25 January 2016
EMA/216066/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0008

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AE-DC/D	adverse event leading to discontinuation or death
BLA	Biologics License Application
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CSR	clinical study report
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DOP1	Division of Oncology Products 1
DOR	duration of response
DRS	disease related symptoms
ECL	electrochemiluminescence
eCTD	Electronic Common Technical Document
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOP1	End of Phase 1
E-R	exposure-response
ESMO	European Society for Medical Oncology/
EU	European Union
FDA	Food and Drug Administration
FKSI	Functional Assessment of Cancer Therapy-Kidney Symptom Index;
GCP	Good Clinical Practice
GI	gastrointestinal
HIFα	hypoxia inducible factor alfa
HLGT	higer level group term
HR	hazard ratio
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNα	interferon alfa
IHC	immunohistochemistry
IL-2	interleukin 2
IMAE	immune-mediated adverse event
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous(ly)
IVRS	interactive voice response system
K-M	Kaplan-Meier

Abbreviation	Definition
KPS	Karnofsky Performance Score/Status
LDH	lactate dehydrogenase
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
NSQ	non-squamous
OHOP	Office of Hematology and Oncology Products
OOPD	Office of Orphan Products Development
ORR	objective response rate
OS	overall survival
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PPK	population pharmacokinetic(s)
PR	partial response
PSM	pre-submission meeting
Q2W	every two weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of world
RR	risk ratio
SAE	serious adverse event
SAWP	Scientific Advice Working Party
sBLA	supplemental Biologics License Application
SCS	Summary of Clinical Safety
SCE	Summary of Clinical Efficacy
SD	stable disease
SI	International System of Units
smPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	system organ class
SQ	squamous
TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
TTR	time to response
US	United States
VEGF	vascular endothelial growth factor
VEGFr	VEGF-receptor

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 13 October 2015 an application for a variation.

The following variation was requested:

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

Extension of Indication to add treatment as monotherapy of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults, based on Study CA209025; a phase 3 study of nivolumab vs. everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy, and the CA209010 addendum study report; phase 2 dose-ranging study of nivolumab in subjects with progressive advanced/metastatic clear-cell RCC who have received prior anti-angiogenic therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are proposed to be updated and the Package Leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet. An updated RMP version 4.0 was provided as part of the application.

The variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and Risk Management Plan.

Information on paediatric requirements

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

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on January 2012. The Scientific Advice pertained to the clinical development programme.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Pieter de Graeff

Timetable	Actual dates
Start of procedure	31 October 2015
CHMP Rapporteur Assessment Report	04 January 2016
CHMP Co-Rapporteur Assessment Report	23 December 2015
PRAC Rapporteur Assessment Report	04 January 2016
PRAC members comments	06 January 2016
Updated PRAC Rapporteur Assessment Report	07 January 2016
PRAC Outcome	14 January 2016
CHMP members comments	19 January 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 January 2016
Request for Supplementary Information	28 January 2016
Submission of responses	31 January 2016
CHMP Rapporteurs Joint response Assessment Report	11 February 2016
Comments from CHMP	16 February 2016
Updated CHMP Rapporteurs Joint response Assessment Report	17 February 2016
Opinion	25 February 2016

2. Scientific discussion

2.1. Introduction

Opdivo (nivolumab) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the PD-1 receptor and blocks its interaction with PD-1 ligand (PD-L1) and PD-1 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. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Opdivo was granted EU approval through an accelerated assessment procedure on 19-Jun-2015 for the treatment, as monotherapy, of advanced (unresectable or metastatic) melanoma in adult. In parallel, nivolumab was granted EU approval on 20-Jul-2015, under the brand name of Nivolumab BMS, for the treatment of locally advanced or metastatic SQ NSCLC after prior chemotherapy in adults. On 28 October 2015, the indication in treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults was added to Opdivo MA and Nivolumab BMS MA was subsequently withdrawn.

Problem statement

Kidney cancer accounts for approximately 2%-5% of all cancers worldwide[1,2,3]. Rates of kidney cancer are highest in Europe, North America, and Australia and lowest in India, Japan, Africa, and China[4,5].

The incidence of RCC varies widely among European countries, with the highest incidence rates reported for the Czech Republic, with up to 15.3 cases per 100,000 among males[4]. Although RCC incidence rates range widely among individual regions, the incidence rate for men is consistently approximately twice as much as that observed for women across all regions examined[4].

Prognosis of advanced RCC is poor. Approximately 30% of patients with RCC have metastatic disease at the time of diagnosis. For patients initially diagnosed with locally advanced RCC, 40% ultimately develop metastatic disease. . There are several distinct histological subtypes of RCC, including clear cell (reported in approximately 80% of patients), papillary, chromophobe, translocation, and collecting duct tumors.

1. Siegel R, Naishadalam D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 63: 1-30. Doi: 10.3322/caac.21166. Epub 22013 Jan 21117
2. Cho E, Adami HO, Lindblad P. Epidemiology of renal cell cancer. Hematol Oncol Clin North Am 25; 651-665. Doi:610.1016/j.hoc.2011.1004.1002
3. Lipworth L, Tarone RE, McLaughlin JK. The epidemiology of renal cell carcinoma. J Urol 2006; 176:2353-2358.
4. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 22 October 2013)
5. Curado MP, Edward B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P, editors. IARC Scientific Publications No 160. Lyon: IARC; 2007. Cancer Incidence in Five Continents, Volume IX

Important established risk factors that are commonly associated with the development of RCC include smoking and obesity. Patients with a history of smoking were reported to have an increased risk for RCC compared to those with a never-smoker history (RR=1.38; 95% CI: 1.27 1.50), with a dose-dependent increase in risk associated with the number of cigarettes smoked per day. Excess body weight has also been associated with increased risk for RCC, with a 5 kg/m2 increase in BMI resulting in an RR of 1.24 (P < 0.0001) in men and 1.34 (P < 0.0001) in women.

The scientific literature has shown that HIFα signalling is involved in the pathogenesis of clear-cell RCC. The PI3K/Akt/mTOR signalling has been identified as an important target pathway because constitutive activation of the upstream signalling pathway leads to HIFα upregulation and activation. Constitutive HIFα activation has been demonstrated to lead to the upregulation and activation of several proteins including VEGF, which is involved in tumor proliferation and neovasculature formation. Until 2005, the cytokines IL-2 and IFNα were the only active treatment for advanced RCC. Since 2005, targeted agents have been approved for the treatment of RCC that will specifically act at the level of VEGF and mTOR signalling pathways. Agents that target angiogenesis include VEGFr TKI (eg, sorafenib, sunitinib, pazopanib, and axitinib) and VEGF binding monoclonal antibodies (eg, bevacizumab), while agents that target the mTOR pathway include the mTOR inhibitors (eg, everolimus and temsirolimus).

Everolimus and axitinib are considered the two standard therapies for use after first-line TKI therapy in advanced RCC by ESMO clinical practice guidelines. In addition, everolimus and axitinib are the only two targeted therapies with a category 1 recommendation in the NCCN guidelines for use in advanced RCC after first-line TKI therapy.

The MAH applied for an extension of indication to add treatment as monotherapy of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults, based on Study CA209025; a phase 3 study of nivolumab vs. everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy, and the CA209010 addendum study report; phase 2 dose-ranging study of nivolumab in subjects with progressive advanced/metastatic clear-cell RCC who have received prior anti-angiogenic therapy.
The proposed and recommended indication for nivolumab for RCC is as follows:

OPDIVO as monotherapy is indicated for the treatment of patients with advanced renal cell carcinoma after prior therapy in adults.
The recommended dose and schedule of nivolumab monotherapy for RCC is the same as the approved dose of 3 mg/kg IV infusion over 60 minutes Q2W for melanoma and SQ NSCLC.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), nivolumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment

2.2.2. Conclusion on the non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), an ERA justifying the lack of ERA studies is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study Number	Primary Objective	Study Design	Randomization Dosage, Route, and Duration of Treatment	No. of Treated Subjects (No. of Nivolumab-treated subjects)[a]	Subject Population	Study Status
Monotherapy for RCC						
CA209003[12,13]	To characterize the safety and tolerability and determine the MTD	Phase 1, multidose, dose-escalation study	nivolumab 0.1, 0.3, 1, 3, or 10 mg/kg Q2W and 0.1 and 0.3 mg/kg Q2W	306 (306) 34 RCC: 18 (1 mg/kg) 16 (10 mg/kg)	Subjects with metastatic NSCLC, CRC, melanoma, RCC (clear cell), or mCRPC	Completed analysis of primary endpoints, OS follow-up ongoing
CA209009	Pharmacodynamic activity	Phase 1b, open-label, parallel-group (4-arm), randomized (Arms 1-3 only) study	Arms 1-3: nivolumab 0.3, 2, or 10 mg/kg Q3W Arm 4: nivolumab 10 mg/kg Q3W	91 (91)	Subjects with metastatic clear-cell RCC: Arms 1-3: prior treatment with anti-angiogenic therapy Arm 4: no prior systemic treatment	Ongoing
CA209010[10,11]	Dose-response relationship of nivolumab as measured by PFS	Phase 2, randomized, blinded, dose-ranging study	nivolumab 0.3, 2, or 10 mg/kg Q3W	167 (167) 59 (0.3 mg/kg) 54 (2 mg/kg) 54 (10 mg/kg)	Subjects with advanced clear-cell RCC who have received prior anti-angiogenic therapy	Completed
CA209025[9]	OS	Phase 3 randomized, open-label study	nivolumab 3 mg/kg Q2W or everolimus 10 mg continuous daily PO	821 (411)	Subjects with advanced clear-cell RCC who have received prior anti-angiogenic therapy	Ongoing
CA209016	Safety and tolerability	Phase 1 open-label, parallel-group, dose-escalation study	nivolumab + TKI: 2 or 5 mg/kg nivolumab Q3W in a 42 day treatment cycle; 50 mg sunitinib PO on Days 1-28; 800 mg pazopanib PO on Days 1-42. nivolumab + ipilimumab (Q2W for 4 doses): 3 mg/kg + 1 mg/kg; 1 mg/kg + 3 mg/kg; and 3 mg/kg + 3 mg/kg, respectively, followed by nivolumab Q2W.	117 (117)	Subjects with metastatic RCC	Ongoing
CA209214	PFS and OS	Phase 3, randomized, open-label study	Nivolumab 3mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W or sunitinib 50 mg daily PO for 4 weeks followed by 2 weeks off, continuously	Enrolling	Subjects with previously untreated, advanced or metastatic RCC	Ongoing

[a] Approximate number of subjects as of the database snapshot or cutoff dates; some randomized open-label study drug assignments are blinded to the Sponsor. Cutoff dates for ongoing studies: 26-Feb-2014 (CA209009); 21-Mar-2014 (CA209016)

Abbreviations: mCRPC: metastatic Castrate Resistant Prostate Cancer; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression free survival; po: orally; Q2W: every 2 weeks; Q3W: every 3 weeks; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor

2.3.2. Pharmacokinetics

Nivolumab's clinical pharmacology profile, including single- and multiple-dose pharmacokinetics (PK), drug-drug interaction potential, QT prolongation potential, and dose selection for phase 2/3 studies was well characterized at the time of the initial marketing authorization.

The nivolumab PPK model was updated to assess the potential effects of tumor type and immunogenicity on nivolumab PK in subjects with advanced RCC. The E-R relationship for efficacy was assessed in subjects with advanced RCC from studies CA209025 (a global, randomized, open-label Phase 3 study of nivolumab monotherapy vs everolimus for advanced or metastatic RCC) and CA209010 (a randomized, blinded, phase 2 dose-ranging study of nivolumab in subjects with progressive advanced/metastatic RCC who have received anti-angiogenic therapy) and the E-R safety relationship was assessed in subjects from Study CA209025. Additionally, an integrated immunogenicity analysis across the solid tumor patient population was performed to assess the incidence and effect of immunogenicity on the pharmacokinetics and safety of nivolumab.

Population PK analyses

The initial PPK analysis was performed using data from three Phase 1 studies (MDX1106-01, MDX1106-03 and ONO-4538-01 [CA209005]), three Phase 2 studies (CA209010, ONO-4538-02, and CA209063) and three Phase 3 studies (CA209017, CA209057, and CA209025), with a total of 1484 subjects included. Studies CA209010 and CA209025 allowed for the assessment of nivolumab PK in subjects with advanced RCC. Bio-analytical methods used for quantifying nivolumab serum concentrations across the development program were cross-validated, thereby allowed merging of the exposure data for PPK analysis.

The PPK model was developed using a previously developed final model and included the effect of tumor type (RCC, NSCLC, or other), immunogenicity, and albumin on CL and VC. The final model was a 2-compartment model with zero-order IV infusion input and first-order elimination with a proportional residual error model. The final PPK model included effects of baseline WT, eGFR, and ECOG on CL and baseline WT, sex, and NSCLC histology (using the combined SQ and NSQ groups) on VC.

Parameter estimates from the final PPK model are provided in table 1.

