS < 70%	1 (0.2)	1 (0.2)	2 (0.2)
SUBJECT WHO RECEIVED PRIOR SYSTEMIC ANTI-CANCER THERAPY	0	0	0
SUBJECT WITH UNCONFIRMED HISTOLOGY	0	1 (0.2)	1 (0.1)
AT ENTRANCE (ONLY FOR INTERMEDIATE/POOR RISK SUBJECTS)			
SUBJECT WITH BASELINE IMDC SCORE < 1	9 (2.1)	8 (1.9)	17 (2.0)
ON-TREATMENT DEVIATIONS			
SUBJECT WHO RECEIVED ANTI-CANCER THERAPY	0	0	0
SUBJECT TREATED DIFFERENTLY AS RANDOMIZED	0	0	0

Efficacy

Overall efficacy results

Overall efficacy results include the co-primary endpoints for the intermediate/poor-risk subjects (primary objective) and all-treated subjects (secondary objective) (Table 22).

Table 22 Summary of Efficacy Results in CA209214 (07-Aug-2017 Database Lock)

	Intermediate/Poor-risk Subjects		All Randomized (Any-Risk) Subjects	
	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	Nivolumab + Ipilimumab N = 550	Sunitinib N = 546
Overall Survival	*Co-primary objective*		*Secondary objective*	
N events (%)	140 (32.9)	188 (44.5)	161 (29.3)	204 (37.4)
Median OS (months)[a]	N.A.	25.95	N.A.	32.92
Exact 95% CI	(28.16, N.A.)	(22.08, N.A.)	-	(N.A., N.A.)
HR (99.8% CI)[b]	0.63 (0.44, 0.89)		0.68 (0.49, 0.95)	
p-value[c]	<0.0001		0.0003	
Overall Survival by PD-L1 Tumor Expression (1% tumor cell membrane expression)				
Subjects with ≥ 1% PD-L1 Expression, n/N	28/100	57/114	30/113	60/127
Median (months) 95% CI	N.A.	19.61 (14.78, N.A)	N.A.	N.A. (15.47, N.A.)
Subjects with < 1% PD-L1 Expression, n/N (%)	93/284	114/278	108/386	126/376
Median (months) 95% CI	N.A. (28.16, N.A.)	N.A. (23.98, N.A)	N.A.	32.92 (N.A., N.A.)
Subjects with Non-quantifiable PD-L1 Expression, n/N (%)	19/41	17/30	23/51	18/43
Median (months) 95% CI	24.34 (10.12, N.A.)	15.70 (9.76, N.A.)	24.34 (16.99, N.A.)	N.A. (15.70, N.A.)
IRRC-assessed Objective Response Rate (CR+PR) [d]	*Co-primary objective*		*Secondary objective*	
N responders (%)	177 (41.6)	112 (26.5)	213 (38.7)	176 (32.2)
Exact 95% CI	36.9, 46.5	22.4, 31.0	34.6, 42.9	28.3, 36.3
Difference in ORR (95% CI)[e,f]	16.0 (9.8, 22.2)		7.2 (1.8, 12.7)	
p-value[g]	<0.0001		0.0191	
Best Overall Response				
Complete Response (CR)	40 (9.4)	5 (1.2)	54 (9.8)	12 (2.2)
Partial Response (PR)	137 (32.2)	107 (25.4)	159 (28.9)	164 (30.0)
Stable Disease (SD)	133 (31.3)	188 (44.5)	199 (36.2)	232 (42.5)
Progressive Disease (PD)	83 (19.5)	72 (17.1)	99 (18.0)	78 (14.3)

	Intermediate/Poor-risk Subjects		All Randomized (Any-Risk) Subjects	
	Nivolumab + Ipilimumab N = 425	**Sunitinib N = 422**	**Nivolumab + Ipilimumab N = 550**	**Sunitinib N = 546**
Unable To Determine (UTD)	31 (7.3)	50 (11.8)	38 (6.9)	59 (10.8)
Time to Response				
Median (Min, Max), months	2.79 (0.9, 11.3)	3.04 (0.6, 15.0)	2.79 (0.9, 11.3)	4.01 (0.6, 20.8)
Duration of Response				
Median (95% CI), months[a]	N.A. (21.82, N.A.)	18.17 (14.82, N.A.)	N.A. (21.82, N.A.)	20.96 (18.17, N.A.)
Min, Max[h]	1.4+, 25.5+	1.3+, 23.6+	1.4+, 27.7+	1.3+, 26.3+
Objective Response Rate by PD-L1 Tumor Expression (1% tumor cell membrane expression)[b, d]				
Subjects with ≥ 1% PD-L1 Expression, n/N (%)	100/422 (23.7)	114/420 (27.1)	113/546 (20.7)	127/541 (23.5)
N responders (%)	58 (58.0)	25 (21.9)	60 (53.1)	28 (22.0)
95% CI	47.7, 67.8	14.7, 30.6	43.5, 62.5	15.2, 30.3
Subjects with < 1% PD-L1 Expression, n/N (%)	284/422 (67.3)	278/420 (66.2)	386/546 (70.7)	376/541 (69.5)
N responders (%)	106 (37.3)	79 (28.4)	139 (36.0)	133 (35.4)
95% CI	31.7, 43.2	23.2, 34.1	31.2, 41.0	30.5, 40.4
Subjects with Non-quantifiable PD-L1 Expression, n/N (%)	38/422 (9.0)	28/420 (6.7)	47/546 (8.6)	38/541 (7.0)
N responders (%)	13 (34.2)	8 (28.6)	14 (29.8)	14 (36.8)
95% CI	19.6, 51.4	13.2, 48.7	17.3, 44.9	21.8, 54.0
IRRC-assessed Progression-free Survival	***Co-primary objective***		***Secondary objective***	
N events (%)	228 (53.6)	228 (54.0)	296 (53.8)	271 (49.6)
Median PFS (months)[a]	11.56	8.38	12.42	12.32
Exact 95% CI	(8.71, 15.51)	(7.03, 10.81)	(9.89, 16.53)	(9.79, 15.24)
HR (99.1% CI)[b]	0.82 (0.64, 1.05)		0.98 (0.79, 1.23)	
p-value[c]	0.0331		0.8498	

	Intermediate/Poor-risk Subjects		All Randomized (Any-Risk) Subjects	
	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	Nivolumab + Ipilimumab N = 550	Sunitinib N = 546
PFS by PD-L1 Tumor Expression (1% tumor cell membrane expression) [i]				
Subjects with ≥ 1% PD-L1 Expression, n/N	45/100	66/114	54/113	69/127
Median (months) 95% CI	22.80 (9.40, N.A.	5.85 (4.44, 7.13)	21.42 (9.40, 23.56)	6.83 (5.55, 8.74)
Subjects with < 1% PD-L1 Expression, n/N (%)	160/284	143/278	211/386	179/376
Median (months) 95% CI	11.01 (8.08, 14.92)	10.41 (7.52, 13.83)	11.56 (8.74, 15.47)	15.24 (12.22, 19.35)
Subjects with Non-quantifiable PD-L1 Expression, n/N (%)	21/38	17/28	28/47	20/38
Median (months) 95% CI	8.25 (3.09, 23.49)	8.54 (4.53, 15.05)	10.84 (5.32, 16.99)	13.01 (7.00, 21.32)

[a] Median computed using Kaplan-Meier method.

[b] Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sunitinib.

[c] Log-rank Test stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.

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

[e] Strata adjusted difference in ORR (nivolumab + ipilimumab – sunitinib) based on DerSimonian and Laird method.

[f] Stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (United States of America, Canada/western Europe/northern Europe, Rest of World) as entered into the IVRS.

[g] Two-sided p-value from DerSimonian and Laird Test.

[h] Symbol + indicates a censored value.

[i] PD-L1 tumor expression results from validated assay.

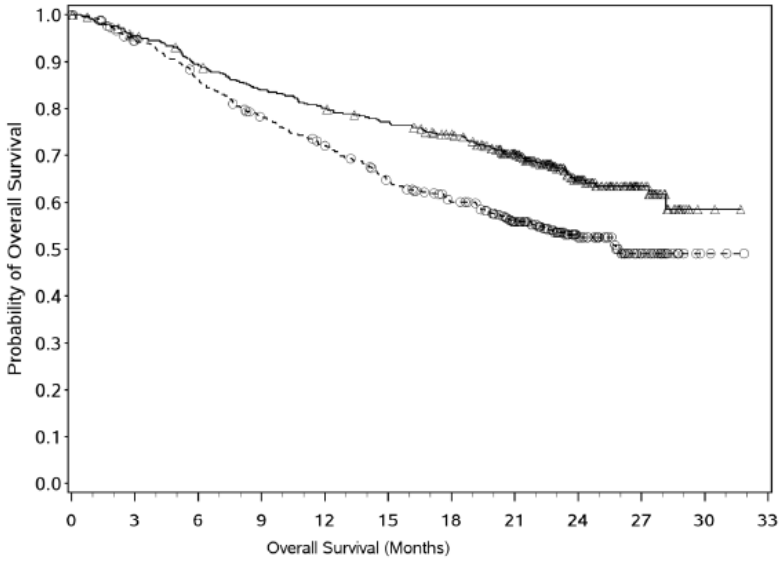
Overall survival

OS results are presented for the intermediate/poor-risk, all randomised, and favourable-risk subjects.

In intermediate/poor-risk subjects, nivolumab + ipilimumab demonstrated statistically significant and superior OS compared with sunitinib at the planned interim OS analysis (HR: 0.63 [99.8% CI: 0.44, 0.89]; stratified log-rank 2-sided p-value < 0.0001) at the adjusted alpha of 0.002 (Figure 13, Table 23). Upon request, the applicant provided an OS update (database lock 01-Mar-2018) (Figure 14).

- Median OS was not reached at the time of analysis in the nivolumab + ipilimumab group and was 25.95 months in the sunitinib group (Figure 13).
- OS rates in the nivolumab + ipilimumab and the sunitinib groups, respectively, were 89.5% and 86.2% at 6 months, and 80.1% and 72.1% at 12 months.
- The K-M curves for OS separated early, favouring nivolumab + ipilimumab (Figure 13).
- 285 (67.1%) subjects in the nivolumab + ipilimumab group and 234 (55.5%) subjects in the sunitinib group were censored. At the time of database lock, a higher proportion of subjects in the nivolumab + ipilimumab group vs. the sunitinib group were still on treatment (24.2% vs. 13.5%), and a similar proportion were in follow-up (39.1% vs. 35.1%). 3.8% of subjects were off-study in the nivolumab + ipilimumab group and 6.9% in the sunitinib group.

Figure 13 Overall Survival, Primary Analysis (Database Lock 07-Aug-2017) – All Intermediate/Poor-risk Subjects

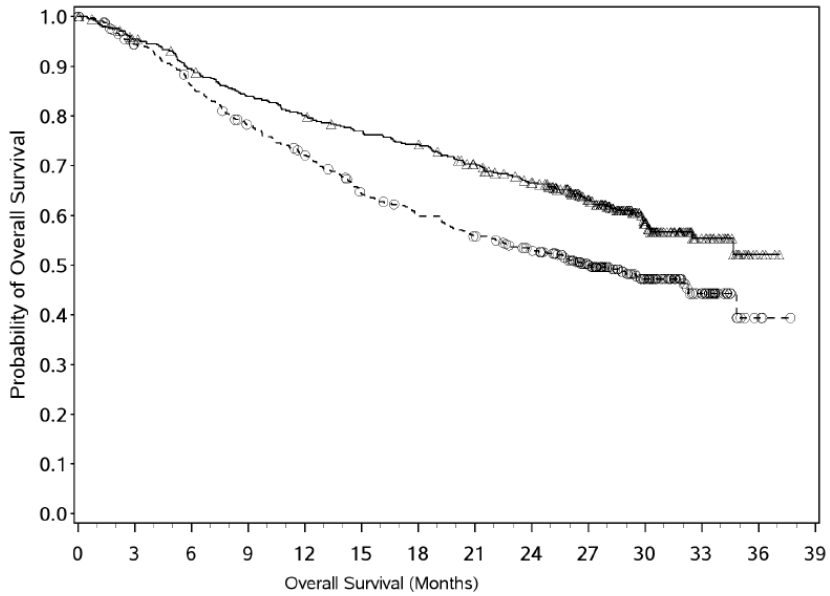


Number of Subjects at Risk

Nivolumab + Ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

Nivolumab + Ipilimumab (events: 140/425), median and 95% CI: N.A. (28.16, N.A.)
Sunitinib (events: 188/422), median and 95% CI: 25.95 (22.08, N.A.)
Hazard Ratio (Nivolumab + Ipilimumab vs Sunitinib) and 99.8% CI: 0.63 (0.44, 0.89); p-value: <0.0001

Figure 14 Kaplan-Meier Plot of Overall Survival in study CA209214, Follow-Up Analysis (Database Lock 01-Mar-2018) – Intermediate/Poor-risk Subjects



Number of Subjects at Risk

Nivolumab + Ipilimumab	425	399	372	348	332	317	306	282	257	201	102	33	4	0
Sunitinib	422	387	352	316	288	253	233	216	196	147	87	36	3	0

Nivolumab + Ipilimumab (events: 166/425), median and 95% CI: N.A. (32.49, N.A.)
Sunitinib (events: 209/422), median and 95% CI: 26.97 (22.08, 34.83)
Hazard Ratio (Nivolumab + Ipilimumab vs Sunitinib) and 95% CI: 0.66 (0.54, 0.81); p-value: <0.0001

Table 23 Overall Survival, Primary Analysis (Database Lock 07-Aug-2017) – All Intermediate/Poor-risk subjects

	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	HR (1) 99.8% CI	P-Value (2)
# EVENTS / # SUBJECTS (%)	140/425 (32.9)	188/422 (44.5)	0.63	<0.0001
MEDIAN OS (MONTHS) (3) (95% CI)	N.A. (28.16, N.A.)	25.95 (22.08, N.A.)	(0.44, 0.89)	

(1) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sunitinib.
(2) Log-rank Test stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.
(3) Based on Kaplan-Meier Estimates.
The boundary for statistical significance requires the p-value to be less than 0.002.
Source: Table S.5.12A

In all randomised subjects, treatment with nivolumab + ipilimumab was statistically significant compared with sunitinib (HR = 0.68, 99.8% CI: 0.49, 0.95; p-value: 0.0003) at the adjusted alpha of 0.002 (Figure 15, Table 24). Upon request, the applicant provided an OS update (database lock 01-Mar-2018) (Figure 16).

- OS rates in the nivolumab + ipilimumab and the sunitinib groups, respectively, were 91.3% and 89.3% at 6 months, and 83.1% and 77.4% at 12 months.

- 389 (70.7%) subjects in the nivolumab + ipilimumab group and 342 (62.6%) subjects in the sunitinib group were censored. At the time of this database lock, a higher proportion of subjects in the nivolumab + ipilimumab group vs. the sunitinib group were still on treatment (23.3% vs. 17.8%), and a similar proportion were in follow-up (43.3% vs. 38.3%). 4.2% ofsubjects were off-study in the nivolumab + ipilimumab group and 6.6% in the sunitinib group.

Figure 15 Overall Survival, Secondary Analysis (Database Lock 07-Aug-2017) – All Randomised Subjects

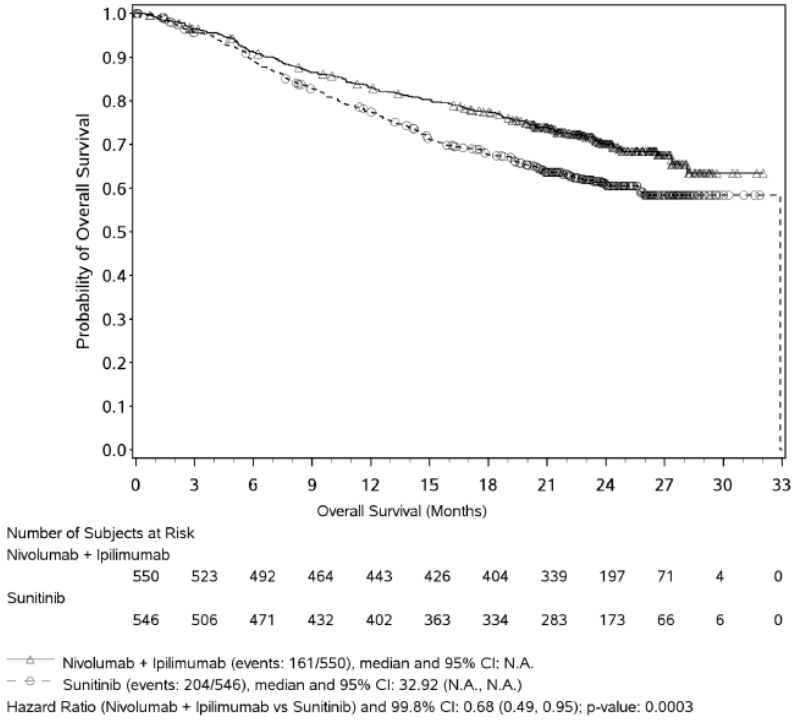
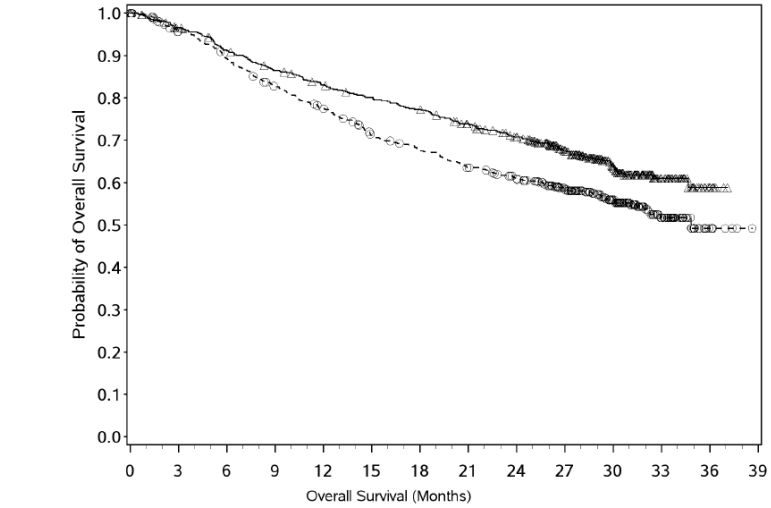


Figure 16 Kaplan-Meier Plot of Overall Survival in Study CA209214, Follow-Up Analysis (Database Lock 01-Mar-2018) - All Randomised Subjects



Number of Subjects at Risk

Nivolumab + Ipilimumab	550	523	492	464	443	425	410	384	356	290	172	59	8	0
Sunitinib	546	506	471	433	402	363	342	321	299	242	164	65	7	0

Nivolumab + Ipilimumab (events: 191/550), median and 95% CI: N.A.
Sunitinib (events: 232/546), median and 95% CI: 34.83 (31.44, N.A.)
Hazard Ratio (Nivolumab + Ipilimumab vs Sunitinib) and 95% CI: 0.70 (0.58, 0.85); p-value: 0.0003

Table 24 Overall Survival, Secondary Analysis – All Randomised Subjects

	Nivolumab + Ipilimumab N = 550	Sunitinib N = 546	HR (1) 99.8% CI	P-Value (2)
# EVENTS / # SUBJECTS (%)	161/550 (29.3)	204/546 (37.4)	0.68	0.0003
MEDIAN OS (MONTHS) (3) (95% CI)	N.A.	32.92 (N.A., N.A.)	(0.49, 0.95)	

(1) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sunitinib.
(2) Log-rank Test stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.
(3) Based on Kaplan-Meier Estimates.
The boundary for statistical significance requires the p-value to be less than 0.002.
Source: Table S.5.12B

In favourable-risk subjects, the OS was observed to favour sunitinib (HR=1.45, 99.8% CI 0.51-4.12), though very few events (p=0.2715, 37/249) (Figure 17). Upon request, the applicant provided an OS update (database lock 01-Mar-2018) (Figure 18).

Figure 17 Overall Survival, Exploratory Analysis (Database Lock 07-Aug-2017) – All Favourable Risk Subjects

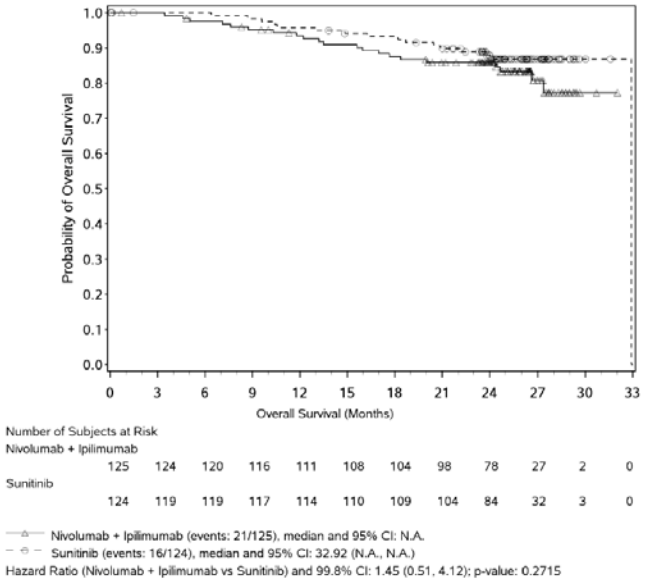
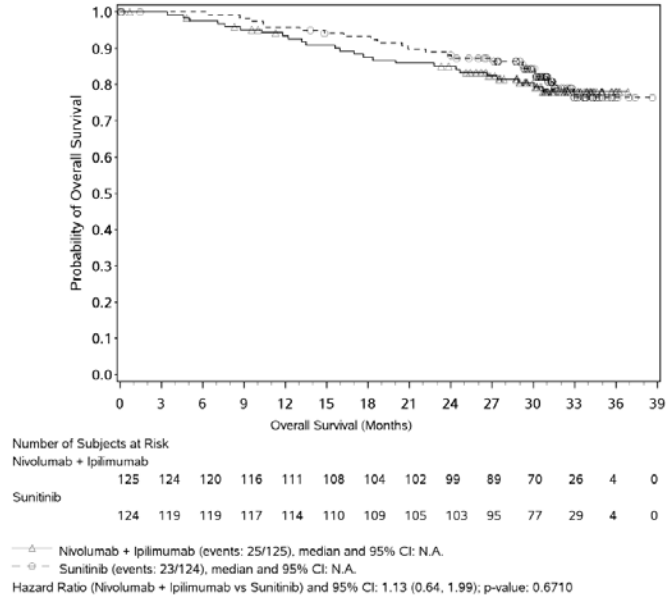


Figure 18 Kaplan-Meier Plot of Overall Survival in Study CA209214, Follow-Up Analysis (Database Lock 01-Mar-2018) - All Favourable-Risk Subjects



Progression-free survival

Progression-free survival per IRRC

In intermediate/poor-risk subjects, the analysis of IRRC-assessed PFS (co-primary endpoint) using RECIST v1.1, and censoring for subsequent therapy (primary PFS definition) favoured nivolumab + ipilimumab vs. sunitinib (HR = 0.82, [99.1% CI: 0.64, 1.05], stratified 2-sided p-value = 0.0331) (Figure 19, Table 25). This difference did not meet the stringent pre-specified α = 0.009 for statistical significance.

- The median PFS was 11.56 months (95% CI: 8.71,15.51) in the nivolumab + ipilimumab group and 8.38 months (95% CI: 7.03, 10.81) in the sunitinib group, representing a difference in median PFS of 3.2 months (Figure 19).

- The 12-month PFS rate was 49.6% in the nivolumab + ipilimumab group and 42.6% in the sunitinib group. Rates at 24-months were not available due to censoring at this later time point.

- The K-M curves overlapped until approximately 6-7 months and then separated, favouring nivolumab + ipilimumab (Figure 19).

- The piece-wise HR ≤ 6 months (HR = 0.90) and > 6 months (HR = 0.69) favours the nivolumab + ipilimumab treatment during the first 6 months and thereafter (S.5.1E -CSR). The weighted log-rank 2-sided p-value = 0.0024.

- 228 (53.6%) subjects had a PFS event in the nivolumab + ipilimumab group (197 progression and 31 deaths) and 228 (54.0%) subjects had a PFS event in the sunitinib group (185 progression and 43 deaths) (Table 25).

- Censoring for PFS per IRRC:

- 46.4% and 46.0% of subjects in the nivolumab + ipilimumab and sunitinib groups, respectively, were censored.

- 44.0% of subjects in the nivolumab + ipilimumab and 40.8% of subjects in the sunitinib group had their PFS time censored on date of last tumour assessment on-study or last assessment prior to subsequent anti-cancer therapy, including 14.8% of subjects in the nivolumab + ipilimumab and 26.8% of subjects in the sunitinib group who were censored due to receiving subsequent anti-cancer therapy.

- The most common reason for censoring between the 2 groups was 'received subsequent anti-cancer therapy'.

Figure 19 Progression Free Survival per IRRC, Primary Analysis, Primary Definition (Database Lock 07-Aug-2017) – All Intermediate/Poor-risk Subjects

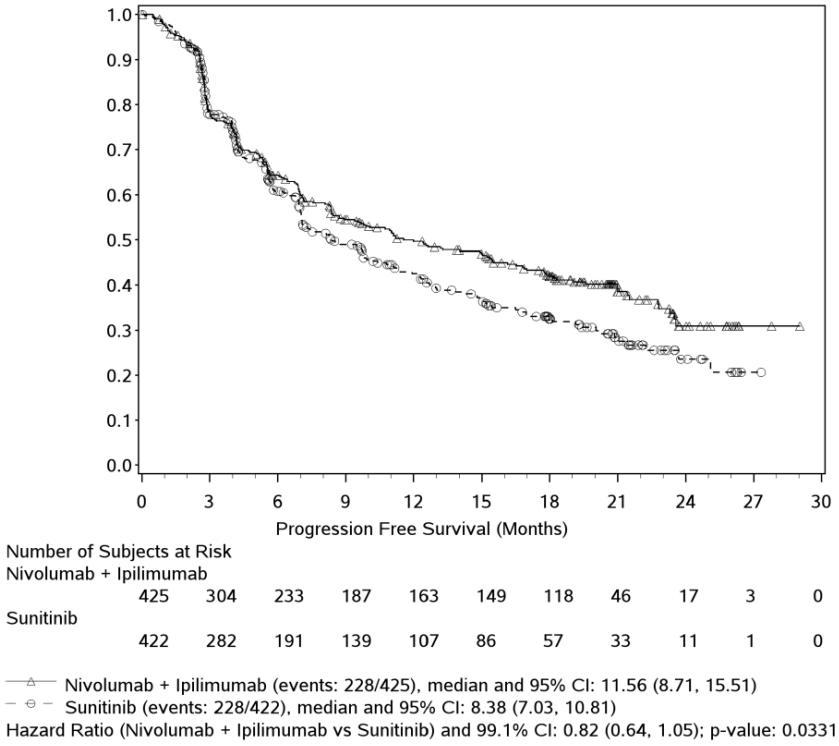


Table 25 Progression Free Survival per IRRC, Primary Analysis, Primary Definition (Database Lock 07-Aug-2017) – All Intermediate/Poor Risk Subjects

	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422	HR <= 6 months (1) 99.1% CI	HR > 6 months (1) 99.1% CI	P-Value (2)
# EVENTS / # SUBJECTS (%)	228/425 (53.6)	228/422 (54.0)	0.90	0.69	0.0024
MEDIAN PFS (MONTHS) (3) (95% CI)	11.56 (8.71, 15.51)	8.38 (7.03, 10.81)	(0.66, 1.23)	(0.46, 1.04)	

(1) Stratified time dependent Cox model. Hazard Ratio before and after 6 months is Nivolumab + Ipilimumab over Sunitinib.
(2) Weighted log-rank Test stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.
(3) Based on Kaplan-Meier Estimates.
Source: Table S.5.1E

In all randomised subjects, IRRC-assessed PFS analysis was only for qualitative purposes due to hierarchical testing.

- PFS observed in all randomised subjects (with censoring for subsequent therapy), including favourable-risk subjects, showed HR=0.98, 99.1% CI: 0.79, 1.23, stratified log-rank 2-sided p = 0.8498 in the nivolumab + ipilimumab group vs. the sunitinib group (Table 7.4.1.1-2,Figure 20, Table 26).

- The median PFS was 12.42 months (95% CI 9.89-16.53) for nivolumab + ipilimumab and 12.32 months (95% CI 9.79-15.24) for sunitinib (Table 26).

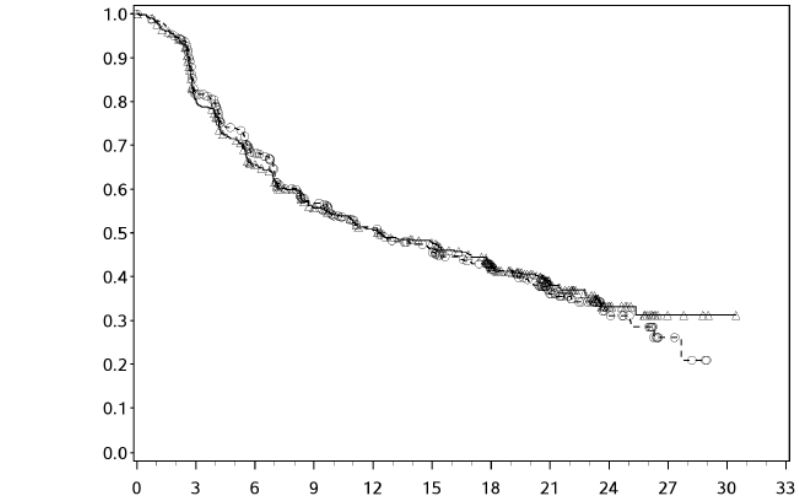
- The 12-month PFS rate was 50.6% in the nivolumab + ipilimumab group and 51.1% in the sunitinib. Rates at 24-months were not available due to censoring at this later time point.

- Among the 1096 randomised subjects, 567 subjects (51.7%) had PFS events.

- 296 (53.8%) subjects had a PFS event in the nivolumab + ipilimumab group (259 progression and 37 deaths) and 271 (49.6%) subjects had a PFS event in the sunitinib group (227 progression and 44 deaths) (Table 26).

- 46.2% and 50.4% of subjects in the nivolumab + ipilimumab and sunitinib groups, respectively, were censored. Most of these subjects were censored on date of last tumour assessment on-study or last assessment prior to subsequent anti-cancer therapy (44.0% in the nivolumab + ipilimumab group, 44.7% in the sunitinib group), including 14.7% in the nivolumab + ipilimumab group and 26.6% in the sunitinib group who were censored due to subsequent anti-cancer therapy. The most common reason for censoring between the 2 groups was 'received subsequent anti-cancer therapy.'

Figure 20 Progression Free Survival per IRRC, Secondary Analysis, Primary Definition (Database Lock 07-Aug-2017) – All Randomised Subjects



Number of Subjects at Risk

Nivolumab + Ipilimumab	550	406	313	249	215	196	157	72	26	5	1	0
Sunitinib	546	388	290	219	181	153	113	67	28	6	0	0

Nivolumab + Ipilimumab (events: 296/550), median and 95% CI: 12.42 (9.89, 16.53)
Sunitinib (events: 271/546), median and 95% CI: 12.32 (9.79, 15.24)
Hazard Ratio (Nivolumab + Ipilimumab vs Sunitinib) and 99.1% CI: 0.98 (0.79, 1.23); p-value: 0.8498

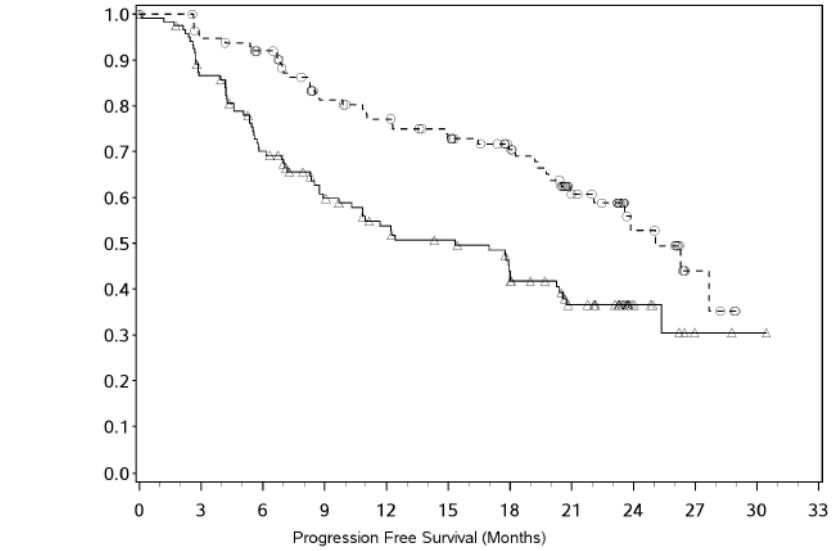
Table 26 Progression Free Survival per IRRC, Secondary Analysis, Primary Definition – All Randomised Subjects

	Nivolumab + Ipilimumab N = 550	Sunitinib N = 546	HR (1) 99.1% CI	P-Value (2)
# EVENTS / # SUBJECTS (%)	296/550 (53.8)	271/546 (49.6)	0.98	0.8498
MEDIAN PFS (MONTHS) (3) (95% CI)	12.42 (9.89, 16.53)	12.32 (9.79, 15.24)	(0.79, 1.23)	

(1) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sunitinib.
(2) Log-rank Test stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.
(3) Based on Kaplan-Meier Estimates.
Source: Table S.5.1C

In favourable-risk subjects, the nivolumab + ipilimumab group showed improved median PFS (15.34 months, 95% CI: 9.69, 20.27) compared with the intermediate and poor-risk subjects, and even stronger improvements were observed in the sunitinib group (25.07 months, 95% CI 20.93 - NA). The HR in PFS (nivolumab + ipilimumab group vs. sunitinib group) was 2.18 (99.1% CI: 1.29, 3.68); p-value <0.0001 (Figure 21).

Figure 21 Progression free survival per IRRC, primary analysis, primary definition – all favourable risk subjects



Objective response rate

Objective response rate per IRRC

In intermediate/poor-risk subjects, the IRRC-assessed ORR using RECIST v1.1 (co-primary endpoint) was higher in the nivolumab + ipilimumab group (41.6% [95% CI: 36.9, 46.5]) than in the sunitinib group (26.5% [95% CI: 22.4, 31.0]), with non-overlapping 95% CIs. The stratified difference in ORR (nivolumab + ipilimumab - sunitinib) was 16.0% (95% CI: 9.8, 22.2), p-value < 0.0001; see Table 27.

- BOR was CR in 9.4% of subjects in the nivolumab + ipilimumab group and 1.2% of subjects in the sunitinib group
- BOR was PR in 32.2% and 25.4% of subjects, respectively
- BOR was SD in 31.3% and 44.5% of subjects, respectively

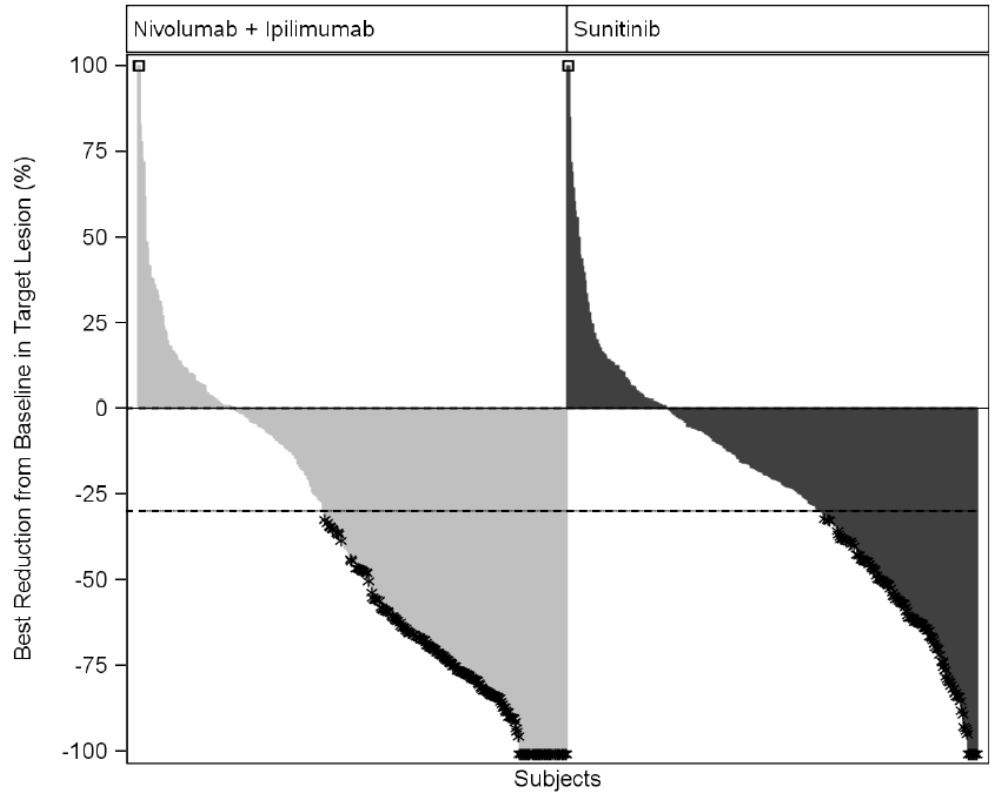
The waterfall plot for intermediate/poor-risk subjects showed a greater magnitude of target lesion tumour burden reductions in the nivolumab + ipilimumab group compared with the sunitinib group (Figure 22).

Table 27 Best Overall Response per IRRC (Database Lock 07-Aug-2017) – Intermediate/Poor-risk Subjects – Co-primary Endpoint

	Number of Subjects (%)	
	Nivolumab + Ipilimumab N = 425	Sunitinib N = 422
BEST OVERALL RESPONSE (RECIST 1.1)		
COMPLETE RESPONSE (CR)	40 (9.4)	5 (1.2)
PARTIAL RESPONSE (PR)	137 (32.2)	107 (25.4)
STABLE DISEASE/NON-CR/NON-PD (SD/NON-CR/NON-PD)	133 (31.3)	188 (44.5)
PROGRESSIVE DISEASE (PD)	83 (19.5)	72 (17.1)
UNABLE TO DETERMINE (UTD)	31 (7.3)	50 (11.8)
NOT REPORTED	1 (0.2)	0
OBJECTIVE RESPONSE RATE (1) (95% CI)	177/425 (41.6%) (36.9, 46.5)	112/422 (26.5%) (22.4, 31.0)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2,3) (95% CI)	16.0% (9.8, 22.2)	
P-VALUE (4)	<0.0001	

(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivolumab+Ipilimumab - Sunitinib) based on DerSimonian and Laird method.
(3) Stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.
(4) Two-sided p-value from DerSimonian and Laird Test
Source: Table S.5.21A

Figure 22 Waterfall Plot of Best Percentage Reduction from Baseline in Sum of Diameters of Target Lesions per IRRC – Intermediate/Poor-risk Subjects



Subjects with target lesion at Baseline and at Least One On-Treatment Tumor Assessment.
Best reduction is maximum reduction in sum of diameters of target lesions (negative value means true reduction, positive value means increase only observed over time).
Horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response.
Asterisk symbol represents responders.
Square symbol represents % change truncated to 100%.
Source: Figure S.5.12A

In all randomised subjects, the IRRC-assessed ORR using RECIST v1.1 (secondary endpoint) was numerically higher in the nivolumab + ipilimumab group (38.7% [95% CI: 34.6, 42.9]) than the sunitinib group (32.2% [95% CI: 28.3, 36.3]); see Table 28. The strata-adjusted difference in ORR (nivolumab + ipilimumab - sunitinib) was 7.2% (95% CI: 1.8, 12.7), p = 0.0191. 9.8% vs. 2.2% of subjects achieved a CR in the nivolumab + ipilimumab and sunitinib groups, respectively.

Table 28 Best Overall Response per IRRC (Database Lock 07-Aug-2017) – All Randomised Subjects – Secondary Endpoint

	Number of Subjects (%)	
	Nivolumab + Ipilimumab N = 550	Sunitinib N = 546
BEST OVERALL RESPONSE (RECIST 1.1)		
COMPLETE RESPONSE (CR)	54 (9.8)	12 (2.2)
PARTIAL RESPONSE (PR)	159 (28.9)	164 (30.0)
STABLE DISEASE/NON-CR/NON-PD (SD/NON-CR/NON-PD)	199 (36.2)	232 (42.5)
PROGRESSIVE DISEASE (PD)	99 (18.0)	78 (14.3)
UNABLE TO DETERMINE (UTD)	38 (6.9)	59 (10.8)
NOT REPORTED	1 (0.2)	1 (0.2)
OBJECTIVE RESPONSE RATE (1)	213/550 (38.7%)	176/546 (32.2%)
(95% CI)	(34.6, 42.9)	(28.3, 36.3)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2,3)	7.2%	
(95% CI)	(1.8, 12.7)	
P-VALUE (4)	0.0191	

(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivolumab+Ipilimumab - Sunitinib) based on DerSimonian and Laird method.
(3) Stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (USA, Canada/W Europe/N Europe, ROW) as entered into the IVRS.
(4) Two-sided p-value from DerSimonian and Laird Test.
Source: Table S.5.21B in the CA209214 Final CSR[1]

In favourable-risk subjects, the IRRC-assessed ORR using RECIST v1.1 (exploratory endpoint) was 28.8% (95% CI: 21.1, 37.6) and 51.6% (95% CI: 42.5, 60.7) in the nivolumab + ipilimumab and sunitinib groups, respectively (Table 29). 11.2% vs. 5.6% of subjects achieved a CR in the nivolumab + ipilimumab and sunitinib groups, respectively.

Table 29 Best Overall Response per IRRC (Database Lock 07-Aug-2017) – All Favourable Risk Subjects

	Number of Subjects (%)	
	Nivolumab + Ipilimumab N = 125	Sunitinib N = 124
BEST OVERALL RESPONSE (RECIST 1.1)		
COMPLETE RESPONSE (CR)	14 (11.2)	7 (5.6)
PARTIAL RESPONSE (PR)	22 (17.6)	57 (46.0)
STABLE DISEASE/NON-CR/NON-PD (SD/NON-CR/NON-PD)	66 (52.8)	44 (35.5)
PROGRESSIVE DISEASE (PD)	16 (12.8)	6 (4.8)
UNABLE TO DETERMINE (UTD)	7 (5.6)	9 (7.3)
NOT REPORTED	0	1 (0.8)
OBJECTIVE RESPONSE RATE (1)	36/125 (28.8%)	64/124 (51.6%)
(95% CI)	(21.1, 37.6)	(42.5, 60.7)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2,3)	-23.0%	
(95% CI)	(-34.5, -11.4)	
P-VALUE (4)	0.0002	

Time to response and duration of response

In intermediate/poor-risk subjects, median TTR was 2.79 months in the nivolumab + ipilimumab group and 3.04 months in the sunitinib group. In intermediate/poor-risk subjects, the median DOR in the nivolumab + ipilimumab group was not reached at the time of database lock, and 18.17 months in the sunitinib group. There was a median follow-up of 25.2 months (minimum follow-up was 17.5 months), providing a robust assessment of duration of response.

In all randomised subjects, median TTR was 2.79 in the nivolumab + ipilimumab group and 4.01 in the sunitinib group. Median DOR had not been achieved in the nivolumab + ipilimumab group and was 20.96 months in the sunitinib group.

In favourable-risk subjects, median TTR was 2.82 months in the nivolumab + ipilimumab group and 4.17 months in the sunitinib group. Median DOR had not been achieved in the nivolumab + ipilimumab group and was 23.49 months in the sunitinib group.

Ancillary analyses

Overall survival subgroup results

In intermediate/poor-risk subjects, OS favoured the nivolumab + ipilimumab group vs. the sunitinib group in all pre-defined subgroups (Figure 23). The CIs for the HRs in the majority of subgroups were wide due to small subgroup sizes. Results were similar in all randomised subjects (Figure 24). Corrected calcium based on "yes" or "no" response, respectively, to corrected calcium > 10 mg/dL was provided by the applicant upon request (Figure 25).