Table 1: Parameter Estimates of the Final PPK Model

Parameter	Fixed Effects		Interindividual Variability[a] / Residual Variability	
	Estimate	%RSE	Estimate	%RSE
CL: Clearance (L/h)[b]	0.00815	2.47		
CL: Power of BBWT Effect on CL[c]	0.707	6.19		
CL: Power of BGFR Effect on CL[c]	0.180	21.4		
CL: PS ≥ 1 Effect on CL[d]	0.135	17.6		
CL: Power of BALB Effect on CL[c]	-0.854	10.5	0.134	6.06
CL: Effect of ADA=1 (positive) for AIMG=1,2,3 on CL[d]	1.13	4.02		
CL: Effect of ADA=-99 on CL[d]	0.939	1.86		
CL: Effect of Tumor Type=RCC on CL[d]	0.0730	38.5		
CL: Effect of Tumor Type=OTHER on CL[d]	0.184	19.3		
VC: Central Volume (L)[b]	3.98	1.95		
VC: Power of BBWT Effect on VC[c]	0.580	6.05		
VC: Effect of Male Gender on VC[d]	0.129	17.0	0.0929	18.6
VC: Effect of (Squamous and Non-squamous) Cell Type on VC[d]	-0.139	13.6		
Q: Intercompartmental CL (L/h)	0.0296	5.31	NE	NA
VP: Peripheral Volume (L)	3.65	2.18	0.257	9.65
cov(IIV in VC, IIV in CL; r=0.266)[e]	NA	NA	0.0297	14.4
RV: Proportional Error (-)	NE	NA	0.204	2.11
Minimum value of the objective function = 61790.326				

Source: KIWI Run ID 147574

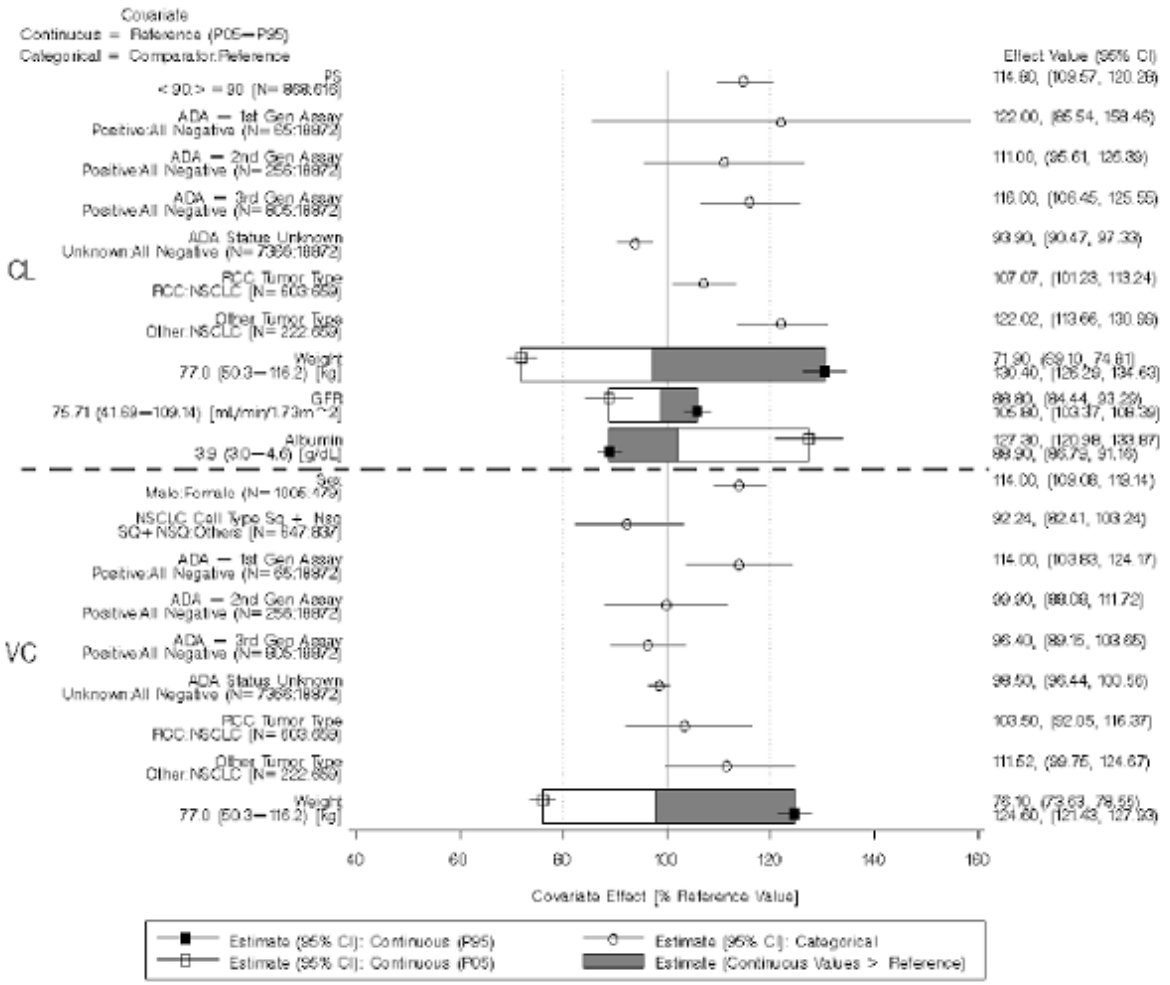
[a] Eta shrinkage: ETA_CL: 9.90%, ETA_VC: 14.4%, ETA_VP: 27.7%; Epsilon shrinkage: 13.9%

[b] CL_{REF} and VC_{REF} are typical values of CL and VC at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a female, weighing 80 kg, eGFR of 80 mL/min/1.73 m^2, serum albumin of 4 gm/dL, cell type/histology of Other (ie, not squamous or non-squamous), performance status of 0, tumor type of NSCLC, and ADA assay negative. The reference values for continuous valued covariates were selected to be approximately the median of the covariate values in the analysis dataset.

[c] The typical value of CL and VC corresponding to continuous valued covariates of subject i are modeled as:

The magnitude of the effect of covariates on CL, accounting for uncertainty, was within the ± 20% boundaries for all covariates, except BW, serum albumin, other tumor type, and immunogenicity.

Figure 1: Covariate effects on PPK model parameters (full PPK model)



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

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

Note 3: Reference subject is female, performance status/ECOG=0, eGFR=80 mL/min/1.73m^2, body weight=80kg, albumin=4 gm/dL, other cell type/histology, NSCLC tumor type, and ADA assay negative. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

A summary of the individual PK parameter estimates obtained from the final PPK model is provided in Table 2. A separate table summarizing the individual measures of exposure for only the subjects enrolled in Study CA209025 (receiving 3 mg/kg Q2W) is provided in Table 3.

Table 2: Summary statistics of individual PK parameters (n=1484)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Clearance (L/h)	0.01 (0.00455)	0.00921 (45.4)	0.00909 (0.00138,0.0438)
Volume of the Central Cmt (L)	4.15 (1.27)	3.95 (30.7)	4.01 (0.141,9.86)
Volume of the Peripheral Cmt (L)	3.92 (1.68)	3.65 (43)	3.68 (0.794,22.7)
Volume of Distribution (L)[a]	8.06 (2.35)	7.76 (29.1)	7.77 (2.49,27.6)
Alpha Half-life (h)	41.7 (10.9)	40.2 (26.3)	40.7 (2.58,103)
Beta Half-life (d)	28.8 (20.7)	26.4 (72)	26.3 (5.72,564)

Source: M:\bms\nivolumab\002522\d1pk\tables\rtf\sumstat-exp.rtf

[a] Volume of Distribution (L) at steady-state = Volume of the Central Cmt (L) + Volume of the Peripheral Cmt (L)

SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; Cmt: compartment

Table 3: Summary statistics of individual measures of nivolumab exposure for subjects enrolled in CA209025 (3mg/kg Q2W) (n=402)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
C_{min1} (mcg/mL)	18.5 (4.73)	17.8 (25.6)	18.2 (5.91, 38)
C_{max1} (mcg/mL)	63 (80.6)	56.4 (128)	54.6 (20.6, 1230)
C_{avg1} (mcg/mL)	27.6 (6.11)	26.9 (22.2)	27.1 (13.2, 47.1)
C_{minss} (mcg/mL)	66.5 (26)	61 (39.1)	64.6 (9.25, 169)
C_{maxss} (mcg/mL)	129 (84.3)	121 (65.2)	121 (48.5, 1270)
C_{avgss} (mcg/mL)	84.4 (27.8)	79.6 (33)	83.6 (20.8, 196)

Source: M:\bms\nivolumab\002522\d1pk\tables\rtf\s25-sumstat-exp

SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; Conc: concentration

Pharmacokinetic interaction studies

No further pharmacokinetic interaction studies have been submitted for this application.

Pharmacokinetics using human biomaterials

No further pharmacokinetics studies using human biomaterials have been submitted for this application.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Justification of Recommended Nivolumab Dose

The recommended dose for nivolumab monotherapy is 3 mg/kg every 2 weeks which has been investigated across melanoma, NSCLC, and RCC indications.

Immunogenicity of Nivolumab

Immunogenicity Analysis

During the clinical development of nivolumab, three assays were used to detect the presence of nivolumab ADA. The primary study in this submission, Study CA209025, and all of the studies included in the integrated summary of immunogenicity used assay ICDIM 140 V1.00/V2.02 for immunogenicity analysis.

Immunogenicity Results from Study CA209025

A summary of the ADA assessments for nivolumab subjects on Study CA209025 who had evaluable ADA data at baseline and on treatment is presented in the table below.

Table 4: Summary of anti drug antibody assessments in study CA209025, based on 16-week definition for persistent positive-all nivolumab treated subjects with baseline and at least one post-baseline assessment.

	Number of Subjects (%)
	Nivolumab N = 371
BASELINE ADA POSITIVE	10 (2.7)
ADA POSITIVE	27 (7.3)
PERSISTENT POSITIVE[a]	1 (0.3)
ONLY AT LAST SAMPLE POSITIVE	7 (1.9)
OTHER POSITIVE	19 (5.1)
NEUTRALIZING ADA POSITIVE	0
ADA NEGATIVE	344 (92.7)

Source: Table 8.7.10 of the CA209025 CSR

[a] See the narrative for Subject CA209025-31-317 in Appendix 7.4A of the CSR

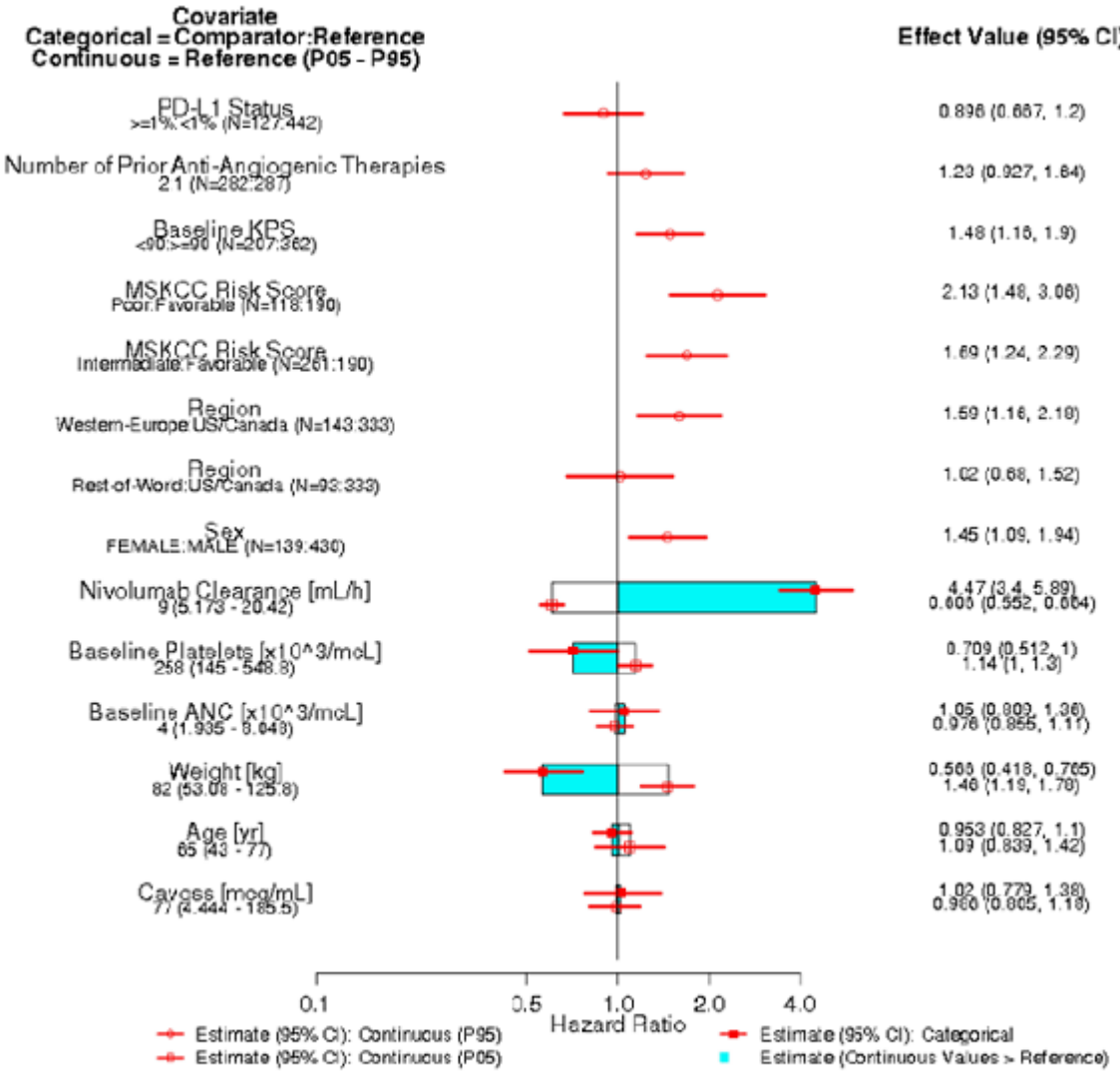
There were 27 (7.3%) subjects who were ADA positive, of which 1 (0.3%) subject was considered persistent positive and no subjects were neutralizing ADA positive. The highest titer value observed in ADA positive subjects was 256, which occurred in only one subject. This subject had only one ADA positive sample observed at 2 weeks after initiation of nivolumab dosing and no other ADA positive samples (Other category). All other ADA positive subjects had titer values less than 16.