Figure 23 Forest Plot of Treatment Effect on OS in Pre-defined Subsets – All Intermediate/Poor-risk Subjects

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mOS (95% CI)	Sunitinib N of events (N of subjects)	Sunitinib mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs Sunitinib
Overall	847	140 (425)	N.A. (28.16, N.A.)	188 (422)	25.95 (22.08, N.A.)	0.66 (0.53, 0.82)
Age Categorization						
< 65	524	77 (265)	N.A.	118 (259)	25.66 (20.76, N.A.)	0.53 (0.40, 0.71)
>= 65 and < 75	258	46 (125)	27.33 (23.43, N.A.)	55 (133)	N.A. (19.61, N.A.)	0.86 (0.58, 1.27)
>= 75	65	17 (35)	21.52 (8.41, N.A.)	15 (30)	19.19 (11.66, N.A.)	0.97 (0.48, 1.95)
Gender						
Male	615	104 (314)	N.A.	130 (301)	N.A. (22.37, N.A.)	0.71 (0.55, 0.92)
Female	232	36 (111)	N.A. (28.16, N.A.)	58 (121)	23.36 (15.47, N.A.)	0.52 (0.34, 0.78)
Race						
White	737	128 (369)	N.A. (28.16, N.A.)	170 (368)	25.66 (20.67, N.A.)	0.66 (0.52, 0.83)
Black or African American	13	2 (7)	N.A. (5.68, N.A.)	4 (6)	16.30 (0.89, N.A.)	0.30 (0.05, 1.70)
Asian	77	7 (38)	N.A.	9 (39)	N.A.	0.78 (0.29, 2.09)
Other	19	2 (10)	N.A. (5.39, N.A.)	5 (9)	17.68 (3.52, N.A.)	0.31 (0.06, 1.58)
Not Reported	1	1 (1)	0.95 (N.A., N.A.)	0 (0)		
Region						
US	222	33 (112)	N.A. (27.33, N.A.)	43 (110)	N.A. (20.67, N.A.)	0.64 (0.40, 1.00)
Canada/W Europe/N Europe	295	51 (148)	N.A.	68 (147)	25.79 (19.61, N.A.)	0.70 (0.49, 1.01)
Rest of World	330	56 (165)	N.A. (28.16, N.A.)	77 (165)	25.66 (17.87, N.A.)	0.63 (0.45, 0.89)
Karnofsky Performance Status						
90-100	581	75 (295)	N.A.	117 (286)	N.A. (23.98, N.A.)	0.55 (0.41, 0.73)
< 90	266	65 (130)	21.52 (18.73, N.A.)	71 (136)	17.81 (12.09, N.A.)	0.86 (0.61, 1.20)
Baseline IMDC Prognostic Score (CRF)						
0	17	1 (9)	N.A. (10.71, N.A.)	1 (8)	N.A. (11.60, N.A.)	
1-2	631	87 (314)	N.A.	121 (317)	N.A. (25.79, N.A.)	0.66 (0.50, 0.87)
3-6	199	52 (102)	22.21 (16.69, N.A.)	66 (97)	9.72 (6.67, 12.94)	0.57 (0.39, 0.82)
Prior Neo-adjuvant or Adjuvant Therapy						
Yes	5	0 (3)	N.A.	0 (2)	N.A.	
No	842	140 (422)	N.A. (28.16, N.A.)	188 (420)	25.79 (21.82, N.A.)	0.66 (0.53, 0.82)
Prior Nephrectomy						
Yes	660	103 (341)	N.A.	127 (319)	N.A. (25.66, N.A.)	0.69 (0.53, 0.89)
No	187	37 (84)	N.A. (20.40, N.A.)	61 (103)	14.55 (12.62, 22.08)	0.63 (0.42, 0.94)
Prior Radiotherapy						
Yes	104	20 (52)	N.A. (20.44, N.A.)	28 (52)	17.94 (11.17, N.A.)	0.64 (0.36, 1.14)
No	743	120 (373)	N.A. (28.16, N.A.)	160 (370)	N.A. (22.60, N.A.)	0.66 (0.52, 0.83)
Time From Initial Diagnosis To Randomization (Years)						
< 1 Year	590	100 (294)	N.A.	139 (296)	22.87 (19.19, N.A.)	0.61 (0.48, 0.80)
>= 1 Year	257	40 (131)	N.A. (28.16, N.A.)	49 (126)	N.A. (25.79, N.A.)	0.77 (0.50, 1.16)
LDH Level						
<= 1.5*ULN	787	122 (393)	N.A.	167 (394)	N.A. (23.98, N.A.)	0.65 (0.52, 0.83)
> 1.5*ULN	45	15 (25)	7.49 (5.29, N.A.)	17 (20)	4.37 (1.97, 10.32)	
Not Reported	15	3 (7)	N.A. (2.20, N.A.)	4 (8)	8.18 (0.89, 8.90)	
Hemoglobin						
< LLN	465	80 (223)	N.A. (27.33, N.A.)	125 (242)	20.04 (14.78, 25.95)	0.60 (0.46, 0.80)
>= LLN	371	58 (199)	N.A. (28.16, N.A.)	59 (172)	N.A.	0.81 (0.56, 1.16)
Not Reported	11	2 (3)	2.35 (2.20, 2.50)	4 (8)	8.18 (0.89, 8.90)	
Corrected Calcium						
<= 10 mg/dl	124	28 (63)	28.16 (16.13, N.A.)	29 (61)	23.98 (15.47, N.A.)	0.94 (0.56, 1.58)
> 10 mg/dl	27	6 (9)	20.40 (0.56, N.A.)	10 (18)	12.68 (2.69, N.A.)	
Not Reported	696	106 (353)	N.A.	149 (343)	N.A. (22.08, N.A.)	0.60 (0.47, 0.77)
Alkaline phosphatase						
< ULN	642	88 (333)	N.A.	120 (309)	N.A. (25.66, N.A.)	0.61 (0.47, 0.81)
>= ULN	191	50 (89)	20.37 (13.90, 27.33)	63 (102)	11.63 (8.51, 17.81)	0.80 (0.55, 1.16)
Not Reported	14	2 (3)	2.35 (2.20, 2.50)	5 (11)	8.18 (0.89, N.A.)	
Baseline PD-L1 + Status 1% Cut Off						
Yes	214	28 (100)	N.A.	57 (114)	19.61 (14.78, N.A.)	0.45 (0.29, 0.71)
No	562	93 (284)	N.A. (28.16, N.A.)	114 (278)	N.A. (23.98, N.A.)	0.73 (0.56, 0.96)
Not Reported	71	19 (41)	24.34 (10.12, N.A.)	17 (30)	15.70 (9.76, N.A.)	0.75 (0.39, 1.45)
Baseline PD-L1 + Status 5% Cut Off						
Yes	143	21 (63)	N.A.	42 (80)	16.20 (11.04, N.A.)	0.53 (0.31, 0.89)
No	633	100 (321)	N.A. (28.16, N.A.)	129 (312)	N.A. (23.98, N.A.)	0.68 (0.52, 0.88)
Not Reported	71	19 (41)	24.34 (10.12, N.A.)	17 (30)	15.70 (9.76, N.A.)	0.75 (0.39, 1.45)
Baseline PD-L1 + Status 10% Cut Off						
Yes	125	18 (55)	N.A. (22.97, N.A.)	38 (70)	15.80 (10.02, N.A.)	0.50 (0.28, 0.88)
No	651	103 (329)	N.A. (28.16, N.A.)	133 (322)	N.A. (23.98, N.A.)	0.68 (0.52, 0.88)
Not Reported	71	19 (41)	24.34 (10.12, N.A.)	17 (30)	15.70 (9.76, N.A.)	0.75 (0.39, 1.45)

Figure 24 Forest Plot of Treatment Effect on OS in Pre-defined Subsets – All Randomised Subjects

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mOS (95% CI)	Sunitinib N of events (N of subjects)	Sunitinib mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs Sunitinib
Overall	1096	161 (550)	N.A.	204 (546)	32.92 (N.A., N.A.)	0.73 (0.59, 0.89)
Age Categorization						
< 65	668	86 (340)	N.A.	125 (328)	N.A. (25.95, N.A.)	0.57 (0.44, 0.76)
>= 65 and < 75	342	54 (164)	N.A. (27.33, N.A.)	63 (178)	32.92 (N.A., N.A.)	0.92 (0.64, 1.33)
>= 75	86	21 (46)	N.A. (10.58, N.A.)	16 (40)	N.A. (13.31, N.A.)	1.27 (0.66, 2.43)
Gender						
Male	808	121 (413)	N.A.	141 (395)	32.92 (N.A., N.A.)	0.79 (0.62, 1.01)
Female	288	40 (137)	N.A. (28.16, N.A.)	63 (151)	N.A. (22.08, N.A.)	0.58 (0.39, 0.87)
Race						
White	969	149 (486)	N.A.	186 (483)	32.92 (N.A., N.A.)	0.73 (0.59, 0.91)
Black or African American	13	2 (7)	N.A. (5.68, N.A.)	4 (6)	16.30 (0.89, N.A.)	0.30 (0.05, 1.70)
Asian	93	7 (46)	N.A.	9 (47)	N.A.	0.79 (0.29, 2.12)
Other	20	2 (10)	N.A. (5.39, N.A.)	5 (10)	N.A. (3.52, N.A.)	0.35 (0.07, 1.81)
Not Reported	1	1 (1)	0.95 (N.A., N.A.)	0 (0)		
Region						
US	306	39 (154)	N.A.	49 (152)	32.92 (N.A., N.A.)	0.70 (0.46, 1.07)
Canada/W Europe/N Europe	401	58 (201)	N.A.	76 (200)	N.A.	0.74 (0.53, 1.04)
Rest of World	389	64 (195)	N.A. (28.16, N.A.)	79 (194)	N.A. (25.66, N.A.)	0.73 (0.53, 1.02)
Karnofsky Performance Status						
90-100	808	93 (412)	N.A.	133 (396)	32.92 (N.A., N.A.)	0.62 (0.48, 0.81)
< 90	288	68 (138)	21.52 (18.73, N.A.)	71 (150)	20.67 (13.80, N.A.)	0.96 (0.69, 1.35)
Baseline IMDC Prognostic Score (CRF)						
0	231	19 (120)	N.A.	15 (111)	32.92 (N.A., N.A.)	1.30 (0.65, 2.60)
1-2	665	90 (328)	N.A.	123 (337)	N.A. (25.95, N.A.)	0.69 (0.53, 0.91)
3-6	199	52 (102)	22.21 (16.69, N.A.)	66 (97)	9.72 (6.67, 12.94)	0.57 (0.39, 0.82)
Not Reported	1	0 (0)		0 (1)	N.A.	
Prior Neo-adjuvant or Adjuvant Therapy						
Yes	13	1 (10)	N.A. (27.37, N.A.)	0 (3)	N.A.	
No	1083	160 (540)	N.A.	204 (543)	32.92 (N.A., N.A.)	0.73 (0.59, 0.90)
Prior Nephrectomy						
Yes	890	121 (453)	N.A.	143 (437)	32.92 (N.A., N.A.)	0.78 (0.61, 0.99)
No	206	40 (97)	N.A. (21.45, N.A.)	61 (109)	15.70 (13.01, 23.98)	0.62 (0.41, 0.92)
Prior Radiotherapy						
Yes	133	25 (63)	N.A. (20.44, N.A.)	30 (70)	32.92 (17.68, 32.92)	0.94 (0.55, 1.60)
No	963	136 (487)	N.A.	174 (476)	N.A.	0.70 (0.56, 0.87)
Time From Initial Diagnosis To Randomization (Years)						
< 1 Year	597	100 (297)	N.A.	139 (300)	23.98 (19.71, N.A.)	0.62 (0.48, 0.80)
>= 1 Year	499	61 (253)	N.A.	65 (246)	32.92 (N.A., N.A.)	0.94 (0.66, 1.33)
LDH Level						
<= 1.5*ULN	1026	142 (513)	N.A.	183 (513)	32.92 (N.A., N.A.)	0.73 (0.59, 0.91)
> 1.5*ULN	47	15 (27)	16.69 (5.49, N.A.)	17 (20)	4.37 (1.97, 10.32)	
Not Reported	23	4 (10)	N.A. (2.20, N.A.)	4 (13)	8.18 (0.89, N.A.)	
Hemoglobin						
< LLN	470	80 (224)	N.A. (27.33, N.A.)	125 (246)	21.82 (15.70, N.A.)	0.62 (0.47, 0.82)
>= LLN	609	78 (322)	N.A.	75 (287)	32.92 (N.A., N.A.)	0.94 (0.68, 1.29)
Not Reported	17	3 (4)	2.50 (2.20, 15.97)	4 (13)	8.18 (0.89, N.A.)	
Corrected Calcium						
<= 10 mg/dl	167	34 (87)	N.A. (23.66, N.A.)	30 (80)	N.A. (23.98, N.A.)	1.12 (0.69, 1.83)
> 10 mg/dl	29	6 (10)	20.40 (0.56, N.A.)	11 (19)	12.88 (5.72, N.A.)	
Not Reported	900	121 (453)	N.A.	163 (447)	32.92 (N.A., N.A.)	0.66 (0.52, 0.84)
Alkaline phosphatase						
< ULN	870	105 (451)	N.A.	136 (419)	32.92 (N.A., N.A.)	0.68 (0.53, 0.88)
>= ULN	206	53 (95)	20.44 (13.90, 24.67)	63 (111)	14.95 (9.76, N.A.)	0.91 (0.63, 1.31)
Not Reported	20	3 (4)	2.50 (2.20, 15.97)	5 (16)	8.90 (0.89, N.A.)	
Baseline PD-L1 + Status 1% Cut Off						
Yes	240	30 (113)	N.A.	60 (127)	N.A. (15.47, N.A.)	0.46 (0.29, 0.71)
No	762	108 (386)	N.A.	126 (376)	32.92 (N.A., N.A.)	0.80 (0.62, 1.03)
Not Reported	94	23 (51)	24.34 (16.99, N.A.)	18 (43)	N.A. (15.70, N.A.)	1.13 (0.61, 2.10)
Baseline PD-L1 + Status 5% Cut Off						
Yes	158	21 (71)	N.A.	44 (87)	19.61 (12.62, N.A.)	0.48 (0.29, 0.81)
No	844	117 (428)	N.A.	142 (416)	32.92 (N.A., N.A.)	0.75 (0.59, 0.96)
Not Reported	94	23 (51)	24.34 (16.99, N.A.)	18 (43)	N.A. (15.70, N.A.)	1.13 (0.61, 2.10)
Baseline PD-L1 + Status 10% Cut Off						
Yes	132	18 (58)	N.A.	39 (74)	16.20 (11.70, N.A.)	0.49 (0.28, 0.86)
No	870	120 (441)	N.A.	147 (429)	32.92 (N.A., N.A.)	0.74 (0.58, 0.94)
Not Reported	94	23 (51)	24.34 (16.99, N.A.)	18 (43)	N.A. (15.70, N.A.)	1.13 (0.61, 2.10)

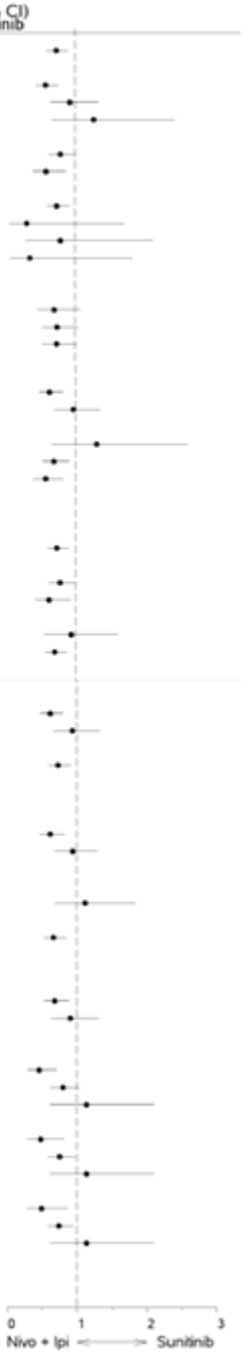
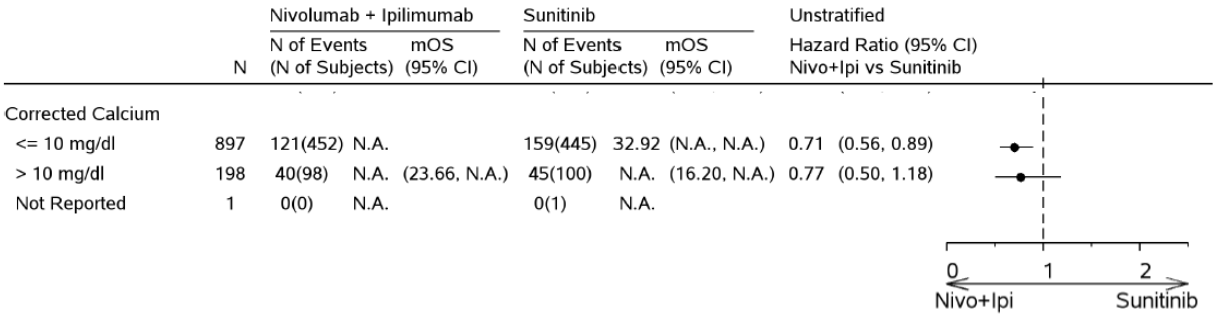


Figure 25 Forest Plot of Treatment Effect on OS in Pre-defined Subsets (corrected calcium update) – All Randomised Subjects



HR is not computed for subset category with less than 21 subjects per treatment group.

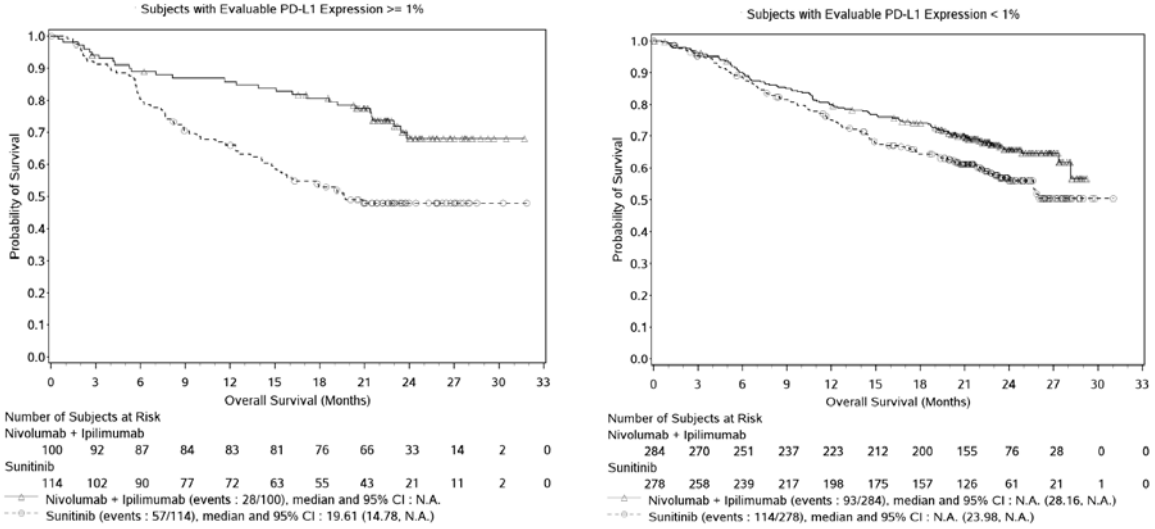
Baseline PD-L1 expression in relation to overall survival

In intermediate/poor-risk subjects, exploratory analyses were performed to investigate the effect of PD-L1 tumour expression on OS.

- Median OS for ≥ 1% PD-L1 tumour expression in nivolumab + ipilimumab subjects was not reached at the time of this report, and was 19.61 months in the sunitinib group (Figure 26). For nivolumab + ipilimumab vs. sunitinib for baseline PD-L1 tumour expression ≥ 1%, HR = 0.45 (95% CI: 0.29, 0.71) (Figure S.5.6A -CSR).

- Median OS for < 1% PD-L1 tumour expression in nivolumab + ipilimumab and sunitinib subjects was not reached at the time of this report. For nivolumab + ipilimumab vs. sunitinib for baseline PD-L1 tumour expression < 1%, HR = 0.73 (0.56, 0.96).

Figure 26 Overall Survival – For each PD-L1 Expression Results Group and for each PD-L1 Status Group by Treatment – Intermediate/Poor-risk Subjects



In all randomised subjects, including favourable risk, results of OS by baseline PD-L1 tumour expression were consistent with those in intermediate/poor-risk subjects (Figure 27, Figure 28).

- PD-L1 positive: HR (95% CI): 0.46 (0.29, 0.71)
- PD-L1 negative: HR (95% CI): 0.80 (0.62, 1.03)

In an analysis of the predictive relationship of PD-L1 tumour expression for OS, OS was similar in all PD-L1 evaluable subjects with PD-L1 tumour expression ≥ 1% compared with those with PD-L1 tumour expression < 1% in the nivolumab + ipilimumab group (HR 0.93, 95% CI: 0.62, 1.39).

However, in the sunitinib group, OS was favoured in subjects with PD-L1 tumour expression < 1% compared to those with PD-L1 tumour expression ≥ 1% (HR 1.64, 95% CI: 1.20, 2.23; Table S.10.12-CSR).

Additional information is provided in the following:

- Forest Plot of OS and PFS per IRRC - Hazard Ratios by PD-L1 Expression Result Group and by PD-L1 Status Group - All Randomised Subjects - Figure S.10.8 – CSR.

Figure 27 Overall Survival – For each PD-L1 Expression Results Group and for each PD-L1 Status Group by Treatment – All Randomised Subjects

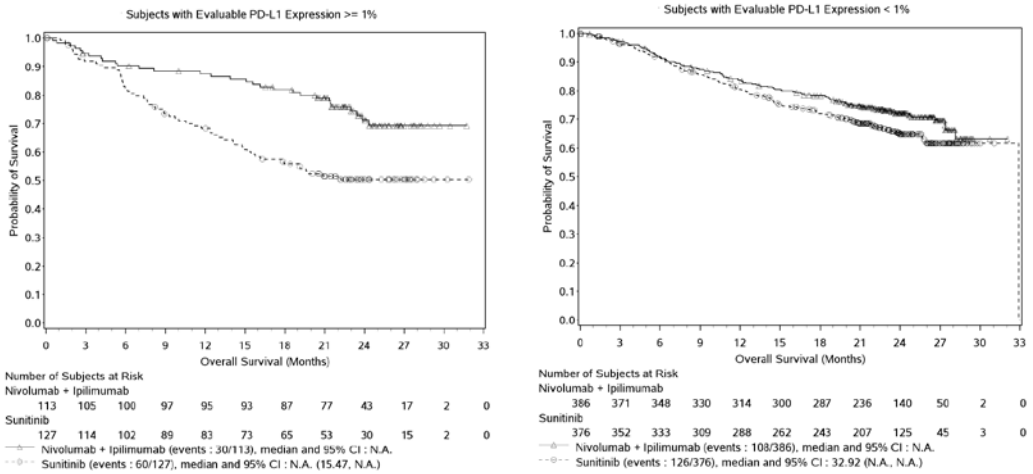
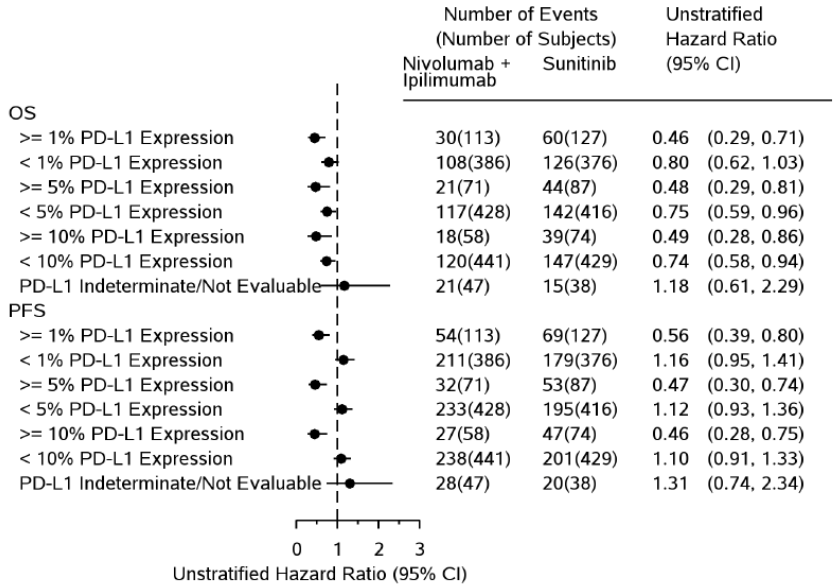


Figure 28 Forest Plot of OS and PFS per IRRC – Hazard Ratios by PD-L1 Expression result Group and by PD-L1 status Group – All Randomised Subjects



Baseline peripheral MDSC expression in relation to overall survival

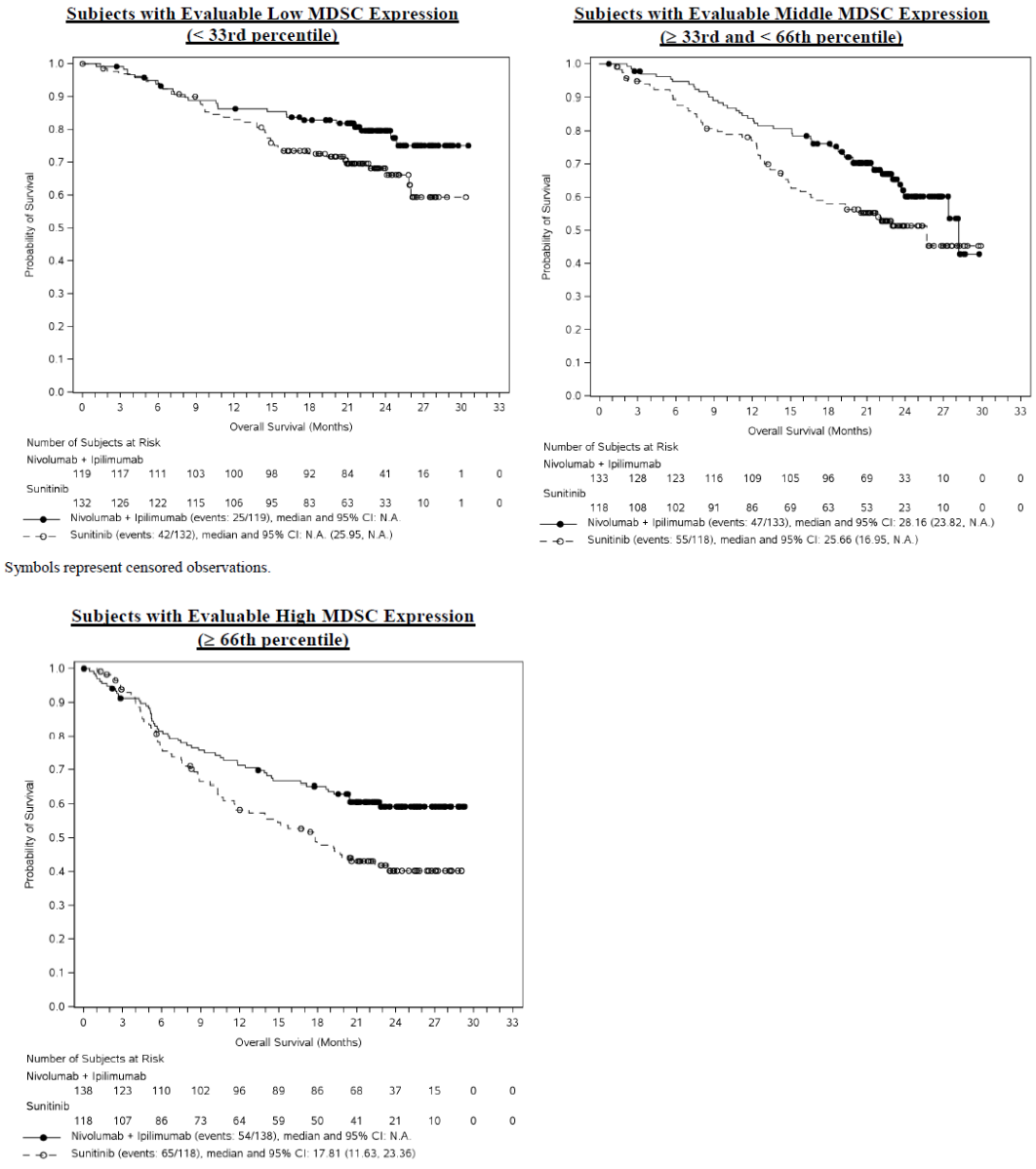
In intermediate/poor-risk subjects, exploratory analyses were performed to investigate the effect of MDSC tumour expression on OS based on baseline peripheral MDSC (% of CD14+LIN-) (Figure 29).

- Median OS for low MDSC expression expression in nivolumab + ipilimumab subjects was not reached at the time of the analysis, and was not reached in the sunitinib group.

- Median OS for middle MDSC expression expression in nivolumab + ipilimumab subjects was 28.15 (23.82 – N.A.) at the time of the analysis, and was 25.66 (16.95, N.A.) in the sunitinib group.

- Median OS for high MDSC expression expression in nivolumab + ipilimumab subjects was not reached at the time of the analysis, and was 17.81 (11.63, 23.36) in the sunitinib group.

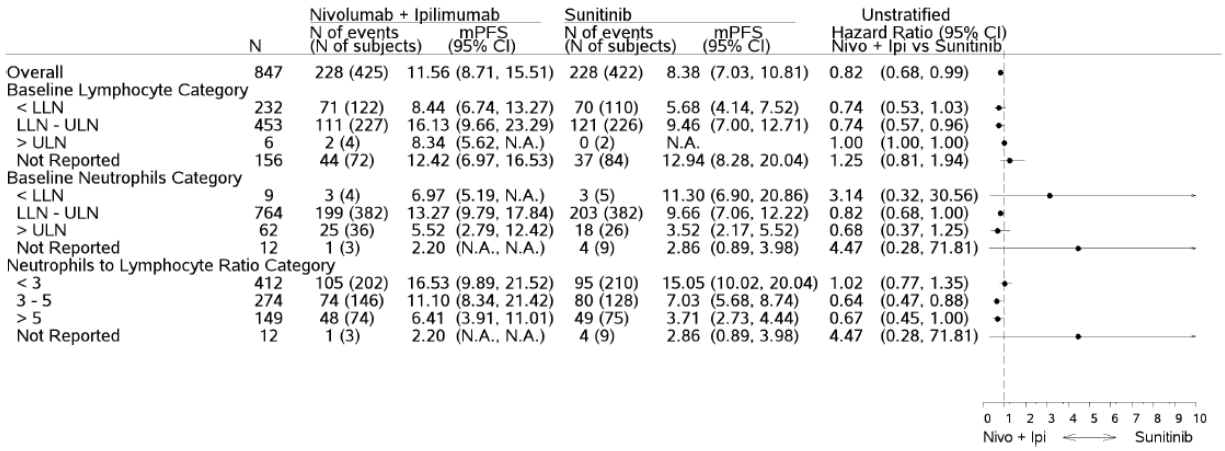
Figure 29 Kaplan-Meier Plot of Overall Survival per IRRC, MDSC Expression Results Group by Treatment – All Intermediate/Poor-Risk Subjects



Blood neutrophil lymphocyte ratio (NLR) and overall survival

In intermediate/poor-risk subjects, exploratory analyses were performed to investigate the effect of NLR on OS based on peripheral absolute lymphocyte and neutrophil counts (Figure 30).

Figure 30 Forest Plot of Treatment Effect on Progression-free Survival per IRRC in Neutrophil Lymphocyte Ratio Subsets, Primary Analysis, Primary Definition - All Intermediate/Poor-Risk Subjects



Progression-free survival subgroup results

Unweighted differences between treatment groups in PFS were analysed using the Cox model for PFS (time to events) endpoints to assess the impact of specific baseline characteristics.

In intermediate/poor-risk subjects, the IRRC-assessed ORR using RECIST v1.1 favoured the nivolumab + ipilimumab group vs. the sunitinib group in all pre-defined subgroups except for Black or African American, and Asian, time from initial diagnosis to randomisation (years) ≥ 1 year, and corrected calcium ≤ 10 mg/dl (Figure 31). The CIs for the odds ratios in the majority of subgroups were wide due to small subgroup sizes.

Results were similar in all randomised subjects (Figure 32). [note: the labels for sunitinib and nivolumab + ipilimumab seem to be switched at the bottom of the forest plot (Figure 32), hazard ratios below 1 should be in favour of nivolumab+ ipilimumab instead of sunitinib. Information on the pre-defined patient subsets based on corrected calcium “yes” or “no”, respectively, was provided by the applicant upon request (Figure 33).

Figure 31 Forest plot of Treatment Effect on Progression Free Survival per IRRC in Pre-defined Subsets – Primary Analysis, Primary Definition – All Intermediate/Poor-risk Subjects

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mPFS (95% CI)	Sunitinib N of events (N of subjects)	Sunitinib mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs Sunitinib
Overall	847	228 (425)	11.56 (8.71, 15.51)	228 (422)	8.38 (7.03, 10.81)	0.82 (0.68, 0.99)
Age Categorization						
< 65	524	137 (265)	12.62 (8.71, 18.30)	141 (259)	7.06 (5.85, 9.69)	0.75 (0.59, 0.95)
>= 65 and < 75	258	69 (125)	11.01 (7.13, 16.79)	68 (133)	11.33 (7.52, 14.92)	0.98 (0.70, 1.37)
>= 75	65	22 (35)	8.34 (3.91, 23.29)	19 (30)	9.76 (5.75, 12.32)	0.84 (0.45, 1.60)
Gender						
Male	615	168 (314)	11.20 (8.31, 16.79)	166 (301)	9.79 (7.03, 12.45)	0.86 (0.70, 1.07)
Female	232	60 (111)	11.99 (8.34, 19.06)	62 (121)	7.06 (5.75, 9.72)	0.69 (0.48, 0.99)
Race						
White	737	197 (369)	11.20 (8.71, 16.13)	201 (368)	7.52 (6.97, 9.79)	0.80 (0.66, 0.97)
Black or African American	13	5 (7)	5.65 (1.74, N.A.)	4 (6)	11.30 (0.89, 19.35)	1.03 (0.27, 3.87)
Asian	77	20 (38)	15.01 (7.13, N.A.)	17 (39)	12.68 (9.72, N.A.)	1.12 (0.59, 2.15)
Other	19	5 (10)	8.34 (1.48, N.A.)	6 (9)	5.39 (2.79, 18.10)	0.58 (0.18, 1.94)
Not Reported	1	1 (1)	0.95 (N.A., N.A.)	0 (0)		
Region						
US	222	56 (112)	11.56 (6.28, N.A.)	59 (110)	7.03 (5.55, 9.79)	0.64 (0.44, 0.93)
Canada/W Europe/N Europe	295	85 (148)	9.40 (6.80, 15.51)	80 (147)	9.76 (7.00, 15.05)	0.97 (0.72, 1.32)
Rest of World	330	87 (165)	13.27 (8.94, 17.84)	89 (165)	9.72 (6.93, 12.68)	0.83 (0.62, 1.12)
Karnofsky Performance Status						
90-100	581	158 (295)	14.98 (10.05, 18.17)	155 (286)	9.76 (7.03, 12.45)	0.79 (0.63, 0.99)
< 90	266	70 (130)	8.08 (5.52, 12.45)	73 (136)	7.13 (5.55, 10.41)	0.93 (0.67, 1.29)
Baseline IMDC Prognostic Score (CRF)						
0	17	6 (9)	8.90 (2.66, N.A.)	3 (8)	21.32 (1.71, N.A.)	
1-2	631	167 (314)	12.62 (8.71, 17.84)	163 (317)	9.79 (8.11, 12.68)	0.88 (0.71, 1.10)
3-6	199	55 (102)	9.79 (4.21, 16.85)	62 (97)	5.22 (3.98, 6.24)	0.57 (0.40, 0.83)
Prior Neo-adjuvant or Adjuvant Therapy						
Yes	5	1 (3)	N.A. (15.21, N.A.)	1 (2)	N.A. (6.77, N.A.)	
No	842	227 (422)	11.20 (8.44, 15.51)	227 (420)	8.38 (7.03, 10.81)	0.82 (0.68, 0.99)
Prior Nephrectomy						
Yes	660	181 (341)	12.55 (8.71, 16.99)	171 (319)	8.34 (7.03, 12.45)	0.84 (0.68, 1.04)
No	187	47 (84)	9.40 (5.62, 20.99)	57 (103)	8.38 (5.68, 11.14)	0.76 (0.51, 1.12)
Prior Radiotherapy						
Yes	104	29 (52)	8.08 (4.14, 20.99)	32 (52)	7.33 (4.53, 10.41)	0.79 (0.47, 1.31)
No	743	199 (373)	12.55 (9.53, 16.85)	196 (370)	8.74 (7.03, 11.33)	0.83 (0.68, 1.01)
Time From Initial Diagnosis To Randomization (Years)						
< 1 Year	590	158 (294)	11.56 (8.25, 16.99)	165 (296)	7.00 (5.68, 9.66)	0.75 (0.60, 0.94)
>= 1 Year	257	70 (131)	11.10 (8.34, 17.77)	63 (126)	12.68 (8.54, 17.97)	1.03 (0.73, 1.45)
LDH Level						
<= 1.5*ULN	787	208 (393)	12.62 (9.66, 17.74)	213 (394)	9.69 (7.06, 11.93)	0.82 (0.68, 0.99)
> 1.5*ULN	45	17 (25)	5.19 (2.60, 8.38)	12 (20)	2.73 (1.64, 4.30)	
Not Reported	15	3 (7)	8.59 (2.20, N.A.)	3 (8)	3.40 (0.89, 3.98)	
Hemoglobin						
< LLN	465	114 (223)	12.42 (7.06, 20.99)	138 (242)	7.13 (6.24, 9.79)	0.73 (0.57, 0.93)
>= LLN	371	113 (199)	11.56 (8.71, 16.13)	87 (172)	11.14 (7.26, 16.49)	1.00 (0.75, 1.32)
Not Reported	11	1 (3)	2.20 (N.A., N.A.)	3 (8)	3.40 (0.89, 3.98)	
Corrected Calcium						
<= 10 mg/dl	124	37 (63)	11.10 (4.17, 17.74)	27 (61)	15.18 (5.72, N.A.)	1.41 (0.86, 2.31)
> 10 mg/dl	27	6 (9)	6.80 (0.56, N.A.)	9 (18)	7.13 (1.64, N.A.)	
Not Reported	696	185 (353)	12.62 (8.71, 17.77)	192 (343)	8.15 (7.00, 9.79)	0.74 (0.61, 0.91)
Alkaline phosphatase						
< ULN	642	174 (333)	15.31 (10.74, 18.30)	159 (309)	11.07 (8.28, 13.83)	0.84 (0.67, 1.04)
>= ULN	191	53 (89)	5.62 (4.01, 11.04)	64 (102)	5.55 (4.17, 7.00)	0.82 (0.57, 1.18)
Not Reported	14	1 (3)	2.20 (N.A., N.A.)	5 (11)	6.41 (0.89, N.A.)	
Baseline PD-L1 + Status 1% Cut Off						
Yes	214	45 (100)	22.80 (9.40, N.A.)	66 (114)	5.85 (4.44, 7.13)	0.46 (0.31, 0.67)
No	562	160 (284)	11.01 (8.08, 14.92)	143 (278)	10.41 (7.52, 13.83)	1.00 (0.80, 1.26)
Not Reported	71	23 (41)	8.25 (3.91, 17.74)	19 (30)	9.76 (4.53, 13.01)	0.92 (0.49, 1.71)
Baseline PD-L1 + Status 5% Cut Off						
Yes	143	28 (63)	23.29 (6.28, N.A.)	51 (80)	5.72 (3.71, 7.00)	0.43 (0.27, 0.69)
No	633	177 (321)	11.20 (8.38, 15.44)	158 (312)	9.92 (7.26, 12.94)	0.95 (0.76, 1.17)
Not Reported	71	23 (41)	8.25 (3.91, 17.74)	19 (30)	9.76 (4.53, 13.01)	0.92 (0.49, 1.71)
Baseline PD-L1 + Status 10% Cut Off						
Yes	125	25 (55)	23.29 (5.55, N.A.)	46 (70)	5.72 (3.71, 7.00)	0.43 (0.26, 0.71)
No	651	180 (329)	11.56 (8.71, 15.51)	163 (322)	9.79 (7.26, 12.94)	0.93 (0.75, 1.15)
Not Reported	71	23 (41)	8.25 (3.91, 17.74)	19 (30)	9.76 (4.53, 13.01)	0.92 (0.49, 1.71)

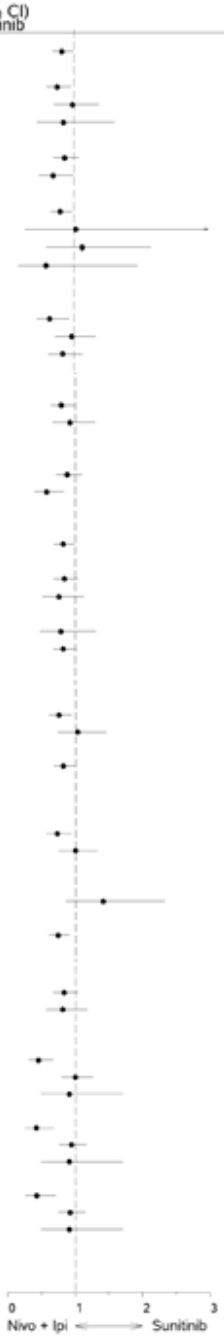


Figure 32 Forest Plot of Treatment Effect on PFS per IRRC in Pre-defined Subsets – Secondary Analysis, Primary Definition – All Randomised Subjects

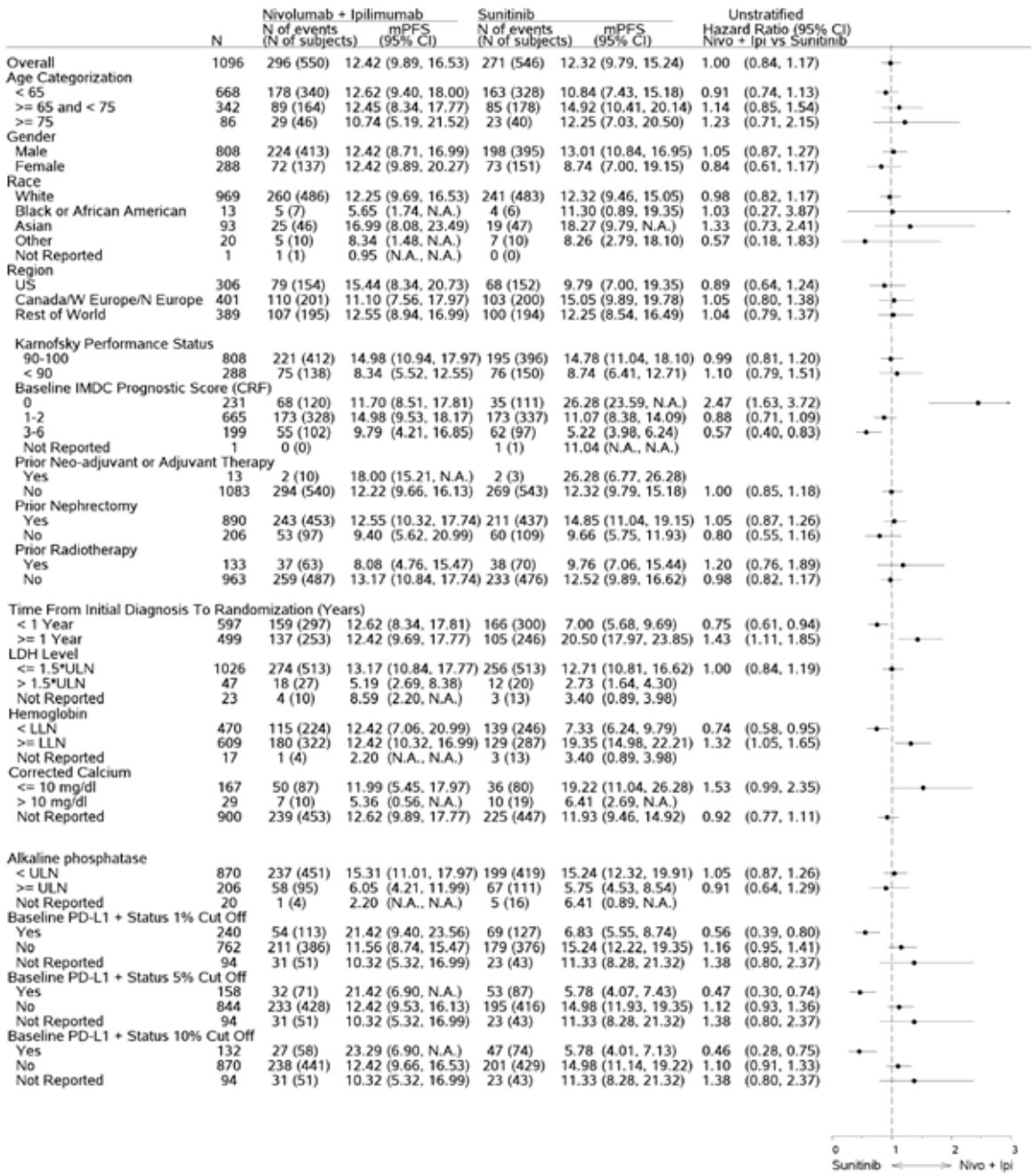
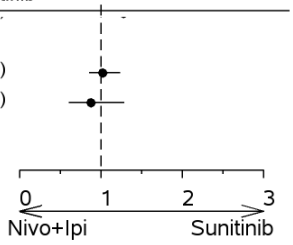


Figure 33 Forest Plot of Treatment Effect on PFS per IRRC in Pre-defined Subsets (corrected calcium) – All Randomised Subjects

		Nivolumab + Ipilimumab		Sunitinib		Unstratified
	N	N of Events (N of Subjects)	mOS (95% CI)	N of Events (N of Subjects)	mOS (95% CI)	Hazard Ratio (95% CI) Nivo+Ipi vs Sunitinib
Corrected Calcium						
<= 10 mg/dl	897	238(452)	12.42 (9.53, 16.99)	218(445)	12.45 (9.92, 16.62)	1.03 (0.85, 1.23)
> 10 mg/dl	198	58(98)	11.99 (7.56, 18.30)	52(100)	8.31 (6.41, 17.02)	0.88 (0.60, 1.28)
Not Reported	1	0(0)	N.A.	1(1)	11.04 (N.A., N.A.)	



HR is not computed for subset category with less than 21 subjects per treatment group.

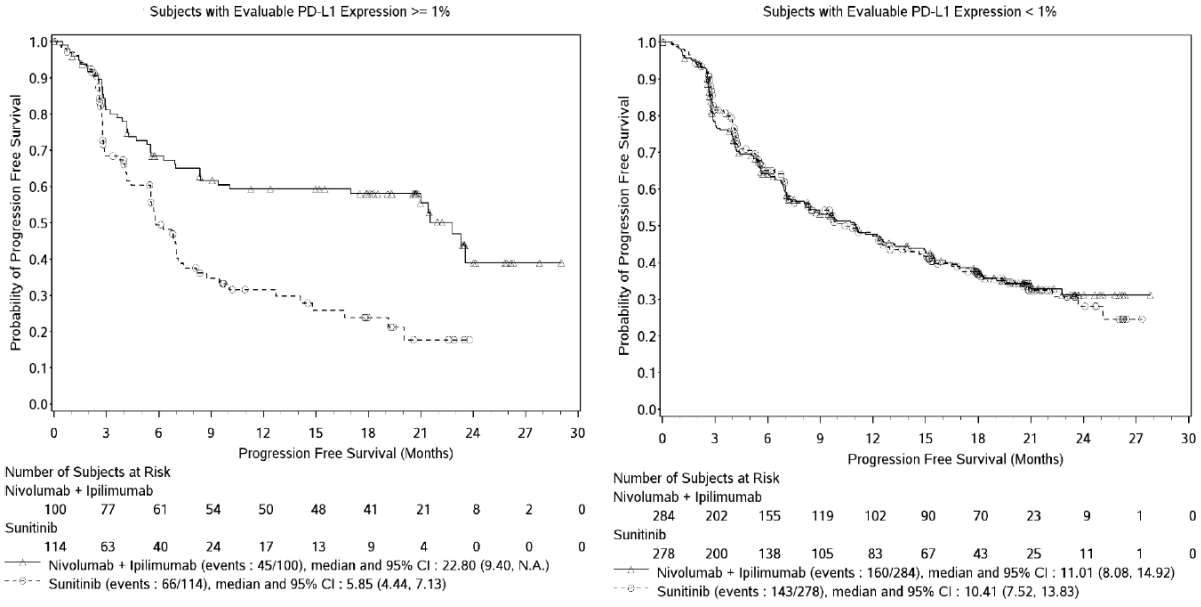
Baseline PD-L1 expression in relation to progression-free survival

In intermediate/poor-risk subjects, exploratory analyses suggest that the improvement in PFS per IRRC with nivolumab + ipilimumab vs. sunitinib were more pronounced in subjects with PD-L1 tumour expression ≥ 1% (Figure 34).

- Median PFS was longer in nivolumab + ipilimumab subjects with ≥ 1% PD-L1 tumour expression than in sunitinib subjects (22.80 months vs. 5.85 months, respectively).
- Median PFS in nivolumab + ipilimumab subjects with < 1% PD-L1 tumour expression was 11.01 months, and 10.41 months in sunitinib subjects.

In all randomised subjects, including favourable risk, PFS was longer in nivolumab + ipilimumab subjects with ≥ 1% PD-L1 tumour expression than in sunitinib subjects (21.42 months vs. 6.83 months, respectively). Refer to Figure S.10.7 in the CA209214 Final CSR. In nivolumab + ipilimumab subjects with < 1% PD-L1 tumour expression, PFS was shorter than in sunitinib subjects (11.56 months vs. 15.24 months, respectively). The K-M plot of PFS for each PD-L1 expression group for favourable-risk subjects is provided in Figure S.10.7.2 in the CA209214 Final CSR.

Figure 34 Progression Free Survival per IRRC – for each PD-L1 Expression Results Group and for each PD-L1 Status Group by Treatment – All Intermediate/Poor-risk Subjects



Objective response rate subgroup results

Unweighted differences between treatment groups in ORR were analysed using the Newcombe method, to assess the impact of specific baseline characteristics. In intermediate/poor-risk subjects, the IRRC-assessed ORR using RECIST v1.1 favored the nivolumab + ipilimumab group vs. the sunitinib group in all pre-defined subgroups except for Black or African American and corrected calcium ≤ 10 mg/dl (Figure 35). The CIs for the odds ratios in the majority of subgroups were wide due to small subgroup sizes. Results were similar in all randomised subjects (Figure 36). Information on the pre-defined patient subsets based on corrected calcium “yes” or “no”, respectively, was provided by the applicant upon request (Figure 27).