A total of 26 nivolumab treated subjects experienced hypersensitivity/infusion reaction category events and all were ADA negative. Thus, the presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions. Overall, it does not appear that immunogenicity had an effect on the safety of nivolumab in Study CA209025. A pooled analysis of nivolumab ADA assessments with data available from several BMS-sponsored studies in which ADA was assessed by a sensitive and drug tolerant assay showed similar results.

2.3.4. PK/PD modelling

The exposure-response relationship was characterized for nivolumab exposure (Cavgss) and OS using 596 previously treated subjects with advanced RCC from studies CA209025 and CA209010, who had exposure data available. The relationship between the nivolumab exposure and OS was characterized using a CPH model that incorporated the effects of covariates that may modulate the E-R relationship. The estimated effects of all of the predictor variables (Cavgss, CL, and covariates) on the hazard ratio of OS in the full model are presented in figure 2. Nivolumab Cavgss was not a significant predictor of hazard of death (95% CI of effect included 1) in the full model after accounting for nivolumab CL.

Figure 2: Effect of predictors on OS (full model) for RCC (studies CA209025 and CA209010)



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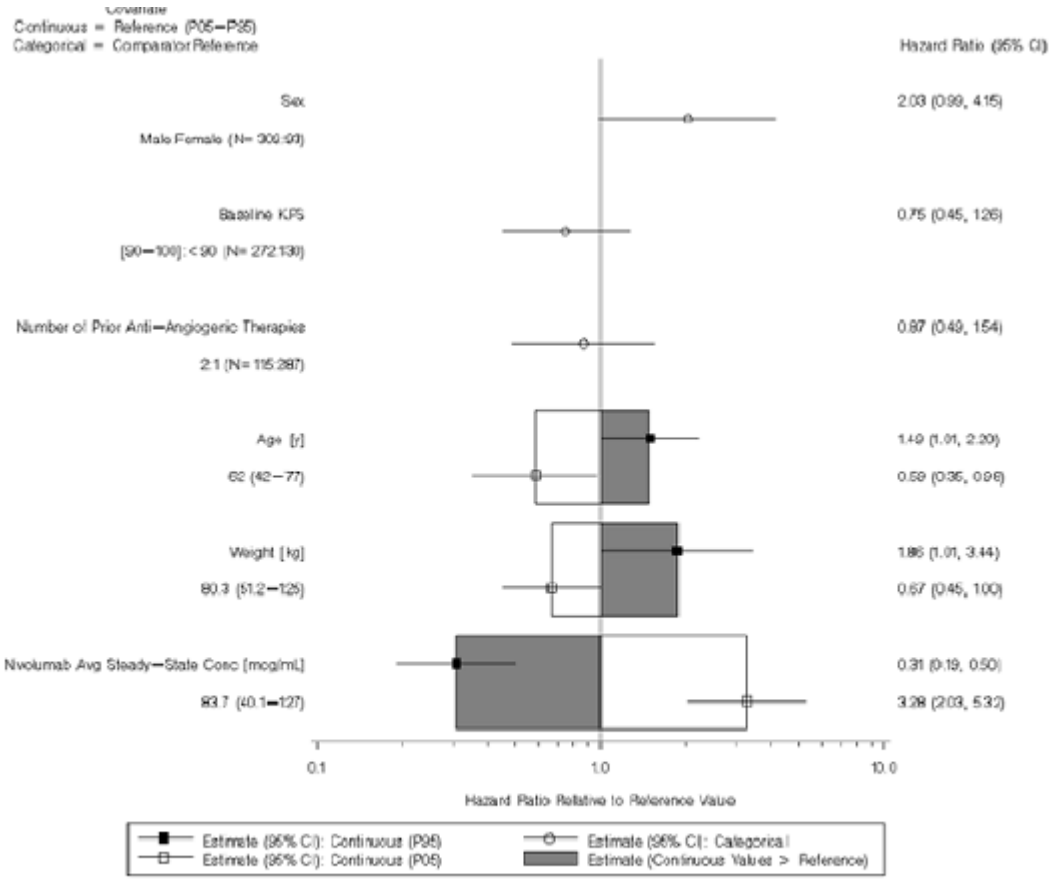
Exposure-Response Analysis for Safety in RCC

The E-R relationship for safety was characterized for nivolumab exposure and AE-DC/D in 402 previously treated subjects with RCC in studies CA209025 and CA209010. The relationship between nivolumab exposure (Cavgss) and time to AE-DC/D was described by a semiparametric CPH model, and included assessments of the modulatory effect of covariates on the E-R relationship. The covariate variables investigated in the E-R analysis of AE-DC/D included age, baseline body weight, sex, number of prior anti-angiogenic therapies, and baseline performance status (Karnofsky scale).

Figure 3 presents the estimated effects of all of the predictor variables on the hazard of AEDC/ D in the Full Model.

Figure 3: Estimated covariate effects of E-R (AE-DC/D) full model for RCC



Source: M:\bms\nivolumab\002522\d1pkpd-saf\graphs\pnghi\rpt-s-forest-saf-ae-full.png

2.3.5. Discussion on clinical pharmacology

The PPK analysis included in this submission has shown that nivolumab volume of distribution was similar across tumor types (data not shown).

Overall, immunogenicity was not considered clinically meaningful based on low ADA titers, low persistent positive rates, low incidence of neutralizing antibodies, and minimal impact on nivolumab clearance, with no evidence of altered safety profile and no evidence of loss of activity with neutralizing antibodies.

The results of the analysis demonstrated that Cavgss was not a significant predictor of hazard of death after accounting for nivolumab CL.

The risk of AE-DC/D, appeared to increase with decreasing Cavgss, but this may be due to confounding with variables not included in the analysis.

2.3.6. Conclusions on clinical pharmacology

Pharmacology data are overall in line with previous observed data in NSCLC and melanoma patients. No relevant differences have been observed.

2.4. Clinical efficacy

2.4.1. Dose response study

CA209010 was a randomised, double-blind, 3-arm dose-ranging, Phase 2 study of nivolumab (0.3, 2, or 10 mg/kg) in adult (aged ≥18 years) subjects with advanced RCC with a clear-cell component who had received prior treatment with at least 1 anti-angiogenic therapy in the advanced setting. Subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups (0.3, 2, or 10 mg/kg) and received nivolumab as an IV infusion over 60 minutes Q3 wks.

CA209010 was designed to investigate the dose-response relationship in the nivolumab treatment groups. The primary objective of this study was to evaluate the dose-response relationship in the 0.3, 2, and 10 mg/kg nivolumab groups as measured by PFS. Secondary objectives included the estimation of PFS, ORR, OS, and the rate of adverse events (AEs) in each nivolumab treatment group.

Subjects were evaluated for response according to the RECIST v1.1 criteria every 6 weeks (± 1 week) for the first 12 months from randomisation and then every 12 weeks (± 1 week) until progressive disease (PD) was documented.

The data reported was based on a cutoff date of 15-May-2013. The database lock point for this final analysis occurred on 02-Jul-2013. At the time of this final CSR, the analysis of PFS was completed and evaluation of OS was ongoing. The median number of doses subjects received during the treatment period was 6.0, 7.5, and 8.0 in the 0.3, 2, and 10 mg/kg treatment groups, respectively. A CSR addendum (database lock 12-Mar-2015) was completed to update the results of PFS, DOR, OS, and safety.

Results

Of the 168 randomized subjects, 167 were treated with nivolumab (59, 54, and 54 subjects in the 0.3, 2, and 10 mg/kg groups, respectively). One subject randomized to the 0.3 mg/kg group was not treated because the subject no longer met study criteria.

- Median age was 61.0 years, with 6.5% aged 75 years or older. Most subjects were white (93.5%) and male (72.0%).
- 33.0%, 42.0%, and 25.0% of randomized subjects in the favorable, intermediate, and poor-risk MSKCC prognostic categories, respectively (IVRS source).
- The median duration of time from initial diagnosis to randomization was 4 years.
- The most common tumor sites reported were visceral/lung (74% overall) and lymph nodes (58% overall).
- Most subjects had a baseline KPS of 80 to 100 (87.5%).
- Most subjects had a quantifiable PD-L1 expression at baseline (88.1%)

PFS (primary endpoint)

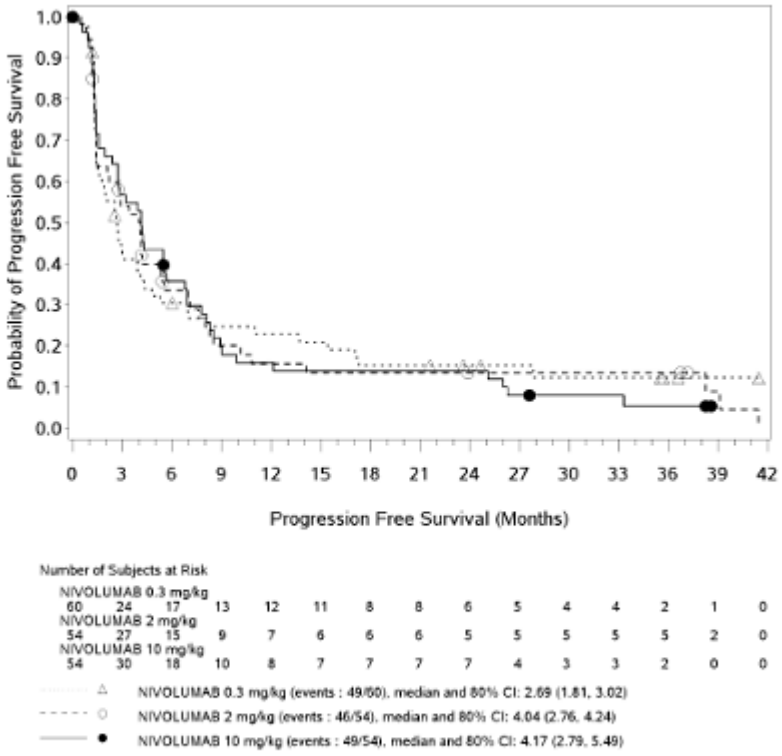
In the CA209010 Addendum, the PFS was similar across treatment groups (Table 5 and Figure 4) and consistent with results reported in the CA209010 Final CSR. Median PFS was reached for each treatment group (2.7, 4.0, and 4.2 months in the 0.3, 2, and 10 mg/kg treatment groups, respectively). In the CA209010 Final CSR, a stratified log-rank trend test indicated no dose relationship for PFS and was confirmed by estimated HRs with 80% CI including 1. The estimated HRs for the addendum likewise indicated no difference in PFS between treatment groups.

Table 5: Comparison of PFS between nivolumab treatment groups – all randomized subjects in CA209010 addendum

	NIVOLUMAB 0.3 mg/kg N = 60	NIVOLUMAB 2 mg/kg N = 54	NIVOLUMAB 10 mg/kg N = 54
NUMBER OF EVENTS (%)	49 (81.7)	46 (85.2)	49 (90.7)
MEDIAN PFS (80% CI) (MONTHS)	2.69 (1.81 - 3.02)	4.04 (2.76 - 4.24)	4.17 (2.79 - 5.49)
6-MONTH PFS RATE (80% CI)	0.304 (0.228 - 0.383)	0.334 (0.250 - 0.420)	0.357 (0.273 - 0.441)
HAZARD RATIO (a) (80% CI)			
2 MG/KG VS. 0.3 MG/KG		0.98 (0.74 - 1.29)	
10 MG/KG VS. 0.3 MG/KG		1.05 (0.80 - 1.37)	
10 MG/KG VS. 2 MG/KG		1.07 (0.80 - 1.42)	

(a) Stratified Cox proportional hazard model.
Source: refer to Table S.5.1 of CA209010 CSR Addendum

Figure 4: Kaplan-Meier plot of PFS – all randomized subjects in CA209010 addendum



Symbols represent censored observations.
Source: Refer to Figure S.5.6 of the CA209010 CSR Addendum

OS (secondary endpoint)

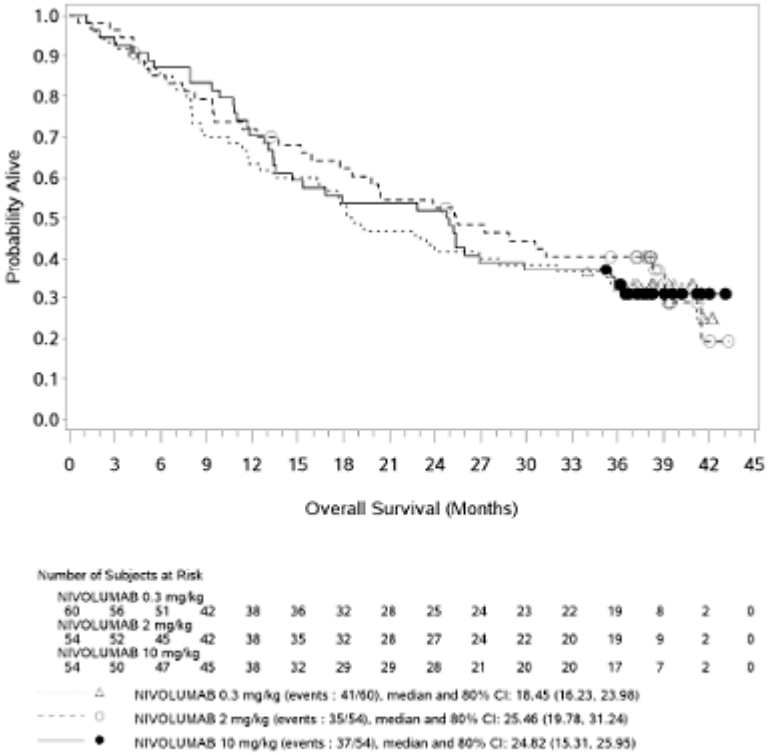
As of the cut-off date, median OS was reached for all three treatment groups in CA209010 (18.5, 25.5, and 24.8 months for the 0.3, 2, and 10 mg/kg treatment groups, respectively). Estimated HRs indicated no statistically significant difference in OS between treatment groups. Updated OS (estimated using K-M methodology) for each treatment group was plotted along with the median and its 80% CI. At the time of the data cut-off, 113 (67%) of 168 randomized subjects had died. The K-M estimations of OS are shown in Table 6 and Figure 5.

Table 6: Overall survival – all randomized subjects in CA209010 addendum

	NIVOLUMAB 0.3 mg/kg N = 60	NIVOLUMAB 2 mg/kg N = 54	NIVOLUMAB 10 mg/kg N = 54
# EVENTS / # SUBJECTS (%)	41/60 (68.3)	35/54 (64.8)	37/54 (68.5)
MEDIAN OS (MONTHS) (80% CI) (a)	18.45 (16.23 - 23.98)	25.46 (19.78 - 31.24)	24.82 (15.31 - 25.95)
12-MONTH OS RATE (80% CI)	0.633 (0.548 - 0.707)	0.718 (0.630 - 0.789)	0.704 (0.616 - 0.775)
18-MONTH OS RATE (80% CI)	0.533 (0.447 - 0.612)	0.622 (0.530 - 0.701)	0.537 (0.446 - 0.619)
24-MONTH OS RATE (80% CI)	0.417 (0.335 - 0.497)	0.525 (0.433 - 0.609)	0.519 (0.428 - 0.601)
30-MONTH OS RATE (80% CI)	0.383 (0.303 - 0.463)	0.444 (0.354 - 0.530)	0.370 (0.287 - 0.454)
36-MONTH OS RATE (80% CI)	0.332 (0.255 - 0.410)	0.404 (0.315 - 0.490)	0.331 (0.251 - 0.414)
HAZARD RATIO (b) (80% CI)			
2 MG/KG VS. 0.3 MG/KG		0.76 (0.56 - 1.02)	
10 MG/KG VS. 0.3 MG/KG		0.89 (0.66 - 1.20)	
10 MG/KG VS. 2 MG/KG		1.18 (0.86 - 1.62)	

(a) Base on Kaplan-Meier Estimates.
(b) Stratified Cox proportional hazard model.
Source: Refer to Table S.5.3 in CA209010 CSR Addendum

Figure 5: Kaplan-Meier plot of overall survival – all randomized subjects in CA209010 addendum



Symbols represent censored observations.
Source: Refer to Figure S.5.1 in CA209010 CSR Addendum

ORR (secondary endpoint)

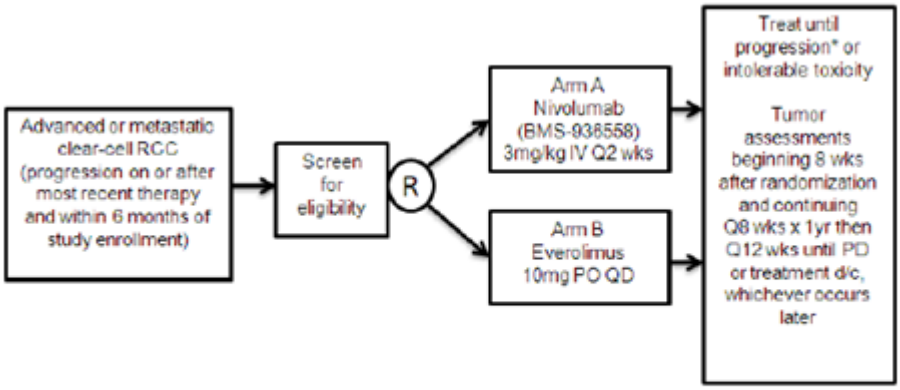
CR or PR was achieved in 12 out of 60 subjects, 12 out of 54 subjects, and 11 out of 54 subjects in the 0.3, 2, and 10 mg/kg groups, respectively. Time to response ranged from approximately 1.2 to 10 months across treatment groups. The median DOR was achieved in the 2 and 10 mg/kg groups (21.6 and 22.3 months, respectively).

2.4.2. Main study

Study CA209025: a randomized, open-label, phase 3 study of nivolumab versus everolimus in subjects with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy

This was an open-label, randomized, global Phase 3 study of nivolumab monotherapy (3 mg/kg administered by 60 minute intravenous [IV] infusion Q2W) vs everolimus (10 mg orally [po] daily) in subjects with advanced RCC with a clear-cell component who have received one or two prior anti-angiogenic therapy regimens in the advanced setting.

Figure 6: CA209025 study design schema



*Treatment beyond initial investigator-assessed, RECIST 1.1-defined progression was considered in subjects experiencing investigator-assessed clinical benefit and tolerating study drug. Such subjects must discontinue therapy when further progression was documented.

Methods

Study participants

Key Inclusion Criteria

The study enrolled adults, who signed an ICF and met the following key target disease and other criteria:

- Histological confirmation of RCC with a clear cell component
- Advanced or metastatic RCC
- Measurable disease as defined by RECIST v.1.1 criteria
- Must have received at least one but not more than 2 prior anti-angiogenic therapy regimens in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics was also allowed
- Must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting, and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment
- Karnofsky Performance Score (KPS) ≥70%
- Tumor tissue (FFPE archival or recent acquisition) must have been received by the central vendor (block or unstained slides) for correlative studies in order to randomize a subject to study treatment.
- Serum creatinine ≤ 1.5xULN OR CrCl ≥40 mL/min (measured or calculated using the Cockcroft-Gault formula)

Main Exclusion Criteria

- Subjects with any history or current CNS metastases.
- Subjects who had prior treatment with an mTOR inhibitor
- Any active known or suspected autoimmune disease.
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug.
- Uncontrolled adrenal insufficiency
- Any known active chronic liver disease
- Prior malignancy active within the previous 3 years except for locally curable cancers that had been apparently cured
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.
- 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
- Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug.
- Minor surgery less than 14 days prior to the first dose of study drug
- Anti-cancer therapy less than 14 days prior to the first dose of study drug (less than 28 days for bevacizumab) or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug
- Presence of any toxicities attributed to prior anti-cancer therapy other than alopecia that have not resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug
- Concurrent use of any medications or substances known to be moderate CYP3A4 or PgP inhibitors or strong CYP3A4 inhibitors or inducers
- Presence of a malabsorption syndrome, gastrointestinal disorder, or gastrointestinal surgery that could affect the absorption of everolimus
- History of severe hypersensitivity reaction to any monoclonal antibody

Treatments

Subjects received one of the following treatments:

- Nivolumab group: nivolumab at 3 mg/kg Q2W by IV infusion.
- Everolimus group: everolimus 10 mg as a daily oral dose.

Method of Assigning Subjects to Treatment

The IVRS randomly assigned subjects in a 1:1 ratio to either nivolumab or everolimus.

Duration

Patients were allowed to continue their assigned treatment (nivolumab or everolimus) beyond progression as long as a clinical benefit was observed or until unacceptable toxicity occurred.

Dose reductions/Interruptions

For nivolumab, no dose escalations or dose reductions were allowed.

For everolimus, dose reductions and escalations were allowed as per the approved product label or as per standard practice in countries where everolimus is not approved for the treatment of advanced RCC.

Dose delays were permitted for nivolumab and everolimus for up to 6 weeks from the last dose. Delays longer than 6 weeks were allowed only in cases where a prolonged steroid taper was required to manage drug-related AEs, or in some cases, if the delay was due to a non-drug related cause. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS Medical Monitor must have been consulted. Subjects were to be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay) were to be based on specific laboratory and AE criteria.

Prohibited and/or Restricted Treatments

The following medications were prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except to treat a drug-related AE).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, or standard or investigational agents for treatment of cancer).
- Live vaccines.
- Strong or moderate CYP3A4 inhibitors and/or PgP inhibitors and strong CYP3A4 inducers were to be avoided by all enrolled subjects. If subjects who received everolimus required moderate CYP3A4 and/or PgP inhibitors or strong CYP3A4 inducers during the course of study drug treatment, dose modifications should have occurred as outlined in the study protocol.

Objectives and endpoints

See Table 7.

Table 7: Study CA209025 Objectives and endpoints

Objective	Endpoint	Endpoint Definition
Primary		
To compare the clinical benefit, as measured by the duration of OS, provided by nivolumab vs everolimus in subjects with advanced RCC who have received prior anti angiogenic therapy	OS	Overall survival (OS) was defined as the time from randomization to the date of death. A subject who had not died was to be censored at last known date alive.
Secondary		
To compare the ORR of nivolumab vs everolimus	Investigator-assessed ORR	Objective response rate (ORR) was defined as the number of subjects with a best response of CR or PR divided by the number of randomized subjects. Best overall response (BOR) was defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST v.1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations were to be contributed to the BOR determination. For subjects who continued treatment beyond progression, the BOR was to be determined based on response designations recorded up to the time of the initial RECIST v.1.1-defined progression.
To compare the duration of PFS of nivolumab vs everolimus	Investigator-assessed PFS	Progression-free survival (PFS) was defined as the time from randomization to the date of the first documented tumor progression as determined by the investigator (per RECIST v.1.1 criteria or clinical) or death due to any cause whichever occurs first. Subjects who died without a reported prior progression were to be considered to have progressed on the date of their death. Subjects who did not progress or die were to be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die were to be censored on the date they were randomized. Subjects who received any subsequent anti-cancer therapy without a prior reported progression were to be censored at the last evaluable tumor assessment prior to or on the date of the initiation of the subsequent anti-cancer therapy.
To assess the duration of objective response of nivolumab vs everolimus	DOR	Duration of objective response (DOR)was defined as the time from first response (CR or PR) to the date of the first documented tumor progression as determined by the investigator using RECIST v.1.1 criteria or death due to any cause, whichever occurred first. For subjects who neither progressed nor died, the duration of objective response was to be censored at the same time they were censored for the primary definition of PFS. This endpoint was only to be evaluated in subjects with objective response of CR or PR.
To evaluate whether PD-L1 is a predictive biomarker for OS	OS, ORR, and PFS, based on PD-L1 status at baseline	PD-L1 expression was defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity in a minimum of 100 evaluable tumor cells using the validated Dako PD-L1 IHC assay.
To assess the overall safety and tolerability of nivolumab vs everolimus	Frequency of deaths, AEs, SAEs, AEs leading to discontinuation and dose delays, select AEs and specific laboratory abnormalities (worst grade) in each treatment group	The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, select AEs, and specific clinical laboratory assessments. Select AE analyses included incidence, time-to-onset, and time-to-resolution. 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 17.1. AEs and laboratory values were graded for severity using the NCI CTCAE Version 4.0.
To assess the disease-related symptom progression rate in each treatment arm based on the FKSI-DRS subscale of the FKSI-15.	Proportion of randomized subjects who had disease-related symptom progression as measured by the	The 9 items of the FKSI-DRS were summarized into a symptom scale ranging in score from 0 to 36, with 0 being the worst possible score and 36 being the best possible score Disease-related symptom progression was defined as a

Sample size

The sample size was calculated in order to compare the OS between subjects randomized to receive nivolumab and subjects randomized to receive everolimus. Approximately 569 events (ie, deaths) with an interim analysis after 398 events (70% of total OS events needed for final analysis) provides 90% power to detect a hazard ratio (HR) of 0.76 with an overall type 1 error of 0.05 (two-sided).

The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab. The stopping boundaries at interim and final analyses were to be derived based on the number of deaths using O'Brien and Fleming α spending function. It was projected that an observed hazard ratio of 0.845 or less, which corresponds to a 2.7 months or greater improvement in median OS (14.8 mo vs 17.5 mo), would result in a statistically significant improvement in OS for nivolumab at the final OS analysis. The final analysis was planned to take place after 569 events (ie, deaths).

Approximately 822 subjects were to be randomized to the two arms in a 1:1 ratio. Assuming a piecewise constant accrual rate (with a maximum rate of 63 subjects/month and an average rate of 41 subjects/month), the accrual was expected to be approximately 20 months. The total duration of the study from start of randomization to final analysis of OS was expected to be 42 months (20 months of accrual + 22 months of follow-up). The table below summarizes the expected timing of each analysis.

Table 8: Schedule of analysis

	Interim Analysis	Final Analysis
Conditions	at least 398 OS events	569 OS events
Expected timing	30 months (20 months of accrual + 10 months of follow-up)	42 months (20 months + 22 months of follow-up)
Nominal significance level	Interim OS projected at 0.0148 level[a]	Final OS analysis projected at 0.0455 level[a]
Lower boundary for statistical significance	Observed hazard ratio of 0.782 (ie 14.8 vs 18.9 mo for median OS)	Observed hazard ratio of 0.845 (ie 14.8 vs 17.5 mo for median OS)

[a] Using O'Brien and Fleming alpha spending function in case exact 398 OS events are observed at the interim OS analysis.

Source: Appendix 1.11A

Randomisation

An IVRS randomly assigned subjects in a 1:1 ratio to either nivolumab or everolimus, and stratified by the following factors: MSKCC risk group (favorable- vs. intermediate- vs poor-risk); number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting (1 vs. 2) and region (US/Canada vs. Western Europe vs Rest of World).