Figure 35 Forest Plot of Treatment Effect on Objective Response Rate per IRRC in Pre-defined Subsets – Intermediate/Poor-risk Subjects

	N	Nivolumab + Ipilimumab N of responses (N of subjects)	Nivolumab + Ipilimumab ORR (95% Exact CI)	Sunitinib N of responses (N of subjects)	Sunitinib ORR (95% Exact CI)	Unweighted ORR Difference (95% CI)
Overall	847	177(425)	41.6% (36.9, 46.5)	112(422)	26.5% (22.4, 31.0)	15.1% (8.7, 21.3)
Age Categorization						
< 65	524	118(265)	44.5% (38.4, 50.7)	67(259)	25.9% (20.6, 31.7)	18.7% (10.5, 26.5)
>= 65 and < 75	258	46(125)	36.8% (28.4, 45.9)	40(133)	30.1% (22.4, 38.6)	6.7% (-4.7, 18.0)
>= 75	65	13(35)	37.1% (21.5, 55.1)	5(30)	16.7% (5.6, 34.7)	20.5% (-1.5, 39.4)
Gender						
Male	615	130(314)	41.4% (35.9, 47.1)	82(301)	27.2% (22.3, 32.6)	14.2% (6.7, 21.4)
Female	232	47(111)	42.3% (33.0, 52.1)	30(121)	24.8% (17.4, 33.5)	17.5% (5.4, 29.1)
Race						
White	737	155(369)	42.0% (36.9, 47.2)	98(368)	26.6% (22.2, 31.5)	15.4% (8.5, 22.0)
Black or African American	13	1(7)	14.3% (0.4, 57.9)	1(6)	16.7% (0.4, 64.1)	-2.4% (-43.8, 37.1)
Asian	77	17(38)	44.7% (28.6, 61.7)	12(39)	30.8% (17.0, 47.6)	14.0% (-7.4, 33.7)
Other	19	4(10)	40.0% (12.2, 73.8)	1(9)	11.1% (0.3, 48.2)	28.9% (-10.9, 59.0)
Region						
US	222	46(112)	41.1% (31.9, 50.8)	23(110)	20.9% (13.7, 29.7)	20.2% (8.0, 31.5)
Canada/W Europe/N Europe	295	64(148)	43.2% (35.1, 51.6)	43(147)	29.3% (22.0, 37.3)	14.0% (3.0, 24.5)
Rest of World	330	67(165)	40.6% (33.0, 48.5)	46(165)	27.9% (21.2, 35.4)	12.7% (2.5, 22.6)
Karnofsky Performance Status						
90-100	581	141(295)	47.8% (42.0, 53.7)	85(286)	29.7% (24.5, 35.4)	18.1% (10.2, 25.7)
< 90	266	36(130)	27.7% (20.2, 36.2)	27(136)	19.9% (13.5, 27.6)	7.8% (-2.4, 17.9)
Baseline IMDC Prognostic Score (CRF)						
0	17	3(9)	33.3% (7.5, 70.1)	2(8)	25.0% (3.2, 65.1)	8.3% (-31.8, 44.3)
1-2	631	133(314)	42.4% (36.8, 48.0)	98(317)	30.9% (25.9, 36.3)	11.4% (3.9, 18.8)
3-6	199	41(102)	40.2% (30.6, 50.4)	12(97)	12.4% (6.6, 20.6)	27.8% (15.8, 38.8)
Prior Neo-adjuvant or Adjuvant Therapy						
Yes	5	2(3)	66.7% (9.4, 99.2)	1(2)	50.0% (1.3, 98.7)	16.7% (-44.6, 65.5)
No	842	175(422)	41.5% (36.7, 46.3)	111(420)	26.4% (22.3, 30.9)	15.0% (8.7, 21.2)
Prior Nephrectomy						
Yes	660	145(341)	42.5% (37.2, 48.0)	94(319)	29.5% (24.5, 34.8)	13.1% (5.7, 20.2)
No	187	32(84)	38.1% (27.7, 49.3)	18(103)	17.5% (10.7, 26.2)	20.6% (7.8, 32.9)
Prior Radiotherapy						
Yes	104	17(52)	32.7% (20.3, 47.1)	12(52)	23.1% (12.5, 36.8)	9.6% (-7.6, 26.1)
No	743	160(373)	42.9% (37.8, 48.1)	100(370)	27.0% (22.6, 31.9)	15.9% (9.0, 22.5)
Time From Initial Diagnosis To Randomization (Years)						
< 1 Year	590	127(294)	43.2% (37.5, 49.1)	70(296)	23.6% (18.9, 28.9)	19.5% (12.0, 26.8)
>= 1 Year	257	50(131)	38.2% (29.8, 47.1)	42(126)	33.3% (25.2, 42.3)	4.8% (-6.8, 16.3)
LDH Level						
<= 1.5*ULN	787	169(393)	43.0% (38.0, 48.1)	110(394)	27.9% (23.5, 32.6)	15.1% (8.4, 21.6)
> 1.5*ULN	45	6(25)	24.0% (9.4, 45.1)	2(20)	10.0% (1.2, 31.7)	14.0% (-9.7, 34.7)
Hemoglobin						
< LLN	465	98(223)	43.9% (37.3, 50.7)	50(242)	20.7% (15.7, 26.3)	23.3% (14.9, 31.3)
>= LLN	371	79(199)	39.7% (32.8, 46.9)	62(172)	36.0% (28.9, 43.7)	3.7% (-6.2, 13.4)
Corrected Calcium						
<= 10 mg/dl	124	19(63)	30.2% (19.2, 43.0)	26(61)	42.6% (30.0, 55.9)	-12.5% (-28.4, 4.4)
> 10 mg/dl	27	3(9)	33.3% (7.5, 70.1)	3(18)	16.7% (3.6, 41.4)	16.7% (-14.3, 49.7)
Alkaline phosphatase						
< ULN	642	145(333)	43.5% (38.1, 49.1)	90(309)	29.1% (24.1, 34.5)	14.4% (7.0, 21.6)
>= ULN	191	32(89)	36.0% (26.1, 46.8)	22(102)	21.6% (14.0, 30.8)	14.4% (1.6, 26.8)
Baseline PD-L1 + Status 1% Cut Off						
Yes	214	58(100)	58.0% (47.7, 67.8)	25(114)	21.9% (14.7, 30.6)	36.1% (23.1, 47.4)
No	562	106(284)	37.3% (31.7, 43.2)	79(278)	28.4% (23.2, 34.1)	8.9% (1.1, 16.5)
Baseline PD-L1 + Status 5% Cut Off						
Yes	143	37(63)	58.7% (45.6, 71.0)	17(80)	21.3% (12.9, 31.8)	37.5% (21.5, 51.1)
No	633	127(321)	39.6% (34.2, 45.1)	87(312)	27.9% (23.0, 33.2)	11.7% (4.3, 18.9)
Baseline PD-L1 + Status 10% Cut Off						
Yes	125	34(55)	61.8% (47.7, 74.6)	14(70)	20.0% (11.4, 31.3)	41.8% (24.7, 55.8)
No	651	130(329)	39.5% (34.2, 45.0)	90(322)	28.0% (23.1, 33.2)	11.6% (4.3, 18.7)

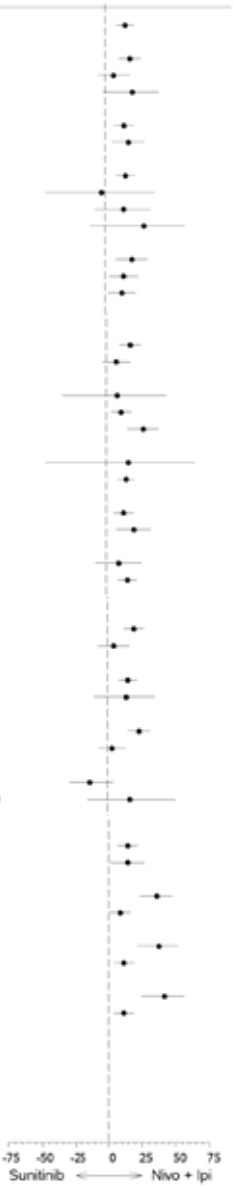
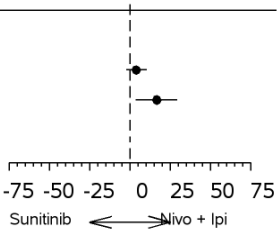


Figure 36 Forest Plot of Treatment Effect on ORR per IRRC in Pre-Defined Subsets – All Randomised Subjects

	N	Nivolumab + Ipilimumab N of responses (N of subjects)	Nivolumab + Ipilimumab ORR (95% Exact CI)	Sunitinib N of responses (N of subjects)	Sunitinib ORR (95% Exact CI)	Unweighted ORR Difference (95% CI)
Overall	1096	213(550)	38.7% (34.6, 42.9)	176(546)	32.2% (28.3, 36.3)	6.5% (0.8, 12.1)
Age Categorization						
< 65	668	143(340)	42.1% (36.8, 47.5)	99(328)	30.2% (25.3, 35.5)	11.9% (4.6, 19.0)
>= 65 and < 75	342	54(164)	32.9% (25.8, 40.7)	67(178)	37.6% (30.5, 45.2)	-4.7% (-14.6, 5.4)
>= 75	86	16(46)	34.8% (21.4, 50.2)	10(40)	25.0% (12.7, 41.2)	9.8% (-9.6, 27.8)
Gender						
Male	808	158(413)	38.3% (33.5, 43.1)	129(395)	32.7% (28.1, 37.5)	5.6% (-1.0, 12.1)
Female	288	55(137)	40.1% (31.9, 48.9)	47(151)	31.1% (23.8, 39.2)	9.0% (-2.0, 19.8)
Race						
White	969	190(486)	39.1% (34.7, 43.6)	156(483)	32.3% (28.1, 36.7)	6.8% (0.8, 12.8)
Black or African American	13	1(7)	14.3% (0.4, 57.9)	1(6)	16.7% (0.4, 64.1)	-2.4% (-43.8, 37.1)
Asian	93	18(46)	39.1% (25.1, 54.6)	17(47)	36.2% (22.7, 51.5)	3.0% (-16.2, 21.8)
Other	20	4(10)	40.0% (12.2, 73.8)	2(10)	20.0% (2.5, 55.6)	20.0% (-18.7, 52.1)
Region						
US	306	57(154)	37.0% (29.4, 45.2)	37(152)	24.3% (17.8, 32.0)	12.7% (2.3, 22.6)
Canada/W Europe/N Europe	401	83(201)	41.3% (34.4, 48.4)	75(200)	37.5% (30.8, 44.6)	3.8% (-5.7, 13.2)
Rest of World	389	73(195)	37.4% (30.6, 44.6)	64(194)	33.0% (26.4, 40.1)	4.4% (-5.0, 13.8)
Karnofsky Performance Status						
90-100	808	175(412)	42.5% (37.7, 47.4)	138(396)	34.8% (30.2, 39.8)	7.6% (0.9, 14.2)
< 90	288	38(138)	27.5% (20.3, 35.8)	38(150)	25.3% (18.6, 33.1)	2.2% (-7.9, 12.4)
Baseline IMDC Prognostic Score (CRF)						
0	231	34(120)	28.3% (20.5, 37.3)	57(111)	51.4% (41.7, 61.0)	-23.0% (-34.7, -10.4)
1-2	665	138(328)	42.1% (36.7, 47.6)	107(337)	31.8% (26.8, 37.0)	10.3% (3.0, 17.5)
3-6	199	41(102)	40.2% (30.6, 50.4)	12(97)	12.4% (6.6, 20.6)	27.8% (15.8, 38.8)
Prior Neo-adjuvant or Adjuvant Therapy						
Yes	13	2(10)	20.0% (2.5, 55.6)	2(3)	66.7% (9.4, 99.2)	-46.7% (-77.4, 8.7)
No	1083	211(540)	39.1% (34.9, 43.3)	174(543)	32.0% (28.1, 36.2)	7.0% (1.3, 12.7)
Prior Nephrectomy						
Yes	890	179(453)	39.5% (35.0, 44.2)	156(437)	35.7% (31.2, 40.4)	3.8% (-2.5, 10.1)
No	206	34(97)	35.1% (25.6, 45.4)	20(109)	18.3% (11.6, 26.9)	16.7% (4.6, 28.4)
Prior Radiotherapy						
Yes	133	18(63)	28.6% (17.9, 41.3)	25(70)	35.7% (24.6, 48.1)	-7.1% (-22.3, 8.7)
No	963	195(487)	40.0% (35.7, 44.5)	151(476)	31.7% (27.6, 36.1)	8.3% (2.3, 14.3)
Time From Initial Diagnosis To Randomization (Years)						
< 1 Year	597	127(297)	42.8% (37.1, 48.6)	71(300)	23.7% (19.0, 28.9)	19.1% (11.6, 26.3)
>= 1 Year	499	86(253)	34.0% (28.2, 40.2)	105(246)	42.7% (36.4, 49.1)	-8.7% (-17.1, -0.2)
LDH Level						
<= 1.5*ULN	1026	204(513)	39.8% (35.5, 44.1)	174(513)	33.9% (29.8, 38.2)	5.8% (-0.1, 11.7)
> 1.5*ULN	47	7(27)	25.9% (11.1, 46.3)	2(20)	10.0% (1.2, 31.7)	15.9% (-7.9, 36.0)
Hemoglobin						
< LLN	470	98(224)	43.8% (37.2, 50.5)	51(246)	20.7% (15.8, 26.3)	23.0% (14.6, 31.0)
>= LLN	609	115(322)	35.7% (30.5, 41.2)	125(287)	43.6% (37.7, 49.5)	-7.8% (-15.5, -0.1)
Corrected Calcium						
<= 10 mg/dl	167	24(87)	27.6% (18.5, 38.2)	38(80)	47.5% (36.2, 59.0)	-19.9% (-33.5, -5.2)
> 10 mg/dl	29	4(10)	40.0% (12.2, 73.8)	3(19)	15.8% (3.4, 39.6)	24.2% (-7.6, 54.7)
Alkaline phosphatase						
< ULN	870	180(451)	39.9% (35.4, 44.6)	149(419)	35.6% (31.0, 40.4)	4.4% (-2.1, 10.7)
>= ULN	206	33(95)	34.7% (25.3, 45.2)	27(111)	24.3% (16.7, 33.4)	10.4% (-2.0, 22.6)
Baseline PD-L1 + Status 1% Cut Off						
Yes	240	60(113)	53.1% (43.5, 62.5)	28(127)	22.0% (15.2, 30.3)	31.1% (18.9, 42.0)
No	762	139(386)	36.0% (31.2, 41.0)	133(376)	35.4% (30.5, 40.4)	0.6% (-6.1, 7.4)
Baseline PD-L1 + Status 5% Cut Off						
Yes	158	39(71)	54.9% (42.7, 66.8)	19(87)	21.8% (13.7, 32.0)	33.1% (18.0, 46.4)
No	844	160(428)	37.4% (32.8, 42.2)	142(416)	34.1% (29.6, 38.9)	3.2% (-3.2, 9.7)
Baseline PD-L1 + Status 10% Cut Off						
Yes	132	36(58)	62.1% (48.4, 74.5)	15(74)	20.3% (11.8, 31.2)	41.8% (25.2, 55.5)
No	870	163(441)	37.0% (32.4, 41.7)	146(429)	34.0% (29.6, 38.7)	2.9% (-3.4, 9.2)

Figure 37 Forest Plot of Treatment Effect on ORR per IRRC in Pre-Defined Subsets (corrected calcium) – All Randomised Subjects

	N	Nivlumab + Ipilimumab N of responses (N of subjects)	Nivlumab + Ipilimumab ORR (95% Exact CI)	Sunitinib N of responses (N of subjects)	Sunitinib ORR (95% Exact CI)	Unweighted ORR Difference (95% CI)
Corrected Calcium						
<= 10 mg/dl	897	172(452)	38.1% (33.6, 42.7)	151(445)	33.9% (29.5, 38.5)	4.1% (-2.2, 10.3)
> 10 mg/dl	198	41(98)	41.8% (31.9, 52.2)	25(100)	25.0% (16.9, 34.7)	16.8% (3.7, 29.2)
Not Reported	1	0(0)	N.A.	0(1)	0.0% (0.0, 97.5)	N.A.



Baseline PD-L1 expression in relation to objective response rate

In intermediate/poor-risk subjects, objective responses per IRRC were observed in the nivolumab + ipilimumab group regardless of PD-L1 tumour expression (Table 30).

- A higher ORR was observed in nivolumab + ipilimumab subjects than in sunitinib subjects, in both subjects with ≥ 1% PD-L1 tumour expression as well as those with < 1% PD-L1 tumour expression.

In all randomised subjects, results of ORR by baseline PD-L1 tumour expression were consistent with those in intermediate/poor-risk subjects (Refer to Table S.10.11 in the CA209214 Final CSR).

Table 30 Best Overall Response and Objective Response Rate per IRRC by Baseline PD-L1 Expression – Intermediate/Poor-risk Subjects

PD-L1 Expression Result Group	Nivolumab + Ipilimumab N = 422	Sunitinib N = 420
SUBJECTS WITH PD-L1 EXPRESSION >= 1%	100 (23.7)	114 (27.1)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	16/100 (16.0)	1/114 (0.9)
PARTIAL RESPONSE (PR)	42/100 (42.0)	24/114 (21.1)
STABLE DISEASE/NON-CR/NON-PD (SD/NON-CR/NON-PD)	19/100 (19.0)	46/114 (40.4)
PROGRESSIVE DISEASE (PD)	14/100 (14.0)	28/114 (24.6)
UNABLE TO DETERMINE (UTD)	9/100 (9.0)	15/114 (13.2)
OBJECTIVE RESPONSE RATE (1)	58/100 (58.0%)	25/114 (21.9%)
(95% CI)	(47.7, 67.8)	(14.7, 30.6)
ODDS RATIO (2)	4.92	
(95% CI)	(2.61, 9.34)	
SUBJECTS WITH PD-L1 EXPRESSION < 1%	284 (67.3)	278 (66.2)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	21/284 (7.4)	4/278 (1.4)
PARTIAL RESPONSE (PR)	85/284 (29.9)	75/278 (27.0)
STABLE DISEASE/NON-CR/NON-PD (SD/NON-CR/NON-PD)	102/284 (35.9)	130/278 (46.8)
PROGRESSIVE DISEASE (PD)	57/284 (20.1)	36/278 (12.9)
UNABLE TO DETERMINE (UTD)	19/284 (6.7)	33/278 (11.9)
OBJECTIVE RESPONSE RATE (1)	106/284 (37.3%)	79/278 (28.4%)
(95% CI)	(31.7, 43.2)	(23.2, 34.1)
ODDS RATIO (2)	1.50	
(95% CI)	(1.04, 2.17)	

In intermediate/poor-risk subjects, time to responses and duration of responses per IRRC were assessed in the nivolumab + ipilimumab and sunitinib groups regardless of PD-L1 tumour expression, and were determined to be consistent across PD-L1 tumour expression levels (Table 3.1.3.11-1 in the CA209214 Final CSR).

- In the nivolumab + ipilimumab group vs. sunitinib, median TTR was similar for PD-L1 tumour expression level ≥1% 2.76 and 2.86 months, respectively. PD-L1 tumour expression level <1 resulted in a TTR of 2.83 and 4.01 in nivolumab+ipilimumab and sunitinib.

- In the nivolumab + ipilimumab group, median DOR was not reached in subjects with PD-L1 tumour expression level <1% and ≥1%. In the sunitinib group, median DOR was 18.23 months in subjects with PD-L1 tumour expression < 1%. Median DOR was 17.22 months in subjects with PD-L1 tumour expression ≥ 1%.

In all randomised subjects, results of TTR and DOR by baseline PD-L1 tumour expression were consistent with those in intermediate/poor-risk subjects (Refer to Table S.10.15.1 in the CA209214 Final CSR).

Additional information is provided in the following:

- Time to objective response and duration of response per IRRC for each PD-L1 expression result group and for each PD-L1 status group by treatment, all favourable-risk PD-L1 tested at baseline subjects - Refer to Table S.10.15.2 in the CA209214 Final CSR.

Patient-reported general health status (EQ-5D)

Utility index scores (Table S.10.6 - CSR)

Mobility:

The proportion of subjects reporting “no problems” on mobility was 75.7 % in the nivolumab + ipilimumab group and 76.3 % in the sunitinib group. After 52 weeks post-baseline, the proportion of subjects reporting “no problems” on mobility was 83.5 % in the nivolumab + ipilimumab group and 71.8 % in the sunitinib group.

The proportion of subjects reporting “no problems” on self-care was 92.3 % in the nivolumab + ipilimumab group and 93.1 % in the sunitinib group. After 52 weeks post-baseline, the proportion of subjects reporting “no problems” on mobility was 95.0 % in the nivolumab + ipilimumab group and 92.2 % in the sunitinib group.

The proportion of subjects reporting “no problems” on activity was 70.3 % in the nivolumab + ipilimumab group and 69.4 % in the sunitinib group. After 52 weeks post-baseline, the proportion of subjects reporting “no problems” on mobility was 78.5 % in the nivolumab + ipilimumab group and 63.1 % in the sunitinib group.

The proportion of subjects reporting “no problems” on pain was 54.0 % in the nivolumab + ipilimumab group and 55.3 % in the sunitinib group. After 52 weeks post-baseline, the proportion of subjects reporting “no problems” on mobility was 66.9 % in the nivolumab + ipilimumab group and 46.6 % in the sunitinib group.

The proportion of subjects reporting “no problems” on anxiety was 61.9 % in the nivolumab + ipilimumab group and 59.9 % in the sunitinib group. After 52 weeks post-baseline, the proportion of subjects reporting “no problems” on mobility was 76.7 % in the nivolumab + ipilimumab group and 77.7 % in the sunitinib group.

Patient-reported health related quality of life assessed by the functional assessment of cancer therapy – general (FACT-G) – All randomised subjects

The mean FACT-G score was 23.9 for nivolumab + ipilimumab group and 23.7 in the sunitinib group at baseline (screening – week 1). After 52 weeks post-baseline, the mean scores were 25.1 in the nivolumab + ipilimumab group and 23.3 in the sunitinib group.

Patient-reported disease related symptoms based on the functional assessment of cancer therapy-kidney symptom index (FKSI-19)

The mean FKSI-19 score was 61.1 for nivolumab + ipilimumab group and 60.0 in the sunitinib group at baseline (screening – week 1). After 52 weeks post-baseline, the mean scores were 65.1 in the nivolumab + ipilimumab group and 61.8 in the sunitinib group.

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 31 Summary of Efficacy

Title: A phase III, randomised, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma			
Study identifier	CA209214		
Design	Randomised, phase III, open-label, study		
	Duration of main phase:		16/Oct/2014 – 07/Aug/2017
Hypothesis	Superiority of nivolumab + ipilimumab over sunitinib		
Treatments groups	Nivolumab + ipilimumab		Nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks, 425 subjects randomised
	Sunitinib		Sunitinib 50 mg p.o. once daily for 4 weeks followed by 2 weeks off, every cycle, 422 subjects randomised
Endpoints and definitions	Co-primary endpoint	OS	Intermediate/poor-risk subjects Defined as the time from randomisation to the date of death from any cause. Survival time was censored at the date of last contact ("last known alive date") for subjects who were alive.
	Co-primary endpoint	PFS	Intermediate/poor-risk subjects Defined as the time between the date of randomisation and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first.
	Co-primary endpoint	ORR	Intermediate/poor-risk subjects Defined as the proportion of randomised subjects who achieved a best response of complete response (CR) or partial response (PR) using the RECIST v1.1 criteria based on IRRC assessment
	Secondary endpoints	OS	All-treated subjects Defined as the time from randomisation to the date of death from any cause. Survival time was censored at the date of last contact ("last known alive date") for subjects who were alive.
	Secondary endpoints	PFS	All-treated subjects Defined as the time between the date of randomisation and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first
	Secondary endpoints	ORR	All-treated subjects Defined as the proportion of randomised subjects who achieved a best response of complete response (CR) or partial response (PR) using the RECIST v1.1 criteria based on IRRC assessment
Database lock	07/Aug/2017		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intermediate/poor-risk subjects Other: The independent DMC reviewed the interim OS data on 06-Sep-2017 and confirmed that the pre-specified boundary for OS (nominal significance level p < 0.002) was crossed, and unanimously recommended that the study be stopped early by the Sponsor.			
Descriptive statistics and estimate variability	Treatment group	Nivolumab + ipilimumab	Sunitinib	
	Number of subject	423	416	
	OS, median (95% CI)	Not reached	25.95 months	
	PFS, median (95% CI)	11.56 months (8.71, 15.51)	8.38 months (7.03, 10.81)	
	ORR, N responders (%) (95% CI)	177 (41.6) (36.9,46.5)	112 (26.5) (22.4, 31.0)	
Effect estimate per comparison	Intermediate/poor-risk subjects			
	OS	Comparison groups	Nivolumab + ipilimumab vs. sunitinib	
		HR	0.63	
		99.8% CI	(0.44, 0.89)	
		P-value	<0.0001	
	PFS	Comparison groups	Nivolumab + ipilimumab vs. sunitinib	
		HR	0.82	
		99.1% CI	(0.64, 1.05)	
		P-value	0.0331	
	ORR	Comparison groups	Nivolumab + ipilimumab vs. sunitinib	
		Stratified difference in ORR	16.0	
		95% CI	(9.8, 22.2)	
		P-value	<0.0001	
	OS Update*	Comparison groups	Nivolumab + ipilimumab vs. sunitinib	
		HR	0.66	
		95% CI	(0.54, 0.81)	
		P-value	<0.0001	
Analysis description	**Secondary analysis**			
Analysis population and time point description	All-treated subjects Other: The independent DMC reviewed the interim OS data on 06-Sep-2017 and confirmed that the pre-specified boundary for OS (nominal significance level p < 0.002) was crossed, and unanimously recommended that the study be stopped early by the Sponsor.			
Descriptive statistics and estimate variability	Treatment group	nivolumab + ipilimumab	Sunitinib	
	Number of subject	547	535	
	OS, median (95% CI)	Not reached -	32.92 (N.A., N.A.)	

	PFS, median (95% CI)	12.42 months (9.89,16.53)	12.32 months (21.8, 54.0)
	ORR, N responders (%) (95% CI)	213 (38.7) (34.6,42.9)	176 (32.2) (28.3,26.3)
Effect estimate per comparison	OS	Comparison groups	Nivolumab + ipilimumab vs. sunitinib
		HR	0.68
		99.8% CI	(0.49, 0.95)
		P-value	0.0003
	PFS	Comparison groups	Nivolumab + ipilimumab vs. sunitinib
		HR	0.98
		99.1% CI	(0.79, 1.23)
		P-value	0.8498
	ORR	Comparison groups	Nivolumab + ipilimumab vs. sunitinib
		Stratified difference in ORR	7.2
		95% CI	(1.8, 12.7)
		P-value	0.0191
	OS update*	Comparison groups	Nivolumab + ipilimumab vs. sunitinib
		HR	0.70
		99.8% CI	(0.58, 0.85)
		P-value	<0.0003

* Database lock 01-Mar-2018

Clinical studies in special populations

In intermediate/poor-risk subjects, OS favoured the nivolumab + ipilimumab group vs. the sunitinib group in all pre-defined subgroups (Figure 19). However, this effect appeared to decrease with increasing age (age ≥65 and <75 – HR 0.86 [0.58, 1.27], age ≥75 – HR 0.97 [0.48, 1.95]).

Supportive study

Study **CA209016** was a phase 1 open-label study of nivolumab plus sunitinib or pazopanib, or nivolumab plus ipilimumab in subjects with mRCC.

Study objectives, methodology, number of subjects, diagnosis and main criteria for inclusion of the supportive study have been summarised in the dose response (4.4.1.) section of this report.

Efficacy results

Disposition of subjects

The enrolment period lasted approximately 27.5 months (Feb 2012 to May 2014). The last patient started first dose on 29/5/2014, and the clinical cut-off date for the clinical study report (CSR) occurred on 16/3/2016, providing a minimum follow-up for survival of approximately 22 months.

A total of 14 sites in 2 countries of North America enrolled and treated subjects. Of the 194 subjects enrolled, 153 (78.9%) were treated; 33 in arm S, 20 in arm P, 47 in Arm I-1, 47 in arm I-3, and 6 in Arm IN-3 (Table 5.1-1). Within arm S, 7 subjects were treated with sunitinib + nivolumab 2 mg/kg, and 26 were treated with sunitinib + nivolumab 5 mg/kg. All subjects in arm P received pazopanib + nivolumab 2 mg/kg.

A summary of the number of subjects enrolled, randomised and treated is presented in Table 32.

Baseline demographic and characteristics

Among all treated subjects, the majority of subjects were under the age of 65, white and male. At baseline, the majority of subjects were diagnosed with clear-cell RCC with KPS of 90 or 100, had favourable or intermediate-risk MSKCC prognostic scores and PD-L1 level ≤ 5%. The lung, lymph node and liver were the most common site of disease reported outside of the kidney (Table 33).

Table 32 Subject Status Summary – All Enrolled, Randomised and Treated Subjects

	Arm S		Arm P	Arm I-1	Arm I-3	Arm IN-3	Total
	SUN + NIV2	SUN + NIV5	PAZ + NIV2	IPI1 + NIV3	IPI3 + NIV1	IPI3 + NIV3	
SUBJECTS ENROLLED							194
SUBJECTS NOT ENTERING THE TREATMENT PERIOD (%)							41 (21.1)
REASON FOR NOT ENTERING TREATMENT PERIOD (%)							
SUBJECT WITHDREW CONSENT							5 (2.6)
SUBJECT NO LONGER MEETS STUDY CRITERIA							32 (16.5)
ADMINISTRATIVE REASON BY SPONSOR							1 (0.5)
OTHER							3 (1.5)
SUBJECTS TREATED	7	26	20	47	47	6	153
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	1 (14.3)	4 (15.4)	1 (5.0)	8 (17.0)	9 (19.1)	0	
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	6 (85.7)	22 (84.6)	19 (95.0)	39 (83.0)	38 (80.9)	6(100.0)	
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)							
DISEASE PROGRESSION	4 (57.1)	10 (38.5)	12 (60.0)	31 (66.0)	22 (46.8)	3 (50.0)	
STUDY DRUG TOXICITY	2 (28.6)	9 (34.6)	4 (20.0)	6 (12.8)	13 (27.7)	2 (33.3)	
DEATH	0	0	0	0	1 (2.1)	0	
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	0	0	0	1 (2.1)	0	
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	3 (11.5)	1 (5.0)	1 (2.1)	0	0	
SUBJECT WITHDREW CONSENT	0	0	0	0	0	1 (16.7)	
POOR/NON-COMPLIANCE	0	0	0	0	1 (2.1)	0	
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	1 (5.0)	0	0	0	
COMPLETED	0	0	0	1 (2.1)	0	0	
SUBJECTS CONTINUING IN THE STUDY (%)	4 (57.1)	15 (57.7)	5 (25.0)	31 (66.0)	28 (59.6)	5 (83.3)	
SUBJECTS NOT CONTINUING IN THE STUDY (%)	3 (42.9)	11 (42.3)	15 (75.0)	16 (34.0)	19 (40.4)	1 (16.7)	

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=ipilimumab; NIV=Nivolumab

Table 33 Baseline Demographic and Characteristics – All Treated Subjects

	Arm S		Arm P	Arm I-1	Arm I-3	Arm IN-3
	SUN + NIV2 N = 7	SUN + NIV5 N = 26	PAZ + NIV2 N = 20	IPI1 + NIV3 N = 47	IPI3 + NIV1 N = 47	IPI3 + NIV3 N = 6
AGE (Units)						
MEAN	56.9	58.3	56.3	53.0	55.6	54.8
MEDIAN	63.0	56.5	56.0	54.0	56.0	55.0
MIN , MAX	38, 69	43, 75	40, 72	26, 68	20, 76	51, 59
STANDARD DEVIATION	11.36	8.62	8.52	8.97	11.58	2.71
AGE CATEGORIZATION (%)						
< 65	5 (71.4)	19 (73.1)	17 (85.0)	43 (91.5)	36 (76.6)	6 (100.0)
>=65	2 (28.6)	7 (26.9)	3 (15.0)	4 (8.5)	11 (23.4)	0
GENDER (%)						
MALE	7 (100.0)	19 (73.1)	18 (90.0)	33 (70.2)	38 (80.9)	5 (83.3)
FEMALE	0	7 (26.9)	2 (10.0)	14 (29.8)	9 (19.1)	1 (16.7)
RACE (%)						
WHITE	6 (85.7)	22 (84.6)	18 (90.0)	44 (93.6)	45 (95.7)	6 (100.0)
BLACK OR AFRICAN AMERICAN	1 (14.3)	1 (3.8)	1 (5.0)	1 (2.1)	1 (2.1)	0
ASIAN	0	1 (3.8)	0	2 (4.3)	0	0
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (3.8)	0	0	0	0
OTHER	0	1 (3.8)	1 (5.0)	0	1 (2.1)	0
ETHNICITY (%)						
HISPANIC OR LATINO	0	2 (7.7)	0	1 (2.1)	2 (4.3)	1 (16.7)
NOT HISPANIC OR LATINO	7 (100.0)	22 (84.6)	18 (90.0)	42 (89.4)	40 (85.1	5 (83.3)
NOT REPORTED	0	2 (7.7)	2 (10.0)	4 (8.5)	5 (10.6)	0
DISEASE DIAGNOSIS						
CLEAR CELL RENAL CELL CARCINOMA	7 (100.0)	25 (96.2)	18 (90.0)	46 (97.9)	45 (95.7)	6 (100.0)
PAPILLARY NON-CLEAR CELL RCC	0	1 (3.8)	1 (5.0)	1 (2.1)	0	0
CHROMOPHOBE NON-CLEAR CELL RCC	0	0	1 (5.0)	0	0	0
UNCLASSIFIED NON-CLEAR CELL RCC	0	0	0	0	2 (4.3)	0
MSKCC SCORE						
FAVORABLE	3 (42.9)	13 (50.0)	4 (20.0)	21 (44.7)	21 (44.7)	5 (83.3)
INTERMEDIATE	4 (57.1)	12 (46.2)	14 (70.0)	23 (48.9)	23 (48.9)	1 (16.7)
POOR	0	1 (3.8)	2 (10.0)	3 (6.4)	3 (6.4)	0
KARNOFSKY PERFORMANCE STATUS						
<80	0	0	0	0	0	0
80	2 (28.6)	2 (7.7)	6 (30.0)	4 (8.5)	5 (10.6)	0
90	0	7 (26.9)	5 (25.0)	14 (29.8)	22 (46.8)	2 (33.3)
100	5 (71.4)	17 (65.4)	9 (45.0)	29 (61.7)	20 (42.6)	4 (66.7)
SMOKING HISTORY						
YES	6 (85.7)	16 (61.5)	10 (50.0)	16 (34.0)	26 (55.3)	1 (16.7)
NO	1 (14.3)	10 (38.5)	9 (45.0)	31 (66.0)	21 (44.7)	5 (83.3)
UNKNOWN	0	0	1 (5.0)	0	0	0

	Arm S		Arm P	Arm I-1	Arm I-3	Arm IN-3
	SUN + NIV2 N = 7	SUN + NIV5 N = 26	PAZ + NIV2 N = 20	IPI1 + NIV3 N = 47	IPI3 + NIV1 N = 47	IPI3 + NIV3 N = 6
TIME FROM INITIANL DIAGNOSIS TO FIRST DOSING						
< 1 YEAR	1 (14.3)	13 (50.0)	5 (25.0)	26 (55.3)	13 (27.7)	1 (16.7)
>=1 YEAR	6 (85.7)	13 (50.0)	15 (75.0)	21 (44.7)	34 (72.3)	5 (83.3)
PD-L1						
< 1%	3 (42.9)	11 (42.3)	10 (50.0)	26 (55.3)	27 (57.4)	4 (66.7)
1% <= PD-L1 < 5%	3 (42.9)	7 (26.9)	5 (25.0)	9 (19.1)	10 (21.3)	0
5% <= PD-L1 < 10%	0	1 (3.8)	0	4 (8.5)	3 (6.4)	1 (16.7)
>= 10%	0	4 (15.4)	2 (10.0)	6 (12.8)	1 (2.1)	0
NOT REPORTED	1 (14.3)	3 (11.5)	3 (15.0)	2 (4.3)	6 (12.8)	1 (16.7)
TARGET LESION DISEASE SITE # (%)						
ADRENAL GLAND	0	1 (3.8)	1 (5.0)	5 (10.6)	7 (14.9)	1 (16.7)
BLADDER	0	0	0	0	1 (2.1)	0
BONE	0	1 (3.8)	2 (10.0)	2 (4.3)	3 (6.4)	0
CENTRAL NERVOUS SYSTEM	0	0	0	1 (2.1)	0	0
CHEST WALL	0	2 (7.7)	0	0	1 (2.1)	0
ESOPHAGUS	1 (14.3)	0	1 (5.0)	0	0	0
INTESTINE	0	0	0	2 (4.3)	0	0
KIDNEY	1 (14.3)	4 (15.4)	2 (10.0)	5 (10.6)	10 (21.3)	1 (16.7)
LIVER	1 (14.3)	1 (3.8)	1 (5.0)	9 (19.1)	9 (19.1)	0
LUNG	2 (28.6)	12 (46.2)	12 (60.0)	24 (51.1)	27 (57.4)	5 (83.3)
LYMPH NODE	4 (57.1)	11 (42.3)	6 (30.0)	27 (57.4)	17 (36.2)	2 (33.3)
MEDIASTINUM	0	0	0	0	1 (2.1)	0
OTHER	0	1 (3.8)	1 (5.0)	5 (10.6)	4 (8.5)	0
PANCREAS	0	3 (11.5)	1 (5.0)	1 (2.1)	4 (8.5)	0
PELVIS	0	0	0	1 (2.1)	1 (2.1)	0
PERICARDIUM	0	0	0	1 (2.1)	0	0
PERITONEUM	0	2 (7.7)	2 (10.0)	6 (12.8)	1 (2.1)	0
PLEURA	1 (14.3)	0	1 (5.0)	1 (2.1)	1 (2.1)	0
PROSTATE	0	0	1 (5.0)	0	0	0
SKIN/SOFT TISSUE	0	3 (11.5)	4 (20.0)	7 (14.9)	7 (14.9)	0
TESTES	0	0	0	1 (2.1)	0	0
VISCERAL, OTHER	0	0	0	0	0	1 (16.7)

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIV=Nivolumab
Subjects may have disease disseminated in more than one site.

Prior treatment

Among all treatment groups, over 97.9% of subjects received prior surgery; and 14.3 - 50% of subjects received prior radiotherapy (Table 33). 25 (53.2%), 21 (44.7%), and 3 (50.0%) of subjects in arms I-1, I-3, and IN-3 were treatment-naïve, respectively. Of all the subjects who were previously treated with systemic cancer therapy, most subjects received only 1 regimen.

Table 34 Prior Therapy Summary – All Treated Subjects

	Arm S		Arm P	Arm I-1	Arm I-3	Arm IN-3
	SUN + NIV2 N = 7	SUN + NIV5 N = 26	PAZ + NIV2 N = 20	IPI1 + NIV3 N = 47	IPI3 + NIV1 N = 47	IPI3 + NIV3 N = 6
PRIOR SURGERY (%)	7 (100.0)	26 (100.0)	20 (100.0)	46 (97.9)	46 (97.9)	6 (100.0)
PRIOR RADIOTHERAPY (%)	1 (14.3)	4 (15.4)	10 (50.0)	15 (31.9)	12 (25.5)	1 (16.7)
PRIOR SYSTEMIC THERAPY (%)	7 (100.0)	7 (26.9)	20 (100.0)	22 (46.8)	26 (55.3)	3 (50.0)
VEGFR TKI	2 (28.6)	3 (11.5)	17 (85.0)	9 (19.1)	16 (34.0)	1 (16.7)
ANTI ANGIOGENIC	2 (28.6)	5 (19.2)	17 (85.0)	10 (21.3)	16 (34.0)	1 (16.7)
CYTOKINE	5 (71.4)	4 (15.4)	10 (50.0)	17 (36.2)	13 (27.7)	2 (33.3)
MTOR INHIBITOR	0	0	3 (15.0)	5 (10.6)	7 (14.9)	0
OTHER	1 (14.3)	2 (7.7)	4 (20.0)	2 (4.3)	5 (10.6)	0
NUMBER OF REGIMEN (%)						
0	0	19 (73.1)	0	25 (53.2)	21 (44.7)	3 (50.0)
1	7 (100.0)	7 (26.9)	14 (70.0)	14 (29.8)	16 (34.0)	3 (50.0)
2	0	0	4 (20.0)	3 (6.4)	3 (6.4)	0
3	0	0	1 (5.0)	2 (4.3)	3 (6.4)	0
>=4	0	0	1 (5.0)	3 (6.4)	4 (8.5)	0
REGIMEN SETTING* (%)						
ADJUVANT	1 (14.3)	2 (7.7)	4 (20.0)	3 (6.4)	4 (8.5)	1 (16.7)
NEO-ADJUVANT	0	0	2 (10.0)	2 (4.3)	1 (2.1)	0
METASTATIC	6 (85.7)	5 (19.2)	16 (80.0)	20 (42.6)	22 (46.8)	2 (33.3)
SUBJECTS ONLY RECEIVED IL-2 IN ADJUVANT/NEOADJUVANT SETTING (%)	0	1 (3.8)	1 (5.0)	2 (4.3)	1 (2.1)	0

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIV=Nivolumab
* More than one setting per subject may be reflected in the frequency.
Source: Table S.3.2A

Summary of efficacy results

A summary of ORR, PFS and OS for all arms is given in Table 34.

Table 35 Summary of Efficacy – All Treated Subjects

	Arm S N = 33		Arm P PAZ + NIV2 N = 20	Arm I-1 IPI1 + NIV3 N = 47	Arm I-3 IPI3 + NIV1 N = 47	Arm IN-3 IPI3 + NIV3 N = 6
	SUN + NIV2 N = 7	SUN + NIV5 N = 26				
SECONDARY ENDPOINTS						
Objective Response Rate (CR+PR)						
Number of Responders, n (%)[a]	6 (85.7)	11 (42.3)	9 (45.0)	19 (40.4)	19 (40.4)	0
95% CI	(42.1, 99.6)	(23.4, 63.1)	(23.1, 68.5)	(26.4, 55.7)	(26.4, 55.7)	--
Duration of Response						
Ongoing Response, n (%)[a]	2 (33.3)	4 (36.4)	0	8 (42.1)	7 (36.8)	0
Median (95% CI)[b] (weeks)	45.6 (18.14, NA)	78.1 (36.14, NA)	30.1 (12.14, 174.14)	88.7 (37.14, NA)	85.9 (35.14, NA)	--
Min, Max[b] (weeks)	18.1, 183.0+	36.0, 150.1+	12.1, 189.0	9.3, 140.0+	12.1+, 138.0+	--
Progression-free Survival (Primary Definition)						
Events[c], n (%)	5 (71.4)	16 (61.5)	17 (85.0)	37 (78.7)	34 (72.3)	4 (66.7)
Median (95% CI)[b] (months)	11.3 (7.62, N.A.)	12.7 (5.55, 19.38)	7.2 (2.79, 11.07)	7.7 (3.71, 14.29)	9.4 (5.62, 18.63)	8.5 (1.31, NA)
Min, Max[b] (months)	7.6, 43.4+	0.0+, 35.8+	1.0, 44.8	1.1+, 33.7+	1.0, 33.1+	1.3, 21.9+
6-Month Rate[b], % (95% CI)[d]	100 (100, 100)	72.9 (49.3, 86.8)	54.9 (29.4, 74.6)	55.6 (40.0, 68.6)	63.8 (48.4, 75.7)	NC
EXPLORATORY ENDPOINTS						
Overall Survival						
Death, n (%)	3 (42.9)	9 (34.6)	13 (65)	16 (34.0)	18 (38.3)	0
Median (95% CI)[b] (months)	43.8 (15.87, NA)	36.8 (30.92, NA)	27.9 (13.34, NA)	NR (26.68, NA)	32.6 (25.99, NA)	NR
Min, Max[b] (months)	15.9, 45.6+	8.1, 39.2+	7.0, 47.6+	3.5, 35.0+	1.1, 34.3+	4.2+, 23.0+

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIV=Nivolumab
+: censored; NC: Not calculated; NR: The time point at which the percent of survivor drops below 50% has not been reached due to insufficient number of events and/or follow up.

[a] Confirmed Response only. Response assessments are defined by RECIST 1.1 Criteria. Number of Responders (%) is out of the total number of subjects. Ongoing Response (%) is defined as response censored within 6 months of the data cutoff date (16-Mar-2016) and out of the number of responders.

[b] By Kaplan-Meier Method. [c] Events were progression or death. [d] The 95% CIs are derived from Greenwood's formula.

Sources: Tables S.5.1A.1 (ORR), Tables S.5.1C.1 (TTR and DOR), Tables S.5.1F.1 (PFS rates), Tables S.5.1I (OS), Tables S.5.1K.1 (PFS).

Objective response rate

The investigator-assessed confirmed ORR was 40.4% in arm I-1 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg), 40.4% in arm I-3 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg). No confirmed ORR was found for arm IN-3 (Table 35). Five (10.6%) subjects in arm I-1 obtained a complete response. The response evaluable population remained the same as the efficacy population, hence no changes in sensitivity analysis results for the ORR.

Table 36 Best Overall Response per Investigator Assessed by RECIST 1.1 – Efficacy Population

	IPI1 + NIV3 N = 47	IPI3 + NIV1 N = 47	IPI3 + NIV3 N = 6
BEST OVERALL RESPONSE (%)			
COMPLETE RESPONSE	5 (10.6)	0	0
PARTIAL RESPONSE	14 (29.8)	19 (40.4)	0
STABLE DISEASE	19 (40.4)	17 (36.2)	5 (83.3)
PROGRESSIVE DISEASE	8 (17.0)	8 (17.0)	1 (16.7)
UNABLE TO DETERMINE	1 (2.1)	3 (6.4)	0
CONFIRMED ORR (A) (%)	19 (40.4)	19 (40.4)	0
95% CONFIDENCE LIMIT	(26.4, 55.7)	(26.4, 55.7)	

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIV=Nivolumab
(A) Confirmed Response Only.
Source: Table S.5.1A.1

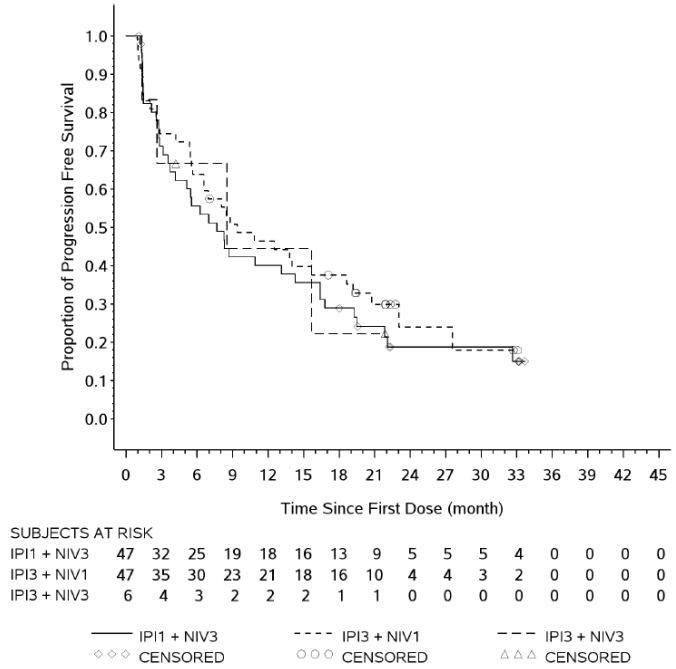
Duration of response

Median DOR was 88.7 and 85.9 weeks in arms I-1 and I-3, respectively. At the time of database lock, 8 (42.1%) and 7 (36.8%) responders had an ongoing response in arms I-1 and I-3.

Progression free survival

The median PFS was 7.7 (95% CI: 3.71, 14.29), 9.4 (95% CI: 5.62, 18.63) and 8.5 (95% CI: 1.31, N.A.) months for arms I-1, I-3, and IN-3 (Figure 38)

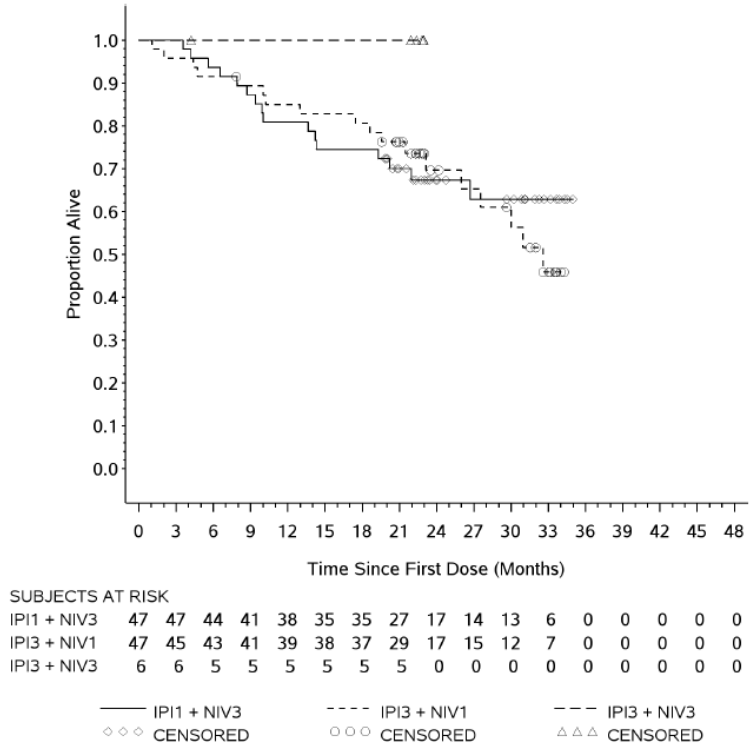
Figure 38 Progression Free Survival – Efficacy Population Arm I



Overall survival

Median OS were 32.6 (95% CI:25.99, N.A.) months in arm I-3; and not reached for both arms I-1 (95% CI:26.68, N.A.) and IN-3 (Figure 39).

Figure 39. Overall Survival – Efficacy Population in Arms I-1, I-3 and IN-3



Prior treatment/treatment naïve

Confirmed ORR between prior treated (n=22) and treatment naïve (n=25) subjects was 45.5% (24.4, 67.8) and 36% (18.0, 57.5) for arm-I. 38.5% (20.2, 59.4) and 42.9 % (21.8, 66.0) confirmed ORR

was reported for prior treated (n=26) and treatment naïve (n=21) subjects in arm I-3. PFS was 6.6 months (1.41, 16.39) and 8.3 months (3.55, 19.29) in prior treated and treatment-naïve subjects in arm I-1 and 10.1 months (5.42, 20,76) and 8.5 months (2,00, NA) in prior treated and treatment-naïve subjects in arm I-3. For both arm I-1 and I-3 OS was not reached, except for prior treatment subjects in arm I-3. In this subgroup, an OS of 30.0 months (25.00, NA) was found.

PD-L1 expression

The ORR in ipilimumab + nivolumab groups was 47.1% for subjects with ≥ 1% baseline PD-L1 expression and 36.8% for subjects with < 1% baseline PD-L1 expression (Table 36). The median PFS in ipilimumab + nivolumab groups was 12.52 months for subjects with ≥ 1% baseline PD-L1 expression, and 8.31 months for subjects with < 1% baseline PD-L1 expression. The median OS in ipilimumab + nivolumab groups was not reached for subjects with ≥ 1% or <1% baseline PD-L1 expression.

Table 37 Best Overall Response and Objective Response by Pre-treatment PD-L1- All Treated Subjects

PRETREATMENT PD-L1 EXPRESSION	SUN + NIV N = 33	PAZ + NIV N = 20	IPI + NIV N = 100
SUBJECTS WITH PRETREATMENT PD-L1 EXPRESSION >=1%	15 (45.5)	7 (35.0)	34 (34.0)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	1 (6.7)	1 (14.3)	1 (2.9)
PARTIAL RESPONSE (PR)	5 (33.3)	2 (28.6)	15 (44.1)
STABLE DISEASE (SD)	5 (33.3)	2 (28.6)	13 (38.2)
RELAPSED/PROGRESSIVE DISEASE (PD)	1 (6.7)	2 (28.6)	5 (14.7)
UNABLE TO DETERMINE (UTD)	3 (20.0)	0	0
NOT REPORTED (NR)	0	0	0
OBJECTIVE RESPONSE RATE (1)	6/ 15 (40.0%)	3/ 7 (42.9%)	16/ 34 (47.1%)
(95% CI)	(16.3, 67.7)	(9.9, 81.6)	(29.8, 64.9)
SUBJECTS WITH PRETREATMENT PD-L1 EXPRESSION < 1%	14 (42.4)	10 (50.0)	57 (57.0)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	0	4 (7.0)
PARTIAL RESPONSE (PR)	9 (64.3)	5 (50.0)	17 (29.8)
STABLE DISEASE (SD)	5 (35.7)	3 (30.0)	26 (45.6)
RELAPSED/PROGRESSIVE DISEASE (PD)	0	2 (20.0)	9 (15.8)
UNABLE TO DETERMINE (UTD)	0	0	1 (1.8)
NOT REPORTED (NR)	0	0	0
OBJECTIVE RESPONSE RATE (1)	9/ 14 (64.3%)	5/ 10 (50.0%)	21/ 57 (36.8%)
(95% CI)	(35.1, 87.2)	(18.7, 81.3)	(24.4, 50.7)

Safety Results

Safety results from study CA209016 are summarised in the section on dose response studies.

2.4.3. Discussion on clinical efficacy

Study CA209214 was the main study submitted for the extension of indication to include combination treatment with nivolumab and ipilimumab in adult patients with intermediate/poor-risk advanced renal cell carcinoma. Study CA209016 was included to support the dose regimen ipilimumab 1 mg/kg + nivolumab 3 mg/kg in mRCC.

Data to support ipilimumab 1 mg/kg + nivolumab 3 mg/kg in renal cell carcinoma

Study CA209016 was performed to explore various combination regimens with nivolumab plus ipilimumab, namely nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm I-3), nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm I-1) and nivolumab 3 mg/kg + ipilimumab 3 mg/kg (arm IN-3) in subjects with advanced or metastatic RCC. The purpose of the study was to determine the maximum tolerated dose and the recommended phase 2 dose of the combination regimens. Because the number of patients in arm IN-3 was low – and probably MTD was reached – the main focus will be on the comparison between arm I-1 and arm I-3. Currently, nivolumab is indicated as second-line treatment in advanced renal cell carcinoma patients, with efficacy demonstrated on OS. Ipilimumab is not indicated for the treatment of advanced RCC and there are limited data from studies performed with

ipilimumab in RCC patients. The combination therapy nivolumab + ipilimumab is indicated for the treatment of advanced melanoma. The recommended dose in melanoma patients is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab for the first 4 doses, followed by 3 mg/kg nivolumab every 2 weeks. Thus, the approved doses of the ipilimumab and nivolumab combination in melanoma are different from those in the current application, i.e. ipilimumab – approved dose 3 mg/kg vs. the proposed dose of 1 mg/kg in the current application, and nivolumab approved dose 1 mg/kg vs. 3 mg/kg in the current application.

In both arm I-1 and arm I-3, 47 subjects were enrolled; 6 patients were enrolled in arm IN-3. The majority of subjects where white males under the age of 65 with a KPS >90. Baseline patient demographics and characteristics were not balanced between arm I-1 and arm I-3, resulting in a suboptimal comparison of efficacy between the two arms. Arm I-1 contained patients who had more favourable prognostic factors for efficacy on different characteristics (refer to effects of these factors on efficacy in the main study; see forest plots), including more subjects below the age of 65 (91.5% vs. 76.6%), more patients with a Karnofsky Performance Status of 100 (61.7% vs. 42.6%) and more patients with PD-L1 expression ≥1% (40.4% vs. 29.8%). Thus, arm I-1 contained patients who might respond better to treatment compared to patients in arm I-3, hampering comparison of efficacy and most likely also safety. In addition, the cohorts of patients enrolled in arm I-1 and I-3 were a mix of previously treated and treatment-naïve patients, further complicating the comparison. MSKCC risk scores were similar between arms. The applicant explained that the KPS 90-100 patients are classified as ECOG 1 and that age is not incorporated in the IMDC prognostic model. It is agreed that small differences in KPS might not have a detrimental effect on efficacy/safety. However, based on the forest plots of ORR (Figure 35 and Figure 36) it seems that ORR is lower in patients above the age of 65 compared to younger patients, thus the imbalance in age between arm I-1 and arm I-3 cannot be ignored. As a result, it remains unclear to which extent the imbalances in baseline characteristics will have an effect on anti-tumour activity and safety observed in arm I-1 and arm I-3.

Safety/tolerability was the primary objective in study CA209016. Based on the safety results, arm I-1 appeared to have a more favourable safety profile compared to arm I-3 (and arm IN-3). However, as discussed above, patient characteristics were not balanced between arms and therefore also comparison of safety is hampered. Frequently observed AEs in both arm I-1 and arm I-3, regardless of causality as well as drug-related, were consistent with the common AEs known for nivolumab + ipilimumab in melanoma. The amount of treatment-related AEs (grade 3-4) was higher in arm I-3 than in arm I-1. There were also more drug-related AEs (any grade) leading to discontinuation of treatment in arm I-3 compared to arm I-1. This was mainly due to the increased frequency of subjects in Arm I-3 experiencing ALT increased, colitis and diarrhoea. The frequency of subjects experiencing SAEs was higher in arm I-3, whereas ALT increased, colitis and diarrhoea were observed most frequently and were all grade 3-4. Both the select AEs (any grade) and IMAEs (any grade) were more present in the arm I-3, except for renal select AE.

Although these data suggest poorer tolerability with I-3 than with I-1, the imbalances in baseline characteristics hamper drawing definitive conclusions regarding tolerability of I-1 and I-3.

When analysing the secondary objective of ORR, no clear differences were found in preliminary anti-tumour activity between arm I-1 and arm I-3. The confirmed ORR was the same in arm I-1 and arm I-3 (40.4%), but complete responses were only observed in the arm I-1 (10.6% vs. 0%). The duration of response was similar between arm I-1 and arm I-3, namely 88.7 weeks and 85.9 weeks, as well as the ongoing responses for both arms (42.1% vs. 36.8%). Therefore, arm I-1 and arm I-3 seemed comparable with regard to ORR. However, as outlined above, differences in baseline characteristics hamper drawing conclusions on relative efficacy of I-1 and I-3. No clear differences in PFS and OS were observed between the two arms. Importantly, it should be noted that both the I-1 arm and I-3 arm included patients with favourable risk according to MSKCC, further limiting the possibility to make

comparisons regarding the efficacy of I-1 and I-3 in the target population. In the subgroup of first-line patients with IMDC intermediate/poor risk (based on retrospective IMDC risk-score assignment - 17 subjects in arm I-1 and 15 subjects in arm I-3), the ORR was slightly higher in arm I-3 (46.7%) compared to arm I-1 (41.1%) (data not shown). However, no complete responses were observed in arm I-3, while 2 subjects (11.8%) had a complete response in arm I-1. Efficacy for arm IN-3 was based on 6 subjects, but these did not obtain a confirmed ORR. PFS was 8.5 months and OS not reached. These results should be analysed with caution, as sample size was small and, in addition, five out of six of these patients had favourable risk.

In conclusion, the applicant selected arm I-1 as the dosing schedule to be used in the pivotal study based on the more favourable safety profile of arm I-1 compared to arm I-3 and the lack of difference in observable anti-tumour activity between I-1 and I-3. However, sample sizes were small in the dose-response study and imbalances in baseline characteristics hamper interpretation of the data for ORR, PFS and OS and the safety results.

Importantly, the applicant did not compare the anti-tumour activity of the combination treatment with nivolumab monotherapy. Nivolumab has been shown to be effective in the target population, as it is approved for the treatment of advanced RCC after prior therapy in adults. In contrast, the benefit of ipilimumab is little characterised in the target population. In the guideline on the evaluation of anticancer medicinal products in man, it is stated that ''In phase II, the new combination should be compared to both combination partners as single agents at efficacious doses and preferably a reference treatment: AB vs. A vs. B vs. reference treatment*''. Depending on the phase II results one or both monotherapy arms may be dispensable in phase III.* In the pivotal study (CA209214) performed by the applicant, monotherapy arms are lacking, and the co-enhancement effect of combination therapy compared to nivolumab monotherapy has also not been demonstrated in phase I/II. The lack of demonstration of the contribution to efficacy of ipilimumab is considered an important issue, because the efficacy of nivolumab in RCC is evident, while the clinical benefit from ipilimumab in RCC has not been demonstrated. This is especially relevant considering that addition of ipilimumab leads to a more unfavourable safety profile than nivolumab monotherapy as shown by the applicant. In addition, the benefit/risk balance for ipilimumab monotherapy (MDX010-11) was not considered sufficiently favourable by the applicant to warrant further development in advanced RCC. The applicant included exposure-effect relationships to support the combination therapy by comparing the efficacy parameters (ORR and OS) for nivolumab monotherapy with the combination nivolumab + ipilimumab. However, it was unclear whether with the current dataset the contribution of each component to efficacy can be elucidated because of insufficient data on nivolumab c.q. ipilimumab monotherapy in first-line RCC and lack of data of the combination therapy in second-line RCC. This uncertainty was discussed by the applicant with the request for supplementary information. The applicant claims that the ORR of nivolumab monotherapy and ipilimumab monotherapy were not considered to be sufficient to warrant testing in a phase 3 randomised study in first-line advanced RCC patients. However, there is no clear correlation observed between ORR/PFS and OS for immune checkpoint inhibitors (PD-1, PD-L1 and CTLA-4) (Kaufman *et al.* Journal of Oncology – abstract, Mushti *et al.* Clin Cancer Res. 2018). Real-world survival data of first-line nivolumab monotherapy in patients with RCC was provided. A small number of patients (n=32) was treated off-label with nivoluamb monotherapy (real-world data) and some of the patients in study CA209009 who received nivolumab were previous untreated (n=24). However, this concerns only a limited number of patients and cross-study comparison between these studies with study CA209214 has its limitations a.o. in terms of patient selection. Therefore, it cannot be determined whether an added benefit of ipilimumab in combination with nivolumab over nivolumab alone is obtained; the lack of demonstration of the contribution to efficacy of ipilimumab is considered a major issue.

In addition, there are questions regarding the chosen dose of ipilimumab, i.e. 1 mg/kg. It is not clear whether 1 mg/kg ipilimumab contributes to clinical benefit in patients with RCC. Limited dose-response data for ipilimumab monotherapy in RCC are available. Study MDX010-11 was presented by the applicant to demonstrate that ipilimumab monotherapy has an effect in patients with stage IV RCC. One subject (5%) who received a single dose of ipilimumab 3 mg/kg followed by 1 mg/kg Q3W (cohort A) experienced a partial response out of the 21 subjects. Four subjects experienced a partial response (12.5%) of the 40 subjects who received a first dose of ipilimumab 3 mg/kg followed by 3 mg/kg Q3W (cohort B). Duration of response in the single patient in cohort A was 18 months, and 7.8 months in cohort B (Yang *et al.* J Immunother. 2007;30: 825-830). In both cohorts, patients started with a dose of 3 mg/kg ipilimumab, and dosing schedules containing only 1 mg/kg ipilimumab appear not to have been tested in RCC patients as concluded from the data submitted by the applicant.

As a result, the dose-response relationship of ipilimumab in RCC is poorly defined, and it cannot be concluded that 1 mg/kg ipilimumab contributes to a relevant extent to efficacy. Especially in view of the additional toxicity that is conferred by ipilimumab, this is considered another important uncertainty in the dossier. In the second round, the applicant provided data regarding the dose-dependent increase in peripheral blood absolute lymphocyte counts (ALC), which has been observed in phase II/III melanoma studies. However, ALC is not a validated surrogate marker for clinical benefit. Further, as elaborated by the applicant, study CA209016 aimed to show the anti-tumour response for first-line intermediate/poor-risk subjects. Anti-tumour effect observed in study CA209016 for the combination therapy does not mean that there will be an added benefit of ipilimumab *per se*, due to the lack of a head-to-head comparison with nivolumab monotherapy. Besides, due to the imbalances in baseline characteristics in study CA209016, it remains difficult to compare anti-tumour activity between arm I-1 and I-3. Whether 1 mg/kg ipilimumab contributes to efficacy of the combination therapy cannot be determined. This means that the MO remains unresolved. What is further notable, is that the dose-response data for ipilimumab that are available in melanoma patients show that 1 mg/kg ipilimumab might be on a low part of the dose-response curve (Figure 10). A statistically significant trend (p=0.0015) between increasing dose and higher best overall response was found in melanoma (EPAR of Yervoy; EMA/CHMP/557664/2011). This dose-response relationship was confirmed in a comparative phase 3 study comparing ipilimumab 3 mg/kg with 10 mg/kg monotherapy for treatment of melanoma, which showed a statistically significantly longer overall survival for 10 mg/kg compared to 3 mg/kg ipilimumab (EMEA/H/C/002213/II/0042).

For nivolumab, it is known that in RCC the dose-efficacy relationship is flat between 1 mg/kg and 10 mg/kg. Also for toxicity there appears to be no difference between 1 mg/kg and 3 mg/kg. The dose of nivolumab is therefore not questioned.

CA209214 - Main study

Study CA209214 was a randomised, open-label, phase III study, comparing nivolumab + ipilimumab with sunitinib. The administered dose of the combination regimen was nivolumab 1 mg/kg + ipilimumab 3 mg/kg for 4 doses followed by nivolumab 3 mg/kg every 2 weeks, based on the results of the dose response study CA209016. As outlined above, it can not be concluded what the single agent contribution of ipilimumab is regarding the observed anti-tumour activity and clinical benefit, and whether 1 mg/kg ipilimumab is an efficacious dose. The dose of sunitinib was 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2 week rest period to comprise a complete cycle of 6 weeks, which is the recommended dose for mRCC (Sutent SmPC).

Design and conduct of clinical studies

Subjects were ≥18 years of age with previously untreated advanced RCC (not amenable for surgery or radiotherapy) or mRRC, with a clear-cell component. No patients with non-clear cell RCC were treated with nivolumab + ipilimumab. However, restrictions to the indication based on histology subtype are not deemed appropriate in this case because in view of the mechanism of action of the combination it is not expected that efficacy is restricted to the clear-cell histological subtype. This is confirmed by available data showing efficacy of nivolumab in non-clear cell RCC (e.g. Koshkin et al. 2017, JCO 35, no. 15_suppl p.4586-4586) and has a regulatory precedent (nivolumab in the second line treatment of RCC; EMEA/H/C/003985/II/0008). The lack of clinical data for nivolumab plus ipilimumab in patients with non-clear cell RCC should be mentioned in section 5.1 of the SmPC. Prior systemic therapy was not permitted except for one prior adjuvant or neoadjuvant therapy, not including agents that target VEGF or VEGF receptors. The patient population was adequate and inclusion/exclusion criteria are acceptable, although the list of exclusion criteria was relatively long. However, this is understood, since these criteria are related to three drugs that patients were potentially eligible for (sunitinib, ipilimumab, and nivolumab). CA209214 was an open-label study. As nivolumab and ipilimumab are administered intravenously and sunitinib orally, and the known safety profiles of sunitinib and nivolumab+ipilimumab are very different, it is understood that an open-label study instead of a blinded study was performed. Since OS is the main endpoint of interest, no relevant bias due to the open-label design is expected.

Of these 1096 subjects, 547 subjects received nivolumab + ipilimumab and 535 subjects received sunitinib (all randomised subjects).

Baseline demographics and disease characteristics were balanced for the nivolumab+ipilimumab and the sunitinib arms (all randomised subjects, as well as intermediate/poor-risk subjects). Stratification was based on region (US vs. Canada/Western Europe/Northern Europe vs. Rest of World) and IMDC prognostic score (0 vs. 1-2 vs. 3-6), which is acceptable. PD-L1 expression was not used as a stratification factor, but expression appeared balanced between study arms. The MAH states that sunitinib is currently a widely used standard-of-care agent in the selected patient population. Indeed, standard first-line treatment of patients with favourable or intermediate prognosis is with sunitinib or pazopanib and for poor-risk patients both temsirolimus or VEGF inhibitors can be used. Therefore, sunitinib is considered acceptable as comparator in favourable, intermediate and poor-risk patients.

Relevant protocol deviations were reported in 2.4% of patients in each study arm from the intermediate/poor-risk population. One patient in each study arm has a baseline KPS<70, 1 patient in the sunitinib arm had no confirmed histology of RCC and 9 patients and 8 patients in the nivo+ipi and sunitinib arm, respectively, had a baseline IDMC score <1, but were however included in the intermediate/poor-risk population. It is unlikely that this had any impact on study results.
Dose reductions and increases were allowed for subjects receiving sunitinib, while no dose reductions and increases were allowed in subjects receiving nivolumab and ipilimumab. A lower proportion of subjects received 90% to 110% of the planned dose in the sunitinib arm, namely 54.0% for sunitinib and 87.6% and 80.3 % for nivolumab + ipilimumab, respectively. The number of dose delays was highest for ipilimumab, mainly caused by adverse events. Patients (all treated) in the sunitinib arm received more subsequent therapy compared to nivolumab + ipilimumab (57.7% vs. 45.6%). Patients in the sunitinib arm mainly received nivolumab or pembrolizumab as subsequent systemic treatment (28.2%) and patients in the nivolumab + ipilimumab arm mainly received sunitinib as subsequent treatment (20.2%). The number of patients (intermediate/poor-risk) receiving subsequent therapy was higher in the sunitnib group compared to the nivolumab+ipilimumab group (55.21% vs. 40.47%). Common subsequent therapies in the nivolumab + ipilimumab group were suntinib (20.47%), pazopanib (13.18%) and axitinib (12.94%). Common subsequent therapies for the sunitinib group

were nivolumab (27.96 %), axitinib 20.62 and evirolimub (10.19%). It is not expected that subsequent therapy hinders the interpretation of the primary objectives of the study.

One of the six prognostic factors determining the RCC risk groups (favourable, intermediate or poor) of the subjects was not reported in approximately 80% of the patients in each arm, i.e. corrected calcium. It is expected that the calcium levels were known at the time of randomisation, since the lack of corrected calcium data would bias the enrolment of patients in their corresponding cohort (poor/intermediate-risk or favourable-risk). If not available, then IMDC risk group could not have been adequately determined, which would be a major issue because the target population is defined based on IMDC risk score. The applicant was asked to confirm whether corrected calcium was available at the time of randomisation, report calcium levels, and discuss whether any patients were misclassified according to IMDC risk score. The applicant clarified that all 6 components of the IMDC risk score, including corrected calcium, were known at the time of randomisation in the 1096 randomised subjects.

Protocol amendments

By means of amendment 13 (4-Aug-2016) ORR was included as the third co-primary endpoint of trial with an "administrative" allocation of alpha=0.001. As the overall alpha for this study was 0.05, which was split in 0.001 to evaluate ORR, 0.009 to evaluate PFS and 0.04 to evaluate OS, it is important to know that the addition of ORR as co-primary endpoint did not change the alpha to evaluate OS determined at primary analysis. Based on the original study protocol (submitted by the applicant on request), it appeared that the inclusion of ORR did not affect the conclusions regarding OS, as the alpha of OS was 0.04 and the alpha of PFS was 0.01 both in the original protocol and the last version of the protocol. An interim analysis was performed on ORR (merely descriptive) on 14-Nov-2016, thus 3 months after protocol amendment 13. Taking into account that this was an open-label study, the integrity of data and the rationale for protocol amendment 13 just before data cut-off for the interim analysis for ORR should be further justified. The applicant mentioned that the reason for adding ORR as primary endpoint was based on communication with the United States (US) Food and Drug Administration in April 2016 for a different tumour type, which supported the potential for accelerated approval in the US. The late inclusion of ORR as a primary endpoint raised initially concerns due to the open-label design of the study, but importantly, the inclusion of ORR as co-primary endpoint did not influence statistical evaluation of OS, as the 0.04 alpha for overall survival was preserved.

The timing of the PFS analysis was advanced due to slowing number of PFS events. Although not stated explicitly, this has probably been done blinded as the study blind was not broken, and this is considered acceptable.

Statistical methods

The primary objective of the study was to describe OS, PFS, and ORR in intermediate/poor-risk subjects. The applicant pragmatically decided *a priori* to focus their primary analysis on the poor/intermediate risk group, because the inclusion of this subset of subjects allowed for potential differences in efficacy to be detected earlier than if favourable-risk patients were included.

The secondary objective of the study was to describe OS, PFS, and ORR in all treated subjects. OS, PFS, and ORR in favourable-risk subjects was added as an exploratory objective. ORR, OS, PFS were not co-primary endpoints in the usual sense (EMA/CHMP/44762/2017), as they do not all need to be statistically significant as they all had their own type I error (0.001, 0.04, 0.009). No formal testing was defined for ORR (only descriptive exact 95%-CI for the ORR in each arm, a descriptive 95%-CI for the difference, and an 'administrative' alpha=0.001), so ORR cannot be formally statistically significant.

The confidence interval of 95% in the updated OS K-M is not in line with the earlier used confidence interval, namely 99.8%. Applicant explained that the primary analysis used 99.8% confidence intervals (CIs) to adjust the type 1 error at the time of the interim analysis based on the pre-specified alpha spending function. The follow-up analyses are considered exploratory so the 95% CI is used for the hazard ratio in the overall survival (OS) Kaplan-Meier plot. Updated figures were also provided.

The primary definition of the PFS analysis censored for start of new cancer-directed therapy, so is not the recommended PFS analysis (EMA/CHMP/27994/2008/Rev.1), although the secondary definition is in line.

Sample size calculations reflect that the primary analysis population is a mixture (different median OS and PFS in the control arm for the poor versus the intermediate risk population assumed). Multiplicity was controlled via alpha splitting for the three primary endpoints and group sequential testing (OS had two interim and one final analysis). The statistical tests and estimation methods (for the proportions such as ORR and time-to-event outcomes such as OS) are considered standard and well-accepted.

Efficacy – Intermediate/poor-risk subjects

In the primary efficacy population of patients with intermediate/poor-risk, a statistically significant difference in OS was found between the nivolumab + ipilimumab group and the sunitinib group, favouring the nivolumab + ipilimumab group (HR 0.63 [99.8 CI: 0.44,0.89] , p-value:<0.0001). The median OS for the sunitinib arm was 25.95 months, whereas the median OS in the nivolumab + ipilimumab group was not reached. At approximately 3 months the K-M curves separated, favouring the nivolumab + ipilimumab group. The amount of censoring was high in the tail of the K-M curves, starting at month 20. The applicant provided an update of the OS data based on a database lock of 01-Mar-2018. No changes in K-M curves are observed in the updated OS curves for patients with intermediate and poor-risk RCC, and the OS benefit remains – as expected – in favour of ipilimumab + nivolumab.

The significant effect on OS was not fully supported by PFS, as PFS was not statistically significant in the nivolumab + ipilimumab group compared with the sunitinib group (HR 0.82 [99.1% CI: 0.64 – 1.05], p-value 0.0331). Nevertheless, the numerical benefit of ipilimumab + nivolumab over sunitinib might still be clinically relevant. A difference of more than three months was found for the median PFS of nivolumab+ipilimumab compared to sunitinib. Piecewise HR for ≤6 months and >6 months favoured nivolumab +ipilimumab, with a HR of 0.90 and 0.69, respectively.

The IRRC-assessed ORR was higher in the nivolumab + ipilimumab group (41.6% [95% CI: 36.9, 46.5]) than in the sunitinib group (26.5% [95% CI: 22.4, 31.0]). A stratified difference in ORR was observed (16% [95% CI: 9.8,22.2], p-value: <0.0001, but no test prespecified so formally not significant), favouring the nivolumab + ipilimumab arm. Both complete responses and partial responses were obtained more frequently in the nivolumab + ipilimumab group compared with the sunitinib group. The time to response was shorter for the nivolumab + ipilimumab group compared to sunitinib group (3.42 months vs. 4.77 months). The duration of response was not reached (95% CI: 21.28, N.A months) for the nivolumab + ipilimumab group and was 20.96 months (95% CI: 18.17, N.A.) for the sunitinib group.

Efficacy – Favourable-risk patients

Based on the exploratory endpoints in the favourable cohort, no clinical benefit from the combination treatment was observed. OS, PFS and ORR all appeared to favour the sunitinib arm. A numerical difference in OS was observed, favouring sunitinib (HR 1.45 [descriptive 99.8% CI: 0.51, 4.12], p-value: 0.2715), however follow-up was too short to definitively determine effects of the treatments on OS. The median OS was not reached for the nivolumab + ipilimumab arm and the median OS of the sunitinib arm (32.92 months) is not precise due to the large extent of censoring at the K-M tail. There were few events observed in the favourable-risk subjects (37/249). Upon request, the applicant provided an update of OS in favourable-risk subjects (database lock 01-Mar-2018). The numerical difference between both groups remained in favour of suntinib, but the number of events observed in these groups was low. A benefit in PFS was seen for sunitinib (HR 2.18 [descriptive 99.1%CI: 1.29, 2.68]). The median PFS difference between the arms was approximately 9 months. The curves separated after 3 months favouring sunitinib. The stratified difference in ORR was -23.0% with a P value of 0.0002, favouring sunitinib. Sunitinib had a longer duration of response in the favourable group compared to the intermediate/poor-risk group (23.49 months vs. 18.18 months). The median duration for nivolumab + ipilimumab in both the intermediate/poor-risk group and favourable-risk group was not reached. Median time to response was increase in the favourable group for both ipilimumab + nivolumab (2.79 months vs. 3.86 months) and sunitinib (3.04 months vs. 5.55 months) compared to the intermediate/poor-risk group. Although the favourable-risk group was an exploratory endpoint, nivolumab + ipilimumab was not superior to sunitinib for OS, PFS or ORR. The sample size was low and follow-up period was short, but favourable-risk patients seemed to benefit more from sunitinib therapy than from ipilimumab + nivolumab. These findings should be clearly reported in the product information(s) in order to inform physicians (see SmPC).

Effects in subgroups – Intermediate/poor-risk subjects

Subgroup analyses were performed in intermediate/poor-risk subjects and all-treated subjects. The unweighted difference in OS and PFS favoured the nivolumab + ipilimumab in almost all subpopulations. For ORR, Black and African American race and ≤10 mg/dl corrected calcium seemed to favour sunitinib. For PFS, Black and African American race, Asian race, year to initial diagnosis to randomisation (years) ≥ 1 year and corrected calcium ≤ 10 mg/dl seemed to favour sunitinib. However, this effect does not seem to be convincing, as samples sizes were small, confidence intervals wide and sometimes subpopulations borderline favoured sunitinib. Most subpopulations favoured nivolumab+ipilimumab for OS. However, different subgroups had hazard ratios close to 1, suggesting limited additional benefit compared to sunitinib. Since serum albumin was not specified as a mandatory laboratory test at cycle 1, serum albumin levels were missing in > 80% of randomised subjects. The applicant provided adjusted forest plots with the ''yes'' / ''no'' data on corrected calcium. There seems to be only a small difference in point estimates for OS HR between patients with corrected calcium > 10 mg/dL or ≤10 mg/dL, both in favour of nivolumab + ipilimumab. Notably, it can be seen that patients with age>65 years and patients with KPS <90 had a HR close to 1. Thus, the benefit of nivolumab + ipilimumab is less obvious in these subpopulations. Patients >65 years of age appear to benefit somewhat less from the combination therapy versus sunitinib compared to younger patients, especially patients age ≥75, although benefit from the combination therapy in these patients appears comparable to patients treated with sunitinib. However, the number of patients with age ≥75 included in the study was small and therefore estimates are relatively imprecise. The applicant showed that patients with a KPS = 80 drove the HR towards 1 in the forest plots and that this might be due to chance. As the point estimate of KPS<80 favours nivolumab + ipilimumab, it is likely that the obtained HR for patients with KPS=80 is an outlier. Also, the benefit of the combination therapy still borderline favours nivolumab + ipilimumab for KPS <90. SmPC includes information regarding elderly (age ≥75).

When comparing IMDC risk groups, it can be seen that the subgroup most favouring the combination therapy vs. sunitinib is the poor-risk group, followed by the intermediate-risk group (for OS, PFS and ORR).

PD-L1 expression

Effects of PD-L1 expression are not conclusive, i.e. due to limitations in the methodology of scoring PD-L1 expression (e.g. not scoring immune cell expression). No quantitative evaluation of immune cell expression of PD-L1 was performed in study CA209214, but the applicant will re-score PD-L1 stained samples in a post hoc evaluation (expected availability date: March 2019). It can be seen, however, that sunitinib performs worse at PD-L1<1% compared to PD-L1 ≥1%. PD-L1 expression seems to predict worse prognosis in advanced RCC patients treated with anti-angiogenesis drugs, as patients with high PD-L1 expression had a worse OS outcome according to literature (Choueiri *et al.* Clin Cancer Res. 2015), which is in line with the obtained results for the sunitinib group in this study. For intermediate/poor-risk subjects, OS by baseline PD-L1 ≥1% expression favoured nivolumab+ipilimumab (HR: 0.45 [95% CI: 0.29, 0.71]). This was also observed in subjects with PD-L1 <1% expression, but the HR was closer to 1 compared to PD-L1 ≥1% expression (HR: 0.73 [95% CI: 0.56, 0.96]) In the favourable risk group, it can be seen that this increased effect in subjects with PD-L1 ≥1 expression is mostly caused by the steeper decrease in OS K-M curve in sunitinib for subjects with PD-L1 ≥1%. In intermediate/poor-risk subjects with PD-L1<1% expression, no difference in PFS was observed between nivolumab + ipilimumab and sunitinib (HR: 1.06 [95% CI: 0.87, 1.36]). For subjects with PD-L1 ≥1% expression, however, a strong PFS benefit was observed for nivolumab + ipilimumab (HR: 0.47 [95% CI: 0.34, 064]). This effect was also caused by the decrease in PFS observed in the sunitinib arm for intermediate/poor-risk subjects with PD-L1 expression ≥1%. A benefit in ORR in the nivolumab + ipilimumab arm was observed regardless of PD-L1 expression in intermediate/poor-risk subjects. The ORR of sunitinib was lower in subjects with PD-L1 ≥1% than in patients with PD-L1 <1%.

Several additional, potentially more relevant biomarkers for nivolumab + ipilimumab efficacy are available, including tumour mutational burden, tumour infiltrating lymphocytes, myeloid-derived suppressor cells in peripheral blood, gene expression profiling, single nucleotide polymorphism in immune-related genes, and correlations between routine lab values and efficacy (e.g. blood lymphocyte counts, neutrophil counts, neutrophil/lymphocyte ratio). These biomarker analyses were planned to be analysed by the applicant. Upon request for supplementary information, the applicant provided additional OS data in relation to myeloid-derived suppressor cells (MDSC) expression and neutrophil/lymphocyte ratio (NLC). It has been observed in mRCC patients that baseline MDSC might have a prognostic value able to predict OS, whereas a lower MDSC results in a more favourable clinical benefit, which is also observed in the Figure 29 (Mizuno *et al.* Cancer Sci. 2017). The OS benefit of nivolumab + ipilimumab compared to sunitinib is observed in subjects with low MDSC expression, intermediate MDSC expression and subjects with high MDSC expression.

An analysis was conducted with available peripheral absolute lymphocyte and neutrophil counts. For NLR, it seems that a favourable OS is observed regardless of neutrophils to lymphocytes ratio, although the benefit was less pronounced for neutrophils to lymphocyte ratio <3. Based on literature, it seems that high neutrophil- to-lymphocyte ratio correlates to a worse treatment outcome, which is not observed in study CA209214 (Sacdalan *et al.* OncoTargets and Therapy. 2018). Data regarding immune profiling in the tumor by IHC was not presented by the applicant due to insufficient tumor tissue material.

Several analysis were asked that have not been submitted yet and it is expected that these data will be available March 2019. This data could be provided as post-marketing measure, including all relevant biomarker data by March 2019.

Additional Biomarkers:

The applicant is committed to submit biomarker data - including tumour infiltrating lymphocytes - will be provided by March 2019. The applicant mentions that the remaining samples for biomarker analysis will be used for analysis of CD8 in tumour tissue, which will be available for only a subset of patients. These biomarker data are considered of importance in the discussion on the identification upfront of those patients that benefit most of the treatment.

Patient-reported outcomes (EQ-5D, FACT-G and FKSI-9) – exploratory endpoints

EQ-5D, FACT-G and NCCN patient-reported outcomes were included to analyse health-related quality of life and patient-reported symptoms. The applicant described that across all 3 patient-reported scales, the nivolumab + ipilimumab group reported numerically higher cores compared to baseline scores and the sunitinib group. However, only small differences were observed between the outcomes and it was not clearly defined in the CSR which the difference in PRO outcome can be considered a clinically relevant difference. Also, after one year the number of subjects included in the PRO assessments was decreased more than 50 percent, while the number of completed questionnaires was even less. In light of these observations, it was not clear what the clinical relevance is of the PRO results. The applicant provided additional data regarding the PRO studies. For the FKSI-19 and the FACT-G, mean scores were numerically different between the sunitinib group and the ipilimumab + nivolumab group, favouring nivolumab + ipilimumab. The applicant's objective was to evaluate disease related symptoms with the FKSI-19. However, the FKSI-19 is not considered optimal to compare the two treatment groups, as the treatment side effects subscale of the questionnaire is developed by input of patients treated with chemotherapy. The items in the questionnaire related to side effects are referring to side effects (fatigue, nausea and diarrhea) more frequently observed with sunitinib than nivolumab + ipilimumab, which might drive the treatment side effect score.

The mean score of the FACT-G favours nivolumab + ipilimumab compared to sunitinib, but the difference is less noticeable than the difference observed with the FKSI-19. It is not clear whether this mean difference was also clinically relevant and remains difficult to interpret with the open-label study design. The applicant did not discuss EQ-5D-3L, but based on the differences in mean score between nivolumab + ipilimumab and sunitinib, it seems that no clinically relevant difference was found with this questionnaire.

2.4.4. Conclusions on the clinical efficacy

In the pivotal study, nivolumab + ipilimumab showed improved efficacy compared to sunitinib in previously untreated intermediate/poor-risk advanced RCC patients. A statistically significant and clinically relevant OS benefit was observed for intermediate/poor-risk subjects treated with nivolumab + ipilimumab compared to sunitinib. The OS data was supported by numerical benefits in PFS and ORR. Benefit of the combination therapy was not observed in favourable-risk patients, in whom sunitinib resulted in a numerically better outcome.

A major issue in the current dossier is that the contribution of ipilimumab (in the studied dose) to the efficacy of the combination therapy has not been demonstrated, whereas it is clear that addition of ipilimumab leads to a more unfavourable safety profile.

2.5. Clinical safety

Introduction

This section describes the safety data from Study CA209214, a phase 3, randomised, open-label study of nivolumab combined with ipilimumab vs. sunitinib monotherapy. The posology in this study is in line with the proposed use of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg at the proposed schedule of every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg every 2 weeks (Q2W) for the treatment of adult patients with intermediate/poor-risk (per International Metastatic RCC Database Consortium criteria) advanced renal cell carcinoma (RCC) (American Joint Committee on Cancer stage IV).

Safety data are presented here for the primary safety population (all treated subjects), nivolumab + ipilimumab group (N = 547 subjects treated) vs. the sunitinib monotherapy treatment group (N = 535 subjects treated), based on the 07-Aug-2017 final analysis database lock (DBL). The all treated population was the primary population for safety analyses to maximise the size of the safety database. In addition, safety data are presented for treated subjects in the primary efficacy population (intermediate/poor-risk subjects) in the nivolumab + ipilimumab group (N = 423) vs. the sunitinib monotherapy treatment group (N = 416). Safety data from the supportive Phase 1 study, CA209016, are not summarised here, a brief summary of safety in study CA209016 is provided in the section on dose response studies. Importantly, the main study is considered most representative for the target population and the safety data from the supportive study show a similar safety profile of nivolumab + ipilimumab as in the main study.

Patient exposure

Safety analyses were conducted in all 1082 treated subjects in study CA2092141 who received at least 1 dose of study drug. Safety presentations of AEs, SAEs, AEs leading to discontinuation, select AEs, and laboratory abnormalities are based on all treated subjects (including favourable risk patients) unless stated otherwise, using a safety window of 30 days after last dose received.

Demographic and Other Characteristics of Study Population

Among all randomised subjects, baseline demographic, disease characteristics, and tumour assessments were well balanced between the nivolumab + ipilimumab and sunitinib groups (refer to section on clinical efficacy). Among intermediate/poor-risk subjects, baseline demographic, disease characteristics, and tumour assessments were consistent with those in all randomised subjects.

Patient exposure

A total of 547 subjects received at least 1 infusion of nivolumab and ipilimumab, and 535 subjects received at least 1 dose of sunitinib. In the nivolumab + ipilimumab group, 87.6% and 80.3% of subjects received 90% to ≥110% of the planned dose intensity of nivolumab and ipilimumab, respectively. In the sunitinib group, 54.0% of subjects received 90% to ≥110% of the planned dose intensity of sunitinib. The higher proportion of subjects receiving ≥90% of the planned dose intensity of nivolumab and ipilimumab than sunitinib can be explained by allowed dose reductions and increases of sunitinib per protocol, while these were not allowed for nivolumab or ipilimumab.
At the time of final DBL, the median duration of therapy was 7.85 months in the nivolumab + ipilimumab group, with a median of 14 nivolumab doses and 4 ipilimumab doses received, and 7.82 months in the sunitinib group, with a median daily dose of 31.33 mg/day (range: 14.2 - 50.0) received.

Dose Modifications and Delays

Most treated subjects in the nivolumab + ipilimumab group received all doses of study medication without an infusion interruption or infusion rate reduction, or dose delay. Reasons for infusion

interruption and infusion rate reduction in the nivolumab + ipilimumab group are provided in (Table 38).

Table 38 Infusion Interruptions and Infusion Rate Reductions - All Treated Subjects in the Nivolumab + Ipilimumab group

	Nivolumab + Ipilimumab N = 547	
	Nivolumab	Ipilimumab
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	29 (5.3)	5 (0.9)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)		
0	518 (94.7)	542 (99.1)
1	23 (4.2)	4 (0.7)
2	2 (0.4)	1 (0.2)
3	2 (0.4)	0
>= 4	2 (0.4)	0
TOTAL NUMBER OF DOSES INTERRUPTED/ TOTAL NUMBER OF DOSES RECEIVED	56/11435 (0.5)	6/ 1983 (0.3)
REASON FOR INFUSION INTERRUPTION (A)		
HYPERSENSITIVITY REACTION	17 (30.4)	1 (16.7)
INFUSION ADMIN ISSUES	32 (57.1)	4 (66.7)
OTHER	7 (12.5)	1 (16.7)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	11 (2.0)	10 (1.8)
NUMBER OF INFUSIONS WITH IV RATE REDUCTIONS PER SUBJECT (%)		
0	536 (98.0)	537 (98.2)
1	8 (1.5)	8 (1.5)
2	1 (0.2)	1 (0.2)
3	1 (0.2)	1 (0.2)
>= 4	1 (0.2)	0
TOTAL NUMBER OF IV RATES REDUCED/ TOTAL NUMBER OF DOSES RECEIVED	17/11435 (0.1)	13/ 1983 (0.7)
REASON FOR IV RATE REDUCTION (B)		
HYPERSENSITIVITY REACTION	9 (52.9)	0
INFUSION ADMIN ISSUES	5 (29.4)	5 (38.5)
OTHER	3 (17.6)	8 (61.5)

(A) Percentages are computed out of the total number of Dose Interrupted by treatment group.
(B) Percentages are computed out of the total number of infusions with iv rate reduction by treatment group.
Source: Table S.4.3 (infusion interruption) and Table S.4.4 (IV rate reduction) of the CA209214 Final CSR[1]

Infusion interruptions: 29 (5.3%) subjects in the nivolumab + ipilimumab group had a nivolumab infusion interruption and 5 (0.9%) subjects had an ipilimumab infusion interruption. Of the subjects who required an infusion interruption, most had only 1 infusion interrupted. Infusion rate reductions: 2.0% of nivolumab + ipilimumab subjects had a nivolumab infusion rate reduction and 1.8% of nivolumab + ipilimumab subjects had an ipilimumab infusion rate reduction.

Dose delay information for the nivolumab + ipilimumab and sunitinib groups is provided in (Table 39).

Table 39 Dose Delays of Study Therapy – All Treated Subjects

	Nivolumab + Ipilimumab N = 547		Sunitinib N = 535
	Nivolumab	Ipilimumab	Sunitinib
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	319 (58.3)	148 (27.1)	315 (58.9)
NUMBER OF DOSES DELAYED PER SUBJECT			
0	228 (41.7)	399 (72.9)	220 (41.1)
1	152 (27.8)	134 (24.5)	123 (23.0)
2	72 (13.2)	13 (2.4)	77 (14.4)
3	39 (7.1)	1 (0.2)	35 (6.5)
>= 4	56 (10.2)	0	80 (15.0)
TOTAL NUMBER OF DOSES DELAYED/ TOTAL NUMBER OF DOSES RECEIVED (A)	728/10888 (6.7)	163/1436 (11.4)	1144/111149 (1.0)
REASON FOR DOSE DELAY (B)			
ADVERSE EVENT	479 (65.8)	139 (85.3)	775 (67.7)
OTHER	247 (33.9)	23 (14.1)	369 (32.3)
NOT REPORTED	2 (0.3)	1 (0.6)	0
LENGTH OF DOSE DELAY (B)			
4 - 7 DAYS	274 (37.6)	56 (34.4)	314 (27.4)
8 - 14 DAYS	219 (30.1)	32 (19.6)	309 (27.0)
15 - 42 DAYS	203 (27.9)	65 (39.9)	169 (14.8)
> 42 DAYS	32 (4.4)	10 (6.1)	5 (0.4)

A dose was considered as actually delayed if the delay is exceeding 3 days for Nivolumab or Ipilimumab.
A dose was considered as actually delayed if the subject did not receive any dose during at least one day for Sunitinib.
(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.
(B) Percentages are computed out of the total number of doses delayed.
Program Source: /projects/bms211276/stats/primary/prog/tables/rt-ex-delay.sas 14AUG2017:09:55:45

Dose delays: Of subjects who experienced dose delays, most experienced only 1 delay: 152 out of 319 subjects experienced at least 1 nivolumab dose delay; 134 out of 148 subjects experienced at least 1 ipilimumab dose delay; and 123 out of 315 subjects experienced at least 1 sunitinib dose delay. The majority of dose delays were ≤ 14 days. The most common reason for dose delays was an AE (accounting for 65.8% of all delayed nivolumab doses; 85.3% of all delayed ipilimumab doses; and 67.7% of all delayed sunitinib doses). Dose reductions: In the sunitinib group, 52.9% of subjects required a dose reduction; dose reductions were not permitted with nivolumab + ipilimumab treatment.

Adverse events

The all treated population was the primary population for safety analyses and is presented below. The safety profile of nivolumab + ipilimumab therapy in intermediate/poor-risk subjects is described at the end of the clinical safety section.

Common Adverse Events

In all treated subjects, the overall frequency of any-grade AEs (regardless of causality) were >90% in both treatment groups. The frequencies of Grade 3-4 AEs and drug-related AEs (any grade and Grade 3-4) were numerically lower in the nivolumab + ipilimumab group than in the sunitinib group.

Adverse Events (Regardless of Causality)

Any-grade AEs (regardless of causality) were reported in 99.5% of subjects in the nivolumab + ipilimumab group and 99.4% of subjects in the sunitinib group (Table 40).

- In the nivolumab + ipilimumab group, the most frequently reported AEs were fatigue (45.0%), diarrhoea (37.5%), pruritus (32.9%) and nausea (29.8%).

- In the sunitinib group, the most frequently reported AEs were diarrhoea (57.9%), fatigue (54.4%), palmar-plantar erythrodysesthesia syndrome (44.3%), hypertension (43.2%), nausea (43.0%) and dysgeusia (34.6%).

Grade 3-4 AEs (regardless of causality) were reported in 65.3% of subjects in the nivolumab + ipilimumab group and 76.1% of subjects in the sunitinib group (Table 40).

- In the nivolumab + ipilimumab group, the most frequently reported Grade 3-4 AEs were lipase increased (11.0%), amylase increased (6.2%) and fatigue (6.2%).

- In the sunitinib group, the most frequently reported Grade 3-4 AEs were hypertension (17.6%), fatigue (10.1%), palmar-plantar erythrodysesthesia syndrome (9.3%), lipase increased (7.7%) and platelet count decreased (7.1%).

Drug-related Adverse Events

Any-grade drug-related AEs were reported in 93.1% of subjects in the nivolumab + ipilimumab group and 97.4% of subjects in the sunitinib group (Table 41).

- In the nivolumab + ipilimumab group, the most frequently reported drug-related AEs were fatigue (36.9%), pruritus (28.2%), diarrhoea (26.5%) and rash (21.6%).

- In the sunitinib group, the most frequently reported drug-related AEs were diarrhoea (52.0%), fatigue (49.3%), palmar-plantar erythrodysesthesia syndrome (43.2%), hypertension (40.4%), nausea (37.8%) and dysgeusia (33.5%).

Grade 3-4 drug-related AEs were reported in 45.7% of subjects in the nivolumab + ipilimumab group and 62.6% of subjects in the sunitinib group (Table 41).

- In the nivolumab + ipilimumab group, the most frequently reported Grade 3-4 drug-related AEs were lipase increased (10.2%), amylase increased (5.7%), alanine aminotransferase (ALT) increased (4.9%), fatigue (4.2%) and diarrhoea (3.8%).
- In the sunitinib group, the most frequently reported Grade 3-4 drug-related AEs reported were hypertension (15.9%), fatigue (9.2%), palmar-plantar erythrodysesthesia syndrome (9.2%), platelet count decreased (6.7%), lipase increased (6.5%), neutropenia (6.0%) and diarrhoea (5.2%).