The randomization was carried out via permuted blocks within each stratum.

Blinding (masking)

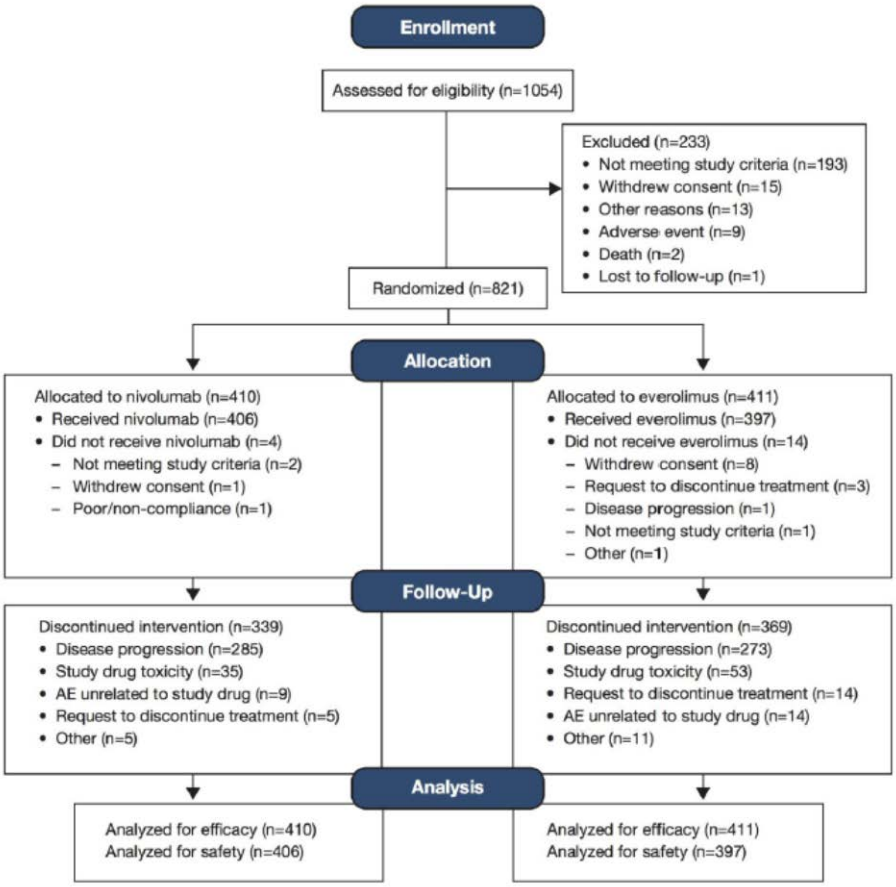
This was an open label study

Statistical methods

Standard statistical methods were used.

Results

Participant flow



Recruitment

The enrolment period lasted approximately 18 months (Oct-2012 to Mar-2014). The last subject was randomized on 11-Mar-2014, and the last patient's last visit date for this CSR occurred on 06-May-2015, providing a minimum follow-up of approximately 14 months.

A total of 146 sites in 24 countries randomized subjects. Of the 821 randomized subjects, 346 (42.1%) were in the US and Canada, 281 (34.2%) were in Western Europe, and 194 (23.6%) were in the 'rest of world'.

Conduct of the study

The original protocol for this study was dated 18-Jun-2012. Eight country-specific amendments and six global amendments were issued for this study.

There were 15 amendments to the protocol. Of them the amendment 12 and 15 were the most relevant. The former changed the order of the secondary objectives, indicating that ORR would be first after testing OS and then PFS. The amendment 15 modified the protocol to allow the crossover from everolimus to nivolumab (nivolumab extension phase) and defined the interim analysis as final analysis.

Relevant protocol deviations were low in frequency (12 subjects [1.5%]) and similar between treatment groups: 7 subjects (1.7%) and 5 subjects (1.2%) in the nivolumab and everolimus groups, respectively. The most common relevant protocol deviation was subjects receiving concurrent anti-cancer therapy while on

study treatment: 8 subjects (1.0%) (3 subjects [0.7%] in the nivolumab group and 5 subjects [1.2%] in the everolimus group).

Baseline data

A total of 821 subjects were randomized (1:1), 410 to nivolumab and 411 to everolimus. Most of the patients received treatment (406 and 397 patients, for nivolumab and everolimus, respectively).

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0- 29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Table 9: Demographic characteristics summary – all randomized subjects

	Nivolumab N = 410	Everolimus N = 411	Total N = 821
AGE (YEARS)			
N	410	411	821
MEAN	60.6	61.9	61.3
MEDIAN	62.0	62.0	62.0
MIN , MAX	23 , 88	18 , 86	18 , 88
STANDARD DEVIATION	10.87	10.43	10.66
AGE CATEGORIZATION (%)			
< 65	257 (62.7)	240 (58.4)	497 (60.5)
>= 65 AND < 75	119 (29.0)	131 (31.9)	250 (30.5)
>= 75	34 (8.3)	40 (9.7)	74 (9.0)
>= 65	153 (37.3)	171 (41.6)	324 (39.5)
GENDER (%)			
MALE	315 (76.8)	304 (74.0)	619 (75.4)
FEMALE	95 (23.2)	107 (26.0)	202 (24.6)
RACE (%)			
WHITE	353 (86.1)	367 (89.3)	720 (87.7)
BLACK OR AFRICAN AMERICAN	1 (0.2)	4 (1.0)	5 (0.6)
ASIAN	42 (10.2)	32 (7.8)	74 (9.0)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.2)	0	1 (0.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (0.2)	1 (0.1)
OTHER	13 (3.2)	7 (1.7)	20 (2.4)

Source: Table S.3.1

The MSKCC and Heng risk group breakdown was as expected for an advanced RCC population:

- 49.2% and 15.1% of subjects were in the intermediate or poor MSKCC risk groups at baseline (IVRS), respectively.
- 58.8% and 21.8% of subjects were in the intermediate or poor Heng risk groups at baseline (CRF), respectively.

Between the 2 treatment groups, the most common site of disease was the lung (67.1%), followed by the lymph node (49.0%), and 'other' (36.2%) sites.

Most randomized subjects had a quantifiable PD-L1 status at pre-study (baseline) (756/821, [92.1%]). Subjects were enrolled regardless of PD-L1 expression level, and PDL1 expression level was not a stratification factor.

Table 10: Baseline disease characteristics and tumor assessment – all randomized subjects

	Nivolumab N = 410	Everolimus N = 411	Total N = 821
PERFORMANCE STATUS (KARNOFSKY) (%)			
100	126 (30.7)	134 (32.6)	260 (31.7)
90	150 (36.6)	130 (31.6)	280 (34.1)
80	110 (26.8)	116 (28.2)	226 (27.5)
70	22 (5.4)	30 (7.3)	52 (6.3)
< 70 (A)	2 (0.5)	1 (0.2)	3 (0.4)
BASELINE MSKCC RISK GROUP (IVRS)			
FAVORABLE	145 (35.4)	148 (36.0)	293 (35.7)
INTERMEDIATE	201 (49.0)	203 (49.4)	404 (49.2)
POOR	64 (15.6)	60 (14.6)	124 (15.1)
HENG RISK GROUP (CRF)			
FAVORABLE	55 (13.4)	70 (17.0)	125 (15.2)
INTERMEDIATE	242 (59.0)	241 (58.6)	483 (58.8)
POOR	96 (23.4)	83 (20.2)	179 (21.8)
NOT REPORTED	17 (4.1)	17 (4.1)	34 (4.1)
SMOKING STATUS			
CURRENT/FORMER	240 (58.5)	207 (50.4)	447 (54.4)
NEVER SMOKED	161 (39.3)	194 (47.2)	355 (43.2)
UNKNOWN	9 (2.2)	10 (2.4)	19 (2.3)
PD-L1 EXPRESSION			
N (B)	370	386	756
MEAN	3.5	3.0	3.2
MEDIAN	0.0	0.0	0.0
MIN , MAX	0 , 90	0 , 80	0 , 90
STANDARD DEVIATION	12.72	10.96	11.85
TIME FROM INITIAL DIAGNOSIS (YEARS)			
N	410	411	821
MEDIAN (MIN - MAX)	2.60 (0.1 - 32.7)	2.59 (0.2 - 31.0)	2.59 (0.1 - 32.7)
TIME FROM INITIAL DIAGNOSIS (%)			
< 1 YEAR	70 (17.1)	77 (18.7)	147 (17.9)
1- < 2 YEARS	99 (24.1)	85 (20.7)	184 (22.4)
2- < 3 YEARS	51 (12.4)	57 (13.9)	108 (13.2)
3- < 4 YEARS	42 (10.2)	34 (8.3)	76 (9.3)
4- < 5 YEARS	22 (5.4)	32 (7.8)	54 (6.6)
>= 5 YEARS	126 (30.7)	126 (30.7)	252 (30.7)
SUBJECTS WITH AT LEAST ONE LESION (B) (%)	409 (99.8)	409 (99.5)	818 (99.6)
SITE OF LESION (C) (D) (%)			
ADRENAL GLAND	59 (14.4)	51 (12.4)	110 (13.4)
ASCITES	2 (0.5)	3 (0.7)	5 (0.6)
BONE	76 (18.5)	70 (17.0)	146 (17.8)
EFFUSION	20 (4.9)	18 (4.4)	38 (4.6)
INTESTINE	7 (1.7)	6 (1.5)	13 (1.6)
KIDNEY	81 (19.8)	89 (21.7)	170 (20.7)
LIVER	100 (24.4)	87 (21.2)	187 (22.8)
LUNG	278 (67.8)	273 (66.4)	551 (67.1)
LYMPH NODE	197 (48.0)	205 (49.9)	402 (49.0)
MEDIASTINUM	22 (5.4)	27 (6.6)	49 (6.0)
OTHER	150 (36.6)	147 (35.8)	297 (36.2)
PERITONEUM	29 (7.1)	40 (9.7)	69 (8.4)
SKIN/SOFT TISSUE	43 (10.5)	60 (14.6)	103 (12.5)
VISCERAL, OTHER	49 (12.0)	58 (14.1)	107 (13.0)
NUMBER OF SITES WITH AT LEAST ONE LESION (D) (%)			
1	68 (16.6)	71 (17.3)	139 (16.9)
2	126 (30.7)	119 (29.0)	245 (29.8)
3	116 (28.3)	105 (25.5)	221 (26.9)
4	65 (15.9)	77 (18.7)	142 (17.3)
>=5	34 (8.3)	37 (9.0)	71 (8.6)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	409 (99.8)	409 (99.5)	818 (99.6)
SITE OF TARGET LESION (C) (%)			
ADRENAL GLAND	51 (12.4)	46 (11.2)	97 (11.8)
INTESTINE	4 (1.0)	4 (1.0)	8 (1.0)
KIDNEY	67 (16.3)	77 (18.7)	144 (17.5)
LIVER	83 (20.2)	71 (17.3)	154 (18.8)
LUNG	214 (52.2)	204 (49.6)	418 (50.9)
LYMPH NODE	147 (35.9)	149 (36.3)	296 (36.1)
MEDIASTINUM	13 (3.2)	20 (4.9)	33 (4.0)
OTHER	108 (26.3)	106 (25.8)	214 (26.1)
PERITONEUM	23 (5.6)	31 (7.5)	54 (6.6)
SKIN/SOFT TISSUE	35 (8.5)	47 (11.4)	82 (10.0)
VISCERAL, OTHER	44 (10.7)	49 (11.9)	93 (11.3)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)			
MEDIAN (MIN - MAX)	76.0 (10 - 426)	73.0 (10 - 504)	75.0 (10 - 504)

(A) Subjects CA209025-43-917 and CA209025-49-828 had KPS >=70% at screening; Subject CA209025-139-198 had KPS < 70% at screening, which was considered a relevant protocol deviation (see Table 4.3-1).
(B) Subjects may have lesions at more than one site.
(C) Includes both target and non-target lesions.
If corrected calcium is missing due to albumin missing, calcium value is used for the corrected calcium.
Source: Table S.3.2 (baseline Karnofsky PS, Heng Risk Group, smoking status, PD-L1 expression), Table S.2.7 (baseline MSKCC per IVRS), Table S.3.3 (time from diagnosis to randomization), and Table S.3.4 (pre-treatment tumor assessment summary)

Medical History

Abnormal physical examination findings were reported at baseline for 42.2% of subjects randomized to nivolumab and 40.6% of subjects randomized to everolimus. The most frequent body system (≥10% of subjects) with abnormal physical exam findings at baseline was skin (14.1%) and musculoskelatal (10.0%) in the nivolumab group and skin (11.7%) in the everolimus group. The most frequent (≥10% of subjects)

pre-treatment events were fatigue (19.3%) and cough (11.0%) in the nivolumab group and fatigue (16.3%) in the everolimus group.

Previous and Subsequent Treatments

The numbers and types of prior cancer therapies (per CRF) were balanced between treatment groups (see table below). The most frequent prior systemic cancer therapies in the metastatic setting (10% of subjects) in the nivolumab and everolimus groups, respectively, were the VEGF receptor tyrosine kinase inhibitors sunitinib (60.0% and 58.9%), pazopanib (29.0% and 31.9%), and axitinib (12.4% and 12.2%).