Table 40 Adverse Events by Worst CTC Grade Reported in ≥ 10% of Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	544 (99.5)	357 (65.3)	17 (3.1)	532 (99.4)	407 (76.1)	18 (3.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	405 (74.0)	53 (9.7)	2 (0.4)	465 (86.9)	94 (17.6)	1 (0.2)
FATIGUE	246 (45.0)	34 (6.2)	0	291 (54.4)	54 (10.1)	0
PYREXIA	136 (24.9)	4 (0.7)	0	91 (17.0)	3 (0.6)	0
ASTHENIA	88 (16.1)	11 (2.0)	0	102 (19.1)	15 (2.8)	0
OEDEMA PERIPHERAL	76 (13.9)	3 (0.5)	0	67 (12.5)	1 (0.2)	0
MUCOSAL INFLAMMATION	18 (3.3)	0	0	157 (29.3)	14 (2.6)	0
GASTROINTESTINAL DISORDERS	398 (72.8)	59 (10.8)	0	468 (87.5)	91 (17.0)	0
DIARRHOEA	205 (37.5)	25 (4.6)	0	310 (57.9)	33 (6.2)	0
NAUSEA	163 (29.8)	11 (2.0)	0	230 (43.0)	8 (1.5)	0
VOMITING	109 (19.9)	5 (0.9)	0	149 (27.9)	11 (2.1)	0
CONSTIPATION	93 (17.0)	2 (0.4)	0	94 (17.6)	0	0
ABDOMINAL PAIN	72 (13.2)	8 (1.5)	0	77 (14.4)	7 (1.3)	0
DYSPEPSIA	29 (5.3)	0	0	112 (20.9)	1 (0.2)	0
STOMATITIS	29 (5.3)	0	0	153 (28.6)	14 (2.6)	0
GASTROOESOPHAGEAL REFLUX DISEASE	11 (2.0)	1 (0.2)	0	67 (12.5)	1 (0.2)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	340 (62.2)	21 (3.8)	0	386 (72.1)	63 (11.8)	0
PRURITUS	180 (32.9)	3 (0.5)	0	58 (10.8)	0	0
RASH	141 (25.8)	8 (1.5)	0	84 (15.7)	0	0
DRY SKIN	55 (10.1)	0	0	53 (9.9)	0	0
RASH MACULO-PAPULAR	55 (10.1)	9 (1.6)	0	28 (5.2)	3 (0.6)	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	9 (1.6)	0	0	237 (44.3)	50 (9.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	288 (52.7)	35 (6.4)	0	275 (51.4)	25 (4.7)	0
ARTHRALGIA	123 (22.5)	7 (1.3)	0	83 (15.5)	0	0
BACK PAIN	88 (16.1)	12 (2.2)	0	91 (17.0)	8 (1.5)	0
MYALGIA	65 (11.9)	3 (0.5)	0	34 (6.4)	0	0
PAIN IN EXTREMITY	63 (11.5)	3 (0.5)	0	76 (14.2)	5 (0.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	280 (51.2)	39 (7.1)	3 (0.5)	285 (53.3)	35 (6.5)	1 (0.2)
COUGH	145 (26.5)	1 (0.2)	0	125 (23.4)	2 (0.4)	0
DYSPNOEA	100 (18.3)	13 (2.4)	0	96 (17.9)	11 (2.1)	1 (0.2)

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
EPISTAXIS	7 (1.3)	1 (0.2)	0	76 (14.2)	3 (0.6)	0
INVESTIGATIONS	267 (48.8)	119 (21.8)	0	263 (49.2)	114 (21.3)	0
LIPASE INCREASED	96 (17.6)	60 (11.0)	0	65 (12.1)	41 (7.7)	0
AMYLASE INCREASED	76 (13.9)	34 (6.2)	0	42 (7.9)	17 (3.2)	0
ASPARTATE AMINOTRANSFERASE INCREASED	70 (12.8)	19 (3.5)	0	57 (10.7)	9 (1.7)	0
BLOOD CREATININE INCREASED	68 (12.4)	2 (0.4)	0	50 (9.3)	4 (0.7)	0
ALANINE AMINOTRANSFERASE INCREASED	67 (12.2)	27 (4.9)	0	60 (11.2)	11 (2.1)	0
PLATELET COUNT DECREASED	9 (1.6)	1 (0.2)	0	78 (14.6)	38 (7.1)	0
METABOLISM AND NUTRITION DISORDERS	260 (47.5)	90 (16.5)	0	256 (47.9)	54 (10.1)	0
DECREASED APPETITE	114 (20.8)	10 (1.8)	0	156 (29.2)	5 (0.9)	0
HYPERGLYCAEMIA	57 (10.4)	22 (4.0)	0	23 (4.3)	4 (0.7)	0
NERVOUS SYSTEM DISORDERS	248 (45.3)	30 (5.5)	1 (0.2)	315 (58.9)	24 (4.5)	1 (0.2)
HEADACHE	103 (18.8)	5 (0.9)	0	121 (22.6)	5 (0.9)	0
DIZZINESS	61 (11.2)	1 (0.2)	0	61 (11.4)	0	0
DYSGEUSIA	40 (7.3)	0	0	185 (34.6)	1 (0.2)	0
ENDOCRINE DISORDERS	175 (32.0)	35 (6.4)	0	152 (28.4)	1 (0.2)	0
HYPOTHYROIDISM	96 (17.6)	2 (0.4)	0	145 (27.1)	1 (0.2)	0
HYPERTHYROIDISM	63 (11.5)	2 (0.4)	0	16 (3.0)	0	0
PSYCHIATRIC DISORDERS	115 (21.0)	5 (0.9)	1 (0.2)	80 (15.0)	3 (0.6)	0
INSOMNIA	58 (10.6)	1 (0.2)	0	35 (6.5)	2 (0.4)	0
VASCULAR DISORDERS	113 (20.7)	30 (5.5)	1 (0.2)	261 (48.8)	102 (19.1)	0
HYPERTENSION	52 (9.5)	18 (3.3)	0	231 (43.2)	94 (17.6)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	91 (16.6)	30 (5.5)	0	209 (39.1)	85 (15.9)	0
ANAEMIA	72 (13.2)	20 (3.7)	0	109 (20.4)	32 (6.0)	0
THROMBOCYTOPENIA	6 (1.1)	2 (0.4)	0	99 (18.5)	26 (4.9)	0
NEUTROPENIA	3 (0.5)	1 (0.2)	0	73 (13.6)	33 (6.2)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.2a of the CA209214 Final CSR[1]

Table 41 Drug-related Adverse Events by Worst CTC Grade Reported in ≥ 5% of Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	509 (93.1)	250 (45.7)	0	521 (97.4)	335 (62.6)	2 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	314 (57.4)	33 (6.0)	0	415 (77.6)	75 (14.0)	0
FATIGUE	202 (36.9)	23 (4.2)	0	264 (49.3)	49 (9.2)	0
PYREXIA	79 (14.4)	2 (0.4)	0	33 (6.2)	1 (0.2)	0
ASTHENIA	72 (13.2)	8 (1.5)	0	91 (17.0)	12 (2.2)	0
OEDEMA PERIPHERAL	25 (4.6)	1 (0.2)	0	29 (5.4)	0	0
MUCOSAL INFLAMMATION	13 (2.4)	0	0	152 (28.4)	14 (2.6)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	289 (52.8)	20 (3.7)	0	358 (66.9)	58 (10.8)	0
PRURITUS	154 (28.2)	3 (0.5)	0	49 (9.2)	0	0
RASH	118 (21.6)	8 (1.5)	0	67 (12.5)	0	0
RASH MACULO-PAPULAR	50 (9.1)	8 (1.5)	0	22 (4.1)	1 (0.2)	0
DRY SKIN	40 (7.3)	0	0	46 (8.6)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	5 (0.9)	0	0	231 (43.2)	49 (9.2)	0
SKIN DISCOLOURATION	2 (0.4)	0	0	27 (5.0)	0	0
HAIR COLOUR CHANGES	0	0	0	29 (5.4)	0	0
YELLOW SKIN	0	0	0	43 (8.0)	0	0
GASTROINTESTINAL DISORDERS	287 (52.5)	41 (7.5)	0	430 (80.4)	67 (12.5)	0
DIARRHOEA	145 (26.5)	21 (3.8)	0	278 (52.0)	28 (5.2)	0
NAUSEA	109 (19.9)	8 (1.5)	0	202 (37.8)	6 (1.1)	0
VOMITING	59 (10.8)	4 (0.7)	0	110 (20.6)	10 (1.9)	0
ABDOMINAL PAIN	38 (6.9)	2 (0.4)	0	38 (7.1)	1 (0.2)	0
CONSTIPATION	35 (6.4)	0	0	39 (7.3)	0	0
DRY MOUTH	31 (5.7)	0	0	32 (6.0)	0	0
STOMATITIS	23 (4.2)	0	0	149 (27.9)	14 (2.6)	0
DYSPEPSIA	15 (2.7)	0	0	96 (17.9)	0	0
ABDOMINAL PAIN UPPER	9 (1.6)	0	0	30 (5.6)	0	0
GASTROOESOPHAGEAL REFLUX DISEASE	6 (1.1)	1 (0.2)	0	55 (10.3)	0	0
FLATULENCE	3 (0.5)	0	0	27 (5.0)	0	0
INVESTIGATIONS	210 (38.4)	111 (20.3)	0	224 (41.9)	100 (18.7)	0
LIPASE INCREASED	90 (16.5)	56 (10.2)	0	58 (10.8)	35 (6.5)	0
AMYLASE INCREASED	71 (13.0)	31 (5.7)	0	41 (7.7)	17 (3.2)	0
ALANINE AMINOTRANSFERASE INCREASED	60 (11.0)	27 (4.9)	0	50 (9.3)	8 (1.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	58 (10.6)	19 (3.5)	0	49 (9.2)	7 (1.3)	0
BLOOD CREATININE INCREASED	35 (6.4)	1 (0.2)	0	35 (6.5)	2 (0.4)	0

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
WEIGHT DECREASED	18 (3.3)	0	0	28 (5.2)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	11 (2.0)	0	0	30 (5.6)	0	0
WHITE BLOOD CELL COUNT DECREASED	6 (1.1)	0	0	40 (7.5)	11 (2.1)	0
PLATELET COUNT DECREASED	4 (0.7)	1 (0.2)	0	73 (13.6)	36 (6.7)	0
NEUTROPHIL COUNT DECREASED	3 (0.5)	1 (0.2)	0	40 (7.5)	23 (4.3)	0
ENDOCRINE DISORDERS	160 (29.3)	34 (6.2)	0	140 (26.2)	1 (0.2)	0
HYPOTHYROIDISM	85 (15.5)	2 (0.4)	0	134 (25.0)	1 (0.2)	0
HYPERTHYROIDISM	59 (10.8)	2 (0.4)	0	12 (2.2)	0	0
ADRENAL INSUFFICIENCY	28 (5.1)	11 (2.0)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	156 (28.5)	48 (8.8)	0	197 (36.8)	33 (6.2)	0
DECREASED APPETITE	75 (13.7)	7 (1.3)	0	133 (24.9)	5 (0.9)	0
HYPERGLYCAEMIA	28 (5.1)	8 (1.5)	0	10 (1.9)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	149 (27.2)	14 (2.6)	0	121 (22.6)	5 (0.9)	0
ARTHRALGIA	76 (13.9)	5 (0.9)	0	39 (7.3)	0	0
MYALGIA	49 (9.0)	3 (0.5)	0	26 (4.9)	0	0
PAIN IN EXTREMITY	17 (3.1)	1 (0.2)	0	36 (6.7)	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	136 (24.9)	11 (2.0)	0	253 (47.3)	7 (1.3)	0
HEADACHE	53 (9.7)	4 (0.7)	0	65 (12.1)	1 (0.2)	0
DYSGEUSIA	31 (5.7)	0	0	179 (33.5)	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	107 (19.6)	8 (1.5)	0	145 (27.1)	10 (1.9)	0
COUGH	45 (8.2)	0	0	31 (5.8)	0	0
PNEUMONITIS	32 (5.9)	6 (1.1)	0	0	0	0
DYSPNOEA	31 (5.7)	1 (0.2)	0	33 (6.2)	2 (0.4)	0
EPISTAXIS	0	0	0	55 (10.3)	3 (0.6)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	47 (8.6)	8 (1.5)	0	183 (34.2)	73 (13.6)	0
ANAEMIA	34 (6.2)	2 (0.4)	0	83 (15.5)	24 (4.5)	0
NEUTROPENIA	3 (0.5)	1 (0.2)	0	69 (12.9)	32 (6.0)	0
THROMBOCYTOPENIA	2 (0.4)	0	0	95 (17.8)	25 (4.7)	0
LEUKOPENIA	1 (0.2)	0	0	30 (5.6)	3 (0.6)	0
VASCULAR DISORDERS	37 (6.8)	9 (1.6)	0	225 (42.1)	87 (16.3)	0
HYPERTENSION	12 (2.2)	4 (0.7)	0	216 (40.4)	85 (15.9)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.3a in CA209214 Final CSR[1]

The overall frequency of AEs (regardless of causality) leading to a dose delay or reduction was 53.6% in the nivolumab + ipilimumab group and 43.2% in the sunitinib group.

Late-Emergent Adverse Events

Late-emergent drug-related AEs were defined as drug-related AEs with an onset date > 100 days after the last dose of study therapy. In the nivolumab + ipilimumab group, 20 (3.7%) subjects had late-emergent drug-related AEs (Table S.6.6 of the CA209214 Final CSR). 15 (3.5%) of these subjects were intermediate/poor-risk subjects (Table S.6.6.1 of the CA209214 Final CSR). Of these AEs, 9 (1.6%) were grade 3-5, and 3 were grade 5 (0.5%). The most frequent late-emergent AEs in the nivolumab + ipilimumab group (in more than 1 patient) occurred in SOCs: infections and infestations (3 patients; disseminated tuberculosis, lung infection, staphylococcal sepsis), investigations (3 patients; ASAT increased, ALAT increased, bilirubin increased), musculoskeletal and connective tissue disorders (3 patients; arthritis, arthralgia, myalgia), gastrointestinal disorders (2 patients; colitis, lower gastrointestinal haemorrhage), general disorders and administration site conditions (2 patients; fatigue, sudden death), immune system disorders (2 patients; contrast media allergy), skin and subcutaneous tissue disorders (2 patients; prurigo, rash). In the sunitinib group, 2 (0.4%) subjects reported late-emergent drug-related AEs, and 1 subject was intermediate/poor-risk (Table S.6.6 and Table S.6.6.1 of the CA209214 Final CSR1). The late-emergent AEs in the sunitinib group occurred in SOCs gastrointestinal disorders (diarrhoea) and investigations (ASAT increased, ALAT increased, and bilirubin increased).

Deaths

As of the 07-Aug-2017 DBL, a lower proportion of treated subjects in the nivolumab + ipilimumab group (29.1%) had died compared with the sunitinib group (37.8%) (Table 41). Disease progression was the most common cause of death for both groups, including deaths occurring within 100 days of last dose. 23 (4.2%) and 25 (4.7%) subjects in each group died within 30 days of last dose, and the most common cause of deaths was due to 'other' in the nivolumab + ipilimumab group and disease progression in the sunitinib group. The causes of death in the 'other' class in the nivolumab + ipilimumab group are provided below.

Table 42 Deaths Summary - All Treated Subjects

	Nivolumab + Ipilimumab N = 547	Sunitinib N = 535
NUMBER OF SUBJECTS WHO DIED (%)	159 (29.1)	202 (37.8)
PRIMARY REASON FOR DEATH (%)		
DISEASE	124 (22.7)	173 (32.3)
STUDY DRUG TOXICITY	7 (1.3)	4 (0.7)
UNKNOWN	6 (1.1)	12 (2.2)
OTHER	22 (4.0)	13 (2.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	23 (4.2)	25 (4.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	10 (1.8)	18 (3.4)
STUDY DRUG TOXICITY	1 (0.2)	3 (0.6)
UNKNOWN	1 (0.2)	1 (0.2)
OTHER	11 (2.0)	3 (0.6)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	50 (9.1)	77 (14.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE	32 (5.9)	63 (11.8)
STUDY DRUG TOXICITY	3 (0.5)	4 (0.7)
UNKNOWN	1 (0.2)	4 (0.7)
OTHER	14 (2.6)	6 (1.1)

Source: Table 8.6.15 in CA209214 Final CSR[1]

Deaths related to study drug toxicity

The following deaths were attributed to study drug toxicity by the investigator:

- 7 (1.3%) deaths in the nivolumab + ipilimumab group: 3 subjects died within 100 days of last dose (1 of these 3 subjects died within 30 days of last dose), and 4 subjects died beyond 100 days of last dose.
- 4 (0.7%) deaths in the sunitinib group: 3 subjects died within 30 days of last dose, and 1 subject died 33 days since the last dose.

The applicant's assessment for the cause of death for the 7 deaths in the nivolumab + ipilimumab group was "not related" in 4, "related" in 2, and "needs more information" in 1 case(s). Among the 4 deaths attributed to sunitinib by the investigators, the applicant's assessment concurred with 3 as "related", and 1 death was considered "unrelated." A listing of the suspected causes of death is provided below (for detailed information refer to Table S.6 of the CA209214 Final CSR).

Deaths in the nivolumab + ipilimumab arm (7 subjects) were the following: Subject […] was a 71-year-old male with RCC diagnosed in Apr-2014 who died due to acute necrotizing pneumonia, Subject […] was a 71-year-old female with RCC diagnosed in 2013 who died due to sudden death, Subject […] was a 79-year-old male with RCC diagnosed in Nov-2014 who died due to hepatic failure, Subject […] was a 70-year-old male with RCC diagnosed in Mar-2011 who died due to pneumonitis, Subject […] was a 71-year-old male with RCC diagnosed in Oct-2012 who died due to immune-mediated bronchitis, Subject […] was an 80-year-old female with RCC diagnosed in Apr-2015 who died due to lower gastrointestinal haemorrhage, Subject […] was a 59-year-old female with RCC diagnosed in Nov-2015 who died due to haemophagocytic syndrome.

Deaths in the sunitinib arm (4 subjects) were the following: Subject […] was a 61-year-old male with RCC diagnosed in Mar-2015 who died due to right heart failure, Subject […] was a 58-year-old male with RCC diagnosed in Apr-2015 who died due to cardiac arrest, Subject […] was a 69-year-old male with RCC diagnosed in Nov-2012 who died due to cardiac arrest, Subject […] was a 62-year-old male with RCC diagnosed in Nov-2012 who died due to multiple organ failure.

Deaths Attributed to 'Other' Reasons

The verbatim terms reported for the 'other' reasons for death are provided below.

Nivolumab + Ipilimumab (22 subjects):

CA209214: cardiac arrest	CA209214: right cerebral infarction
CA209214: suicide	CA209214: pneumonia
CA209214: community acquired pneumonia, metastatic renal cancer	CA209214: acute myocardial infarction
CA209214: sepsis secondary to pancreatitis	CA209214: pulmonary embolism
CA209214: heart failure	CA209214: cardiac arrest
CA209214: bronchopneumonia	CA209214: cardiac arrest
CA209214: pneumonia	CA209214: pneumonia
CA209214: global respiratory insufficiency due to respiratory infection	CA209214: exacerbated chronic heart failure
CA209214: massive thrombotic embolism	CA209214:acute respiratory distress
CA209214: pulmonary embolism suspicion	CA209214: cardiopulmonary arrest
CA209214: sudden cardiac death	
CA209214: stroke	

Sunitinib (13 subjects):

CA209214: complications of procedure	CA209214: cardiac arrest
CA209214: intracranial hemorrhage	CA209214: sepsis
CA209214: secondary to hemorhaggic stroke - not related to study drug	CA209214: pulmonary embolism
CA209214: hydropneumothorax	CA209214: bacterial pneumonia
CA209214: gastrointestinal bleed	CA209214: complications pos surgical
CA209214: fell down due to alcohol intoxication (14-Jul-2016, he stayed in the hospital until death)	CA209214: uncontrolled diabetes
CA209214: bleeding in the gastrointestinal tract	

Serious Adverse Events

In all treated subjects, the overall frequencies of all-causality SAEs and drug-related SAEs were numerically higher in the nivolumab + ipilimumab group than in the sunitinib group. Drug-related SAEs consisted mainly of events in the SOCs of GI and endocrine disorders and infections and infestations disorders in the nivolumab + ipilimumab group, and GI disorders and respiratory, thoracic and mediastinal disorders in the sunitinib group. SAEs were reported in 55.8% of subjects in the nivolumab + ipilimumab group and 39.8% of subjects in the sunitinib group (Table 42). Grade 3-4 SAEs were reported in 41.5% and 30.1% of subjects in the nivolumab + ipilimumab and sunitinib groups, respectively.

- In the nivolumab + ipilimumab group, the most frequently reported SAEs were diarrhoea (4.4%), malignant neoplasm progression (4.0%), pyrexia (3.3%) and pneumonia (3.1%).
- In the sunitinib group, the most frequently reported SAEs were malignant neoplasm progression (5.8%), dyspnoea, pleural effusion, and pyrexia (1.7% each), and acute kidney injury, dehydration, haematuria and pneumonia (1.5% each).

Drug-related SAEs were reported in 29.6% of subjects in the nivolumab + ipilimumab group and 15.1% of subjects in the sunitinib group (Table 43). Grade 3-4 drug-related SAEs were reported in 22.1% and 12.0% of subjects in the nivolumab + ipilimumab and sunitinib groups, respectively.

- In the nivolumab + ipilimumab group, the most frequently reported drug-related SAEs were diarrhoea (3.8%), pneumonitis (2.7%) and hypophysitis (2.4%).
- In the sunitinib group, the most frequently reported drug-related SAE was dehydration (1.3%).

Table 43. SAEs by Worst CTC Grade Reported in ≥1% of Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	305 (55.8)	227 (41.5)	17 (3.1)	213 (39.8)	161 (30.1)	18 (3.4)
GASTROINTESTINAL DISORDERS	59 (10.8)	38 (6.9)	0	38 (7.1)	35 (6.5)	0
DIARRHOEA	24 (4.4)	13 (2.4)	0	3 (0.6)	3 (0.6)	0
COLITIS	10 (1.8)	9 (1.6)	0	0	0	0
NAUSEA	8 (1.5)	4 (0.7)	0	2 (0.4)	2 (0.4)	0
INFECTIONS AND INFESTATIONS	52 (9.5)	45 (8.2)	1 (0.2)	30 (5.6)	21 (3.9)	2 (0.4)
PNEUMONIA	17 (3.1)	15 (2.7)	1 (0.2)	8 (1.5)	3 (0.6)	1 (0.2)
URINARY TRACT INFECTION	6 (1.1)	4 (0.7)	0	0	0	0
SEPSIS	5 (0.9)	5 (0.9)	0	6 (1.1)	3 (0.6)	1 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	46 (8.4)	23 (4.2)	3 (0.5)	35 (6.5)	21 (3.9)	1 (0.2)
PNEUMONITIS	15 (2.7)	6 (1.1)	0	1 (0.2)	1 (0.2)	0
DYSPNOEA	9 (1.6)	7 (1.3)	0	9 (1.7)	5 (0.9)	1 (0.2)
PLEURAL EFFUSION	7 (1.3)	5 (0.9)	0	9 (1.7)	8 (1.5)	0
ENDOCRINE DISORDERS	41 (7.5)	29 (5.3)	0	1 (0.2)	0	0
HYPOPHYSITIS	14 (2.6)	12 (2.2)	0	0	0	0
ADRENAL INSUFFICIENCY	10 (1.8)	9 (1.6)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	37 (6.8)	31 (5.7)	0	22 (4.1)	20 (3.7)	0
HYPONATRAEMIA	9 (1.6)	9 (1.6)	0	5 (0.9)	5 (0.9)	0
DEHYDRATION	7 (1.3)	6 (1.1)	0	8 (1.5)	7 (1.3)	0
HYPERGLYCAEMIA	6 (1.1)	6 (1.1)	0	1 (0.2)	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	34 (6.2)	24 (4.4)	7 (1.3)	41 (7.7)	20 (3.7)	11 (2.1)
MALIGNANT NEOPLASM PROGRESSION	22 (4.0)	13 (2.4)	7 (1.3)	31 (5.8)	17 (3.2)	11 (2.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	33 (6.0)	12 (2.2)	2 (0.4)	27 (5.0)	15 (2.8)	1 (0.2)
PYREXIA	18 (3.3)	2 (0.4)	0	9 (1.7)	1 (0.2)	0
CARDIAC DISORDERS	20 (3.7)	15 (2.7)	3 (0.5)	12 (2.2)	6 (1.1)	2 (0.4)
MYOCARDIAL INFARCTION	6 (1.1)	6 (1.1)	0	1 (0.2)	0	0
RENAL AND URINARY DISORDERS	20 (3.7)	10 (1.8)	0	22 (4.1)	16 (3.0)	0
ACUTE KIDNEY INJURY	8 (1.5)	5 (0.9)	0	8 (1.5)	6 (1.1)	0
HAEMATURIA	2 (0.4)	1 (0.2)	0	8 (1.5)	5 (0.9)	0
INVESTIGATIONS	18 (3.3)	12 (2.2)	0	9 (1.7)	7 (1.3)	0
ALANINE AMINOTRANSFERASE INCREASED	9 (1.6)	8 (1.5)	0	0	0	0
PSYCHIATRIC DISORDERS	8 (1.5)	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	0
CONFUSIONAL STATE	6 (1.1)	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (1.3)	6 (1.1)	0	10 (1.9)	7 (1.3)	0
ANAEMIA	6 (1.1)	5 (0.9)	0	7 (1.3)	6 (1.1)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.18a in CA209214 Final CSR[1]

Table 44 Drug-related SAEs by Worst CTC Grade Reported in at Least 2 Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	162 (29.6)	121 (22.1)	0	81 (15.1)	64 (12.0)	2 (0.4)
GASTROINTESTINAL DISORDERS	39 (7.1)	25 (4.6)	0	21 (3.9)	19 (3.6)	0
DIARRHOEA	21 (3.8)	11 (2.0)	0	2 (0.4)	2 (0.4)	0
COLITIS	9 (1.6)	8 (1.5)	0	0	0	0
NAUSEA	6 (1.1)	3 (0.5)	0	1 (0.2)	1 (0.2)	0
VOMITING	4 (0.7)	3 (0.5)	0	3 (0.6)	3 (0.6)	0
PANCREATITIS	2 (0.4)	1 (0.2)	0	4 (0.7)	3 (0.6)	0
STOMATITIS	0	0	0	2 (0.4)	2 (0.4)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	0	0	0	2 (0.4)	2 (0.4)	0
ENDOCRINE DISORDERS	37 (6.8)	28 (5.1)	0	1 (0.2)	0	0
HYPOPHYSITIS	13 (2.4)	12 (2.2)	0	0	0	0
ADRENAL INSUFFICIENCY	9 (1.6)	8 (1.5)	0	0	0	0
HYPERTHYROIDISM	3 (0.5)	1 (0.2)	0	0	0	0
THYROIDITIS	3 (0.5)	1 (0.2)	0	0	0	0
BASEDOW'S DISEASE	2 (0.4)	2 (0.4)	0	0	0	0
HYPOPITUITARISM	2 (0.4)	0	0	0	0	0
HYPOTHYROIDISM	2 (0.4)	1 (0.2)	0	1 (0.2)	0	0
SECONDARY ADRENOCORTICAL INSUFFICIENCY	2 (0.4)	2 (0.4)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	19 (3.5)	19 (3.5)	0	15 (2.8)	14 (2.6)	0
HYPONATRAEMIA	6 (1.1)	6 (1.1)	0	4 (0.7)	4 (0.7)	0
DEHYDRATION	4 (0.7)	4 (0.7)	0	7 (1.3)	6 (1.1)	0
DIABETES MELLITUS	2 (0.4)	2 (0.4)	0	0	0	0
FULMINANT TYPE 1 DIABETES MELLITUS	2 (0.4)	2 (0.4)	0	0	0	0
HYPERGLYCAEMIA	2 (0.4)	2 (0.4)	0	0	0	0
HYPOGLYCAEMIA	1 (0.2)	1 (0.2)	0	2 (0.4)	2 (0.4)	0
HYPOMAGNESAEMIA	0	0	0	2 (0.4)	2 (0.4)	0
INVESTIGATIONS	18 (3.3)	12 (2.2)	0	5 (0.9)	4 (0.7)	0
ALANINE AMINOTRANSFERASE INCREASED	9 (1.6)	8 (1.5)	0	0	0	0
BLOOD CREATININE INCREASED	5 (0.9)	1 (0.2)	0	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	4 (0.7)	3 (0.5)	0	0	0	0
TRANSAMINASES INCREASED	3 (0.5)	2 (0.4)	0	0	0	0
PLATELET COUNT DECREASED	0	0	0	4 (0.7)	4 (0.7)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	17 (3.1)	6 (1.1)	0	11 (2.1)	4 (0.7)	0
PNEUMONITIS	15 (2.7)	6 (1.1)	0	0	0	0
DYSPNOEA	1 (0.2)	0	0	3 (0.6)	1 (0.2)	0
EPISTAXIS	0	0	0	3 (0.6)	1 (0.2)	0
HAEMOPTYSIS	0	0	0	2 (0.4)	2 (0.4)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13 (2.4)	2 (0.4)	0	9 (1.7)	4 (0.7)	0
PYREXIA	9 (1.6)	0	0	2 (0.4)	0	0
FATIGUE	3 (0.5)	1 (0.2)	0	3 (0.6)	2 (0.4)	0
MALAISE	1 (0.2)	0	0	2 (0.4)	0	0
ASTHENIA	0	0	0	2 (0.4)	2 (0.4)	0
NERVOUS SYSTEM DISORDERS	10 (1.8)	5 (0.9)	0	2 (0.4)	1 (0.2)	0
PERIPHERAL MOTOR NEUROPATHY	2 (0.4)	0	0	0	0	0
CEREBROVASCULAR ACCIDENT	0	0	0	2 (0.4)	1 (0.2)	0
RENAL AND URINARY DISORDERS	8 (1.5)	5 (0.9)	0	10 (1.9)	7 (1.3)	0
ACUTE KIDNEY INJURY	4 (0.7)	4 (0.7)	0	4 (0.7)	3 (0.6)	0
RENAL INJURY	2 (0.4)	0	0	0	0	0
HAEMATURIA	0	0	0	2 (0.4)	1 (0.2)	0
RENAL FAILURE	0	0	0	2 (0.4)	2 (0.4)	0
RENAL IMPAIRMENT	0	0	0	2 (0.4)	1 (0.2)	0
HEPATOBILIARY DISORDERS	7 (1.3)	7 (1.3)	0	1 (0.2)	0	0
HEPATITIS	3 (0.5)	3 (0.5)	0	0	0	0
INFECTIONS AND INFESTATIONS	7 (1.3)	7 (1.3)	0	5 (0.9)	3 (0.6)	0
MENINGITIS ASEPTIC	2 (0.4)	2 (0.4)	0	0	0	0
SEPSIS	2 (0.4)	2 (0.4)	0	3 (0.6)	2 (0.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6 (1.1)	4 (0.7)	0	1 (0.2)	1 (0.2)	0
RASH	2 (0.4)	1 (0.2)	0	0	0	0
RASH MACULO-PAPULAR	2 (0.4)	2 (0.4)	0	0	0	0
IMMUNE SYSTEM DISORDERS	4 (0.7)	3 (0.5)	0	0	0	0
CONTRAST MEDIA ALLERGY	3 (0.5)	2 (0.4)	0	0	0	0
CONTRAST MEDIA REACTION	2 (0.4)	2 (0.4)	0	0	0	0
VASCULAR DISORDERS	4 (0.7)	3 (0.5)	0	4 (0.7)	4 (0.7)	0
HYPOTENSION	2 (0.4)	2 (0.4)	0	0	0	0
HYPERTENSION	0	0	0	3 (0.6)	3 (0.6)	0

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547 Any Grade	Grade 3-4	Grade 5	Sunitinib N = 535 Any Grade	Grade 3-4	Grade 5
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.2)	1 (0.2)	0	4 (0.7)	2 (0.4)	0
ANAEMIA	0	0	0	2 (0.4)	2 (0.4)	0
CARDIAC DISORDERS	1 (0.2)	1 (0.2)	0	9 (1.7)	5 (0.9)	2 (0.4)
CARDIAC ARREST	0	0	0	2 (0.4)	0	2 (0.4)
CARDIAC FAILURE CONGESTIVE	0	0	0	3 (0.6)	3 (0.6)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table 8.6.19a in CA209214 Final CSR[1]

Adverse Events Leading to Discontinuation of Study Therapy

In all treated subjects, the overall frequencies of all-causality and drug-related AEs leading to discontinuation numerically higher in the nivolumab + ipilimumab group compared to the sunitinib group. AEs leading to discontinuation were reported in 30.7% of subjects in the nivolumab + ipilimumab group and 21.3% of subjects in the sunitinib group (Table 44). Grade 3-4 AEs leading to discontinuation were reported in 21.6% and 13.8% of the subjects in the nivolumab + ipilimumab and sunitinib group, respectively.

- In the nivolumab + ipilimumab group, AEs leading to discontinuation reported in at least 1% of subjects included ALT increased and diarrhoea (2.7% each), malignant neoplasm progression (2.6%), aspartate aminotransferase (AST) increased (2.2%), pneumonitis (2.0%), and colitis and hypophysitis (1.3% each).
- In the sunitinib group, AEs leading to discontinuation reported in at least 1% of subjects was malignant neoplasm progression (2.2%) and fatigue (1.3%).

Drug-related AEs leading to discontinuation were reported in 21.6% of subjects in the nivolumab + ipilimumab group and 11.8% of subjects in the sunitinib group (Table 45). Grade 3-4 drug-related AEs leading to discontinuation were reported in 15.4% and 6.9% of the subjects in the nivolumab + ipilimumab and sunitinib group, respectively.

- In the nivolumab + ipilimumab group, the drug-related AE leading to discontinuation reported in at least 1% of subjects was ALT increased (2.7%), diarrhoea (2.6%), AST increased (2.2%), pneumonitis (2.0%), and colitis and hypophysitis (1.3% each).
- In the sunitinib group, the drug-related AE leading to discontinuation reported in at least 1% of subjects was fatigue (1.3%).

Table 45 Adverse Events Leading to Discontinuation (Reported in ≥1% of Subjects) by Worst CTC Grade - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	168 (30.7)	118 (21.6)	6 (1.1)	114 (21.3)	74 (13.8)	8 (1.5)
INVESTIGATIONS	28 (5.1)	23 (4.2)	0	12 (2.2)	8 (1.5)	0
ALANINE AMINOTRANSFERASE INCREASED	15 (2.7)	15 (2.7)	0	5 (0.9)	4 (0.7)	0
ASPARTATE AMINOTRANSFERASE	12 (2.2)	10 (1.8)	0	3 (0.6)	2 (0.4)	0
GASTROINTESTINAL DISORDERS	25 (4.6)	17 (3.1)	0	21 (3.9)	14 (2.6)	0
DIARRHOEA	15 (2.7)	9 (1.6)	0	4 (0.7)	2 (0.4)	0
COLITIS	7 (1.3)	7 (1.3)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	21 (3.8)	10 (1.8)	2 (0.4)	10 (1.9)	6 (1.1)	1 (0.2)
PNEUMONITIS	11 (2.0)	5 (0.9)	0	1 (0.2)	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	17 (3.1)	12 (2.2)	1 (0.2)	18 (3.4)	13 (2.4)	2 (0.4)
MALIGNANT NEOPLASM PROGRESSION	14 (2.6)	9 (1.6)	1 (0.2)	12 (2.2)	9 (1.7)	2 (0.4)
ENDOCRINE DISORDERS	12 (2.2)	10 (1.8)	0	1 (0.2)	1 (0.2)	0
HYPOPHYSITIS	7 (1.3)	6 (1.1)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (1.1)	3 (0.5)	1 (0.2)	15 (2.8)	9 (1.7)	0
FATIGUE	2 (0.4)	1 (0.2)	0	7 (1.3)	3 (0.6)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.23a in CA209214 Final CSR[1]

Table 46 Drug-related Adverse Events Leading to Discontinuation (Reported in ≥1% of Subjects) by Worst CTC Grade - All Treated Subjects

Table 2.4-2: Drug-related Adverse Events Leading to Discontinuation (Reported in ≥ 1% of Subjects) by Worst CTC Grade - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	118 (21.6)	84 (15.4)	0	63 (11.8)	37 (6.9)	2 (0.4)
INVESTIGATIONS	27 (4.9)	22 (4.0)	0	10 (1.9)	7 (1.3)	0
ALANINE AMINOTRANSFERASE INCREASED	15 (2.7)	15 (2.7)	0	5 (0.9)	4 (0.7)	0
ASPARTATE AMINOTRANSFERASE INCREASED	12 (2.2)	10 (1.8)	0	3 (0.6)	2 (0.4)	0
GASTROINTESTINAL DISORDERS	23 (4.2)	16 (2.9)	0	17 (3.2)	10 (1.9)	0
DIARRHOEA	14 (2.6)	9 (1.6)	0	4 (0.7)	2 (0.4)	0
COLITIS	7 (1.3)	7 (1.3)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14 (2.6)	6 (1.1)	0	3 (0.6)	2 (0.4)	0
PNEUMONITIS	11 (2.0)	5 (0.9)	0	0	0	0
ENDOCRINE DISORDERS	12 (2.2)	10 (1.8)	0	1 (0.2)	1 (0.2)	0
HYPOPHYSITIS	7 (1.3)	6 (1.1)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.7)	2 (0.4)	0	11 (2.1)	5 (0.9)	0
FATIGUE	2 (0.4)	1 (0.2)	0	7 (1.3)	3 (0.6)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.24a in CA209214 Final CSR[1]

Selected Adverse Events

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, the applicant identified select AEs based on the following 4 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.
- 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.
Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively. Hypersensitivity/infusion reactions were analysed along with the select AE categories because multiple event terms may be used to describe such events and pooling of terms was therefore necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs.

Endocrine Events

The endocrine select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders and thyroid disorders. Endocrine select AEs (all-causality, any grade) were reported in 195 (35.6%) subjects in the nivolumab + ipilimumab group and 175 (32.7%) subjects in the sunitinib group. In the nivolumab + ipilimumab group, 178 (32.5%) subjects had endocrine select AEs considered to be drug-related by the investigator, vs. 30.5% in the sunitinib group (Table 47). The most commonly reported drug-related event was hypothyroidism (15.5% of subjects). Most of the drug-related endocrine events were Grade 1-2, but 38 (6.9%) subjects had Grade 3-4 drug-related events in the ipilimumab + nivolumab group vs. 0.2% in the sunitinib group. 16 (2.9%) subjects had drug-related endocrine select AEs that led to permanent discontinuation of nivolumab + ipilimumab, versus 0% in the sunitinib group.

The median time to onset of drug-related endocrine AEs was 8.43 weeks (Table 2.5.1-2).

In total 68 subjects (12.4%) were treated with immune-modulating medication for a median duration of 16.36 weeks. 45 subjects received high dose corticosteroids for a median duration of 2.14 weeks. 21 subjects treated with immune-modulating medication had resolution of their events. Overall, 76 of the 178 subjects with drug-related endocrine select AEs resolved; the median time to resolution was not available at the time of DBL.

Table 47 Summary of Drug-related Endocrine Select Adverse Events Reported Up to 30 days after Last Dose - All Treated Subjects

Sub Category (%) Preferred Term (%)	NIVOLUMAB + IPILIMUMAB N = 547			SUNITINIB N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	178 (32.5)	38 (6.9)	0	163 (30.5)	1 (0.2)	0
THYROID DISORDER	149 (27.2)	7 (1.3)	0	163 (30.5)	1 (0.2)	0
HYPOTHYROIDISM	85 (15.5)	2 (0.4)	0	134 (25.0)	1 (0.2)	0
HYPERTHYROIDISM	59 (10.8)	2 (0.4)	0	12 (2.2)	0	0
THYROIDITIS	16 (2.9)	1 (0.2)	0	0	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	11 (2.0)	0	0	30 (5.6)	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	5 (0.9)	0	0	1 (0.2)	0	0
BASEDOW'S DISEASE	2 (0.4)	2 (0.4)	0	0	0	0
THYROXINE FREE INCREASED	2 (0.4)	0	0	0	0	0
AUTOIMMUNE HYPOTHYROIDISM	1 (0.2)	0	0	0	0	0
AUTOIMMUNE THYROIDITIS	1 (0.2)	0	0	0	0	0
THYROID FUNCTION TEST ABNORMAL	1 (0.2)	0	0	0	0	0
THYROXINE DECREASED	1 (0.2)	0	0	1 (0.2)	0	0
ADRENAL DISORDER	33 (6.0)	14 (2.6)	0	0	0	0
ADRENAL INSUFFICIENCY	28 (5.1)	11 (2.0)	0	0	0	0
SECONDARY ADRENOCORTICAL INSUFFICIENCY	2 (0.4)	2 (0.4)	0	0	0	0
ADRENOCORTICAL INSUFFICIENCY ACUTE	1 (0.2)	1 (0.2)	0	0	0	0
BLOOD CORTICOTROPHIN DECREASED	1 (0.2)	0	0	0	0	0
BLOOD CORTICOTROPHIN INCREASED	1 (0.2)	0	0	0	0	0
PITUITARY DISORDER	24 (4.4)	15 (2.7)	0	0	0	0
HYPOPHYSITIS	22 (4.0)	15 (2.7)	0	0	0	0
HYPOPITUITARISM	2 (0.4)	0	0	0	0	0
DIABETES	10 (1.8)	6 (1.1)	0	0	0	0
DIABETES MELLITUS	6 (1.1)	2 (0.4)	0	0	0	0
TYPE 1 DIABETES MELLITUS	3 (0.5)	1 (0.2)	0	0	0	0
FULMINANT TYPE 1 DIABETES MELLITUS	2 (0.4)	2 (0.4)	0	0	0	0
DIABETIC KETOACIDOSIS	1 (0.2)	1 (0.2)	0	0	0	0

MedDRA Version: 20.0, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.107 of the CA209214 Final CSR[1]

Gastrointestinal Events

Gastrointestinal select AEs (all-causality, any grade) were reported in 212 (38.8%) subjects in the nivolumab + ipilimumab group and 312 (58.3%) subjects in the sunitinib group. In the nivolumab + ipilimumab group, 154 (28.2%) subjects had GI select AEs considered to be drug-related by the investigator, versus 52.0% in the sunitinib group (Table 48).

Table 48 Summary of Drug-related Gastrointestinal Select Adverse Events Reported Up to 30 days after Last Dose - All Treated Subjects

Preferred Term (%)	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	154 (28.2)	27 (4.9)	0	278 (52.0)	28 (5.2)	0
DIARRHOEA	145 (26.5)	21 (3.8)	0	278 (52.0)	28 (5.2)	0
COLITIS	18 (3.3)	11 (2.0)	0	2 (0.4)	0	0
AUTOIMMUNE COLITIS	2 (0.4)	1 (0.2)	0	0	0	0
COLITIS ULCERATIVE	1 (0.2)	0	0	0	0	0
ENTERITIS	1 (0.2)	0	0	0	0	0
ENTEROCOLITIS	1 (0.2)	0	0	1 (0.2)	0	0
FREQUENT BOWEL MOVEMENTS	1 (0.2)	0	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Most drug-related events were Grade 1-2. 27 (4.9%) subjects had Grade 3-4 drug-related events. 22 (4.0%) subjects had drug-related GI select AEs that led to permanent discontinuation of nivolumab + ipilimumab, versus 4 patients (0.7%) in the sunitinib group. The median time to onset of drug-related GI select AEs was 5.36 weeks. 47 subjects (8.6%) were treated with immune-modulating medication for a median duration of 7.86 weeks. 40 subjects were treated with high dose corticosteroids for a median duration of 3.14 weeks. 44 subjects treated with immune-modulating medication had resolution of their events. Overall, 140 of the 154 subjects with drug-related GI select AEs had resolution of their events, with a median time to resolution of 2.43 weeks.

Hepatic Events

Hepatic select AEs (all-causality, any grade) were reported in 115 (21.0%) subjects in the nivolumab + ipilimumab group and 97 (18.1%) subjects in the sunitinib group.
In the nivolumab + ipilimumab group, 101 (18.5%) subjects had hepatic select AEs considered to be drug-related by the investigator. Most drug-related events were Grade 1-2, and 45 (8.2%) subjects had Grade 3-4 drug-related events (Table 49).

Table 49 Summary of Drug-related Hepatic Select Adverse Events Reported Up to 30 days after Last Dose - All Treated Subjects

	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	101 (18.5)	45 (8.2)	0	77 (14.4)	20 (3.7)	0
ALANINE AMINOTRANSFERASE INCREASED	60 (11.0)	27 (4.9)	0	50 (9.3)	8 (1.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	58 (10.6)	19 (3.5)	0	49 (9.2)	7 (1.3)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	25 (4.6)	9 (1.6)	0	12 (2.2)	1 (0.2)	0
BLOOD BILIRUBIN INCREASED	13 (2.4)	1 (0.2)	0	17 (3.2)	3 (0.6)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	12 (2.2)	5 (0.9)	0	7 (1.3)	4 (0.7)	0
TRANSAMINASES INCREASED	12 (2.2)	4 (0.7)	0	6 (1.1)	2 (0.4)	0
HEPATIC ENZYME INCREASED	6 (1.1)	2 (0.4)	0	0	0	0
HYPERBILIRUBINAEMIA	4 (0.7)	1 (0.2)	0	2 (0.4)	0	0
HEPATITIS	3 (0.5)	3 (0.5)	0	1 (0.2)	1 (0.2)	0
HEPATOTOXICITY	3 (0.5)	1 (0.2)	0	0	0	0
AUTOIMMUNE HEPATITIS	2 (0.4)	0	0	0	0	0
HEPATITIS ACUTE	1 (0.2)	1 (0.2)	0	0	0	0
LIVER FUNCTION TEST INCREASED	1 (0.2)	1 (0.2)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

A total of 24 (4.4%) subjects had drug-related select hepatic AEs that led to permanent discontinuation of nivolumab + ipilimumab, versus 7 patients (1.3%) in the sunitinib group. The median time to onset of drug-related hepatic events was 8.86 weeks. 39 subjects (7.1%) were treated with immune-modulating medication for a median duration of 6.14 weeks. 35 subjects received high dose corticosteroids for a median duration of 4.00 weeks. 31 subjects treated with immune-modulating medication had resolution of their events. Overall, 86 of the 101 subjects with drug related hepatic select AEs had resolution of their events, with a median time to resolution of 6.14 weeks.

Pulmonary Events

Pulmonary select AEs (all-causality, any grade) were reported in 35 (6.4%) subjects in the nivolumab + ipilimumab group and 5 (0.9%) subjects in the sunitinib group. Most events in the nivolumab + ipilimumab group (32) concerned pneumonitis. In the nivolumab + ipilimumab group, 34 (6.2%) subjects had pulmonary select AEs (pneumonitis and interstitial lung disease) considered to be drug-related by the investigator. Most drug-related events were Grade 1-2, while 6 (1.1%) subjects had Grade 3-4 drug-related events (pneumonitis). 12 (2.2%) subjects had drug-related pulmonary select AEs that led to permanent discontinuation of nivolumab + ipilimumab, versus 0% in the sunitinib group. The median time to onset of drug-related pulmonary events was 11.36 weeks. 21 subjects (3.8%) were treated with immune-modulating medication for a median duration of 5.71 weeks. 20 subjects were treated with high dose corticosteroids for a median duration of 2.36 weeks. 20 subjects treated with immune-modulating medication had resolution of their events. Overall, 31 of the 34 subjects with drug-related pulmonary select AEs had resolution of their events; the median time to resolution was 6.14 weeks.

Renal Events

Renal select AEs (all-causality, any grade) were reported in 90 (16.5%) subjects in the nivolumab + ipilimumab group and 73 (13.6%) subjects in the sunitinib group. In the nivolumab + ipilimumab group, 48 (8.8%) subjects had renal select AEs considered to be drug-related by the investigator, versus 8.6% in the sunitinib group (Table 50).

Table 50 Summary of Drug-related Renal Select Adverse Events Reported Up to 30 days after Last Dose - All Treated Subjects

	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	48 (8.8)	7 (1.3)	0	46 (8.6)	6 (1.1)	0
BLOOD CREATININE INCREASED	35 (6.4)	1 (0.2)	0	35 (6.5)	2 (0.4)	0
ACUTE KIDNEY INJURY	10 (1.8)	4 (0.7)	0	9 (1.7)	3 (0.6)	0
NEPHRITIS	4 (0.7)	1 (0.2)	0	0	0	0
AUTOIMMUNE NEPHRITIS	1 (0.2)	1 (0.2)	0	0	0	0
TUBULOINTERSTITIAL NEPHRITIS	1 (0.2)	1 (0.2)	0	0	0	0
URINE OUTPUT DECREASED	1 (0.2)	0	0	0	0	0
BLOOD UREA INCREASED	0	0	0	3 (0.6)	0	0
RENAL FAILURE	0	0	0	4 (0.7)	2 (0.4)	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

In total 7 (1.3%) subjects had Grade 3-4 drug-related events in the nivolumab + ipilimumab group versus 1.1% in the sunitinib group. 7 (1.3%) subjects had drug-related renal select AEs that led to permanent discontinuation of nivolumab + ipilimumab. 2 of the 7 subjects who discontinued nivolumab + ipilimumab treatment had Grade 4 events: 1 increased blood creatinine and 1 acute kidney injury. The median time to onset of drug-related renal events was 8.93 weeks. 19 subjects were treated with immune-modulating medication for a median duration of 5.29 weeks. 13 subjects received high dose corticosteroids for a median duration of 2.14 weeks. 13 subjects treated with immune-modulating medication had resolution of their events. Overall, 37 of the 48 subjects with drug-related renal select AEs had resolution of their events; the median time to resolution was 13.21 weeks.

Skin Events

Skin select AEs (all-causality, any grade) were reported in 305 (55.8%) subjects in the nivolumab + ipilimumab group and 324 (60.6%) subjects in the sunitinib group.

In the nivolumab + ipilimumab group, 267 (48.8%) subjects had skin select AEs considered to be drug-related by the investigator, versus 56.8% in the sunitinib group. The most frequently reported drug-related events were pruritus and rash. There was no event of toxic epidermal necrolysis reported; however, 1 subject had a SAE of Stevens-Johnson syndrome in the ipilimumab + nivolumab group (grade 3-4). 20 (3.7%) subjects had Grade 3-4 events in the ipilimumab + nivolumab group, versus 9.9% in the sunitinib group. 8 (1.5%) subjects had drug-related skin select AEs that led to permanent discontinuation of nivolumab + ipilimumab, versus 4 patients (0.7%) in the sunitinib group. The median time to onset of drug-related skin select AEs was 4.00 weeks. 100 subjects were treated with immune-modulating medication for a median duration of 13.50 weeks (19 received a corticosteroid at a dose ≥ 40 mg for a median duration of 2.29 weeks). In total 51 subjects (9.3%) treated with immune-modulating medication had resolution of their events. Overall, 192 of 267 subjects with skin select AEs had resolution of their events with a median time to resolution of 11.57 weeks.

Hypersensitivity/infusion Reactions

Hypersensitivity/infusion reactions (all-causality, any grade) were reported in 29 (5.3%) subjects in the nivolumab + ipilimumab group and 12 (2.2%) subjects in the sunitinib group.

In the nivolumab + ipilimumab group, 22 (4.0%) subjects had hypersensitivity/infusion reactions select AEs considered to be drug-related by the investigator, versus 1.1% in the sunitinib group. None of the events led to permanent discontinuation of nivolumab + ipilimumab. The median time to onset of drug-related hypersensitivity/infusion reactions select AEs was 3.14 weeks. 6 subjects were treated with immune-modulating medication for a median duration of 0.14 weeks. 2 subjects received high dose corticosteroids for a median duration of 0.14 weeks. 5 subjects treated with immune-modulating medication had resolution of their events. Overall, 20 of the 22 subjects with hypersensitivity/infusion reactions select AEs had resolution of their events with a median time to resolution of 0.14 weeks.

Other Events of Special Interest

Other events of special interest (OESIs) were events that do not fulfil all criteria to qualify as select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100-day window). OESIs included the following categories: myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, encephalitis, myocarditis, myositis, and rhabdomyolysis. OESI included the following categories: myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, encephalitis, myocarditis, myositis and rhabdomyolysis. A summary of OESI is presented below in Table 51.

It can be seen that grade≥3 OESIs were more frequent in the ipilimumab + nivolumab arm (11 patients, 2.0%) than in the sunitinib arm (4 patients, 0.7%). All but 3 OESIs in the ipilimumab + nivolumab arm resolved, within 1-62 days. In the sunitinib arm, all OESIs resolved.

Table 51 Summary of All Other Events of Special Interest (Regardless of Causality or Immune Modulating Medication Treatment) with Extended Follow-up - All Treated Subjects

	Nivolumab + Ipilimumab N = 547			Sunitinib N = 535		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
MYASTHENIC SYNDROME						
TOTAL SUBJECTS WITH AN EVENT	1 (0.2)	1 (0.2)	0	0	0	0
MYASTHENIA GRAVIS	1 (0.2)	1 (0.2)	0	0	0	0
DEMYELINATION EVENT						
TOTAL SUBJECTS WITH AN EVENT	0	0	0	0	0	0
GUILLAIN-BARRE SYNDROME						
TOTAL SUBJECTS WITH AN EVENT	0	0	0	0	0	0
PANCREATITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	13 (2.4)	6 (1.1)	0	7 (1.3)	4 (0.7)	0
PANCREATITIS	13 (2.4)	6 (1.1)	0	6 (1.1)	3 (0.6)	0
PANCREATITIS ACUTE	0	0	0	1 (0.2)	1 (0.2)	0
UVEITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	2 (0.4)	0	0	1 (0.2)	0	0
IRIDOCYCLITIS	1 (0.2)	0	0	0	0	0
UVEITIS	1 (0.2)	0	0	1 (0.2)	0	0
ENCEPHALITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	1 (0.2)	1 (0.2)	0	0	0	0
ENCEPHALITIS	1 (0.2)	1 (0.2)	0	0	0	0
MYOCARDITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	1 (0.2)	1 (0.2)	0	0	0	0
MYOCARDITIS	1 (0.2)	1 (0.2)	0	0	0	0
MYOSITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	3 (0.5)	1 (0.2)	0	0	0	0
MYOSITIS	3 (0.5)	1 (0.2)	0	0	0	0
RHABDOMYOLYSIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	1 (0.2)	1 (0.2)	0	0	0	0
RHABDOMYOLYSIS	1 (0.2)	1 (0.2)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 100 days after last dose of study therapy.