Table 11: Prior cancer therapy summary – all randomized subjects

	Number (%) of Subjects		
	Nivolumab N = 410	Everolimus N = 411	Total N = 821
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED IN ADVANCED/METASTATIC SETTING (CRF)			
0	0	0	0
1	278 (67.8)	256 (62.3)	534 (65.0)
2	110 (26.8)	139 (33.8)	249 (30.3)
3	21 (5.1)	16 (3.9)	37 (4.5)
> 3	1 (0.2)	0	1 (0.1)
NUMBER OF PRIOR SYSTEMIC REGIMEN WITH ANTI-ANGIOGENIC AGENT RECEIVED			
0	0	0	0
1	317 (77.3)	312 (75.9)	629 (76.6)
2	90 (22.0)	99 (24.1)	189 (23.0)
> 2	3 (0.7)	0	3 (0.4)
PRIOR SYSTEMIC REGIMEN WITH FDA APPROVED VEGF TKI AGENT IN ADVANCED/METASTATIC SETTING			
YES	394 (96.1)	395 (96.1)	789 (96.1)
NO	16 (3.9)	16 (3.9)	32 (3.9)
PRIOR SYSTEMIC REGIMEN WITH CYTOKINE AGENT IN ADVANCED/METASTATIC SETTING			
YES	68 (16.6)	74 (18.0)	142 (17.3)
NO	342 (83.4)	337 (82.0)	679 (82.7)
PRIOR SYSTEMIC REGIMEN IN NEO-ADJUVANT OR ADJUVANT SETTING			
YES	34 (8.3)	27 (6.6)	61 (7.4)
NO	376 (91.7)	384 (93.4)	760 (92.6)
PRIOR SURGERY RELATED TO CANCER			
YES	401 (97.8)	397 (96.6)	798 (97.2)
NO	9 (2.2)	14 (3.4)	23 (2.8)
PRIOR RADIOTHERAPY			
YES	115 (28.0)	115 (28.0)	230 (28.0)
NO	295 (72.0)	296 (72.0)	591 (72.0)

Source: Table S.3.7

Subsequent systemic anti-cancer therapy was received by 67.3% of nivolumab subjects and 69.1% of everolimus subjects (Table 12).

Table 12: Subsequent cancer therapy summary – all randomized subjects

Subsequent Cancer Therapy Summary
All Randomized Subjects

	Number of Subjects (%)	
	Nivolumab N = 410	Everolimus N = 411
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%)	276 (67.3)	284 (69.1)
SUBSEQUENT RADIOTHERAPY (%)		
YES	138 (33.7)	118 (28.7)
NO	272 (66.3)	293 (71.3)
SUBSEQUENT SURGERY (%)		
YES	54 (13.2)	48 (11.7)
NO	356 (86.8)	363 (88.3)
SUBSEQUENT SYSTEMIC THERAPY (%)	227 (55.4)	259 (63.0)
IMMUNOTHERAPY	10 (2.4)	21 (5.1)
ANTI-PD1 AGENTS	1 (0.2)	7 (1.7)
INVESTIGATIONAL IMMUNOTHERAPY	0	1 (0.2)
NIVOLUMAB	1 (0.2)	4 (1.0)
PEMBROLIZUMAB	0	2 (0.5)
ANTI-PDL1 AGENTS	0	1 (0.2)
INVESTIGATIONAL IMMUNOTHERAPY	0	1 (0.2)
ANTI-CTLA4 AGENTS	1 (0.2)	1 (0.2)
IPILIMUMAB	1 (0.2)	1 (0.2)
OTHER IMMUNOTHERAPY	8 (2.0)	14 (3.4)
INTERFERON	1 (0.2)	6 (1.5)
INTERFERON ALFA	0	5 (1.2)
INTERFERON ALFA 2B	1 (0.2)	3 (0.7)
INTERLEUKIN	1 (0.2)	0
INTERLEUKIN 2	2 (0.5)	3 (0.7)
INVESTIGATIONAL IMMUNOTHERAPY	3 (0.7)	1 (0.2)
OTHER APPROVED AGENT	221 (53.9)	250 (60.8)
AXITINIB	99 (24.1)	149 (36.3)
BEVACIZUMAB	13 (3.2)	22 (5.4)
CABOZANTINIB	18 (4.4)	7 (1.7)
CAPECITABINE	1 (0.2)	2 (0.5)
CARFILZOMIB	1 (0.2)	0
DOXORUBICIN	1 (0.2)	1 (0.2)
EVEROLIMUS	105 (25.6)	23 (5.6)
GEMCITABINE	3 (0.7)	5 (1.2)
GIMER/TEGFUR/OTERA	0	1 (0.2)
IXABEPILONE	1 (0.2)	0
LAETRILE	1 (0.2)	0
PAZOPANIB	37 (9.0)	64 (15.6)
RAMUCIRUMAB	0	1 (0.2)
SORAFENIB	26 (6.3)	38 (9.2)
SUNITINIB	28 (6.8)	34 (8.3)
TEMSIROLIMUS	11 (2.7)	13 (3.2)
VORINOSTAT	1 (0.2)	0
OTHER INVESTIGATIONAL AGENT	13 (3.2)	22 (5.4)
INVESTIGATIONAL ANTINEOPLASTIC	13 (3.2)	22 (5.4)

Numbers analysed

The all-randomized population was the primary population used for the primary efficacy analysis and the all-treated population was the primary population for the safety analyses. A description of analysis populations is provided in table 13.

Table 13: Analysis populations

Table 5.2-1: Analysis Populations

Population	Nivolumab Group N	Everolimus Group N	Total N
All enrolled subjects: All subjects who signed an ICF and were registered into the IVRS.	NA	NA	1054
All-randomized population: All subjects who were randomized to any treatment group in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, outcome research and PD-L1expression.	410	411	821
All-treated population: All subjects who received at least one dose of nivolumab or everolimus. This is the primary dataset for analyses for dosing and safety.	406	397	803
Response-evaluable subjects: Randomized subjects whose change in the sum of diameters of target lesions was assessed (ie, target lesion measurements were made at baseline and at least one on-study tumor assessment).	387	363	750
PD-L1 quantifiable subjects: All randomized subjects with quantifiable PD-L1 expression at baseline	370	386	756
Immunogenicity subjects: All nivolumab-treated subjects with baseline and at least one post-baseline assessment for ADA	371	NA	371

Source: Table S.2.4 (enrolled), Table S.2.5 (randomized), Table S.2.6 (treated), Table S.5.14 (response evaluable [CR+PR+SD+PD]), Table S.10.6 (PD-L1 quantifiable), Table S.7.10 (immunogenicity)

Outcomes and estimation

Nivolumab demonstrated superior OS and ORR compared with everolimus. Responses to nivolumab occurred early (median time to objective response: 3.52 months) and were durable.

PFS was not statistically significant, but the available data suggested a benefit with nivolumab vs. everolimus (HR: 0.88 [95%CI: 0.75, 1.03], stratified log-rank test p-value = 0.1135), with separation of the K-M curves after 6 months favouring nivolumab.

Of 803 treated subjects, 179/406 (44.1%) subjects in the nivolumab group and 183/397 (46.1%) subjects in the everolimus group were treated beyond initial RECIST v1.1 progression. Of the 179 subjects in the nivolumab group treated beyond initial RECIST v1.1 progression, 51 experienced non-conventional benefit (ie, durable reductions and/or stabilization in the size of target lesions after initial progression).

Table 14: Summary of key efficacy results – all randomized subjects

Efficacy Parameter	Nivolumab (N = 410)	Everolimus (N = 411)
PRIMARY ENDPOINT		
Overall Survival		
Events, n (%)	183/410 (44.6)	215/411 (52.3)
Stratified log-rank test p-value [a,b]	0.0018	
HR (98.52% CI) [c]	0.73 (0.57, 0.93)	
Median (95% CI), months [d]	25.00 (21.75, NR)	19.55 (17.64, 23.06)
Rate at 6 months (95% CI), % [d]	89.2 (85.7, 91.8)	81.2 (77.0, 84.7)
Rate at 12 months (95% CI), % [d]	76.0 (71.5, 79.9)	66.7 (61.8, 71.0)
SECONDARY ENDPOINTS		
Objective Response Rate per Investigator (CR+PR) [e]		
n (%)	103 (25.1)	22 (5.4)
95% CI [f]	(21.0, 29.6)	(3.4, 8.0)
Odds ratio estimate (95% CI) [g,h]	5.98 (3.68, 9.72)	
p-value [i]	< 0.0001	
Duration of Response		
Ongoing responders, n/N (%)	49/103 (47.6)	10/22 (45.5)
Median (95% CI), months [d]	11.99 (7.85, 23.03)	11.99 (6.44, NR)
Min, Max [j]	0.0, 27.6+	0.0+, 22.2+
Progression-free Survival		
Events, n (%)	318 (77.6)	322 (78.3)
Stratified log-rank test p-value [a]	0.1135	
HR (95% CI) [c]	0.88 (0.75, 1.03)	
Median (95% CI), months [d]	4.60 (3.71, 5.39)	4.44 (3.71, 5.52)
Overall Survival by PD-L1 Expression Level (1% tumor cell membrane expression)		
Subjects with quantifiable PD-L1 expression, n (%)	370/410 (90.2)	386/411 (93.9)
Subjects with ≥ 1% PD-L1 expression, n (%)	94/370 (25.4)	87/386 (22.5)
Unstratified HR (95% CI)	0.79 (0.53, 1.17)	
Median (95% CI), months	21.82 (16.46, 28.06)	18.79 (11.86, 19.91)
Subjects with < 1% PD-L1 expression, n (%)	276/370 (74.6)	299/386 (77.5)
Unstratified HR (95% CI)	0.77 (0.60, 0.97)	
Median (95% CI), months	27.37 (21.39, NR)	21.22 (17.71, 26.22)
Subjects with indeterminate or not evaluable PD-L1 expression, n (%)	40/410 (9.8)	25/411 (6.1)
Unstratified HR (95% CI)	0.56 (0.27, 1.13)	
Median (95% CI), months	25.00 (15.38, NR)	15.84 (6.93, NR)

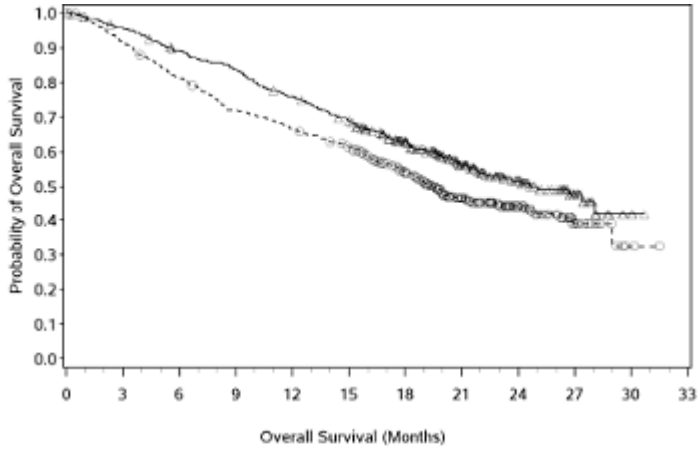
a Log-rank Test stratified by the MSKCC risk group (poor vs. intermediate vs. favorable), the number of prior antiangiogenic therapies in the advanced/metastatic setting (1 vs. 2) and the region (W. Europe, US/Canada vs. Rest of the World) as entered into the IVRS.
b Based on the 398 observed deaths and O'Brian-Fleming alpha spending function, the boundary for statistical significance requires the p-value to be less than 0.0148.
c Stratified Cox proportional hazard model. Hazard ratio is nivolumab over everolimus.
d Based on Kaplan-Meier Estimates.
e The ORR with a confirmatory scan after at least 4 weeks (ie, confirmed ORR) was 88/410 (21.5%) in the nivolumab group and 16/411 (3.9%) in the everolimus group (stratified CMH test p-value: < 0.0001).
f CR+PR, confidence interval based on the Clopper and Pearson method.
g Cochran-Mantel-Haenszel Test stratified by the MSKCC risk group (poor vs intermediate vs favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (1 vs 2) and the region (Western Europe vs US/Canada vs. Rest of the World) as entered into the IVRS.
h Ratio of nivolumab over everolimus.
i Two-sided p-value from CMH Test for the comparison of the odds ratio of nivolumab over everolimus.
j Symbol + indicates a censored value.
Source: Table S.5.1 (OS), Table S.5.2 (OS rate), Table S.5.14 (ORR), Table S.5.14A (confirmed ORR) Table S.5.16 (DOR), Table S.5.11 (PFS), Table S.10.6 (frequencies of PD-L1 expression) Figure S.10.1 (OS by PD-L1 expression level), Figure S.10.7 (OS by PD-L1 expression level HRs).

OS (primary endpoint)

Nivolumab demonstrated 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 in the nivolumab group and 19.55 months in the everolimus group. OS rates were higher in the nivolumab group than the everolimus group at 6 months (89.2% vs 81.2%, respectively) and 12 months (76.0 % vs 66.7%, respectively).

The Kaplan-Meier curves for OS separated early, favouring nivolumab.

Figure 7: Kaplan-Meier overall survival plot – all randomized subjects



Number of Subjects at Risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Nivolumab (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
Everolimus (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)
Nivolumab vs Everolimus - hazard ratio and 98.52% CI: 0.73 (0.57, 0.93); p-value: 0.0018

Symbols represent censored observations.
Hazard ratios are estimated using Cox proportional hazard model with treatment group as a sing le covariate, stratified by MSKCC risk group (poor vs. intermediate vs. favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (1 vs. 2) and the region (W. Europe, US/Canada vs. Rest of the World) as entered into the IVRS.
The boundary for statistical significance requires the p-value to be less than 0.0148.
Source: Figure S.5.1

A total of 227 (55.4%) subjects in the nivolumab group and 196 (47.7%) subjects in the everolimus group were censored. At the time of this database lock point, a higher proportion of subjects in the nivolumab group vs the everolimus group were still on treatment (16.3% vs 6.8%), and a similar proportion were either in follow-up (36.6% vs 36.7%) or off study (2.4% vs 4.1%).

Median follow-up for OS (time between randomization and death or last known date alive) was 18.25 months (range: 0.0 to 30.7 months) in the nivolumab group and 17.22 months (range: 0.0 to 31.5 months) in the everolimus group.

Follow-up for OS was current for the majority of subjects; 96.1% and 93.9% of randomized subjects in the nivolumab and everolimus groups, respectively, either died or had a last known alive date on or after the last patient last visit date for the CSR of 06-May-2015.

Results of 3 sensitivity analyses (unstratified analysis, analysis using stratification factors as determined at baseline [CRF source], and analysis of all treated subjects) were consistent with the primary OS analysis. In a multivariate analysis of OS, the treatment effect when adjusted for time from diagnosis to start of first systemic therapy in metastatic regimen (< 1 year), baseline ANC > ULN, and baseline platelets > ULN, was consistent with the primary OS analysis (HR: 0.73; stratified Cox model p-value = 0.0030). Time from diagnosis to start of first systemic therapy in metastatic regimen, baseline ANC, and baseline platelets were significant prognostic variables for OS.

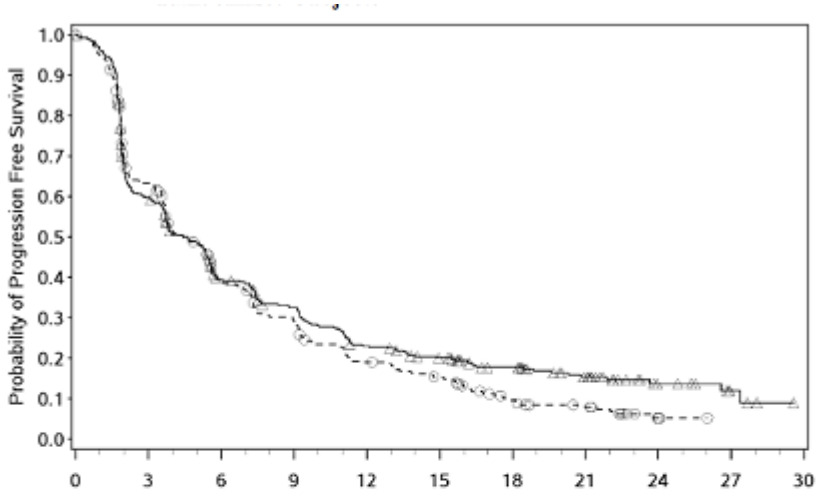
PFS (secondary endpoint)

While not statistically significant, PFS data suggested a benefit with nivolumab vs everolimus (HR: 0.88 [95%CI: 0.75 to 1.03], stratified log-rank test p-value = 0.1135), with separation of the K-M curves after 6 months favouring nivolumab; see Table 14 and Figure 8.

- The median PFS was 4.60 months in the nivolumab group and 4.44 months in the everolimus group.
- The 6-month PFS rate was 39% in both treatment groups and the 12-month PFS rate was 23% in the nivolumab group and 19% in the everolimus group.
- The K-M curves overlapped until approximately 6 months and then separated, favouring nivolumab beyond this time point and more pronounced over time when looking at the tail of the curve (Figure 8).
  - 318 (77.6%) subjects had a PFS event in the nivolumab group (311 progression and 7 deaths) and 322 (78.3%) subjects had a PFS event in the everolimus group (312 progression and 10 deaths);
  - 92 (22.4%) subjects in the nivolumab group and 89 (21.7%) subjects in the everolimus group were censored. Among the randomized subjects censored on the date of last on study tumor assessment (72 [17.6%] nivolumab and 55 [13.4%] everolimus), the most common reason for censoring was 'still on treatment' in the nivolumab group (47 [11.5%] subjects) and 'received subsequent anti-cancer therapy' in the everolimus group (28 [6.8%] subjects).

Results of 3 sensitivity analyses of PFS (analysis using stratification factors as determined at baseline [CRF source], analysis accounting for assessment after subsequent therapy, and analysis accounting for radiographic progression or death) were consistent with the primary PFS analysis.

Figure 8: Kaplan-Meier of progression-free survival per investigator – all randomized subjects



Number of Subjects at Risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0

Nivolumab (events: 318/410), median and 95% CI: 4.60 (3.71, 5.39)
Everolimus (events: 322/411), median and 95% CI: 4.44 (3.71, 5.52)
Nivolumab vs Everolimus - hazard ratio and 95% CI: 0.88 (0.75, 1.03); p-value: 0.1135

Symbols represent censored observations.
Hazard ratios are estimated using Cox proportional hazard model with treatment group as a single covariate, stratified by MSKCC risk group (poor vs. intermediate vs. favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (1 vs. 2) and the region (W. Europe, US/Canada vs. Rest of the World) as entered into the IVRS.
Source: Figure S.5.8

ORR

The investigator-assessed ORR using RECIST v1.1 which was superior in the nivolumab group (103/410, 25.1%) compared with the everolimus group (22/411, 5.4%), with a stratified CMH test p-value of < 0.0001 (Table 15).

- BOR was CR in 4 subjects (1.0%) in the nivolumab group and 2 subjects (0.5%) in the everolimus group
- BOR was PR in 99 (24.1%) subjects in the nivolumab group and 20 (4.9%) subjects in the everolimus group.
- BOR was unable to be determined (UTD) in 23 (5.6%) subjects in the nivolumab group and 47 (11.4%) subjects in the everolimus group (see Table 15 for all reasons for UTD).
  - In both treatment groups, the main reason for BOR UTD was 'death prior to disease assessment.'
  - For the 2 subjects in the everolimus group with 'not reported' as the reason for BOR UTD, the BOR was reported as 'not evaluable', with no specified reason provided.

Reductions in target lesion tumor burden appeared to be deeper in the nivolumab group as compared to the everolimus group.

Table 15: Best objective response per investigator – all randomized subjects

Table 7.3-1: Best Objective Response per Investigator - All Randomized Subjects

	Nivolumab N = 410	Everolimus N = 411
BEST OVERALL RESPONSE (RECIST v1.1):		
COMPLETE RESPONSE (CR)	4 (1.0)	2 (0.5)
PARTIAL RESPONSE (PR)	99 (24.1)	20 (4.9)
STABLE DISEASE (SD)	141 (34.4)	227 (55.2)
PROGRESSIVE DISEASE (PD)	143 (34.9)	114 (27.7)
UNABLE TO DETERMINE (UTD)	23 (5.6)	47 (11.4)
NEVER TREATED	4 (1.0)	14 (3.4)
DEATH PRIOR TO DISEASE ASSESSMENT	9 (2.2)	16 (3.9)
EARLY DISCONTINUATION DUE TO TOXICITY	4 (1.0)	7 (1.7)
OTHER	6 (1.5)	8 (1.9)
NOT REPORTED	0	2 (0.5)
NOT REPORTED	0	1 (0.2)
OBJECTIVE RESPONSE RATE (1)	103/410 (25.1%)	22/411 (5.4%)
(95% CI)	(21.0, 29.6)	(3.4, 8.0)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2)	19.9%	
(95% CI)	(15.1, 24.6)	
CMH ESTIMATE OF COMMON ODDS RATIO (3, 4)	5.98	
(95% CI)	(3.68, 9.72)	
P-VALUE (5)	<0.0001	

(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Estimate of (Nivolumab - Everolimus) is based on Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the MSKCC risk group (poor vs. intermediate vs. favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (1 vs. 2) and the region (W. Europe, US/Canada vs. Rest of the World) as entered into the IVRS.
(3) Cochran-Mantel-Haenszel Test Stratified by the MSKCC risk group (poor vs. intermediate vs. favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (1 vs.2) and the region (W. Europe, US/Canada vs. Rest of the World) as entered into the IVRS.
(4) Ratio of nivolumab over everolimus.
(5) Two-sided p-value from CMH Test for the comparison of the odds ratio of nivolumab over everolimus.
Source: Table S.5.14

The ORR with a confirmatory scan after at least 4 weeks (ie, confirmed ORR) was superior in the nivolumab group (88/410, 21.5%) compared with the everolimus group (16/411, 3.9%), with a stratified CMH test p-value of < 0.0001.

DOR

Median TTR was 3.52 months in the nivolumab group and 3.70 months in the everolimus group (see table below). The majority of responses occurred within the first 4 months (77/103 [74.8%] for nivolumab and 14/22 [63.6%] for everolimus).

At the time of the database lock point, the proportion of responders with an ongoing response of PR or CR (as of the last tumor assessment before censoring) was 49/103 (47.6%) subjects in the nivolumab group and 10/22 (45.5%) subjects in the everolimus group (Table 14, Table 16, and Figure 9).

Median DOR was 11.99 months in both treatment groups. In the nivolumab group, 49 responders were censored (36 still on treatment, 9 in follow-up, and 4 received subsequent anti-cancer therapy). In the everolimus group, 10 responders were censored (7 still on treatment, 1 in follow-up, 1 received subsequent anti-cancer therapy, and 1 withdrew consent).

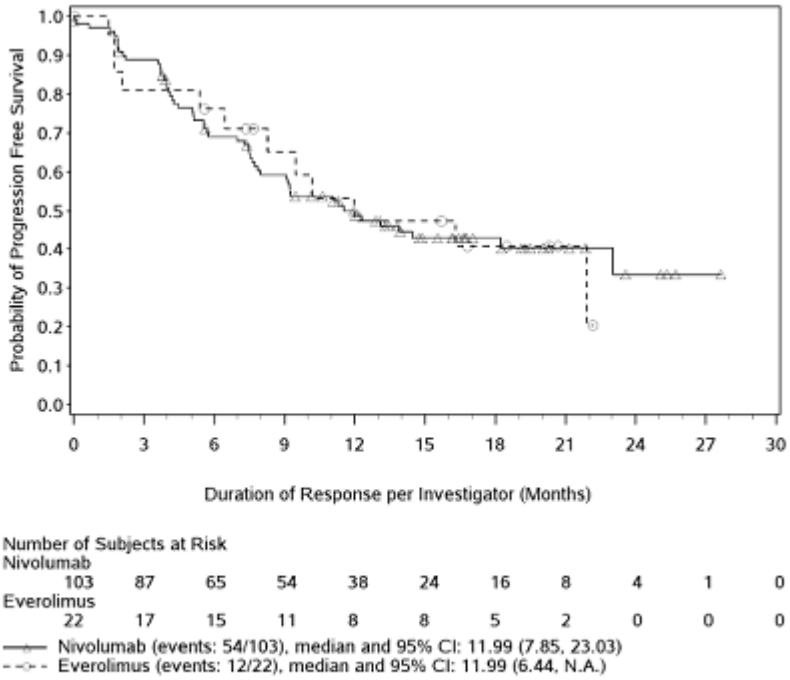
Among subjects with a BOR of SD, the median duration of SD was 5.59 months (95% CI: 5.36, 7.36) in the nivolumab group (25/141 [17.7%] subjects with ongoing SD) and 7.29 months (95% CI: 5.88, 7.75) in the everolimus group (47/227 [20.7%] subjects with ongoing SD).

Table 16: Time to objective response and duration of response per investigator – all randomized subjects with response

	Nivolumab N = 103	Everolimus N = 22
TIME TO OBJECTIVE RESPONSE (MONTHS)		
NUMBER OF RESPONDERS	103	22
MEAN	4.34	4.65
MEDIAN	3.52	3.70
MIN, MAX	1.4, 24.8	1.5, 11.2
STANDARD DEVIATION	4.070	3.115
DURATION OF OBJECTIVE RESPONSE (MONTHS)		
MIN, MAX	0.0, 27.6 (A)	0.0 (A), 22.2 (A)
MEDIAN (95% CI) (B)	11.99 (7.85, 23.03)	11.99 (6.44, N.A.)
N EVENT/N RESP (%)	54/103 (52.4)	12/22 (54.5)

RECIST v1.1 response criteria.
(A) Censored observation.
(B) Median computed using Kaplan-Meier method.
Source: Table 8.5.16

Figure 9: Kaplan-Meier plot of duration of response per investigator – all randomized subjects with response



RECIST v1.1 Response Criteria.
Symbols represent censored observations.
Source: Figure S.5.13

Quality of life results

Overall survival could be accompanied by an improvement over time in disease related symptoms and non-disease specific quality of life (QoL) as assessed using valid and reliable scales in the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and the EuroQoL EQ-5D. Apparently, meaningful symptom improvement (MID=2 point change in FKSI-DRS score; $p<0.001$) and time to improvement (HR= 1.66 (1.33,2.08), $p<0.001$) were significantly better for patients on the nivolumab arm. While both arms of the study received active therapy, the QoL data should be interpreted in the context of the open-label study design and therefore cautiously taken.

Nivolumab Subjects Treated Beyond RECIST v1.1-Defined Progression

A total of 44.1% (179/406) of treated subjects in the nivolumab group and 46.1% (183/397) of subjects in the everolimus group were treated beyond progression (defined as a last dosing date after a RECIST v1.1 progression date).

Of the 179 subjects treated beyond progression in the nivolumab group, 51 were considered non-conventional benefiters, defined as subjects who had not experienced a BOR of PR/CR prior to initial RECIST v1.1-defined progression, and met at least 1 of the following criteria:

Criterion 1: Appearance of a new lesion followed by decrease from baseline of at least 10% in the sum of the target lesions (15 subjects).

Criterion 2: Initial increase from nadir ≥20% in the sum of the target lesions followed by reduction from baseline of at least 30% (5 subjects).