Laboratory findings

Haematology

- In the nivolumab + ipilimumab group, absolute lymphocytes (5.2%) were the only Grade 3-4 haematologic abnormality reported in ≥ 5% of subjects.

- In the sunitinib group, the Grade 3-4 haematologic abnormalities reported in ≥ 5% of subjects were decreased absolute neutrophil count (19.3% Grade 3, 1.0% Grade 4), decreased absolute lymphocytes (13.2% Grade 3, 1.3% Grade 4), decreased platelet count (12.2% Grade 3, 1.5% Grade 4), and decreased haemoglobin (9.0% Grade 3).

Liver function tests

Abnormalities in liver function tests are described in Table 52.

Table 52 Summary of liver function test abnormalities - All Treated Subjects

	Nivolumab + Ipilimumab N = 547	Sunitinib N = 535
	N = 538	N = 525
ALT OR AST > 3XULN	71 (13.2)	51 (9.7)
ALT OR AST > 5XULN	38 (7.1)	20 (3.8)
ALT OR AST > 10XULN	14 (2.6)	8 (1.5)
ALT OR AST > 20XULN	9 (1.7)	0
	N = 535	N = 524
TOTAL BILIRUBIN > 2XULN	9 (1.7)	21 (4.0)
	N = 535	N = 524
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	7 (1.3)	7 (1.3)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	7 (1.3)	8 (1.5)

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

Kidney function tests

In the nivolumab + ipilimumab and sunitinib groups, the majority of subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period. In both groups, the majority of reported abnormalities in creatinine (increases) were Grade 1 or 2. 9 (1.7%) subjects in the nivolumab + ipilimumab group and 7 (1.3%) subjects in the sunitinib group had a Grade 3 abnormality in creatinine; two Grade 4 abnormalities and one Grade 4 abnormality were reported in the nivolumab + ipilimumab and sunitinib groups, respectively.

Thyroid Function Tests

Abnormalities in thyroid function tests are described in Table 53.

Table 53 Summary of thyroid function test abnormalities - All Treated Subjects

	Nivolumab + Ipilimumab N = 532	Sunitinib N = 521
TSH > ULN	213 (40.0)	380 (72.9)
TSH > ULN WITH TSH <= ULN AT BASELINE	174 (32.6)	326 (62.6)
TSH > ULN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	117 (22.0)	179 (34.4)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	64 (12.0)	127 (24.4)
WITH FT3/FT4 TEST MISSING (A) (B)	32 (6.0)	74 (14.2)
TSH < LLN	246 (46.2)	120 (23.0)
TSH < LLN WITH TSH >= LLN AT BASELINE	229 (43.0)	114 (21.9)
TSH < LLN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	149 (28.0)	66 (12.7)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	74 (13.9)	44 (8.4)
WITH FT3/FT4 TEST MISSING (A) (B)	23 (4.3)	10 (1.9)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date.
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Safety in special populations

In CA209214, the frequency of total AEs, AEs leading to discontinuation and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented in Table 54. The frequencies of SAEs including fatal events appeared to increase with increasing age.

Table 54 Summary of Safety Results by Age Group - All Subjects Treated with Ipilimumab + Nivolumab

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 338	65-74 N = 163	75-84 N = 43	>= 85 N = 3	Total N = 547
TOTAL SUBJECTS WITH AN EVENT	337 (99.7)	161 (98.8)	43 (100.0)	3 (100.0)	544 (99.5)
SERIOUS AE - TOTAL	177 (52.4)	98 (60.1)	28 (65.1)	2 (66.7)	305 (55.8)
FATAL (DEATH)	8 (2.4)	9 (5.5)	7 (16.3)	1 (33.3)	25 (4.6)
HOSPITALIZATION/PROLONGATION	166 (49.1)	93 (57.1)	27 (62.8)	2 (66.7)	288 (52.7)
LIFE THREATENING	6 (1.8)	5 (3.1)	2 (4.7)	1 (33.3)	14 (2.6)
CANCER	3 (0.9)	0	1 (2.3)	0	4 (0.7)
DISABILITY/INCAPACITY	0	0	2 (4.7)	0	2 (0.4)
IMPORTANT MEDICAL EVENT	19 (5.6)	10 (6.1)	5 (11.6)	0	34 (6.2)
AE LEADING TO DISCONTINUATION	91 (26.9)	59 (36.2)	17 (39.5)	1 (33.3)	168 (30.7)
PSYCHIATRIC DISORDERS	73 (21.6)	33 (20.2)	8 (18.6)	1 (33.3)	115 (21.0)
NERVOUS SYSTEM DISORDERS	165 (48.8)	66 (40.5)	16 (37.2)	1 (33.3)	248 (45.3)
ACCIDENT AND INJURIES	31 (9.2)	18 (11.0)	5 (11.6)	0	54 (9.9)
CARDIAC DISORDERS	35 (10.4)	17 (10.4)	4 (9.3)	1 (33.3)	57 (10.4)
VASCULAR DISORDERS	77 (22.8)	31 (19.0)	5 (11.6)	0	113 (20.7)
CEREBROVASCULAR DISORDERS	8 (2.4)	2 (1.2)	6 (14.0)	0	16 (2.9)
INFECTIONS AND INFESTATIONS	176 (52.1)	72 (44.2)	22 (51.2)	1 (33.3)	271 (49.5)
ANTICHOLINERGIC SYNDROME	157 (46.4)	68 (41.7)	13 (30.2)	2 (66.7)	240 (43.9)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	53 (15.7)	21 (12.9)	9 (20.9)	0	83 (15.2)

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Immunogenicity

The immunogenicity of nivolumab and ipilimumab was assessed when administered in combination in Study CA209214. The incidence of nivolumab anti-drug antibodies (ADAs) was 26.0% (107/411 subjects) when nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg. 2 subjects (0.5%) were neutralizing ADA (NAb) positive and 9 subjects (2.2%) were considered persistent positive. The incidence of ipilimumab ADA was 6.3% (26/415 subjects) and no subject was NAb positive (to ipilimumab) or considered persistent positive.
The presence of nivolumab or ipilimumab ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions. In the analysis of hypersensitivity/infusion reaction AEs by ADA status (positive, negative) in all treated subjects who were ADA positive or negative, nivolumab and ipilimumab ADA occurrence did not appear to impact safety. Out of all subjects who received nivolumab + ipilimumab combination therapy who were evaluable for ADA, 5/107 (4.7%) nivolumab ADA positive subjects experienced AEs in the hypersensitivity/infusion reaction category. In comparison, 14/304 (4.6%) nivolumab ADA negative subjects experienced AEs in the hypersensitivity/infusion reaction category. No ipilimumab ADA positive subjects experienced hypersensitivity/infusion reaction AEs, whereas 19 (4.9%) ipilimumab ADA negative subjects experienced AEs in the hypersensitivity/infusion reaction category.

Safety in Intermediate/Poor-risk patients

The safety profile of nivolumab + ipilimumab combination therapy when compared to sunitinib monotherapy in intermediate/poor-risk subjects was consistent with that reported above for the all treated population, and no notable differences between the frequency of all-causality and drug-related SAEs or AEs were observed between the all treated population and the intermediate/poor-risk subjects (Table 55).

Table 55 Summary of All-Causality AEs (≥20% of Any Grade in Either Treatment Group) and Drug-related AEs (≥15% of Any Grade in Either Treatment Group) - Intermediate/Poor-risk Subjects and All Treated Subjects

	Intermediate/Poor-risk Subjects				All Treated Subjects			
	Nivolumab + Ipilimumab (N = 423)		Sunitinib (N = 416)		Nivolumab + Ipilimumab (N = 547)		Sunitinib (N = 535)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-Causality AEs, N (%)	**420 (99.3)**	**275 (65.0)**	**413 (99.3)**	**315 (75.7)**	**544 (99.5)**	**357 (65.3)**	**532 (99.4)**	**407 (76.1)**
Most Frequent AEs (≥ 20% of Any Grade in Either Treatment Group)								
Fatigue	177 (41.8)	27 (6.4)	208 (50.0)	39 (9.4)	246 (45.0)	34 (6.2)	291 (54.4)	54 (10.1)
Pyrexia	104 (24.6)	3 (0.7)	64 (15.4)	2 (0.5)	136 (24.9)	4 (0.7)	91 (17.0)	3 (0.6)
Mucosal inflammation	14 (3.3)	0	118 (28.4)	11 (2.6)	18 (3.3)	0	157 (29.3)	14 (2.6)
Diarrhoea	148 (35.0)	16 (3.8)	224 (53.8)	23 (5.5)	205 (37.5)	25 (4.6)	310 (57.9)	33 (6.2)
Nausea	122 (28.8)	8 (1.9)	167 (40.1)	7 (1.7)	163 (29.8)	11 (2.0)	230 (43.0)	8 (1.5)
Vomiting	86 (20.3)	4 (0.9)	117 (28.1)	10 (2.4)	109 (19.9)	5 (0.9)	149 (27.9)	11 (2.1)
Dyspepsia	18 (4.3)	0	77 (18.5)	1 (0.2)	29 (5.3)	0	112 (20.9)	1 (0.2)
Stomatitis	19 (4.5)	0	104 (25.0)	12 (2.9)	29 (5.3)	0	153 (28.6)	14 (2.6)
Pruritus	143 (33.8)	3 (0.7)	43 (10.3)	0	180 (32.9)	3 (0.5)	58 (10.8)	0
Rash	99 (23.4)	8 (1.9)	63 (15.1)	0	141 (25.8)	8 (1.5)	84 (15.7)	0
Palmar-plantar erythrodysaesthesia syndrome	6 (1.4)	0	168 (40.4)	32 (7.7)	9 (1.6)	0	237 (44.3)	50 (9.3)
Arthralgia	93 (22.0)	5 (1.2)	57 (13.7)	0	123 (22.5)	7 (1.3)	83 (15.5)	0
Cough	102 (24.1)	1 (0.2)	93 (22.4)	2 (0.5)	145 (26.5)	1 (0.2)	125 (23.4)	2 (0.4)
Decreased appetite	89 (21.0)	7 (1.7)	121 (29.1)	4 (1.0)	114 (20.8)	10 (1.8)	156 (29.2)	5 (0.9)
Headache	72 (17.0)	4 (0.9)	86 (20.7)	5 (1.2)	103 (18.8)	5 (0.9)	121 (22.6)	5 (0.9)
Dysgeusia	28 (6.6)	0	133 (32.0)	1 (0.2)	40 (7.3)	0	185 (34.6)	1 (0.2)
Hypothyroidism	74 (17.5)	2 (0.5)	107 (25.7)	1 (0.2)	96 (17.6)	2 (0.4)	145 (27.1)	1 (0.2)
Hypertension	38 (9.0)	11 (2.6)	164 (39.4)	66 (15.9)	52 (9.5)	18 (3.3)	231 (43.2)	94 (17.6)
Anaemia	64 (15.1)	20 (4.7)	99 (23.8)	30 (7.2)	72 (13.2)	20 (3.7)	109 (20.4)	32 (6.0)

	Intermediate/Poor-risk Subjects				All Treated Subjects			
	Nivolumab + Ipilimumab (N = 423)		Sunitinib (N = 416)		Nivolumab + Ipilimumab (N = 547)		Sunitinib (N = 535)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Drug-Related AEs, N (%)	**388 (91.7)**	**190 (44.9)**	**403 (96.9)**	**254 (61.1)**	**509 (93.1)**	**250 (45.7)**	**521 (97.4)**	**335 (62.6)**
Most Frequent Drug-related AEs (≥ 15% of Any Grade in Either Treatment Group)								
Fatigue	140 (33.1)	16 (3.8)	183 (44.0)	34 (8.2)	202 (36.9)	23 (4.2)	264 (49.3)	49 (9.2)
Asthenia	55 (13.0)	6 (1.4)	64 (15.4)	10 (2.4)	72 (13.2)	8 (1.5)	91 (17.0)	12 (2.2)
Mucosal inflammation	11 (2.6)	0	113 (27.2)	11 (2.6)	13 (2.4)	0	152 (28.4)	14 (2.6)
Pruritus	122 (28.8)	3 (0.7)	35 (8.4)	0	154 (28.2)	3 (0.5)	49 (9.2)	0
Rash	84 (19.9)	8 (1.9)	47 (11.3)	0	118 (21.6)	8 (1.5)	67 (12.5)	0
Palmar-plantar erythrodysaesthesia syndrome	2 (0.5)	0	162 (38.9)	32 (7.7)	5 (0.9)	0	231 (43.2)	49 (9.2)
Diarrhoea	102 (24.1)	15 (3.5)	199 (47.8)	19 (4.6)	145 (26.5)	21 (3.8)	278 (52.0)	28 (5.2)
Nausea	78 (18.4)	6 (1.4)	142 (34.1)	5 (1.2)	109 (19.9)	8 (1.5)	202 (37.8)	6 (1.1)
Vomiting	42 (9.9)	3 (0.7)	88 (21.2)	9 (2.2)	59 (10.8)	4 (0.7)	110 (20.6)	10 (1.9)
Stomatitis	14 (3.3)	0	100 (24.0)	12 (2.9)	23 (4.2)	0	149 (27.9)	14 (2.6)
Dyspepsia	8 (1.9)	0	66 (15.9)	0	15 (2.7)	0	96 (17.9)	0
Lipase increased	67 (15.8)	40 (9.5)	43 (10.3)	26 (6.3)	90 (16.5)	56 (10.2)	58 (10.8)	35 (6.5)
Decreased appetite	55 (13.0)	4 (0.9)	102 (24.5)	4 (1.0)	75 (13.7)	7 (1.3)	133 (24.9)	5 (0.9)
Hypothyroidism	65 (15.4)	2 (0.5)	97 (23.3)	1 (0.2)	85 (15.5)	2 (0.4)	134 (25.0)	1 (0.2)
Dysgeusia	24 (5.7)	0	128 (30.8)	1 (0.2)	31 (5.7)	0	179 (33.5)	1 (0.2)
Anaemia	27 (6.4)	2 (0.5)	75 (18.0)	22 (5.3)	34 (6.2)	2 (0.4)	83 (15.5)	24 (4.5)
Hypertension	7 (1.7)	1 (0.2)	151 (36.3)	60 (14.4)	12 (2.2)	4 (0.7)	216 (40.4)	85 (15.9)
Thrombocytopenia	2 (0.5)	0	69 (16.6)	19 (4.6)	2 (0.4)	0	95 (17.8)	25 (4.7)

Safety data to Support the Adverse Reactions in the Nivolumab and Ipilimumab Summary of Product Characteristics and Package Leaflets and PIs

To support an update of the Undesirable Effects section of the Summary of Product Characteristics (SmPC), safety data were further integrated across studies in multiple indications. Safety results for CA209214 nivolumab 3 mg/kg + ipilimumab 1 mg/kg combination safety data were presented side by side with the integrated safety from previous nivolumab 1 mg/kg + ipilimumab 3 mg/kg combination studies (thus excluding CA209214). The 3 studies (melanoma) included in the analyses for nivolumab 1 mg/kg + ipilimumab 3 mg/kg combination were CA209067 (nivolumab + ipilimumab combination arm), CA209069, and CA209004 (Cohort 8 only).

The presentation of adverse drug reactions (ADRs) in Section 4.8 of the approved OPDIVO (nivolumab) SmPC currently displays two columns in Table 2, one for nivolumab monotherapy and one for nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg. The nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg pooled data set includes 3 studies in melanoma; CA209067 (nivolumab + ipilimumab combination arm), CA209069, and CA209004 (Cohort 8 only). In the now proposed SmPC, the ADR table has been split into two, Table 2 for nivolumab monotherapy and Table 3 with two different columns: one for nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg and one for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg. An additional table, Table 4, has been added to Section 4.8 of the nivolumab SmPC to reflect the immune-related ADRs leading to permanent discontinuation or requiring high-dose corticosteroids for nivolumab monotherapy, nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, and nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg.

For nivolumab monotherapy, the proposed SmPC reflects the data for the current pooled nivolumab monotherapy population across other tumour types (n = 2950), as described in the gastric cancer (GC)/gastroesophageal junction (GEJ) cancer procedure (EMEA/H/C/003985/II/039, ongoing review). The table of adverse reactions included in the updated SmPC provided as part of this application (Table 2 of Section 4.8) is identical to the table submitted for GC/GEJ cancer (Procedure EMEA/H/C/003985/II/039, ongoing review). For ipilimumab monotherapy, the proposed SmPC reflects the currently approved data for the current pooled ipilimumab monotherapy population (n = 767).

Two additional tables have been added to Section 4.8 of the YERVOY (ipilimumab) SmPC: Table 3, to reflect the ADRs for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg; and Table 4, to reflect the immune-related ADRs leading to permanent discontinuation or requiring high-dose corticosteroids for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg.

2.5.1. Discussion on clinical safety

The safety profile of the combination of nivolumab 3 mg/kg with ipilimumab 1 mg/kg is assessed primarily based on the data of the 'all treated subjects' safety population, including favourable, intermediate and poor-risk patients, in order to maximise the size of the safety database. Safety data for the primary efficacy population (intermediate/poor-risk subjects, i.e. the target population) were highly similar to the safety data of the all treated population (Table 55).
The combination regimen of nivolumab + ipilimumab used in the current pivotal study is nivolumab 3 mg/kg + ipilimumab 1 mg/kg, which is different from the regimen approved for melanoma, i.e. nivolumab 1 mg/kg + ipilimumab 3 mg/kg. The observed safety profile in the current study is similar to that observed in the pooled melanoma studies, where nivolumab 1 mg/kg + ipilimumab 3 mg/kg was used, although the frequencies of some AEs which are known to be ipilimumab dose-dependent (e.g. gastrointestinal toxicities) appear somewhat lower with 1 mg/kg than with 3 mg/kg ipilimumab.
The most frequently reported AEs in the nivolumab + ipilimumab group (AEs regardless of causality and grade) were fatigue, diarrhoea, pruritus and nausea. In the sunitinib group, the most frequently reported AEs were diarrhoea, fatigue, palmar-plantar erythrodysesthesia syndrome, hypertension, nausea and dysgeusia. Grade 3-4 AEs regardless of causality were reported in 65.3% of subjects in the nivolumab + ipilimumab group and 76.1% of subjects in the sunitinib group. The most frequently reported drug-related AEs in the nivolumab + ipilimumab group were fatigue (36.9%), pruritus (28.2%), diarrhoea (26.5%) and rash (21.6%). In the sunitinib group, the most frequently reported drug-related AEs were diarrhoea (52.0%), fatigue (49.3%), palmar-plantar erythrodysesthesia syndrome (43.2%), hypertension (40.4%), nausea (37.8%) and dysgeusia (33.5%). Grade 3-4 drug-related AEs were reported in 45.7% of subjects in the nivolumab + ipilimumab group and 62.6% of subjects in the sunitinib group (Table 40). In the nivolumab + ipilimumab group, the most frequently reported Grade 3-4 drug-related AEs were lipase increased (10.2%), amylase increased (5.7%), alanine aminotransferase (ALT) increased (4.9%), fatigue (4.2%) and diarrhoea (3.8%). In the sunitinib group, the most frequently reported Grade 3-4 drug-related AEs reported were hypertension (15.9%), fatigue (9.2%), palmar-plantar erythrodysesthesia syndrome (9.2%), platelet count decreased (6.7%), lipase increased (6.5%), neutropenia (6.0%) and diarrhoea (5.2%).

The safety profile of nivolumab + ipilimumab is characterised by a high frequency of immune-related adverse events, i.e. AEs observed during treatment with ipilimumab and/or nivolumab that are believed to have an immune-related aetiology consistent with the mechanism of action of these drugs. The most frequently reported any-grade drug-related immune-related AE categories were skin (48.8%), endocrine (32.5%) and gastrointestinal (28.2%). Most endocrine, GI, hepatic, pulmonary, skin and hypersensitivity/infusion reaction select AEs were considered drug-related by the investigator. A proportion of the immune-related AEs seen with nivolumab + ipilimumab did not resolve, e.g., 102 of the 178 subjects with drug-related endocrine immune-related AEs did not have their AE resolved.

Thus, the safety profile of nivolumab + ipilimumab and the safety profile of sunitinib are very different. Sunitinib treatment is typically associated with low-grade diarrhoea as well as with hypertension, hand-foot syndrome, fatigue, nausea and dysgeusia, while the most notable AEs associated with treatment with nivolumab plus ipilimumab are the immune-related AEs which sometimes require (long-term) treatment with corticosteroids. This means that the comparison of risks is not straightforward. Even so, it appears that overall the combination treatment is less well tolerated than sunitinib. The

combination treatment was associated with a higher frequency of SAEs (55.8% vs. 39.8%), although the overall frequency of AEs regardless of causality was comparable between study arms. The poorer tolerability of the combination treatment is further illustrated by the relatively high frequency of treatment discontinuation. Drug-related AEs leading to discontinuation were reported in 21.6% of patients in the nivolumab + ipilimumab group and in 11.8% of patients in the sunitinib group, and grade 3-4 drug-related AEs leading to discontinuation were reported in 15.4% and 6.9% of the subjects, respectively.

The safety profiles for sunitinib and nivolumab + ipilimumab in the current pivotal study are consistent with existing data on the safety profile of both treatments (EPARs Sutent, Opdivo). When taking into account the available safety data in melanoma patients, no new safety concerns were identified with the combination of nivolumab 3 mg/kg + ipilimumab 1 mg/kg in metastatic renal cell carcinoma. The frequencies of AEs related to important identified risks for nivolumab and ipilimumab, e.g. immune-related adverse reactions, are in line with existing data on the safety profile of the combination.

Death as a result of study drug toxicity (as declared by the investigator) occurred in 7 patients (1.3%) in the nivolumab + ipilimumab arm versus 4 patients (0.7%) in the sunitinib arm. Thus, both arms were associated with a low rate of fatal drug toxicity, although numerically the risk with combination therapy appears higher. However, there was also an imbalance in deaths attributed to “other reasons” between study arms, i.e. 22 deaths in the ipilimumab + nivolumab arm, versus 13 deaths in the sunitinib arm. This imbalance was driven primairily by a higher frequency of infection-related deaths and cardiovascular event-related deaths in the ipilimumab + nivolumab group. Therefore, it is considered that it cannot be excluded that these deaths were to some extent related to treatment with ipilimumab + nivolumab.

The impact of late-emergent drug-related AEs was not sufficiently addressed by the applicant. Late-emergent drug-related AEs were defined as drug-related AEs with an onset date >100 days after the last dose of study therapy. In the sunitinib group, 2 (0.4%) subjects reported late-emergent drug-related AEs, and 1 subject was intermediate/poor-risk. In the nivolumab + ipilimumab group, 20 (3.7%) subjects had late-emergent drug-related AEs. 15 (3.5%) of these subjects were intermediate/poor-risk subjects. Of these AEs, 9 (1.6%) were grade 3-5, and 3 were grade 5 (0.5%). The most frequent late-emergent AEs in the nivolumab + ipilimumab group (in more than 1 patient) occurred in SOCs: infections and infestations (3 patients; disseminated tuberculosis, lung infection, staphylococcal sepsis), investigations (3 patients; ASAT increased, ALAT increased, bilirubin increased), musculoskeletal and connective tissue disorders (3 patients; arthritis, arthralgia, myalgia), gastrointestinal disorders (2 patients; colitis, lower gastrointestinal haemorrhage), general disorders and administration site conditions (2 patients; fatigue, sudden death), immune system disorders (2 patients; contrast media allergy), skin and subcutaneous tissue disorders (2 patients; prurigo, rash).

The frequencies of SAEs, including fatal SAEs, appeared to increase strongly with increasing age. For example, in patients <65 years of age SAEs occurred with a frequency of 52.4%, while in patients 75-84 years of age the frequency was 65.1%. Similarly, fatal AEs occurred in 2.4% of patients <65 years of age, versus 16.3% of patients 75-84 years of age. The applicant was asked to discuss the benefit/risk balance of the combination treatment in elderly patients. It was concluded that safety was somewhat poorer in elderly in both study arms.

The immunogenicity profile of nivolumab + ipilimumab was similar to the profile seen in melanoma, and did not appear to affect safety.

When compared to nivolumab monotherapy in the second-line treatment of RCC, the combination of ipilimumab + nivolumab in first line appears to have much poorer safety, e.g., grade 3-4 drug-related AEs were reported in 45.7% of subjects in the nivolumab + ipilimumab arm in the current study, while nivolumab monotherapy in second line was associated with 18.7% grade 3-4 drug-related AEs.

Although this is a cross-study comparison, these findings indicate that ipilimumab contributes substantially to toxicity in the combination. This is consistent with comparative data between nivolumab monotherapy and the combination therapy in melanoma (grade 3-4 drug-related AEs reported less frequently in the pooled monotherapy group in melanoma [13.7%] than in the pooled combination therapy group [54.1%]; EMA/CHMP/215704/2016).

2.5.2. Conclusions on clinical safety

The combination nivolumab + ipilimumab has a safety profile which is very different from that of sunitinib. The combination appears to be less well tolerated than sunitinib. The safety profiles of nivolumab + ipilimumab and sunitinib in the current pivotal study were consistent with existing data on the safety profile of each treatment. When considering the available safety data on ipilimumab + nivolumab in melanoma patients, no new safety concerns were identified with the combination of nivolumab 3 mg/kg + ipilimumab 1 mg/kg in advanced RCC, and the frequencies of AEs related to important identified risks for nivolumab and ipilimumab, e.g. immune-related adverse reactions, are in line with existing data on combination therapy.

The safety profile of ipilimumab + nivolumab in the current dossier seems to compare unfavourably with nivolumab monotherapy in second-line renal cell carcinoma, as well as with nivolumab monotherapy in other tumour types. It is clear that addition of ipilimumab contributes substantially to toxicity, consistent with data in melanoma. In view of the substantial additional toxicity, the contribution to benefit of ipilimumab in the first-line treatment of RCC remains unclear (refer to clinical efficacy).

2.6. Risk management plan

The CHMP having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan for Opdivo and Yervoy cannot be agreed at this stage.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs have been proposed to be updated. In addition, the Worksharing applicant (WSA) would take the opportunity to correct some typos throughout the Yervoy and Opdivo product information.

In light of the negative recommendation, the proposed changes to the SmPC and Package Leaflet for Opdivo and Yervoy cannot be agreed at this stage.

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 WSA and has been found acceptable for the following reasons:

- The readability of the PL (QRD template Version 9.0) of OPDIVO (nivolumab) and Yervoy (ipilimumab), in English, was assessed during the assessment of the initial Marketing Authorisation Application (MAA) according to the methods outlined in the European Commission's guideline
- The new indication that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indications.

- Administration of is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL remain unchanged.
- The general design and layout of the proposed PL have not changed compared to the tested one.

However, in light of the negative recommendation, the proposed changes to the Package Leaflet for Opdivo and Yervoy cannot be agreed at this stage.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The new claimed indication for nivolumab + ipilimumab is for the treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (first-line treatment).

3.1.2. Available therapies and unmet medical need

According to ESMO guidelines and NCCN guidelines, sunitinib, bevacizumab plus interferon, and pazopanib are all standard treatment options for favourable and intermediate-risk patients in the first-line treatment of RCC. Currently, the median OS of patients with advanced RCC is estimated to be around 8 months for poor-risk patients, 23 months for intermediate-risk patients and 43 months for favourable-risk patients, indicating the need for improved treatments. The standard treatment option in previously untreated RCC patients is sunitinib for favourable/intermediate-risk patients. For poor-risk patients, the standard treatment option can either be sunitinib or temsirolimus. The median OS is less than 4 years for treatment-naive patients with the most favourable prognosis, and less than 1 year in patients with poor prognosis, indicating the need for more efficacious therapies. Nivolumab is currently indicated for second-line treatment of RCC, while ipilimumab currently has no approved indication in RCC.

3.1.3. Main clinical studies

The main study was CA209214, a phase 3, randomised, open-label study of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks, vs. sunitinib monotherapy using the approved dose and schedule (50 mg orally once daily for 4 weeks followed by 2 weeks off, every cycle) in adults (≥ 18 years) with previously untreated advanced RCC. All randomised subjects included previously untreated favourable, intermediate and poor-risk advanced RCC patients (according to Metastatic Renal Cell Carcinoma Database Consortium criteria). The primary objective of the study was to determine OS, PFS and ORR in the subset of intermediate/poor-risk patients, as analysis of this subset of patients in the primary analysis would allow for potential meaningful differences in efficacy to be detected earlier than if favourable-risk patients were also included in the primary efficacy analysis.

3.2. Favourable effects

Only favourable effects in the primary efficacy population, i.e. intermediate/poor-risk patients, which comprise the target population, are discussed here.

A statistically significant difference in OS was observed in the nivolumab + ipilimumab group compared to the sunitinib group in intermediate/poor-risk subjects (HR: 0.63 [99.8% CI: 0.44, 0.89]; stratified log-rank 2-sided p-value < 0.0001). The median OS was not reached for the nivolumab + ipilimumab group and 25.95 months for the sunitinib group. The OS rates were 89.5% and 86.2% at 6 months, and 80.1% and 72.1% at 12 months in the nivolumab + ipilimumab and the sunitinib groups, respectively. K-M curves separated after approximately 3 months, favouring nivolumab + ipilimumab. Updated OS data confirmed previous data (HR: 0.66 [95% CI: 0.54, 0.81]; p-value < 0.0001).

A numerical difference in PFS was found favouring the nivolumab + ipilimumab group (HR = 0.82, [99.1% CI: 0.64,1.05], p-value: 0.0331). Median PFS was 11.56 months (95% CI: 8.71, 15.51) and 8.38 months in the nivolumab + ipilimumab group and the sunitinib group, respectively. The 12-month PFS rate was 49.6% in the nivolumab + ipilimumab group and 42.6% in the sunitinib group. At approximately 6-7 months, the K-M curves separated, favouring nivolumab + ipilimumab.

The independent radiology review committee (IRRC)-assessed ORR was higher in the nivolumab + ipilimumab group (41.6% [95% CI: 36.9, 46.5]) than in the sunitinib group (26.5% [95% CI: 22.4, 31.0]). The stratified difference in ORR (nivolumab + ipilimumab - sunitinib) was 16.0% (95% CI: 9.8, 22.2), p-value < 0.0001. BOR was CR in 9.4% and 1.2 % of subjects, BOR was PR in 32.2% and 25.4% of subjects and BOR was SD in 31.3% and 44.5% of subjects in the nivolumab + ipilimumab group and in the sunitinib group, respectively. TTR was 2.79 months in the nivolumab + ipilimumab group and 3.04 months in the sunitinib group. DOR was not reached at the time of database lock in the nivolumab + ipilimumab group and was 18.17 months in the sunitinib group.

Subgroup analyses showed that the unstratified HR for OS for nivolumab + ipilimumab vs. sunitinib was 0.53 (95% CI: 0.40, 0.71) for patients aged <65 years, as compared to HR 0.86 (95% CI: 0.40, 0.71) and 0.97 (95% CI: 0.40, 0.71) for patients aged ≥65 years and patients aged <75–≥75, respectively.

Subgroup analyses showed that the unstratified HR for OS for nivolumab + ipilimumab vs. sunitinib was 0.55 (95% CI: 0.41, 0.73) for patients with Karnofsky performance status (KPS) 90-100 compared to HR 0.86 (95% CI: 0.61, 1.20) for patients with KPS <90.

Subgroup analyses showed that the unstratified HR for OS for nivolumab + ipilimumab vs. sunitinib was 0.45 (95% CI: 0.29, 0.71) for patients with baseline PD-L1-positive status (≥1%) versus HR 0.73 (95% CI: 0.56, 0.96) for patients with baseline PD-L1-negative status (<1%).

3.3. Uncertainties and limitations about favourable effects

- The most critical uncertainty in this application remains the contribution of ipilimumab to the efficacy of the combination therapy nivolumab + ipilimumab. Nivolumab has previously been shown to be active in the target population, and is approved for the treatment of advanced RCC after prior therapy in adults. In contrast, the benefits of ipilimumab treatment in the target population are insufficiently characterised. In the pivotal study, the applicant did not compare efficacy of the combination therapy with either nivolumab monotherapy or ipilimumab monotherapy. Also in phase I/II studies, the effect of the combination therapy was not investigated in comparison with either nivolumab or ipilimumab monotherapy, although a direct comparison was made between 1 mg/kg ipilimumab + 3 mg/kg nivolumab and 3 mg/kg ipilimumab + 1 mg/kg nivolumab. The performed

exposure-effect analysis aimed at establishing the contribution of ipilimumab is considered inconclusive, due to insufficient data included in the model to determine the effects of nivolumab and ipilimumab in first and second-line treatment of RCC. The lack of demonstration of the contribution of ipilimumab to efficacy of the combination treatment is considered an important issue, especially because it is evident that addition of ipilimumab leads to substantial additional toxicity. Moreover, the benefit/risk balance of ipilimumab monotherapy in advanced RCC (MDX010-11 study) was not considered sufficiently favourable by the applicant to warrant further development.

- There is also still uncertainty regarding the dose of ipilimumab. It is not clear whether 1 mg/kg ipilimumab is an effective dose contributing to clinical benefit in RCC (nor in other cancers). Dosing schedules containing only 1 mg/kg ipilimumab appear not to have been tested in RCC patients (only a study in which patients received first a 3 mg/kg loading dose followed by doses of 1 mg/kg; in which 1/21 patients had a partial response). As a result, the dose-response relationship of ipilimumab in RCC is poorly characterised, and it cannot be concluded that 1 mg/kg ipilimumab contributes to a relevant extent to efficacy of the combination treatment.

- Potentially reduced OS benefit of the combination therapy was observed in patients >65 years, although efficacy still appears comparable to that of sunitinib.

- Tumour PD-L1 expression (<1% vs. ≥1%) had an effect on OS (HR: 0.73 [95% CI: 0.56, 0.96] vs. HR: 0.45 [95% CI: 0.29, 0.71]), PFS (HR: 1.06 [95% CI: 0.87, 1.36] vs. HR: 0.45 [95% CI: 0.29, 0.71]) and ORR (36.8% vs. 47.1%). However, the methods used to score PD-L1 expression in tumour tissue were suboptimal (e.g. immune cell expression was not taken into account). Updated PD-L1 analyses are required to determine the role of PD-L1 expression in the efficacy of the combination therapy.

- Additional biomarkers for efficacy of nivolumab + ipilimumab are available which may have an impact on the benefit/risk of the combination treatment in subgroups of patients. These biomarkers include tumour mutational burden, tumour infiltrating lymphocytes, gene expression profiling, and single nucleotide polymorphism in immune-related genes. These biomarker analyses were not included in the CSR while these were planned to be analysed by the applicant. The applicant should provide these additional biomarker analyses as a post-authorisation measure if the application is approved.

3.4. Unfavourable effects

The most frequently reported drug-related AEs in the nivolumab + ipilimumab group were fatigue (36.9%), pruritus (28.2%), diarrhoea (26.5%), and rash (21.6%). In the sunitinib group, the most frequently reported drug-related AEs were diarrhoea (52.0%), fatigue (49.3%), palmar-plantar erythrodysesthesia syndrome (43.2%), hypertension (40.4%), nausea (37.8%), and dysgeusia (33.5%).

Grade 3-4 drug-related AEs were reported in 45.7% of subjects in the nivolumab + ipilimumab group and 62.6% of subjects in the sunitinib group. In the nivolumab + ipilimumab group, the most frequently reported Grade 3-4 drug-related AEs were lipase increased (10.2%), amylase increased (5.7%), alanine aminotransferase (ALT) increased (4.9%), fatigue (4.2%), and diarrhoea (3.8%). In the sunitinib group, the most frequently reported Grade 3-4 drug-related AEs reported were hypertension (15.9%), fatigue (9.2%), palmar-plantar erythrodysesthesia syndrome (9.2%), platelet count decreased (6.7%), lipase increased (6.5%), neutropaenia (6.0%), and diarrhoea (5.2%).

SAEs were reported in 55.8% of subjects in the nivolumab + ipilimumab group and 39.8% of subjects in the sunitinib group.

In patients <65 years of age SEAs occurred with a frequency of 52.4%, while in patients 75-84 years of age the frequency was 65.1%. Fatal AEs occurred in 2.4% of patients <65 years of age, versus 16.3% of patients 75-84 years of age.

The most frequently reported any-grade drug-related select AE categories in the ipilimumab + nivolumab group were skin (48.8%), endocrine (32.5%), and gastrointestinal (28.2%); versus 56.8%, 30.5%, and 52.0%, respectively, in the sunitinib group.

In the sunitinib group, 2 (0.4%) subjects reported late-emergent drug-related AEs, and 1 subject was intermediate/poor-risk. In the nivolumab + ipilimumab group, 20 (3.7%) subjects had late-emergent drug-related AEs. 15 (3.5%) of these subjects were intermediate/poor-risk subjects.

Death as a result of study drug toxicity (as declared by the investigator) occurred in 7 patients (1.3%) in the nivolumab + ipilimumab arm versus 4 patients (0.7%) in the sunitinib arm. Deaths attributed to "other reasons" occurred in 22 patients in the ipilimumab + nivolumab arm, versus 13 patients in the sunitinib arm. This imbalance was driven primairily by a higher frequency of infection-related deaths and cardiovascular event-related deaths in the ipilimumab + nivolumab group.

Drug-related AEs leading to discontinuation were reported in 21.6% of subjects in the nivolumab + ipilimumab group and 11.8% of subjects in the sunitinib group.

3.5. Uncertainties and limitations about unfavourable effects

The pivotal study was an open-label study, potentially affecting safety reporting.

Follow-up was relatively short in relation to establishing the long-term safety of the combination of ipilimumab + nivolumab.

3.6. Effects Table

Table 56 Effects Table for OPDIVO + YERVOY vs. SUTENT for the intermediate/poor risk population (data cut-off: 07/AUG/2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
OS	Overall survival	Months	Not reached	25.95	Statistically significant Median OS not evaluable yet.
			HR 0.63 (99.8% CI: 0.44, 0.89), stratified log-rank 2-sided p-value < 0.0001		
OS update (database lock 01-Mar-2018)	Overall survival	Months	Not reached	26.97	Statistically significant Median OS not evaluable yet.
			HR 0.66 (95% CI: 0.54, 0.81), stratified log-rank 2-sided p-value < 0.0001		
PFS	Progression-free survival	Months	11.56	8.38	Not statistically significant

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
	by independent radiology review committee		HR 0.82 (99.1% CI: 0.64 - 1.05), stratified 2-sided p-value = 0.0331)		
ORR	Objective response rate by independent radiology review committee	%	41.6 (95% CI:36.9, 46.5)	26.5 (95% CI:22.4,31.0)	ORR analysed initially on a descriptive basis (CSR – CA209214d)
			Stratified difference 16.0% (95% CI: 9.8, 22.2), p-value < 0.0001		
Unfavourable Effects					
Fatigue Grade 3/4	Drug-related AEs	%	4.2	9.2	Open-label study
Diarrhoea Grade 3/4	Drug-related AEs	%	3.8	5.2	
Lipase increased Grade 3/4	Drug-related AEs	%	10.2	6.5	
Nausea Grade 3/4	Drug-related AEs	%	1.5	1.1	
Asthenia Grade 3/4	Drug-related AEs	%	1.5	2.2	
Vomiting Grade 3/4	Drug-related AEs	%	0.7	1.9	
Anaemia Grade 3/4	Drug-related AEs	%	0.4	4.5	
Hypertension Grade 3/4	Drug-related AEs	%	0.7	15.9	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

In the current pivotal study, nivolumab + ipilimumab showed improved efficacy compared to sunitinib in previously untreated intermediate/poor-risk advanced RCC patients. The K-M curves split after approximately 3 months favouring nivolumab + ipilimumab. The observed OS benefit is considered clinically relevant. A difference of more than three months was found for the median PFS of nivolumab+ipilimumab compared to sunitinib. The K-M curves overlapped the first 6-7 months, then separated and favoured nivolumab + ipilimumab. These PFS results further support the observed OS benefit. Also, a convincing difference in ORR was observed favouring nivolumab + ipilimumab.

The lack of demonstration of the contribution of ipilimumab to efficacy of the combination therapy is considered a major issue. While the efficacy of nivolumab in RCC is evident, the (added) benefit from ipilimumab in RCC has not been adequately demonstrated. According to the 'guideline on the evaluation of anticancer medicinal products in man', a new combination of anticancer drugs should be compared to the combination partners as single agents at efficacious doses (EMA/CHMP/205/95/Rev.4). In the pivotal study (CA209214) both monotherapy arms are lacking, and the benefit of the combination therapy over monotherapy has also not been demonstrated in phase I/II. Upon request for supplementary information, the applicant further explored the earlier presented E-R model, comparing ORR and OS data between 1L and 2L+ RCC patients treated with either nivolumab in combination with ipilimumab or ipilimumab alone, and further submitted real world data for nivolumab monotherapy (off-label) and compared ORR data of nivolumab between 1L and 2L patients across tumour types. The E-R model is considered inconclusive, due to insufficient data included in the model to determine the effects of nivolumab and ipilimumab in first and second-line treatment of RCC. The results of the cross-study comparisons to compare ORR between nivolumab alone and nivolumab in combination with ipilimumab are difficult to interpret for several reasons, i.e. due to small sample size, uncertainty on the comparability of the patient populations among the studies, the assumption that the response in the 2nd line is comparable to 1st line, that a difference in ORR translates into OS benefit, as well as other limitations inherent to an indirect comparison of outcome data.

Furthermore, there are questions regarding the dose of ipilimumab of 1 mg/kg. This dose is not used in any other indication (in melanoma 3 mg/kg is used in combination with nivolumab), nor is adequate data available to demonstrate that 1 mg/kg is an efficacious dose in RCC. The dose-response relationship of ipilimumab monotherapy in RCC patients has not been satisfactorily determined (while in melanoma the available dose-response data show a positive trend between dose and efficacy between 1-10 mg/kg and indicate that 1 mg/kg is on the low part of the dose-response curve). The applicant provided ALC data in melanoma and further explored study CA209016 in the second round. These data merely show that ipilimumab at 1 mg/kg increases ALC, but ALC is not a validated surrogate marker for clinical benefit and therefore these data do not contribute to the interpretation of the effect of ipilimumab on the benefits conferred by the combination therapy.

What is evident is that addition of ipilimumab leads to a much worse safety profile compared to nivolumab monotherapy, stressing the importance of determining the added benefit of ipilimumab in combination with nivolumab in the target population of previously untreated advanced RCC patients with intermediate/poor-risk.

It is considered that the uncertainty related to the unknown benefit of ipilimumab at a dose of 1 mg/kg in combination with nivolumab weighs heavily in the assessment of the benefit/risk balance of the combination treatment, since the undesirable consequence would be that many patients would be exposed to an anticancer agent with uncertain benefit and with clear additional risks.

The effect of biomarkers cannot be adequately characterised based on the currently submitted data. The method of PD-L1 immunohistochemistry scoring was not complete, since PD-L1 expression on tumour-associated immune cells was not incorporated in the method of scoring. The applicant should provide additional PD-L1 biomarker data based on adequate scoring methodology. In addition, several other, potentially more relevant biomarkers for nivolumab + ipilimumab efficacy are available (as described in discussion on clinical efficacy). In the second round, the applicant has presented limited biomarker data and several planned biomarker analysis still need to be performed by the applicant. Remaining biomarker data should be provided by the applicant in the context of a post-authorisation measure.

Importance of unfavourable effects

The combination of ipilimumab with nivolumab has a distinct safety profile, characterised by a high frequency of immune-mediated adverse events, and is in that respect very different from the safety profile of sunitinib. The combination treatment appears less well tolerated than sunitinib, and is associated with a higher frequency of SAEs, and drug-related treatment discontinuation. This should, however, be considered in the light of the observed OS benefit.

The safety profile of nivolumab + ipilimumab in the current pivotal study is consistent with existing data on the safety profile of the combination in melanoma and the observed safety profile of sunitinib is also in line with available data, which is re-assuring and does not suggest bias in safety reporting as a result of the open-label design of the study. When taking into account the available safety data on ipilimumab + nivolumab in melanoma, no new safety concerns were identified with the combination of nivolumab 3 mg/kg + ipilimumab 1 mg/kg in mRCC.

As in melanoma, it is clear that the ipilimumab component of treatment contributes substantially to toxicity of the combination in RCC. Whether the additional toxicity is outweighed by the benefits, depends largely on whether a relevant contribution of (the proposed dose) of ipilimumab to efficacy can be demonstrated.

3.7.2. Balance of benefits and risks

In the performed pivotal study, a clinically relevant OS benefit for nivolumab + ipilimumab versus sunitinib was observed in the first-line treatment of intermediate/poor-risk mRCC patients. However, there is great uncertainty about the contribution of ipilimumab to efficacy in the combination therapy, both due to lack of studies on single-agent contribution and uncertainties regarding the 1 mg/kg dose of ipilimumab, which is considered a major issue in assessing the benefit/risk. The response of the applicant upon request for supplementary information was not sufficient to demonstrate the contribution of ipilimumab to efficacy of the combination therapy.

The safety profile of ipilimumab + nivolumab in the current dossier compares unfavourably to nivolumab monotherapy in second-line renal cell carcinoma, as well as with nivolumab monotherapy in other tumour types. It is clear that the addition of ipilimumab contributes substantially to toxicity, consistent with data in melanoma.

In view of the substantial additional toxicity and since the contribution to benefit of ipilimumab in the first-line treatment of RCC remains unclear, the B/R of the combination is considered unsubstantiated.

3.7.3. Additional considerations on the benefit-risk balance

In the favourable-risk group of patients, no benefit for ipilimumab + nivolumab versus sunitinib was observed. In fact, sunitinib tended to perform better than the combination therapy in favourable-risk patients. It is currently not clear why there is such a strong difference between the intermediate/poor-risk cohort and the favourable cohort in terms of the relative efficacy of ipilimumab + nivolumab versus sunitinib.

A major deficiency in the current application is that the contribution of ipilimumab (in the studied dose) to the efficacy of the combination therapy has not been demonstrated. A full assessment of the efficacy associated with the combination and its components is thus prevented, whereas it is clear that addition of ipilimumab leads to a more unfavourable safety profile compared to nivolumab alone. Moreover, considering the lack of relevant efficacy of ipilimumab as monotherapy in first line treatment of RCC and the known efficacy of nivolumab monotherapy in second line treatment of RCC, investigating the efficacy of nivolumab monotherapy in first line advanced RCC is warranted.

The combination of two or more drugs is often an adequate way to achieve or improve efficacy and/or improve safety compared to using single agents. This will often be the way forward to advance therapies in areas of unmet medical need. In this context, the establishment of adequate combinations and doses is crucial, as is outlined in the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5). If information on these aspects is inadequate, there is a clear risk of exposing patients to combinations that have more toxicity compared to the individual components while not being more effective (and potentially even less so). Thus, because of the direct importance to public health, there is a requirement for a justification of the combination and the doses used.

3.8. Conclusions

The B/R for Opdivo in combination with Yervoy for treatment of previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma is negative.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend, by a majority of 24 out of 26 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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 the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs were proposed to be updated. The Package Leaflet and the Risk Management Plan (version 19.0 for Yervoy and version 13.0 for Opdivo) were proposed to be updated in accordance. In addition, the Worksharing applicant (WSA) would take the opportunity to correct some typos throughout the Yervoy and Opdivo product information.

Grounds for refusal:

Whereas:

- There is no basis to establish or to quantify any benefits conferred by 1 mg/kg ipilimumab as used in combination with 3 mg/kg nivolumab in the first-line treatment of intermediate/poor-risk advanced renal cell carcinoma patients, and specifically whether ipilimumab contributes to the efficacy of the combination therapy to an extent that outweighs the substantial additional toxicity. Therefore, the safety and efficacy of the combination cannot be considered properly or sufficiently demonstrated and a comprehensive assessment of the benefits and risks associated with the combination and its components cannot be completed in this case. The benefit-risk balance of the combination treatment with nivolumab and ipilimumab in this setting must thus currently be regarded as unsubstantiated.

Divergent position to the majority recommendation is appended to this report.

5. Re-examination of the CHMP opinion of 26 July 2018

Following the CHMP conclusion that nivolumab + ipilimumab for the treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (first-line treatment) was not approvable nivolumab + ipilimumab for the treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (first-line treatment) was not approvable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

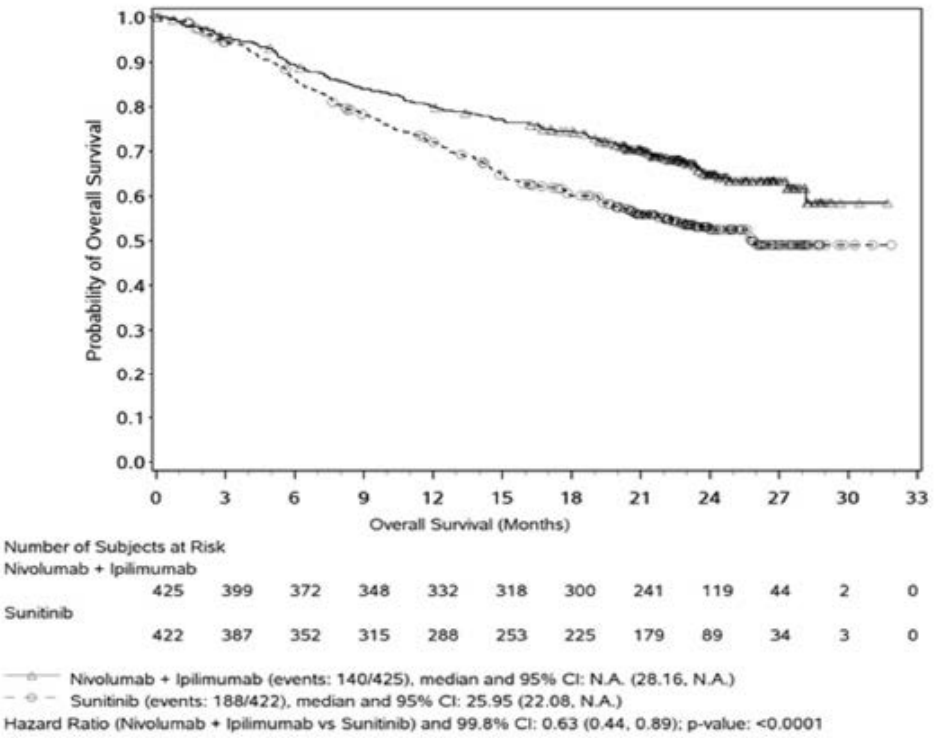
The applicant presented in writing and at an oral explanation arguments refuting the grounds for refusal. The MAH argumentation was as follows:

Ground #1: Favourable benefit-risk profile versus sunitinib based on currently available data

Unprecedented Benefit

The primary analysis population (intermediate/poor risk) in CA209214 represents a population with a high unmet medical need (median OS for favourable risk patients is 43 months but for intermediate risk it is 23 months and poor risk, 8 months) with limited benefit from standard of care, sunitinib. While agents currently approved for treatment of 1L advanced RCC have demonstrated statistically significant benefits in terms of PFS, no agent in this population has been approved based upon OS benefit. In addition, no agent has demonstrated superiority to sunitinib based upon a Ph3 study in over the past ten years.

In the Phase 3 CA209214 study, the nivolumab 3 mg/kg and ipilimumab 1 mg/kg combination regimen has demonstrated an unprecedented, statistically significant improvement in OS compared to the current standard of care, sunitinib, in previously untreated, intermediate or poor risk advanced RCC, reducing the risk of death by 37% (Figure 40).



Symbols represent censored observations.
The boundary for statistical significance requires the p-value to be less than 0.002.

Figure 40 Kaplan-Meier Plot of Overall Survival, Primary Analysis – All Intermdiate/Poor Risk Subjects – 07-Aug-2017 Database Lock

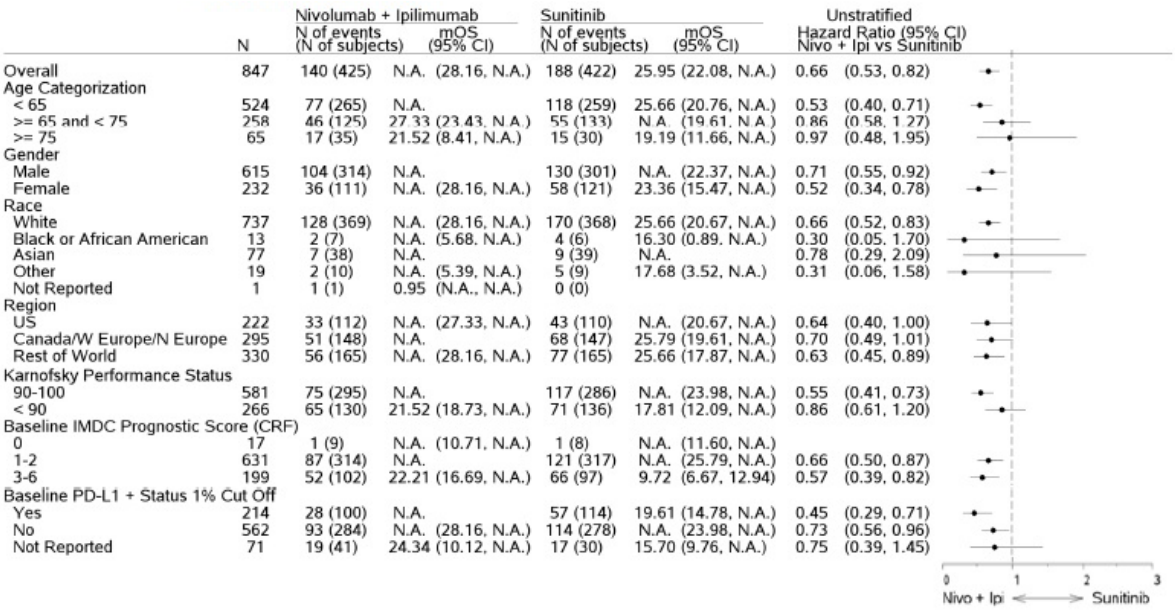
OS was favored with nivolumab + ipilimumab versus sunitinib across all predefined subgroups (Figure 41). This improvement in OS was accompanied by a clinically meaningful 16% improvement in ORR (including complete responses in 9.4% of participants versus 1.2% in the sunitinib arm), as well as a 3.2 month improvement in median PFS (Table 57). Depth of response has been shown to correlate with improved survival outcomes, emphasizing the clinical significance of the complete responses observed.

The magnitude of OS benefit in CA209214 is striking given the availability of multiple effective systemic therapies for advanced RCC, reflected in the subsequent use of nivolumab in 28% of subjects in the sunitinib arm. The unprecedented 9.4% complete response rate, durability of responses, and OS benefit in CA209214 indicate that the nivolumab + ipilimumab combination may have the potential to cure some patients with advanced RCC.

Table 57 Efficacy Results – All Intermediate/Poor Risk Subjects in CA209214-07-Aug-2017 Database Lock

	Nivolumab + Ipilimumab (N = 425)		Sunitinib (N = 422)
Progression-free survival			
Events	228 (53.6%)		228 (54.0%)
Hazard ratio[a]		0.82	
99.1% CI		(0.64, 1.05)	
p-value[b, ,c]		0.0331	
Median (95% CI)	11.6 (8.71, 15.51)		8.4 (7.03, 10.81)
Confirmed objective response (BICR)	177 (41.6%)		112 (26.5%)
(95% CI)	(36.9, 46.5)		(22.4, 31.0)
Difference in ORR (95% CI)[,d]		16.0 (9.8, 22.2)	
p-value[e, ,f]		< 0.0001	
Complete response (CR)	40 (9.4%)		5 (1.2%)
Partial response (PR)	137 (32.2%)		107 (25.4%)
Stable disease (SD)	133 (31.3%)		188 (44.5%)
Median duration of response[g]			
Months (range)	NA (1.4+-25.5+)		18.17 (1.3+-23.6+)
Median time to response			
Months (range)	2.79 (0.9-11.3)		3.04 (0.6-15.0)

a Based on a stratified proportional hazards model.
b Based on a stratified log-rank test.
c p-value is compared to alpha 0.009 in order to achieve statistical significance.
d Strata adjusted difference.
e Based on the stratified DerSimonian-Laird text.
f p-value is compared to alpha 0.001 in order to achieve statistical significance.
g Computed using Kaplan-Meier method.
"+" denotes a censored observation.
NE = non-estimable



HR is not computed for subset (except age, race, region, and gender) category with less than 21 subjects per treatment group.

Figure 41 Forest Plot of Treatment Effect on OS in Pre-Defined Subsets – All Intermediate/Poor Risk Subjects – 07-Aug-2017 Database Lock

Clinical benefit for OS for nivolumab + ipilimumab was seen regardless of tumor PD-L1 expression. Although the magnitude of benefit for nivolumab + ipilimumab compared to sunitinib was greater among PD-L1 positive (≥ 1% tumour expression) subjects (HR = 0.45), much of this difference was derived from the poorer performance of sunitinib in PD-L1 positive subjects (Figure 42) which is consistent with external studies which also found PD-L1 expression to be a significant predictor of worse outcomes in advanced RCC patients treated with anti-angiogenesis agents.3 However, even among PD-L1 negative (< 1% tumour expression) subjects in CA209214, Kaplan Meier curves show improved OS for nivolumab + ipilimumab compared to sunitinib (HR = 0.73).

There was also a higher ORR observed with nivolumab + ipilimumab compared to sunitinib regardless of tumor PD-L1 expression level (Table 58). Only in evaluation of PFS was significant benefit of nivolumab + ipilimumab compared to sunitinib restricted to PD-L1 positive subjects while PFS was similar between treatment groups among PD-L1 negative subjects.

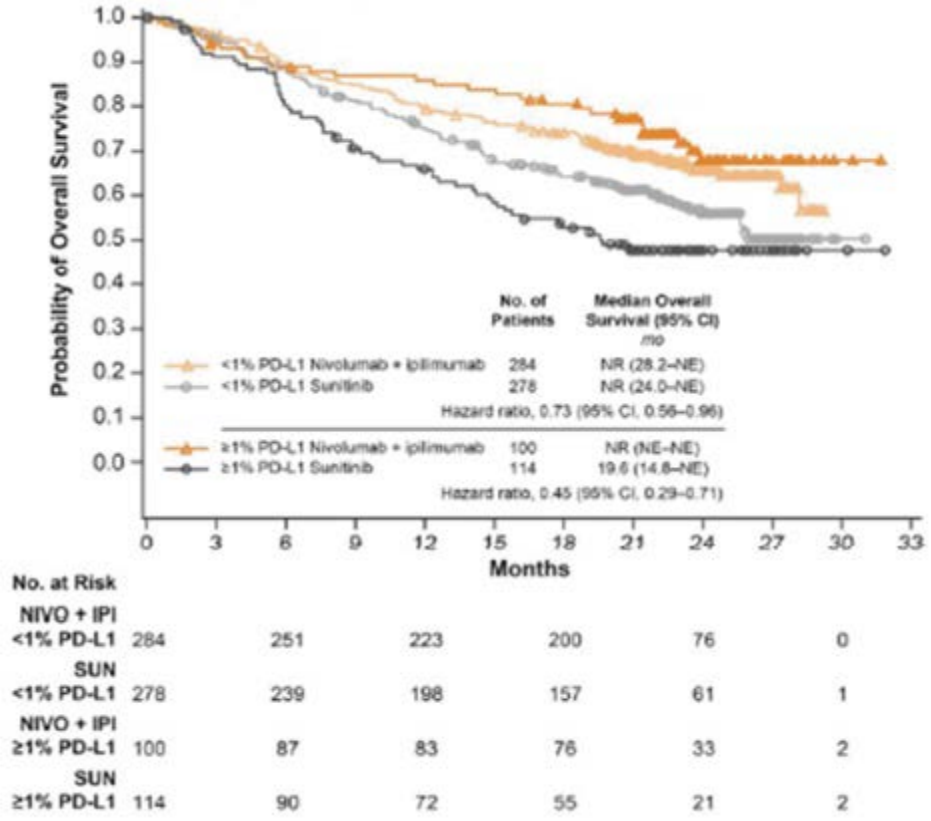


Figure 42 Kaplan-Meier Curves for Overall Survival According to PD-L1 Expression Level in IDMC Intermediate-and Porr-risk Patients-07-Aug-2017 Database Lock

Table 58 Efficacy by Baseline PD-L1 Tunour Expression – Intermediate/Poor Risk Subjects in CA209214-07-Aug-2017 Database Lock

	Intermediate/Poor-risk Subjects			
	PD-L1≥ 1%		PD-L1<1 %	
	Nivo+Ipi N = 100	Sunitinib N = 114	Nivo+Ipi N = 284	Sunitinib N = 278
IRRC-assessed ORR (CR + PR)				
N responders (%)[a]	58 (58.0)	25 (21.9)	106 (37.3)	79 (28.4)
95% CI	(47.7, 67.8)	(14.7, 30.6)	(31.7, 43.2)	(23.2, 34.1)
IRRC-assessed PFS				
Median, mo.[b]	22.80	5.85	11.01	10.41
95% CI	(9.40, N.A.)	(4.44, 7.13)	(8.08, 14.92)	(7.52, 13.83)

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

[b] Median computed using Kaplan-Meier method.

In order to further characterize the incidence of PD-L1 and outcomes based on PD-L1 expression, BMS is fully committed to deliver the results of evaluation of PD-L1 status by immune cells to CHMP by March 2019.

The safety profile of the combination is considered manageable and favourable compared to that of sunitinib (different MoA), supported by patient-reported outcome (PRO) data

The different mechanisms of action of nivolumab in combination with ipilimumab and sunitinib result in differentiated safety profiles. Overall, the safety profile of the combination of nivolumab and ipilimumab is considered favourable compared to that of sunitinib, and together with the patient-reported outcome data, show that, with the distinct safety profiles, the combination is overall, better tolerated than sunitinib.

The combination of nivolumab and ipilimumab has a manageable safety profile with established algorithms for management of drug-related adverse events (AEs). These management algorithms are utilized for the approved nivolumab monotherapy indications as well as the nivolumab + ipilimumab (3 mg) combination approved in 1L advanced melanoma.

The better safety profile of the low dose ipilimumab (1 mg/kg) combination relative to the high dose ipilimumab (3 mg/kg) combination contributed to it being selected as the Phase 3 regimen given the comparable efficacy observed with the 2 combination regimens in CA209016, as well as in the broader combination program.

Safety of N3/I1 vs Sunitinib in RCC (CA209214)

In CA209214, the safety profiles of the nivolumab 3 mg/kg + ipilimumab 1 mg/kg arm and the sunitinib arm were distinct, based on their different mechanisms of action.

The clinical relevance of the safety profiles of the combination relative to sunitinib are further characterized below.

Drug-Related Adverse Events Are Less Common and Frequency Tapers over Time with Nivolumab and Ipilimumab Compared to Sunitinib

Figure 43 shows that among the most common any grade drug-related AEs (occurring in $\geq$ 15% of subjects), the majority had a higher incidence in the sunitinib arm compared to the nivolumab + ipilimumab arm These include general AEs such as fatigue, dysgeusia, nausea and vomiting, which can be debilitating, in particular when chronic, and the prolonged duration of such events often can negatively impact QoL, which may compromise the ability to tolerate further treatment with sunitinib as well as subsequent therapies. Consistent with published safety information for sunitinib and other VEGF targeted therapies, patients in the sunitinib arm more commonly experience other events such diarrhea, palmar planter dysesthesia, stomatitis and haematological toxicities, which require careful management and often dose reductions to maintain tolerability.

Hypertension is a common and often chronic toxicity which typically requires long term use of anti-hypertensive medications and, if not properly managed, may result in serious complications. Notably, the majority of deaths associated with sunitinib-related toxicity were related to cardiac events. The common drug-related AEs that occurred more frequently in the combination of nivolumab with ipilimumab arm included pruritus and rash, which are often manageable and reversible with topical therapy, and an increase in serum lipase level, which is typically asymptomatic and of unknown clinical significance in the absence of clinical symptoms of pancreatitis.

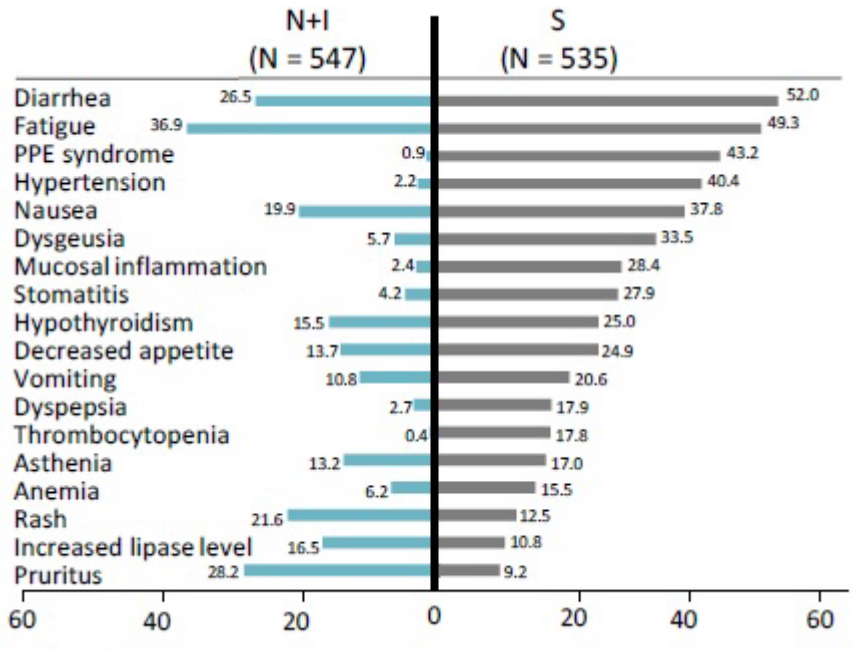


Figure 43 Any-Grade-Drug-Related AEs (%) Occurring in ≥ 15% of Patients in Either Treatment Arm (All Treated Patients) -07-Aug-2017 Database Lock

Given its MoA, the combination of nivolumab and ipilimumab tends to be associated with AEs linked to over-stimulation of the immune system, with the most common events affecting skin, endocrine, and gastrointestinal (GI) systems. High-grade drug-related AEs are manageable with corticosteroid treatment, as recommended by established AE management algorithms, and the vast majority are reversible. Endocrine events may require long term hormone replacement therapy and, for that reason, may not be considered to be resolved.

Figure 44 shows the proportion of subjects in each treatment group with ongoing Grade 3-4 drug - related AEs, from time of onset to resolution, over the course of the study, starting from the first dose of study treatment. This figure shows that high grade drug-related events in the nivolumab + ipilimumab arm are most common early during the course of treatment, peaking at approximately 10% of subjects around Day 80, which coincides with the end of the 4 combination doses, and then tapering off to a prevalence ≤ 2% during the nivolumab monotherapy phase.

Figure 55 is a similar graphical presentation of the proportion of subjects with ongoing Grade 3-4 drug-related AEs over time but broken down by different system organ classes (SOCs). This figure shows that the most common Grade 3-4 drug-related AEs in the nivolumab + ipilimumab arm belonged to the GI, endocrine, and skin disorders SOC, with peak prevalence during the time of the 4 combination doses, followed by a decreased and stable low prevalence during the nivolumab monotherapy phase.

Frequency of Sunitinib Toxicity is greater than Nivolumab and Ipilimumab over time with the frequency of Nivolumab and Ipilimumab Drug-related AEs Tapering over Time

By contrast, high-grade drug-related AEs in the sunitinib arm were characterized by an early peak prevalence of approximately 20% of subjects within the first 40 days of treatment (coinciding with the first treatment cycle), followed by a decreased but saw-tooth pattern, likely coinciding with the 4 weeks on, 2 weeks off dosing in each cycle (Figure 44). Unlike the steadily decreasing prevalence of high-grade drug-related AEs observed in the nivolumab + ipilimumab beyond Day 80, the sunitinib arm continued to demonstrate a saw-tooth pattern well beyond Day 80, with overall prevalence generally higher than that observed in the nivolumab + ipilimumab arm with longer treatment duration. Unlike the nivolumab + ipilimumab arm, the most common high-grade drug-related AEs in the sunitinib arm belonged to the vascular disorders (eg, hypertension), blood and lymphatic disorders (thrombocytopenia, anemia, neutropenia), GI (diarrhea, nausea/vomiting), and skin disorders (eg, palmar-plantar erythrodysesthesia) SOCs (Figure 45).

Since 53% of subjects in the sunitinib arm required dose reductions, it is possible that the decreasing prevalence of high-grade drug-related AEs over time may be related, in part, to dose reductions to manage toxicity.

Overall, drug-related AEs, particularly Grade 3-4 events, were more common with sunitinib compared to nivolumab + ipilimumab. In addition, high-grade AEs related to nivolumab + ipilimumab were most common during the combination dosing phase, with prevalence tapering and stabilizing to $\leq$ 2% during the nivolumab monotherapy phase. In contrast, high-grade AEs related to sunitinib were most common during the first cycle but continued to recur and subside with subsequent cycles, indicating a pattern of waxing and waning but chronic toxicity. The chronicity of overall vascular events in the sunitinib arm was particularly notable reflected in longer times to and low rates of resolution.

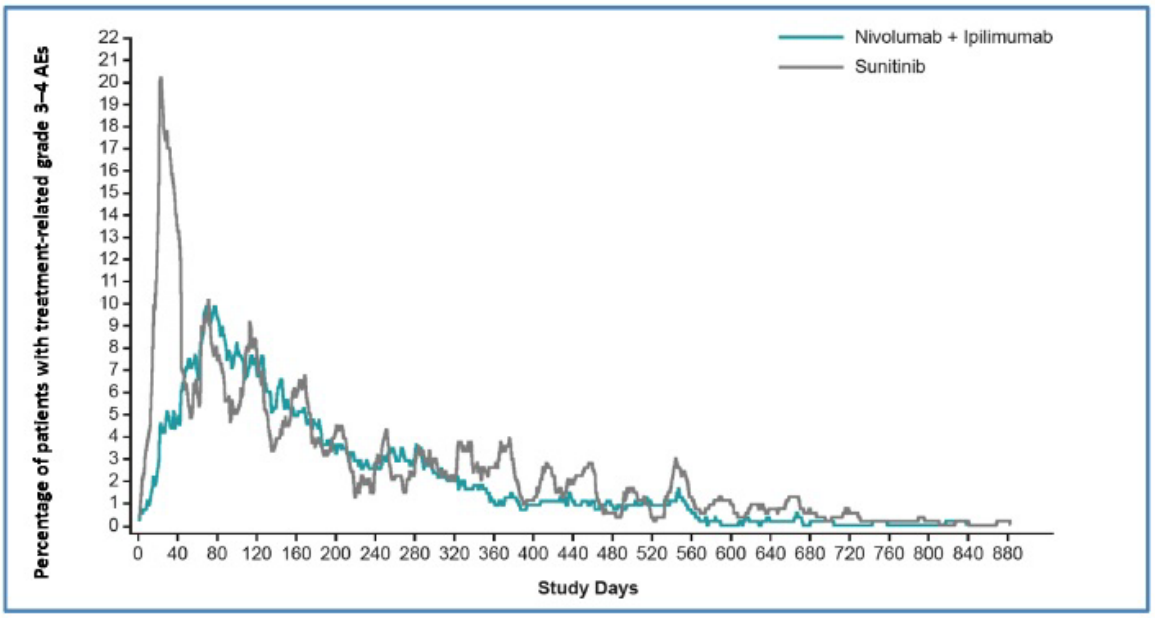


Figure 44 Percentage of patients with drug-related grade 3-4 AEs over time (all treated patients)-07-Aug-2017 Database Lock

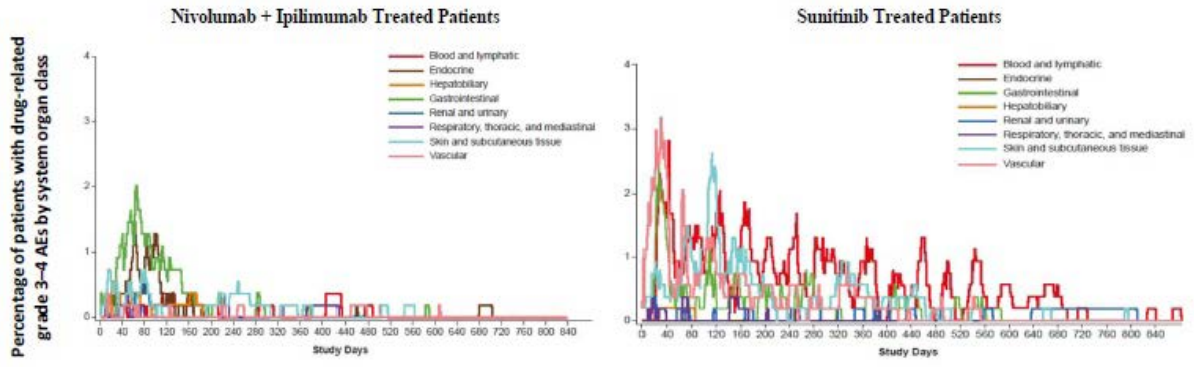


Figure 45 Percentage of patients with drug-related grade 3-4 AEs by system organ class over time-all treated subjects-07-Aug-2017 Database Lock

Select Adverse Events Occurred Early during Nivolumab + Ipilimumab Dosing and the Majority Resolve with Appropriate Management

Select AEs are groupings of pre-specified event terms that reflect immune-mediated reactions affecting certain organ systems and commonly associated with nivolumab or ipilimumab treatment. Because these select AE categories are defined to characterize the safety profile of nivolumab and ipilimumab, these select AEs may not fully capture the safety profile of other therapies. Therefore, direct comparisons of select AEs between the nivolumab + ipilimumab arm and the sunitinib arm may not adequately capture additional sunitinib-associated safety events not seen with nivolumab + ipilimumab, or describe the relative safety between these treatment regimens in CA209214.

With these caveats in mind, the frequencies of drug-related select AEs (any grade) were similar between the 2 arms in CA209214, with the exception of select GI and skin AEs, which were more common in the sunitinib arm (Table 59). The median time to onset of drug-related select AEs across all select AE categories was within 12 weeks of first dose in both treatment arms in CA209214. The majority of drug-related select AEs in the nivolumab + ipilimumab arm resolved within 6-12 weeks of onset with use of established algorithms for toxicity management, including use of immune modulating medications, except for some select endocrine AEs which were not considered resolved due to the continued need for hormone replacement therapy. The majority of drug-related select AEs in the sunitinib arm also resolved within 6-12 weeks, although time to resolution was longer for select GI and skin AEs and resolution of select GI events was less common with sunitinib (77%) compared to nivolumab + ipilimumab (92%). The frequency of resolution of select endocrine AEs in the sunitinib arm was similar to that in the nivolumab + ipilimumab arm.

Table 59 Time to Onset and Resolution of Any-Grade Drug-Related Select AEs – All Treated Subjects-07-Aug-2017 Database Lock[a]

Nivolumab + Ipilimumab				Sunitinib			
Select AEs	**Median Time to Onset (Weeks)**	**Median Time to Resolution (Weeks)**	**Percent of Subjects Resolved**	**Select Aes**	**Median Time to Onset (Weeks)**	**Median Time to Resolution (Weeks)**	**Percent of Subjects Resolved**
Endocrine (n = 178)	8.4	-	43%	Endocrine (n = 163)	9.1	-	37%
GI	5.4	2.4	92%	GI	6.4	6.1	77%

Nivolumab + Ipilimumab				Sunitinib			
Select AEs	**Median Time to Onset (Weeks)**	**Median Time to Resolution (Weeks)**	**Percent of Subjects Resolved**	**Select Aes**	**Median Time to Onset (Weeks)**	**Median Time to Resolution (Weeks)**	**Percent of Subjects Resolved**
(n = 154)				(n = 278)			
Hepatic (n = 101)	8.9	6.1	85%	Hepatic (n = 77)	4.0	5.3	86%
Pulmonary (n = 34)	11.4	6.1	91%	Pulmonary (n = 1)	2.3	10.7	100%
Renal (n = 48)	8.9	13.2	77%	Renal (n = 46)	9.2	3.1	67%
Skin[a] (n = 267)	4.0	11.6	72%	Skin[a] (n = 304)	3.9	21.0	70%

Error! Bookmark not defined. Includes treated patients who experienced ≥1 drug-related select AE from the category and had drug-related AEs.

[a] N for % resolution included 1 fewer patient than was included in AE system onset.

Drug-related Serious Adverse Events (SAEs) Were More Common with Nivolumab + Ipilimumab but Were Manageable and Did Not Lead to Worse Quality of Life Compared to Sunitinib

The overall frequency of drug-related SAEs was higher in the nivolumab + ipilimumab arm compared to the sunitinib arm, 30% vs 15%.

The majority of drug-related SAEs in the nivolumab + ipilimumab arm occurred during the combination dosing cycles, most commonly affecting the GI and endocrine systems, and the vast majority were reported as serious because they involved hospitalizations for management of AEs requiring use of intravenous steroids, which led to resolution in the majority of cases. Based on discussion with investigators, this higher frequency of SAEs in the nivolumab + ipilimumab arm compared to the sunitinib arm may be a reflection of clinicians' limited clinical experience with managing immune mediated AEs at the time of active enrollment of the study. The frequency of total drug related AEs, particularly high grade AEs (Grade 3-4), was higher in the sunitinib arm, but physicians' familiarity and prior experience with sunitinib toxicity led to more frequent management in the outpatient setting. With increasing clinical experience with managing immunotherapy toxicity, the frequency of SAEs related to nivolumab + ipilimumab is anticipated to decline over time. Given the high resolution rate and manageability of AEs related to nivolumab + ipilimumab, including SAEs, and the improved tolerability of the combination relative to sunitinib based on quality of life outcomes (described below), the higher frequency of drug-related SAE with nivolumab + ipilimumab in CA209214 do not indicate a worse safety profile compared to sunitinib.

Drug-related AEs leading to Discontinuation Did Not Compromise Efficacy of Nivolumab + Ipilimumab

Despite the higher discontinuation rate for toxicity in the combination arm, the median duration of therapy was similar in both arms (7.8 months), and 79% of patients on the combination arm were able to receive all 4 combination doses. It should be noted that dose reductions were not permitted on the

combination arm.

While the nature and severity of AEs do lead to a higher rate of discontinuations in the nivolumab + ipilimumab arm than observed with sunitinib, patients who discontinue the combination regimen on account of toxicities continue to derive long term benefit from treatment. This is shown in Figure 46, where responses achieved with combination treatment in CA209214 were durable beyond last dose in patients who discontinued due to drug-related AEs, whereas responses with sunitinib were typically lost soon after the last dose of sunitinib. This durability of response beyond last dose suggests that patients treated with nivolumab + ipilimumab are likely to experience a prolonged treatment-free interval prior to starting subsequent therapy.

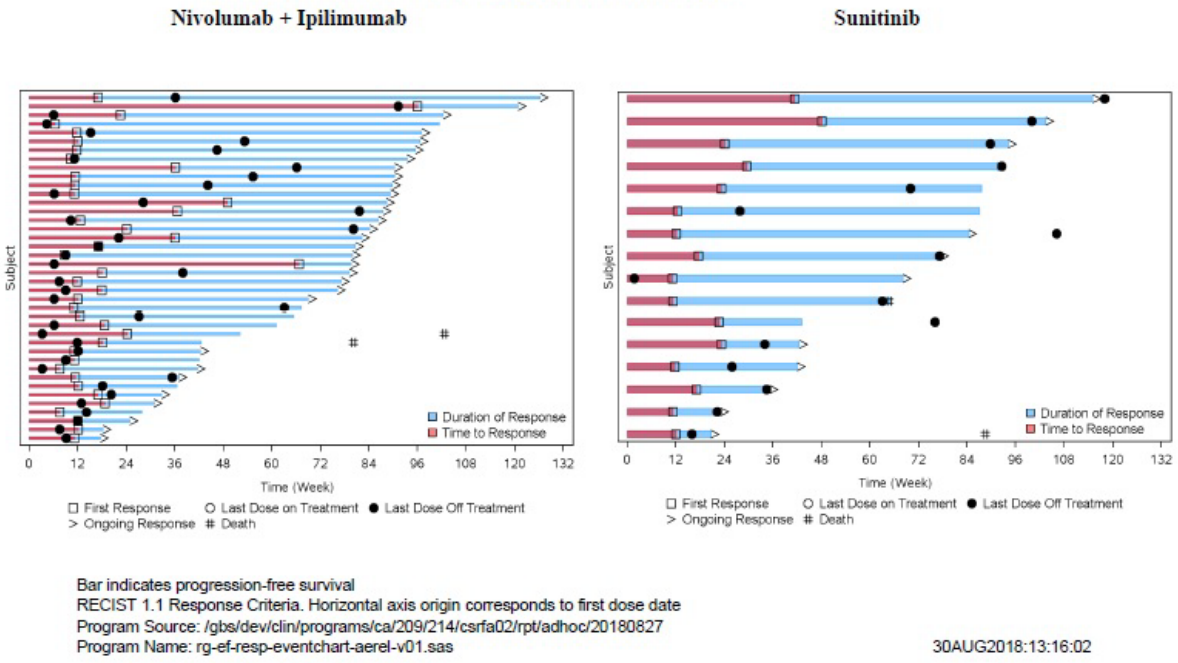


Figure 46 Event Chart for Tumour Response, Tunour Progression, Duration of Therapy and Death, per IRCC – All Intermediate/Poor Risk Subjects with response Who Experienced a Drug-Related Adverse Event Leading to Discontinuation – 07-Aug-2017 Database Lock

Deaths

A lower proportion of treated subjects in the nivolumab + ipilimumab group (29.1%) died compared with the sunitinib group (37.8%). Disease progression was the most common cause of death for both groups, including deaths occurring within 100 days of last dose. The frequency of treatment related deaths was low in both arms, 7 deaths (1.3%) in nivolumab + ipilimumab group and 4 deaths (0.7%) in the sunitinib arm. BMS assessment for the cause of death for the 7 deaths in the nivolumab + ipilimumab group was “not related” in 4 cases, “related” in 2, and “needs more information” in 1. Among the 4 deaths attributed to sunitinib by the investigators, BMS assessment concurred with 3 as “related”, and 1 death was considered “unrelated”. The majority of drugrelated deaths were related to immune mediated adverse effects and complications due to steroid use while in the sunitinib arm it was due to cardiac events.

Overview of safety profiles

Overall, the data above support that although the combination of nivolumab + ipilimumab and sunitinib had differential safety profiles, the combination was in many ways better tolerated than sunitinib based on the overall incidence, type and timing of AEs as well as the total proportion of subjects affected at any given time during the study. Although there was a higher discontinuation rate with nivolumab + ipilimumab arm than sunitinib this is partly due to the ability to dose reduce sunitinib at the expense of efficacy and the majority of patients who discontinued due to toxicity in nivolumab + ipilimumab arm continued to derive efficacy benefit.

Nivolumab + ipilimumab is well tolerated, as indicated by maintenance of high HRQoL and low symptom burden for a longer period of time compared to sunitinib.

Better PRO scores were consistently observed for nivolumab + ipilimumab over sunitinib for all PRO analyses across all instruments. The FKSI-19 scale is of particular interest because it was specifically designed for patients with RCC and outcomes have been reflected in the SmPC for 2L RCC based on evaluation of data from the CA209025 study. Results are presented below for the FKSI Disease Related Symptoms (DRS), since a minimally important difference is established in the literature for this FKSI-19 subscale. Results are similar for additional instruments. Change from baseline showed an advantage for nivolumab + ipilimumab over sunitinib for the FKSI DRS (Figure 47); the mean change from baseline was greater in the nivolumab + ipilimumab group than in the sunitinib group during the first 6 months (P<0.05). Similar results were shown in FACT and EQ-5D. The pattern-mixture model and the mixed model repeated-measures analyses indicated a significant difference in favor of nivolumab + ipilimumab, which substantiated the descriptive results.

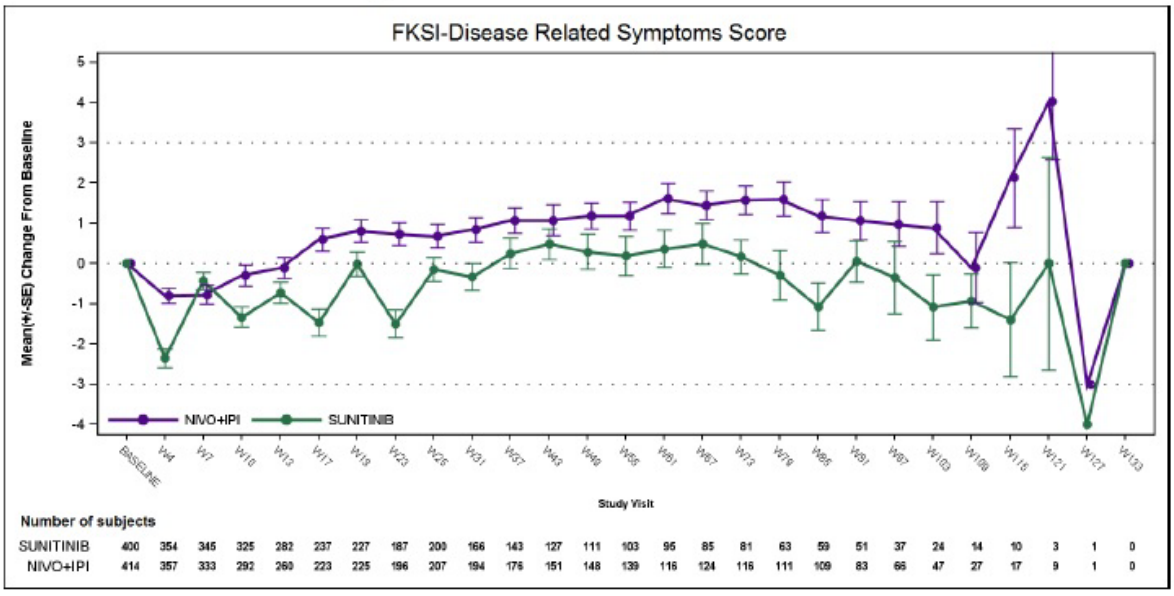


Figure 47 Kaplan-Meier Plot of Change from Baseline in FKSI Disease Related Symptoms Score- Intermediate/Poor Risks – All Randomized Subjects-07-Aug-2017 Database Lock

Time to first deterioration was significantly delayed by nivolumab + ipilimumab for all 3 scales:

FKSI DRS HR=0.66 (95% CI: 0.56–0.78; P < 0.0001); FACT-G total HR=0.63 (95% CI, 0.52–0.75; P < 0.0001); and EQ-5D utility index HR=0.67 (95% CI, 0.57–0.80; P < 0.0001) (Figure 48).

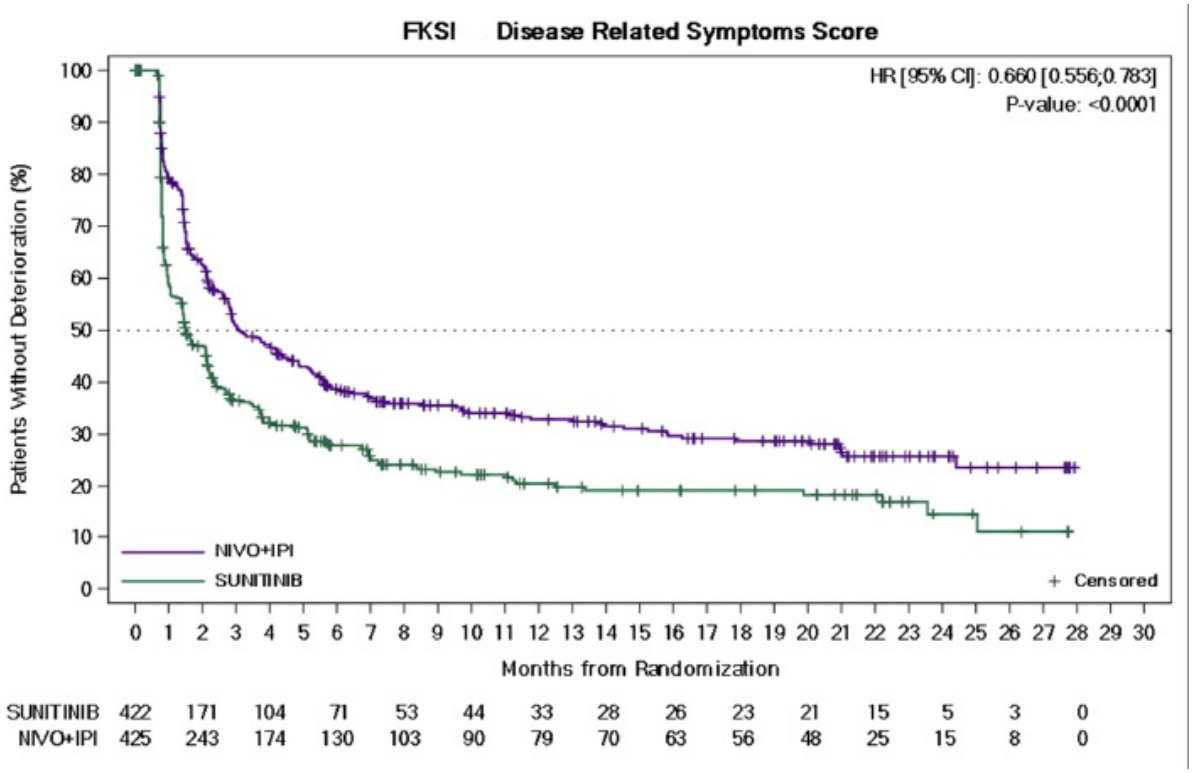


Figure 48 Kaplan-Meier Plot of Time to First Deterioration in FKSI Disease Related Symptoms Score – Intermediate/Poor Risk – All Randomized Subjects – 07-Aug-2017 Database Lock

The applicant acknowledges the concern of the interpretability of data from open label studies; that is, the treatment benefit of experimental therapies may be biased, particularly for subjective outcomes such as HRQoL, when there is a lack of blinding. In this study, blinding was not feasible, since sunitinib was administered orally, and nivolumab + ipilimumab was administered intravenously. However, when coupled with the OS benefit observed, there is increased confidence in the reliability of the PRO assessments despite the open-label nature of the study. Results indicate better tolerability and superior quality of life compared to sunitinib, even in the presence of AEs. The significance of this observation was further supported by feedback from leading investigatorsin RCC.

Overall benefit/risk profile of nivolumab + ipilimumab combination in advanced RCC

The totality of available data support favourable benefit-risk for the combination of nivolumab and ipilimumab compared to sunitinib. The combination of nivolumab and ipilimumab has demonstrated unprecedented efficacy benefit compared to available therapies as evidenced by statistically significant and highly positive OS and ORR benefit (which included a 9.4% CR rate) along with a positive trend in PFS. The safety profile shows that the combination of nivolumab + ipilimumab has distinct toxicities from sunitinib owing to different mechanisms of action, but overall toxicities are less frequent with nivolumab + ipilimumab, the majority occur within the initial few weeks of initiating treatment and are well managed with established treatmentalgorithms which result in resolution in most cases. In contrast, sunitinib toxicity commonly affects skin, GI, and vascular systems, with longer times to resolution and often requiring chronic management as long as sunitinib dosing continues. Approximately 20% of subjects discontinued nivolumab + ipilimumab due to toxicity, but efficacy benefit is still maintained in these patients, with quality of life (PRO) improvements from baseline over time and, importantly, significant delay in time to deterioration relative to sunitinib across all instruments.

The unprecedented OS benefit observed, together with the manageable and well-tolerated safety profile relative to sunitinib, is therefore considered to outweigh the added toxicity of ipilimumab to the combination.

Ground #2: Available data support the additional benefit of the combination relative to nivolumab monotherapy for the treatment of 1L RCC

Available clinical and non-clinical data suggest that the combination of nivolumab and ipilimumab provides greater benefit than nivolumab monotherapy.

- Nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) target distinct immune checkpoint proteins with complementary roles in regulating immune responses.

- At the time of initiation of CA209214, the decision to investigate the combination of nivolumab and ipilimumab was based on the knowledge of the science and data available at the time, with the broader objective of bringing patients an overall survival benefit versus standard of care which had not been demonstrated with any other regimen.

- The activity of nivolumab monotherapy in RCC (1L & 2L) was observed in the Phase 1 studies CA209009 and CA209010.

- The activity of ipilimumab monotherapy in RCC (1L & 2L) was observed in completed trial MDX010-11.

- The incremental activity of the combination of nivolumab and ipilimumab (relative to that observed with nivolumab monotherapy) was observed in CA209004 in advanced melanoma. Given the mechanism of action, a similar incremental benefit was expected in a range of solid tumours susceptible to immunotherapy, including RCC.

- CHMP scientific advice with respect to combination development (in accordance with the EU anticancer guideline) in melanoma was sought in 2012. Additionally, CHMP advice had also been sought earlier for development of nivolumab monotherapy in 2L RCC, where the data from the studies CA209009 and CA209010 were presented to help characterize the patient population for the proposed Phase 3 study.

- CA209016 informed the incremental benefit of the combination in RCC at different dose ratios, with all dose ratios demonstrating incremental benefit (and toxicity) to nivolumab monotherapy, providing evidence of the added benefit of ipilimumab. Comparable outcomes with respect to response were observed with nivolumab 3 mg/kg + ipilimumab 1 mg/kg combination and nivolumab 1 mg/kg + ipilimumab 3 mg/kg and the nivolumab 3 mg/kg and ipilimumab 1 mg/kg combination was selected for Phase 3 based on a better tolerated safety profile.

- Acknowledging the limitations of the available data sources including small sample sizes and patient heterogeneity, based on the biological rationale and knowledge of the science at the time, BMS considered the totality of the available evidence was sufficient to initiate Phase 3 development with the objective of demonstrating a survival benefit.

Table 60 Efficacy of Nivolumab and Ipilimumab as Monotherapy or Combination Therapy in Subjects With RCC

Treatment	Study	ORR (%)	Median PFS (months)
Nivolumab monotherapy	CA209025, (N = 410), 2L	25.1	4.60
	CA209009, Arm 4 (N=24), 1L	12.5	4.79
Ipilimumab monotherapy	MDX010-11, Cohort B (N=12), 1L	25.0	NA
Nivolumab in combination with ipilimumab	CA209016, Arm I-1 (N = 47), 1L/2L	40.4	7.7
	CA209016, Arm I-3 (N = 47), 1L/2L	40.4	9.4

Abbreviations: 1L - first-line; 2L - second-line; NA - not available; ORR - objective response rate; PFS - progression-free survival

Recognising the importance of characterizing the contribution of ipilimumab, in particular to establish the benefit/risk profile of the combination relative to nivolumab monotherapy, BMS proposes to undertake a robust, post-approval clinical study to confirm the magnitude of benefit from the addition of ipilimumab 1 mg/kg to the combination of nivolumab and ipilimumab in 1L RCC. Contemporary data in 1L RCC for PD-1/PD-L1 monotherapies that has recently been published further support the feasibility of this characterisation.

Ground #3: A post-approval clinical study will confirm the contribution of ipilimumab 1 mg/kg to the combination of nivolumab and ipilimumab and labelling proposals will address differential benefit/risk in relevant subgroups (i.e. elderly)

Post-Approval Efficacy Study (PAES) Proposal

In order to address the contribution of ipilimumab at 1 mg/kg to the magnitude of benefit of the combination regimen, BMS proposes a post-approval randomized, double-blind clinical study of nivolumab + ipilimumab versus nivolumab monotherapy + placebo in patients with previously untreated, intermediate/poor risk advanced RCC. A draft study synopsis and draft Statistical Analysis Plan (SAP) is provided by the applicant. The study proposal has been designed in consideration of the feedback received from CHMP during the initial review of the Type II variation (WS1278) as outlined below (Figure 49):

- The study is a double-blind, randomized, controlled study comparing the combination of nivolumab and ipilimumab (as evaluated in CA209214) to nivolumab monotherapy in the same patient population as CA209214.

- The PFS primary endpoint of the study is considered informative in the context of a comparison between 2 cancer immunotherapy regimens and additionally, is expected to provide conclusive evidence of the benefit of the combination relative to nivolumab monotherapy in a reliable and interpretable way within a reasonable timeframe (including sample size determination and timelines for read-out of interim and final results)

- The design of the study factors in feasibility of conduct, including in European subjects, and aims to leverage the enrollment window in Europe following approval, but prior to access.

- In the absence of a clear demonstration of benefit for the combination versus nivolumab monotherapy, the study should enable a robust comparison of nivolumab monotherapy to sunitinib (in CA209214) via a meta-analysis.

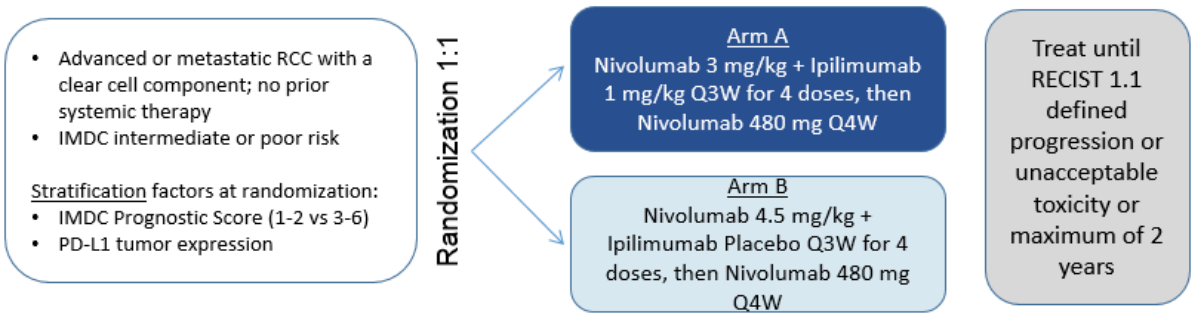


Figure 49 Proposed Draft Study Design of Post-Approval Efficacy Study (PAES)

Dose of nivolumab in Arm B reflects the exposure consistent with approved nivolumab monotherapy dosing in RCC.

The purpose of this study is to establish the benefit/risk of the combination over nivolumab monotherapy in intermediate/poor risk patients in first line metastatic RCC. In the event that superiority of the combination over nivolumab monotherapy is not clearly established by a statistically positive result, the efficacy of nivolumab monotherapy will be compared to sunitinib through a "meta-analysis" of data from this study and CA209214, as described in the draft SAP. This step-wise approach is described in more detail below and illustrated in Figure 50:

Proposed Efficacy Assessment

1) The primary endpoint of PFS will be compared between nivolumab + ipilimumab and nivolumab monotherapy for superiority based on statistical assumptions provided in Section 4.1 of the draft SAP.

2) If the primary endpoint of PFS is not significantly improved, the PFS HR and CI will provide an estimate of the relative difference between the 2 arms. An OS meta-analysis comparing nivolumab to sunitinib will be performed at the time of the primary PFS analysis of nivolumab + ipilimumab and nivolumab monotherapy from the post-approval study.

3) The final OS meta-analysis comparing nivolumab monotherapy to sunitinib will be conducted after a minimum follow-up of approximately 18 months in the post-approval study to match the duration of follow-up at the time of the final analysis of CA209214.

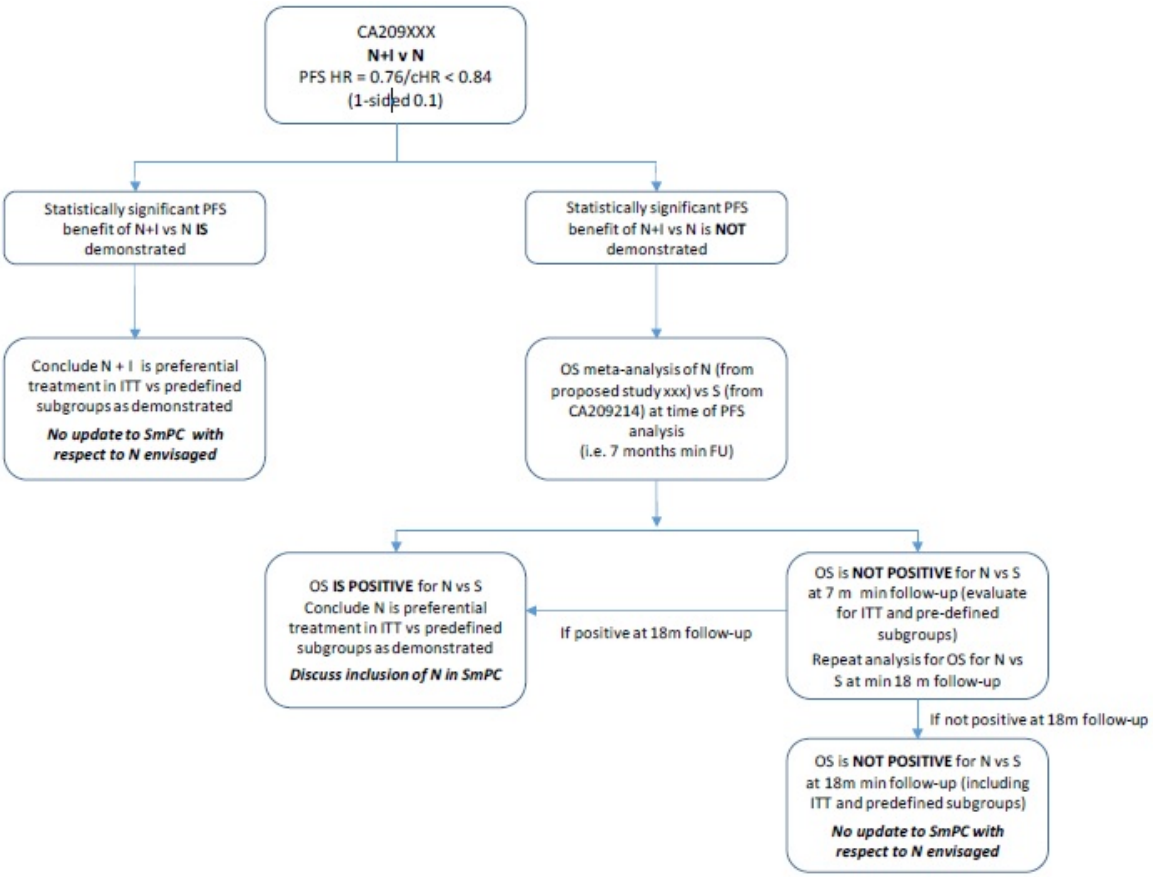


Figure 50 The decision pathway for the step-wise approach to establish the benefit of the combination relative to nivolumab monotherapy

The feasibility of the proposed trial has been confirmed by multiple ongoing investigator-sponsored trials and discussion with several thought leaders.

The MAH commits to working closely with the Rapporteurs and CHMP on next steps including SmPC updates following the availability of the results of the study to ensure appropriate characterization of benefit/risk of the combination and/or nivolumab monotherapy in 1L mRCC.

The proposed study would be initiated by 1Q of 2019 to optimize the enrollment window.

The Study Will Provide a Conclusive Result

The inclusion of the additional stage (meta-analysis of nivolumab versus sunitinib from CA209214) builds in the safeguard of being able to reach a conclusion on the B/R of the combination relative to nivolumab monotherapy conclusively regardless of whether a positive outcome of the primary endpoint is achieved. In the event that the superiority of the combination is not demonstrated over nivolumab monotherapy, it lays out, in a step-wise fashion, a plan to determine if nivolumab monotherapy shows efficacy benefit over sunitinib and, if so, the magnitude of this relative benefit. Planned exploratory analyses based on stratification criteria such as tumour PD-L1 expression and IMDC risk-criteria as well as additional predefined subgroups will attempt to determine if a differential benefit/risk profile is seen in any subgroups.

Choice of Endpoints

In randomized studies, PFS is a generally a reliable measure of antitumor activity that is not confounded by subsequent therapies, and it has historically served as an acceptable regulatory endpoint for approval of new systemic therapies in first-line advanced RCC. Although statistically significant improvement in PFS was not demonstrated in CA209214 or in the Phase 3 study of nivolumab monotherapy in previously treated advanced RCC (CA209025), these studies compared nivolumab + ipilimumab (CA209214) or nivolumab alone (CA209025) to non-immunotherapies (sunitinib and everolimus in CA209214 and CA209025, respectively). PFS as per RECIST v1.1, however, is considered informative in the context of comparison between 2 immunotherapy regimens. In the CA209067 study in melanoma, a clear separation of PFS curves between nivolumab + ipilimumab and nivolumab monotherapy was seen at the time of initial assessment at 3 months, indicating it be an informative endpoint when comparing 2 cancer immunotherapy regimens. In addition to using standard RECIST, evaluation of PFS by irRECIST is also planned as an exploratory analysis. In the event that the combination fails to show PFS superiority over nivolumab monotherapy, the second part of the study will use OS to evaluate the relative benefit of nivolumab monotherapy from the OS results from the proposed study over the sunitinib arm in CA209214. This interim OS analysis would occur at time of primary PFS analysis at approximately 19 months from study start, and final OS analysis would be conducted approximately 12 months later, after a minimum followup of 18 months in the proposed study, when OS is expected to reach full maturity for comparison. ORR, OS, safety, and quality of life will be secondary endpoints. Exploratory analyses of efficacy based on PD-L1 expression, biomarkers, PK and in predefined subgroups will allow evaluation of differential efficacy in subpopulations.

Assumptions for PFS

In the proposed post-approval study of nivolumab + ipilimumab versus nivolumab in first-line advanced RCC, both treatments are immunotherapies which are expected to display a similar delayed effect on PFS, leading to a more valid comparison of this endpoint. Indeed, in the Phase 3 study of nivolumab + ipilimumab or nivolumab versus ipilimumab in first-line advanced melanoma (CA209067), the combination demonstrated PFS benefit compared to nivolumab onotherapy in an exploratory analysis (PFS HR 0.76 [95% CI 0.62, 0.94]). Based on these results, the target PFS HR will be 0.76 for the proposed post-approval study, which is considered clinically meaningful based on results of studies which have supported recent EU approvals in first line RCC. Using a 1-sided alpha of 0.1 and 80% power, the sample size for the proposed post-approval study is 418 subjects (209 per arm). An interim analysis for PFS is planned to be conducted at 75% of events, estimated to occur at approximately 15 months from study start, with the final PFS analysis anticipated to occur at approximately 19 months from study start. Recognising that the study is retrospective and in the post-approval setting, it has been designed/powered to robustly evaluate the benefit/risk of the combination relative to nivolumab monotherapy.

Implementation Plan

Based on the observed accrual rate of ~50 intermediate/poor risk subjects per month observed in CA209214 and recent feedback from RCC investigators in several EU and non-EU countries, an accrual of 35 intermediate/poor risk advanced RCC patients per month is estimated for the postapproval study, anticipated to begin enrollment in 1Q 2019. Given the evolving treatment landscape in first-line advanced RCC, there is currently interest in exploring a PD-1 monotherapy approach in this population. The post-approval study would complete enrollment in approximately 12 months, and the final analysis of PFS would be 19 months after the start of enrollment.

An interim analysis of PFS at 15 months (75% of events) may also be included, with the appropriate alpha spend (Table 61). The meta-analysis of these 2 studies, combining with CA209214, would be used for an indirect treatment comparison of the nivolumab monotherapy arm to the sunitinib arm with the common nivolumab + ipilimumab arm linking the 2 studies.

Given the results of the proposed study and the large treatment effect observed in the CA209214 study, the OS boundary in the meta-analysis is expected to be met, ie superiority of nivolumab over sunitinib would still be demonstrated even if nivolumab + ipilimumab is not shown to be superior to nivolumab in the proposed study. With approximately 209 nivolumab patients compared to 422 sunitinib patients, for a total of 631 patients, an HR<0.81 (nivolumab versus sunitinib) would yield 95% CIs that exclude 1, which is expected due to the large treatment effect of nivolumab + ipilimumab over sunitinib observed in study CA209214. The details of statistical analysis are provided in the study synopsis and draft SAP.

BMS also proposes to seek CHMP scientific advice on the proposed study to ensure that the study can deliver on its objectives. The request for advice is planned to be submitted to ensure that the study can be initiated by 1Q 2019 to optimize the enrolment window (prior to access).

Table 61 Draft Study Endpoints and timelines for Post-Approval Efficacy Study (PAES)

Primary Endpoint	PFS
Power / Alpha	80% / 0.1 (1-sided)
N	418
Target Treatment Effect Δ	HR = 0.76 Target difference in PFS 11.6 vs 8.8 mo
Minimal Statistically Sig Δ	0.84
Accrual rate Accrual duration	35 (post-approval) 12 months
IA for PFS	75% of events (~15 mo) cHR = 0.79
Final PFS read-out	19 mo

SmPC Updates

In the absence of comprehensive clinical data demonstrating the contribution of ipilimumab, the applicant proposes to include a statement in Section 4.4 of the SmPC indicating that the benefit of the combination relative to nivolumab monotherapy in 1L RCC has not been evaluated. The statement is as follows:

"The benefit of the combination of nivolumab and ipilimumab relative to nivolumab monotherapy in the first-line treatment of advanced RCC patients has not been evaluated."

Pending confirmation of the benefit of the combination relative to nivolumab monotherapy and the potential for increased risk (relative to nivolumab monotherapy), efficacy and safety analyses were undertaken to identify any patient population where there is a potential differential benefit/risk for the combination of nivolumab and ipilimumab relative to sunitinib. While benefit of the combination relative to sunitinib was consistently demonstrated across subgroups, BMS are receptive to addressing the outstanding uncertainties through the SmPC and RMP as appropriate.

5.2. Scientific Advisory Group-Oncology consultation

Following a request from the MAH at the time of the re-examination of the CHMP opinion concerning the use of Opidvo/Yervoy for the first-line treatment of renal cell carcinoma (RCC), the CHMP has convened a Scientific Advisory Group (SAG) to discuss the following issues.

1. The experts are invited to provide their views on the CHMP grounds for refusal, taking into account the company's response:

- **There is no basis to establish or to quantify any benefits conferred by 1 mg/kg ipilimumab as used in combination with 3 mg/kg nivolumab in the first-line treatment of intermediate/poor-risk advanced renal cell carcinoma patients, and specifically whether ipilimumab contributes to the efficacy of the combination therapy to an extent that outweighs the substantial additional toxicity. Therefore, the safety and efficacy of the combination cannot be considered properly or sufficiently demonstrated and a comprehensive assessment of the benefits and risks associated with the combination and its components cannot be completed in this case. The benefit-risk balance of the combination treatment with nivolumab and ipilimumab in this setting must thus currently be regarded as unsubstantiated.**

The SAG disagreed with the grounds for refusal noting that the benefit-risk balance for the combination is clearly positive based on a convincing and clinically important improvement in overall survival compared to sunitinib, based on a robust clinical trial and supportive evidence, despite the fact that quantification of the individual contributions in the combination cannot be quantified precisely.

The safety and efficacy of the combination, considered as a whole, is clearly established according to robust evidence and meeting stringent scientific and clinical standards. The benefit-risk balance of the combination has been convincingly substantiated to the extent that it is already included in current clinical guidelines. The possibility that ipilimumab may add more harms than benefits, although considered unlikely, cannot change the overall benefit-risk of the combination, which is clearly favourable.

Given the available evidence, it would be very difficult for physicians and patients to understand how lack of a precise quantification of the effect of the individual elements of a combination could result in an overall negative risk-benefit of a combination that has shown a clinically important increase in overall survival with acceptable toxicity compared to a n adequate control. Such an assessment would deprive patients in a high unmet medical need of a clear opportunity in terms of improving overall survival, with a potential for long-term survival associated with some immunotherapies.

Questions concerning the suboptimal dosing or the potential unnecessary toxicity associated with one element of the combination might be explored in further optimisation studies if considered worthwhile. However, it may be more important to try to identify patients more likely to respond to this particular combination, also given that a number of other treatments and combinations are currently being developed and there will be a need to identify factors to inform clinical decisions.

Concerning patient reported outcomes which were analysed as secondary endpoints using different scales, small differences were observed in the mean score of the FACT-G favouring nivolumab + ipilimumab compared to sunitinib. Although no strong claims can be made on the basis of secondary analyses, the results do not raise any issues about excessive toxicity at end of treatment. From a patient perspective, these results are encouraging. Taken together with the outstanding results in terms of overall survival that have not been observed for other treatments options so far, there is a clear preference for the combination compared to sunitinib.

Concerns about "setting precedents" about methodological principles advocating a fully factorial design were considered unjustified on the basis of the large benefit observed in terms of overall survival that has not been observed with other treatment options, and the convincing scientific rationale and supportive evidence for the combination (see answer to question No. 2). In any case, any arguable deviation from general methodological principles would be considered justified on grounds of improving the outcome for RCC patients. Deviations from general principles and guidelines are justified in situations where dramatic activity is observed in situations with high unmet medical need. Concerns about subsequent therapies and lack of "cross-over" were considered unfounded because the objectives of the trial were to increase overall survival and the design of the study was appropriate to assess this objective.

One expert disagreed, considering that one should be cautious in extrapolating from melanoma to renal cancer because a different response to ant-PD-1 therapies was observed (different slopes of the overall survival curves; lack of a "plateau" in long-term survival in RCC as opposed to melanoma). Furthermore, given the lack of systematic "cross-over" after progression in the pivotal trial (only about 20% of patients assigned to sunitinib received subsequent treatment with nivolumab), the benefit in terms of overall survival may have been over-estimated. Thus, a fully factorial design should thus have been necessary to establish the additive role of the combination. Such trial should be conducted prior to marketing authorisation and the delay in access would not expose patients to unacceptable loss of opportunity given the availability of the kinase inhibitor cabozantinib that was associated with an improvement in progression-free survival compared to sunitinib (albeit based on less comprehensive clinical evidence, i.e., a randomised phase II trial and no significant difference in overall survival, which, however, was not the primary end-point of this trial). The next best option would be to make it mandatory to complete a comparative analysis of ipilimumab/nivolumab versus anti-PD-1 monotherapy within a meaningful time frame, e.g. 2 years post-approval, and to revise the indication accordingly (see also answer to question No. 3).

In addition to providing their views on the CHMP grounds for refusal, the experts are invited to provide input on the following questions.

2. Please discuss the strength of available data for the additive effect of ipilimumab at 1 mg/kg to the efficacy of the combination of nivolumab + ipilimumab in the treatment of 1L RCC.

The trial was not designed to assess the additive effect of ipilimumab or nivolumab to the combination. Thus, robust clinical evidence to assess the individual contribution is lacking. However, concerning ipilimumab at the studied dose, there is evidence of (admittedly low) activity as single-agent in RCC. Also, relevant activity of the combination has been established in melanoma for ipilimumab monotherapy and especially for the combination with nivolumab. With reference to scientific rationale, CTLA-4 being the drug target for ipilimumab and PD-1, being target for nivolumab, these monoclonal antibodies have separate immunological "break functions", indicating the potential value by combining them. The drugs have in addition partly different side-effect profiles. In conclusion, based on mechanistic arguments and extrapolation, there is sufficient evidence to support a role for ipilimumab to the efficacy of the combination.

One SAG expert disagreed, considering that a factorial design should have been necessary and should be conducted prior to marketing authorisation (see answer to question No. 1).

3. Would equipoise remain for randomizing patients to nivolumab alone versus ipilimumab/nivolumab after a marketing authorization for 1L RCC? Does equipoise remain if ipilimumab/nivolumab is not authorized for such use?

This study design implies a hypothesis that similar efficacy might be achieved with less toxicity with nivolumab alone compared to the combination of ipilimumab plus nivolumab. The SAG debated this hypothesis and considered that it was unlikely given the supportive evidence for the added activity of ipilimumab in the combination (other trials with drugs with a similar mechanism of action to nivolumab are exploring the efficacy in monotherapy). Also, because of the widely recognised important effect and magnitude on overall survival of the combination with acceptable toxicity, the goal of minimising toxicity at the possible expense of efficacy is unlikely to be of high priority given the urgent need for further improvement of long-term outcome of RCC patients. Nevertheless, in oncology it is not uncommon to deconstruct or de-escalate established regimens seeking to optimise treatment. Thus, depending on individual judgments on the strength of evidence and need to minimise toxicity, some clinicians and patients might find that equipoise would hold.

It may be more important to try to identify patients more likely to respond to this combination to guide treatment decisions. Even more important will be to determine the relative efficacy of different combinations or monotherapies in first-line treatment of metastatic RCC and sequencing of different options as they become available. Given the number of agents and combinations being developed the task will be challenging. There is an opportunity for academic trials to address some of these questions.

According to one expert, this was indeed a relevant hypothesis and the trial should be conducted before marketing authorisation. Clinical evidence for single-agent anti-PD-1 therapy in 1st line RCC has been observed for pembrolizumab (also an anti-PD-1 agent) in a large exploratory study showing similar activity in terms of ORR with greatly reduced toxicity if indirectly compared to the combination of ipilimumab and nivolumab in RCC (ASCO 2018).

5.3. Discussion and overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group, including clinical experts and patients.

The CHMP considered that based on general methodological principles, in order to establish the efficacy and safety of each product in this combination, an appropriate phase III design would have been a randomised three-arm study of nivolumab+ipilimumab v. nivolumab v. reference treatment.

However, despite the fact that such study has not been submitted by the applicant, the efficacy of nivolumab in the combination can be considered established on the basis of the overall clinical results and monotherapy data. Concerning ipilimumab, although conclusive clinical trials investigating its activity as monotherapy at the proposed dose in RCC are lacking, the inference of the contribution to efficacy can be considered sufficiently established based on a cogent biological and pharmacological rationale, as well as relevant non-clinical and clinical data such as the activity shown in a B16 tumour mouse model in melanoma, evidence of single-agent activity in melanoma, the established contribution of ipilimumab to the combination with nivolumab in melanoma, and the consideration that these effects are relevant for RCC on the basis of the mechanism of action.

Therefore, based on the totality of evidence the CHMP concluded that,

- The benefits of the combination treatment were considered to outweigh the risks, including the uncertainties regarding the precise contribution of ipilimumab at the studied dose, as the combination is associated with clinically important improvement in overall survival compared to sunitinib, with a manageable toxicity profile that is not worse than that of the comparator. The comparator is considered adequate and there are no treatment options that offer similar advantages without additional uncertainty in the target population.

- The inference of the contribution of ipilimumab to the benefits of the combination regimen is sufficiently established on the basis of the complementary mechanisms of action of the two agents in the combination, the activity shown in a B16 tumour mouse model in melanoma, evidence of single-agent activity in melanoma, the established contribution of ipilimumab to the combination with nivolumab in melanoma, and the consideration that these effects are relevant for RCC on the basis of the mechanism of action.

- Further studies will be conducted to address remaining uncertainties and provide a more precise understanding about the contribution of ipilimumab to the combination.

Taken together, the CHMP considered that there was sufficient evidence that efficacy and safety of nivolumab 3 mg/kg and ipilimumab 1 mg/kg have been established and that the remaining uncertainties can be accepted as they are outweighed by the large survival benefit observed for the combination compared to the current standard. Therefore, the safety, efficacy, and a positive balance of benefits and risks of the combination and its components are considered sufficiently established.

5.4. Risk Management Plan

The WSA submitted updated RMP version (revised proposed Risk Management Plan, OPDIVO RMP version 13.2 and YERVOY RMP version 23.1) with this application (re-examination).

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

The PRAC considered that the risk management plan version 13.3 for Opdivo and 23.2 for Yervoy are acceptable.

Safety concerns

Table 62 Summary of the safety concerns - Opdivo

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
	Cardiac Arrhythmias
	Complications of allogeneic HSCT following nivolumab therapy in cHL
	Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Pediatric patients <18 years of age
	Elderly patients with: cHL ≥ 65 years of age SCCHN ≥ 75 years of age
	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab
	Use in patients who have undergone influenza vaccination
	Patients with brain metastases: Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases NSCLC – active brain metastases RCC – any history of or concurrent brain metastases

Table 63 Summary of the safety concerns - Yervoy

Important identified risks	GI irARs (eg, diarrhoea, colitis, GI perforation)
	Hepatic irARs (eg, hepatitis)
	Skin irARs (eg, rash, pruritus, TEN, and DRESS)
	Neurologic irARs (eg, neuropathy)
	Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)
	Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)
	Severe infusion reactions
Important potential risks	Immunogenicity
	Severe skin drug reactions from concurrent or sequential (in any

Important identified risks	GI irARs (eg, diarrhoea, colitis, GI perforation)
	Hepatic irARs (eg, hepatitis)
	Skin irARs (eg, rash, pruritus, TEN, and DRESS)
	Neurologic irARs (eg, neuropathy)
	Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)
	Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)
	Severe infusion reactions
	order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors
Missing information	Reproductive and lactation data
	Long-term safety in adolescent patients > 12 years of age
	Data in ethnic groups
	Potential PD interaction with systemic immunosuppressants
	Patients with severe hepatic impairment
	Patients with severe renal impairment
	Patients with autoimmune disease
	Long-term safety

Pharmacovigilance plan

Table 64 Ongoing and Planned Additional Pharmacovigilance Activities **– Opdivo**

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
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

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
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	With PSUR starting at DLP 03-Jul-2017
			2. Interim CSR submission	06/2019
			3. Final CSR submission	4Q2022

Table 65 Ongoing and Planned Additional Pharmacovigilance Activities **– Yervoy**

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 3 - Required additional pharmacovigilance activities				
CA184143 - A Multi-National, Prospective, Observational Study in Patients with Unresectable or Metastatic Melanoma / Ongoing	1) to estimate the incidence and severity of adverse reactions in adult patients treated with ipilimumab in the post approval setting 2) to describe the management of adverse reactions (eg, diarrhoea, colitis, hepatitis, elevated liver enzymes, hypopituitarism, hypothyroidism, rash, neurologic syndromes) and their outcomes in ipilimumab-treated patients in the post-approval setting 3) to describe patterns of care for adult patients receiving any therapy for unresectable or metastatic melanoma (dosing, regimen, indication, treatment rationales, management of treatment-related AEs, reasons for treatment termination, etc.)	Post-marketing safety	Protocol submission Amended protocol submission addressing extended enrollment period and broader inclusion criteria Amended protocol submission addressing broadening of inclusion to all approved melanoma indications Annual interim reports Final study report	10-Aug-2011 13-Aug-2013 19-Nov-2013 21-May-2012 23-May-2013 21-May-2014 20-May 2015 May 2016 May 2017 4Q 2018
MAH to sponsor extension of the Dutch Melanoma Treatment Registry (DMTR) to include paediatric subjects and to collect their safety data	To obtain additional safety information in paediatric patients	Long-term safety in adolescent patients > 12 years of age	Synopsis of the DMTR Registration of paediatric patients in the DMTR register Interim safety reporting Final study report	16-Apr-2018 4Q 2018 PSUR 4Q 2028

Risk minimisation measures

Table 66 Summary of risk minimization measures - Opdivo

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimization measures: Adverse Reaction Management Guide Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Postmarketing myotoxicity questionnaire (Annex 4) 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
Cardiac arrhythmias (previously treated melanoma indication, only)	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: Adverse Reaction Management Guide Patient Alert Card	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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	measures: Adverse Reaction Management Guide Patient Alert Card	
Pediatric patients <18 years of age	Routine risk minimization measures: SmPC Section 4.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Two PIPs have been agreed by the EMA
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Elderly patients with: cHL ≥ 65 years of age SCCHN ≥ 75 years of age	Routine risk minimization measures: SmPC Sections 4.2, 4.8, and 5.1	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
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
Use in patients who have undergone influenza vaccination	Routine risk minimization measures: Confirmation of a causal or potential relationship between the use of nivolumab and the occurrence of influenza vaccination complications will trigger the update of SmPC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with brain metastases: Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases NSCLC – active brain metastases	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
RCC – any history of or concurrent brain metastases		

Table 67 Summary of risk minimization measures - Yervoy

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified Risks Immune-related Adverse Reactions (GI irARs, hepatic irARs, skin irARs, neurological irARs, endocrine irARs, and other irARs)	Routine risk minimisation measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list Additional risk minimisation measures: Healthcare Professional Frequently Asked Question Brochure Patient Information Brochure and Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Postmarketing targeted questionnaires Additional pharmacovigilance activities: Post-marketing epidemiologic prospective cohort study (CA184143)
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 5.1 Immunogenicity Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Severe skin drug reactions from concurrent or sequential (in any order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Reproductive and lactation data	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety in adolescent patients > 12 years of age	Routine risk minimisation measures: SmPC Section 4.2, 4.4, 4.8, and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU. Reporting of long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy (CA209070 and CA209908) and post-approval data on endocrine AEs in observational studies (CA184332 and CA184338). Monitoring of initial AEs and continued follow-up while on therapy and/or 100 days after the last dose by the treating physician. Follow-up information obtained by BMS using specified procedures (telephone interviews or mailing a questionnaire to the treating physician).
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: MAH to sponsor extension of the DMTR to include paediatric subjects and to their collect safety data.
Data in ethnic groups	Routine risk minimisation measures: SmPC Section 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Potential PD interaction with systemic immunosuppressants	Routine risk minimisation measures: SmPC Section 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Long term safety	Routine risk minimisation measures: N/A	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: N/A
	Additional risk minimisation measures: N/A	Additional pharmacovigilance activities: N/A

5.5. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC for Opdivo and Yervoy have been updated. The Annex II and the Package Leaflet have been updated accordingly.

In addition, the Worksharing applicant (WSA) took the opportunity to correct some typos throughout the Yervoy and Opdivo product information.

5.5.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons:

- The readability of the PL (QRD template Version 9.0) of OPDIVO (nivolumab) and Yervoy (ipilimumab), in English, was assessed during the assessment of the initial Marketing Authorisation Application (MAA) according to the methods outlined in the European Commission's guideline
- The new indication that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indications.
- Administration of is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL remain unchanged.
- The general design and layout of the proposed PL have not changed compared to the tested one.

6. Benefit-risk balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The claimed indication for nivolumab + ipilimumab is for the treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (first-line treatment).

6.1.2. Available therapies and unmet medical need

According to ESMO guidelines and NCCN guidelines, sunitinib, bevacizumab plus interferon, and pazopanib are all standard treatment options for favourable and intermediate-risk patients in the first-line treatment of RCC. Currently, the median OS of patients with advanced RCC is estimated to be around 8 months for poor-risk patients, 23 months for intermediate-risk patients and 43 months for favourable-risk patients, indicating the need for improved treatments. The standard treatment option in previously untreated RCC patients is sunitinib for favourable/intermediate-risk patients. For poor-risk patients, the standard treatment option can either be sunitinib or temsirolimus. Also, cabozantinib was recently approved in this setting. The median OS is less than 4 years for treatment-naive patients with the most favourable prognosis, and less than 1 year in patients with poor prognosis, indicating the need for more efficacious therapies. Nivolumab is currently indicated for second-line treatment of RCC, while ipilimumab currently has no approved indication in RCC.

6.1.3. Main clinical studies

The main study was CA209214, a phase 3, randomised, open-label study of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks, vs. sunitinib monotherapy using the approved dose and schedule (50 mg orally once daily for 4 weeks followed by 2 weeks off, every cycle) in adults (≥ 18 years) with previously untreated advanced RCC. All randomised subjects included previously untreated favourable, intermediate and poor-risk advanced RCC patients (according to Metastatic Renal Cell Carcinoma Database Consortium criteria). The primary objective of the study was to determine OS, PFS and ORR in the subset of intermediate/poor-risk patients, as analysis of this subset of patients in the primary analysis would allow for potential meaningful differences in efficacy to be detected earlier than if favourable-risk patients were also included in the primary efficacy analysis.

6.2. Favourable effects

A statistically significant difference in OS was observed in the nivolumab + ipilimumab group compared to the sunitinib group in intermediate/poor-risk subjects (HR: 0.63 [99.8% CI: 0.44, 0.89]; stratified log-rank 2-sided p-value < 0.0001). The median OS was not reached for the nivolumab + ipilimumab group and 25.95 months for the sunitinib group. The OS rates were 89.5% and 86.2% at 6 months, and 80.1% and 72.1% at 12 months in the nivolumab + ipilimumab and the sunitinib groups, respectively. K-M curves separated after approximately 3 months, favouring nivolumab + ipilimumab. Updated OS data confirmed previous data (HR: 0.66 [95% CI: 0.54, 0.81]; p-value < 0.0001).

A numerical difference in PFS was found favouring the nivolumab + ipilimumab group (HR = 0.82, [99.1% CI: 0.64,1.05], p-value: 0.0331). Median PFS was 11.56 months (95% CI: 8.71, 15.51) and 8.38 months in the nivolumab + ipilimumab group and the sunitinib group, respectively. The 12-month PFS rate was 49.6% in the nivolumab + ipilimumab group and 42.6% in the sunitinib group.

The independent radiology review committee (IRRC)-assessed ORR was higher in the nivolumab + ipilimumab group (41.6% [95% CI: 36.9, 46.5]) than in the sunitinib group (26.5% [95% CI: 22.4, 31.0]). The stratified difference in ORR (nivolumab + ipilimumab - sunitinib) was 16.0% (95% CI: 9.8, 22.2), p-value < 0.0001. BOR was CR in 9.4% and 1.2 % of subjects, BOR was PR in 32.2% and 25.4% of subjects and BOR was SD in 31.3% and 44.5% of subjects in the nivolumab + ipilimumab group and in the sunitinib group, respectively. DOR was not reached at the time of database lock in the nivolumab + ipilimumab group and was 18.17 months in the sunitinib group.

Subgroup analyses showed that the unstratified HR for OS for nivolumab + ipilimumab vs. sunitinib was 0.53 (95% CI: 0.40, 0.71) for patients aged <65 years, as compared to HR 0.86 (95% CI: 0.40, 0.71) and 0.97 (95% CI: 0.40, 0.71) for patients aged ≥65 years and patients aged <75–≥75, respectively.

Subgroup analyses showed that the unstratified HR for OS for nivolumab + ipilimumab vs. sunitinib was 0.55 (95% CI: 0.41, 0.73) for patients with Karnofsky performance status (KPS) 90-100 compared to HR 0.86 (95% CI: 0.61, 1.20) for patients with KPS <90.

Subgroup analyses showed that the unstratified HR for OS for nivolumab + ipilimumab vs. sunitinib was 0.45 (95% CI: 0.29, 0.71) for patients with baseline PD-L1-positive status (≥1%) versus HR 0.73 (95% CI: 0.56, 0.96) for patients with baseline PD-L1-negative status (<1%).

6.3. Uncertainties and limitations about favourable effects

The most critical uncertainty in this application remains the contribution of ipilimumab to the efficacy of the combination therapy nivolumab + ipilimumab. However, a positive contribution of ipilimumab is considered supported on the basis of the plausible mechanism of action of the two agents in the combination, evidence of single-agent activity in melanoma, and the established contribution of ipilimumab to nivolumab in melanoma (which is considered relevant in terms of mechanism of action); the more precise contribution of ipilimumab to efficacy of the combination will be further addressed in future studies [Annex II PAES].

Tumour PD-L1 expression (<1% vs. ≥1%) had an effect on OS (HR: 0.73 [95% CI: 0.56, 0.96] vs. HR: 0.45 [95% CI: 0.29, 0.71]), PFS (HR: 1.06 [95% CI: 0.87, 1.36] vs. HR: 0.45 [95% CI: 0.29, 0.71]) and ORR (36.8% vs. 47.1%). However, the methods used to score PD-L1 expression in tumour tissue were suboptimal (e.g. immune cell expression was not taken into account). Updated PD-L1 analyses are required to determine the role of PD-L1 expression in the efficacy of the combination therapy. This will be further evaluated in the PAES [Annex II].

Additional biomarkers for efficacy of nivolumab + ipilimumab are available which may have an impact on the benefit/risk of the combination treatment in subgroups of patients. These biomarkers include tumour mutational burden, tumour infiltrating lymphocytes, gene expression profiling, and single nucleotide polymorphism in immune-related genes. These biomarker analyses were not included in the CSR while these were planned to be analysed by the applicant. The applicant is recommended to provide these additional biomarker data post approval.

6.4. Unfavourable effects

The most frequently reported drug-related AEs in the nivolumab + ipilimumab group were fatigue (36.9%), pruritus (28.2%), diarrhoea (26.5%), and rash (21.6%). In the sunitinib group, the most frequently reported drug-related AEs were diarrhoea (52.0%), fatigue (49.3%), palmar-plantar erythrodysesthesia syndrome (43.2%), hypertension (40.4%), nausea (37.8%), and dysgeusia (33.5%).

Grade 3-4 drug-related AEs were reported in 45.7% of subjects in the nivolumab + ipilimumab group and 62.6% of subjects in the sunitinib group. In the nivolumab + ipilimumab group, the most frequently reported Grade 3-4 drug-related AEs were lipase increased (10.2%), amylase increased (5.7%), alanine aminotransferase (ALT) increased (4.9%), fatigue (4.2%), and diarrhoea (3.8%). In the sunitinib group, the most frequently reported Grade 3-4 drug-related AEs reported were hypertension (15.9%), fatigue (9.2%), palmar-plantar erythrodysesthesia syndrome (9.2%), platelet count decreased (6.7%), lipase increased (6.5%), neutropaenia (6.0%), and diarrhoea (5.2%).

SAEs were reported in 55.8% of subjects in the nivolumab + ipilimumab group and 39.8% of subjects in the sunitinib group.

In patients <65 years of age SEAs occurred with a frequency of 52.4%, while in patients 75-84 years of age the frequency was 65.1%. Fatal AEs occurred in 2.4% of patients <65 years of age, versus 16.3% of patients 75-84 years of age.

The most frequently reported any-grade drug-related select AE categories in the ipilimumab + nivolumab group were skin (48.8%), endocrine (32.5%), and gastrointestinal (28.2%); versus 56.8%, 30.5%, and 52.0%, respectively, in the sunitinib group.

In the sunitinib group, 2 (0.4%) subjects reported late-emergent drug-related AEs, and 1 subject was intermediate/poor-risk. In the nivolumab + ipilimumab group, 20 (3.7%) subjects had late-emergent drug-related AEs. 15 (3.5%) of these subjects were intermediate/poor-risk subjects.

Death as a result of study drug toxicity (as declared by the investigator) occurred in 7 patients (1.3%) in the nivolumab + ipilimumab arm versus 4 patients (0.7%) in the sunitinib arm. Deaths attributed to "other reasons" occurred in 22 patients in the ipilimumab + nivolumab arm, versus 13 patients in the sunitinib arm. This imbalance was driven primairily by a higher frequency of infection-related deaths and cardiovascular event-related deaths in the ipilimumab + nivolumab group.

Drug-related AEs leading to discontinuation were reported in 21.6% of subjects in the nivolumab + ipilimumab group and 11.8% of subjects in the sunitinib group.

6.5. Uncertainties and limitations about unfavourable effects

The pivotal study was an open-label study, potentially affecting safety reporting.

Follow-up was relatively short in relation to establishing the long-term safety of the combination of ipilimumab + nivolumab (see RMP).

6.6. Effects Table

Table 68 Effects Table for OPDIVO + YERVOY vs. SUTENT for the intermediate/poor risk population (data cut-off: 07/AUG/2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
OS	Overall survival	Months	Not reached	25.95	Statistically significant Median OS not evaluable yet.
			HR 0.63 (99.8% CI: 0.44, 0.89), stratified log-rank 2-sided p-value < 0.0001		
OS update (database lock 01-Mar-2018)	Overall survival	Months	Not reached	26.97	Statistically significant Median OS not evaluable yet.
			HR 0.66 (95% CI: 0.54, 0.81), stratified log-rank 2-sided p-value < 0.0001		
PFS	Progression-free survival	Months	11.56	8.38	Not statistically significant

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
	by independent radiology review committee		HR 0.82 (99.1% CI: 0.64 - 1.05), stratified 2-sided p-value = 0.0331)		
ORR	Objective response rate by independent radiology review committee	%	41.6 (95% CI:36.9, 46.5)	26.5 (95% CI:22.4,31.0)	ORR analysed initially on a descriptive basis (CSR – CA209214d) High proportion of CR for the combination (9.4%)
			Stratified difference 16.0% (95% CI: 9.8, 22.2), p-value < 0.0001		
Unfavourable Effects					
Treatment related AEs	Grade 3-4	%	46	63	
Fatigue Grade 3/4	Drug-related AEs	%	4.2	9.2	Open-label study Short follow-up
Diarrhoea Grade 3/4	Drug-related AEs	%	3.8	5.2	
Lipase increased Grade 3/4	Drug-related AEs	%	10.2	6.5	
Nausea Grade 3/4	Drug-related AEs	%	1.5	1.1	
Asthenia Grade 3/4	Drug-related AEs	%	1.5	2.2	
Vomiting Grade 3/4	Drug-related AEs	%	0.7	1.9	
Anaemia Grade 3/4	Drug-related AEs	%	0.4	4.5	
Hypertension Grade 3/4	Drug-related AEs	%	0.7	15.9	

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

In the current pivotal study, nivolumab + ipilimumab showed significantly improved efficacy compared to sunitinib in previously untreated intermediate/poor-risk advanced RCC patients. The observed OS benefit is considered clinically relevant and unprecedented in this therapeutic context.

A difference of more than three months was found for the median PFS of nivolumab+ipilimumab compared to sunitinib. The K-M curves overlapped the first 6-7 months, then separated and favoured nivolumab + ipilimumab. These PFS results further support the observed OS benefit. Also, a convincing difference in ORR was observed favouring nivolumab + ipilimumab, including a high proportion of CR (9.4%).

The combination of ipilimumab with nivolumab has a distinct safety profile, characterised by a high frequency of immune-mediated adverse events, and is in that respect very different from the safety profile of sunitinib. The safety profile of nivolumab + ipilimumab in the current pivotal study is consistent with existing data on the safety profile of the combination in melanoma and the observed safety profile of sunitinib is also in line with available data, which is reassuring and does not suggest bias in safety reporting as a result of the open-label design of the study. When taking into account the

available safety data on ipilimumab + nivolumab in melanoma, no new safety concerns were identified with the combination of nivolumab 3 mg/kg + ipilimumab 1 mg/kg in mRCC.

6.7.2. Balance of benefits and risks

In the performed pivotal study, a clinically highly relevant OS benefit for nivolumab + ipilimumab versus sunitinib was observed in the first-line treatment of intermediate/poor-risk mRCC patients. The toxicity of the combination is considered acceptable and the proportion of patients experiencing grade 3-4 toxicity was lower in the combination group compared to the comparator group.

Despite the fact that an appropriate phase III three-arm study of nivolumab+ipilimumab v. nivolumab v. reference treatment has not been submitted by the applicant, the efficacy of nivolumab in the combination can be established on the basis of the overall clinical results and monotherapy data. Concerning ipilimumab, although conclusive clinical trials investigating its activity as monotherapy at the proposed dose in RCC are lacking, its use in combination with nivolumab can be considered sufficiently established based on, a cogent biological and pharmacological rationale, as well as relevant non-clinical and clinical data such as the activity shown in a B16 tumour mouse model in melanoma, evidence of single-agent activity in melanoma, the established contribution of ipilimumab to the combination with nivolumab in melanoma, and the consideration that these effects are relevant for RCC on the basis of the mechanism of action.

Therefore, based on the totality of evidence the CHMP concluded that,,

- The benefits of the combination treatment were considered to outweigh the risks, including the uncertainties regarding the precise contribution of ipilimumab at the studied dose, as the combination is associated with clinically important improvement in overall survival compared to sunitinib, with a manageable toxicity profile that is not worse than that of the comparator. The comparator is considered adequate and there are no treatment options that offer similar advantages without additional uncertainty in the target population.

- The inference of the contribution of ipilimumab to the benefits of the combination regimen is based on the complementary mechanisms of action of the two agents in the combination, the activity shown in a B16 tumour mouse model in melanoma, evidence of single-agent activity in melanoma, the established contribution of ipilimumab to the combination with nivolumab in melanoma, and the consideration that these effects are plausibly relevant for RCC on the basis of the mechanism of action.

- Further studies will be conducted to address remaining uncertainties and provide a more precise understanding about the contribution of ipilimumab to the combination.

Taken together, the CHMP considered that there was sufficient evidence that efficacy and safety of nivolumab 3 mg/kg and ipilimumab 1 mg/kg have been established and that the remaining uncertainties can be accepted as they are outweighed by the large survival benefit observed for the combination compared to the current standard. Therefore, the safety, efficacy, and a positive balance of benefits and risks of the combination and its components are considered sufficiently established.

6.7.3. Additional considerations on the benefit-risk balance

A major deficiency in the current application is that the precise contribution of ipilimumab (in the studied dose) to the efficacy and safety of the combination therapy has not been demonstrated. Further data investigating more precisely the contribution of ipilimumab to the combination in first line advanced RCC will be submitted post-approval.

The combination of two or more drugs is often an adequate way to achieve or improve efficacy and/or improve safety compared to using single agents. This will often be the way forward to advance therapies in areas of unmet medical need. In this context, the establishment of adequate combinations and doses is crucial, as is outlined in the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5). If information on these aspects is inadequate, there is a clear risk of exposing patients to combinations that have more toxicity compared to the individual components while not being more effective (and potentially even less so).

The CHMP considered that based on general methodological principles, in order to establish the efficacy and safety of each product in this combination, an appropriate phase III design would have been a randomised three-arm study of nivolumab+ipilimumab v. nivolumab v. reference treatment. However, despite the fact that such study has not been submitted by the applicant, the efficacy of nivolumab in the combination can be established on the basis of the overall clinical results and monotherapy data available from the literature. Concerning ipilimumab, although conclusive clinical trials investigating its activity as monotherapy at the proposed dose in RCC are lacking, the contribution to efficacy can be considered sufficiently established based on the overall clinical results, a cogent biological and pharmacological rationale, as well as relevant non-clinical and clinical data such as the activity shown in a B16 tumour mouse model in melanoma, evidence of single-agent activity in melanoma, the established contribution of ipilimumab to the combination with nivolumab in melanoma, and the consideration that these effects are relevant for RCC on the basis of the mechanism of action.

In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH will submit the results of a randomised study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with a appropriate spectrum of PD-L1 expression. The Applicant is also recommended to provide additional biomarker data that could help identify patients more likely to benefit from the combination compared to standard of care.

6.8. Conclusions

The B/R for Opdivo in combination with Yervoy for first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma is positive.

The CHMP considers the following measures necessary to address issues related to efficacy and safety of the combination:

PAES: In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels.

Divergent position is appended to this report.

7. Recommendations following re-examination

Final outcome

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion considers the following variation

acceptable and therefore recommends, by a majority of 24 out of 31 votes, 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, II and IIIB

Extension of indication to include the first-line combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the Opdivo and Yervoy SmPCs are updated. The Annex II, the Package Leaflet and the Risk Management Plan (version 23.2 for Yervoy and version 13.3 for Opdivo) are updated in accordance. In addition, the MAH took the opportunity to correct some typos throughout the Yervoy and Opdivo product information.

Divergent position to the majority recommendation is appended to this report.

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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Opdivo

Description	Due date
1. Post authorisation efficacy study (PAES): The MAH should submit the addendum to the CA209205 Final CSR reporting the OS data and data from the discontinuation schedule in Cohort C.	30th June 2021
2. The MAH should submit the final OS data for study CA209238: A Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma.	4Q2020
3. The value of biomarkers to predict the efficacy of nivolumab and/or nivolumab + ipilimumab combination therapy should be further explored, specifically:	
To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, etc.) as predictive of nivolumab therapy efficacy. This will be provided for the approved indications: NSCLC: studies CA209017, CA209057 and CA209026 RCC: studies CA209025 and CA209009 UC: studies CA209275 and CA209032.	 30th June 2018 30th June 2018 30th June 2018

To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods/ assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab + ipilimumab combination therapy efficacy in the context of melanoma studies CA209038, CA209067, or CA209069. In addition, levels of myeloid-derived suppressor cells in circulation will be explored in study CA209038.	31st March 2019
To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1 (on tumour- and tumour associated immune cells), PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, Tumour mutational burden) as predictive of nivolumab adjuvant therapy efficacy. This will be provided for the approved indications: Adjuvant treatment of melanoma (monotherapy): study CA209238	31st March 2019
To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies (CA209009, CA209038 and CA209064). The MAH should submit full analytical study methods and validation reports for PD-L1 and PD-L2 assays used in the CA209009, CA209038 and CA209064 studies including discussion on performance characteristics (assay limitations and robustness). Comparison of expression of PD-L1 and PD-L2 in these studies with data reported in literature should also be included The MAH should provide an update on plans to potentially further investigate immune-cell PD-L2 expression on available clinical study samples (for CA209009, CA209038 and CA209064).	 31st December 2017 30th June 2018
To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in studies CA209066, CA209057 and CA209025.	30th June 2018
To further investigate, in CA209141, the association between improved clinical outcomes to nivolumab and the presence of: PD-L2 expression High inflamed phenotype.	 30th September 2018 30th September 2018
To further explore in UC patients the early identification of those who do / do not respond to treatment with nivolumab, as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of: Mutational and neoantigen load, PD-L1 expression on tumour- and tumour associated immune cells using validated approaches as feasible.	30th June 2018
Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	30th September 2021

Yervoy

Description	Due date
Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	30th September 2021

8. EPAR changes

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

Scope

Extension of indication to include the first-line combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the Opdivo and Yervoy SmPCs are updated. The Annex II, the Package Leaflet and the Risk Management Plan (version 23.2 for Yervoy and version 13.3 for Opdivo) are updated in accordance. In addition, the MAH took the opportunity to correct some typos throughout the Yervoy and Opdivo product information.

Summary

Please refer to the published assessment report Opdivo-Yervoy H-C-WS-1278: EPAR – Assessment Report – Variation

9. Attachments

1. Product Information (changes highlighted) for Opdivo as adopted by the CHMP on 15 November 2018

2. Product Information (changes highlighted) for Yervoy as adopted by the CHMP on 15 November 2018

3. Divergent position to the majority recommendation for the initial opinion

4. Divergent position to the majority recommendation for the re-examination

APPENDIX

DIVERGENT POSITION DATED 26 JULY 2018

DIVERGENT POSITION DATED 26 JULY 2018

OPDIVO YERVOY EMEA/H/C/WS1278

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the variation to the terms of the marketing authorisation for OPDIVO and YERVOY.

The reason for divergent opinion was the following:

The B/R in the applied indication is considered positive as a clinically relevant overall survival gain has been demonstrated.

CHMP Member expressing a divergent position:

Kristina Dunder
Jan Mueller-Berghaus

APPENDIX

DIVERGENT POSITION DATED 15 NOVEMBER 2018

DIVERGENT POSITION DATED 15 NOVEMBER 2018

OPDIVO YERVOY EMEA/H/C/WS1278

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the approval of the variation to the terms of the marketing authorisation for OPDIVO and YERVOY.

The reason for divergent opinion was the following:

The combination of drugs can improve efficacy compared to single agents. However, data should be available to describe the contribution of the individual components, justifying their combination, to avoid exposing patients to combinations that have more toxicity compared to the individual components while not necessarily being more effective.

There is no basis to establish or to quantify any benefits conferred by 1 mg/kg ipilimumab as used in combination with 3 mg/kg nivolumab in the first-line treatment of intermediate/poor-risk advanced renal cell carcinoma patients, and specifically whether ipilimumab contributes to the efficacy of the combination therapy to an extent that outweighs the additional toxicity compared to nivolumab monotherapy. Therefore, a comprehensive assessment of the benefits and risks associated with the combination and its components cannot be completed in this case.

The benefit-risk balance of the combination treatment with nivolumab and ipilimumab in this setting must thus be regarded as unsubstantiated.

CHMP Member expressing a divergent position:

Alexandre Moreau
Bruno Sepodes
Concepcion Prieto Yerro
Constantinos Markopoulos
Johann Lodewijk Hillege
Robert Jammes Hemmings
Sol Ruiz
Svein Rune Anderson