Criterion 3: Initial increase from nadir ≥20% in the sum of the target lesions or appearance of new lesion followed by at least 2 tumor assessments showing no further progression defined as a 10% additional increase in sum of target lesions and new lesions (44 subjects).

Ancillary analyses

Results according to PD-L1 expression

Subjects were enrolled regardless of PD-L1 expression. PD-L1 tumor membrane expression levels were evaluated using a novel automated IHC assay incorporating a rabbit-anti-human PD-L1 antibody. PD-L1 expression was defined as the percentage of viable tumor cells demonstrating plasma membrane PD-L1 staining in a minimum of 100 evaluable tumor cells per this validated Dako PD-L1 IHC 28-8 pharmDx assay. All randomized subjects had tumor samples available, and subjects with evaluable pre-study (baseline) tumor samples were tested for PD-L1 expression. The majority of samples (74.7%) were collected at the primary tumor site.

Most subjects (92.1%) had a quantifiable PD-L1 level at pre-study (baseline), and the proportion of subjects with quantifiable PD-L1 expression was balanced between the treatment groups (90.2% nivolumab and 93.9% everolimus) (see table below).

Table 17: Overall frequency of PD-L1 expression at pre-study (baseline) – all randomized subjects

Population PD-L1 Expression Category	Nivolumab N = 410	Everolimus N = 411	Total N = 821
OVERALL	410	411	821
PD-L1 QUANTIFIABLE (N(%))	370 (90.2)	386 (93.9)	756 (92.1)
>= 1%	94/370 (25.4)	87/386 (22.5)	181/756 (23.9)
< 1%	276/370 (74.6)	299/386 (77.5)	575/756 (76.1)
>= 5%	44/370 (11.9)	41/386 (10.6)	85/756 (11.2)
< 5%	326/370 (88.1)	345/386 (89.4)	671/756 (88.8)
>= 10%	32/370 (8.6)	30/386 (7.8)	62/756 (8.2)
< 10%	338/370 (91.4)	356/386 (92.2)	694/756 (91.8)
PD-L1 INDETERMINATE/ NOT EVALUABLE (N(%))	40 (9.8)	25 (6.1)	65 (7.9)

Source: Table S.10.6

Efficacy results were generally consistent across PD-L1 expression levels (1%, 5%, or 10%), with the exception of the OS result in the small subgroup of subjects with ≥10% PD-L1 expression (n = 32 nivolumab and n= 30 everolimus).

OS per PD-L1 expression

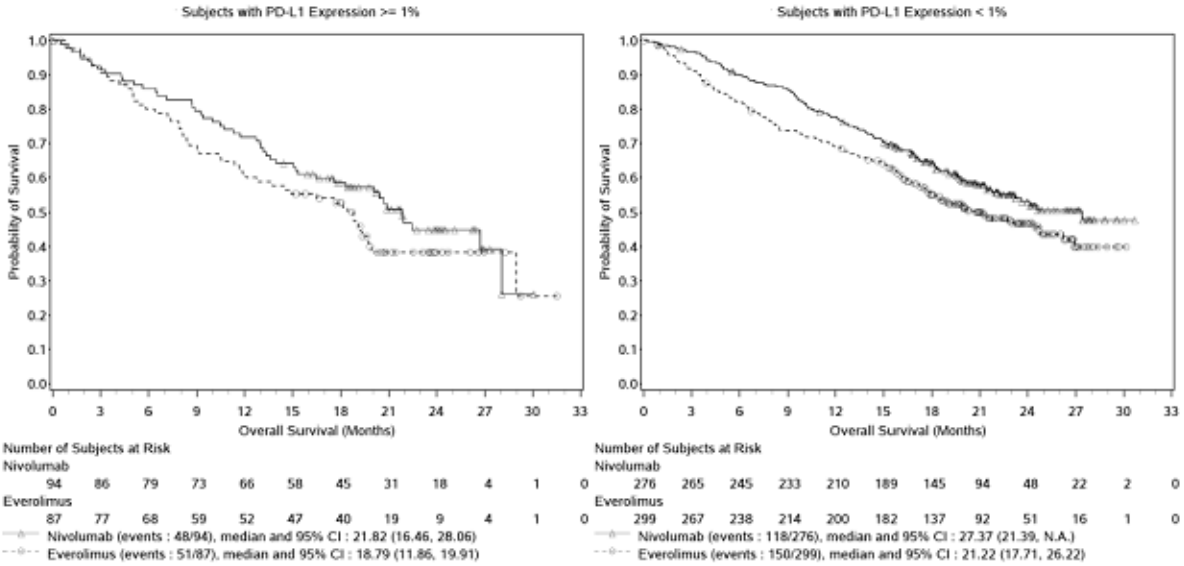
Nivoumab demonstrated superior OS compared with everolimus regardless of PD-L1 expression. Kaplan-Meier plots of OS by PD-L1 expression at the 1% level are provided in Figure 10, with unstratified HRs and 95% CIs provided in Figure 11.

- In subjects with pre-study (baseline) PD-L1 expression ≥ 1%:
  - Median OS (months) was 21.82 for nivolumab subjects compared to 18.79 for everolimus subjects.
  - The OS HR (nivolumab over everolimus) was 0.79 (95% CI: 0.53, 1.17).
- In subjects with pre-study (baseline) PD-L1 expression < 1%:
  - Median OS (months) was 27.37 for nivolumab subjects compared to 21.22 for everolimus subjects.
  - The OS HR (nivolumab over everolimus) was 0.77 (95% CI: 0.60, 0.97).

There was longer median OS in subjects with < 1% PD-L1 expression relative to subjects with ≥ 1% PD-L1 expression (Figure 10).

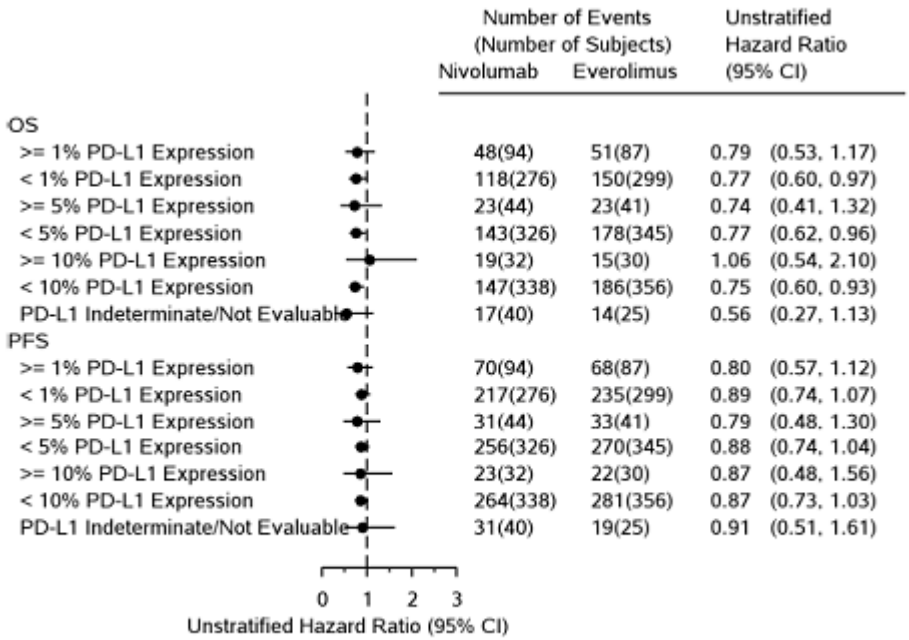
- The OS HR for PD-L1 expression ≥ 1% vs <1% was 1.27 (95% CI: 0.91, 1.78) in the nivolumab group and 1.24 (95% CI: 0.90, 1.70) in the everolimus group.

Figure 10: Kaplan- Meier plot of OS by pre-study (baseline) PD-L1 expression (1% expression level) – all PD-L1 randomized subjects



Symbols represent censored observations.
Source: Figure S.10.1

Figure 11: plot of OS and PFS per investigator hazar ratios by pre-study (baseline) PD-L1 expression – all randomized subjects



Source: Figure S.10.7

PFS per PD-L1 expression

Results across pre-study (baseline) PD-L1 expression subgroups were similar to the PFS result in all randomized subjects.

- In subjects with pre-study (baseline) PD-L1 expression ≥1%:
    - Median PFS was 5.36 months for nivolumab subjects compared to 4.17 months for everolimus subjects.
    - The PFS HR (nivolumab over everolimus) was 0.80 (95% CI: 0.57, 1.12).
- In subjects with pre-study (baseline) PD-L1 expression < 1%:
    - Median PFS was 3.94 months for nivolumab subjects compared to 4.67 months for everolimus subjects.
    - The PFS HR (nivolumab over everolimus) was 0.89 (95% CI: 0.74, 1.07).

Similar to the K-M curve of the all randomized population (Figure 8), the K-M PFS curves for PD-L1 subgroups overlapped initially and then separated, favoring nivolumab, becoming more pronounced over time when looking at the tail of the curve.

ORR per PD-L1 expression

In the nivolumab group, objective responses were observed in subjects regardless of PD-L1 expression. In the everolimus group, no objective responses were observed in the ≥ 5%, ≥ 10%, and indeterminate/not evaluable PD-L1 expression subgroups.

- A higher ORR was observed in nivolumab-treated vs everolimus-treated subjects across PD-L1 expression subgroups.
- In the nivolumab group, the ORR was higher for subjects with ≥ 1% PD-L1 expression (30.9%) than subjects with < 1% PD-L1 expression (22.8%) (see table below). At a cut-off of 5% for pre-treatment tumour PD-L1 expression, nivolumab-treated patients with ≥5%PD-L1 expression had an ORR of 43% (95%CI: 28.3-59.0), compared to 22% (95%CI: 18.0-27.3) for nivolumab-treated patients with <5% baseline PD-L1 expression.

Table 18: Objective response rate per investigator by pre-treatment (baseline) PD-L1 expression (1% expression level) – all PD-L1 randomized subjects

PD-L1 Expression Result Group		Nivolumab N = 410	Everolimus N = 411
SUBJECTS WITH PD-L1 EXPRESSION >= 1%			
	OBJECTIVE RESPONSE RATE (1)	29/94 (30.9%)	3/87 (3.4%)
	(95% CI)	(21.7, 41.2)	(0.7, 9.7)
	ODDS RATIO (95% CI) (2)	12.49 (3.59, 66.09)	
SUBJECTS WITH PD-L1 EXPRESSION < 1%			
	OBJECTIVE RESPONSE RATE (1)	63/276 (22.8%)	19/299 (6.4%)
	(95% CI)	(18.0, 28.2)	(3.9, 9.7)
	ODDS RATIO (95% CI) (2)	4.36 (2.48, 7.94)	

RECIST v1.1 response criteria. PD-L1 expression results from validated assay.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Ratio of Nivolumab over Everolimus.
Source: Table 8.10.7

OS per subgroups

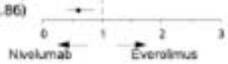
Subgroup analyses were conducted using an unadjusted univariate Cox model to assess the impact of baseline MSKCC risk group, number of prior anti- angiogenic regimens in the advanced/metastatic setting; region, age category, gender, race, smoking status, Karnofsky performance status, prior cytokine in the advanced/metastatic setting, time from diagnosis to start of first systemic therapy in metastatic regimen, and Heng risk group.

The OS unstratified HR favored nivolumab vs. everolimus for all pre-defined subgroups, with the exception of the ≥75 years and Asian subgroups (Figure 12). The CIs in these subgroups were wide and encompassed 1.0 due to small subgroup sizes.

The poor MSKCC risk subgroup and Karnofsky performance status < 90% subgroup showed the greatest OS benefit with nivolumab vs. everolimus.

Figure 12: Forest plot of treatment effect on overall survival in pre-defined subsets - All Randomized Subjects

		Nivolumab		Everolimus		Unstratified
	N	N of events (N of subjects)	mOS (95% CI)	N of events (N of subjects)	mOS (95% CI)	Hazard Ratio (95% CI)
Overall	821	183(410)	25.00 (21.75, N.A.)	215(411)	19.55 (17.64, 23.06)	0.76 (0.62, 0.92)
Baseline MSKCC Risk Group						
Favorable	282	38(137)	N.A.	50(145)	28.98 (26.91, N.A.)	0.80 (0.52, 1.21)
Intermediate	385	95(193)	21.82 (18.27, N.A.)	104(192)	18.43 (16.13, 23.06)	0.81 (0.61, 1.06)
Poor	153	50(79)	15.34 (9.59, 22.44)	61(74)	7.85 (5.42, 9.69)	0.48 (0.32, 0.70)
Number of Prior Anti-Angiogenic Regimen in the Advanced/Metastatic Setting						
1	629	144(317)	23.62 (20.80, N.A.)	162(312)	19.91 (17.71, 24.67)	0.79 (0.63, 0.99)
2	189	37(90)	N.A. (18.14, N.A.)	53(99)	18.43 (14.00, N.A.)	0.65 (0.43, 0.99)
Region						
US/Canada	346	66(174)	N.A. (22.44, N.A.)	87(172)	19.55 (16.43, 24.67)	0.66 (0.48, 0.91)
Western Europe	281	78(140)	20.80 (15.87, 28.06)	84(141)	18.50 (13.34, 22.77)	0.86 (0.63, 1.16)
Rest of World	194	39(96)	26.71 (19.65, N.A.)	44(98)	24.34 (15.74, N.A.)	0.78 (0.51, 1.20)
Age Category I						
< 65	497	111(257)	26.71 (21.75, N.A.)	118(240)	19.94 (17.48, N.A.)	0.78 (0.60, 1.01)
>= 65 and < 75	250	53(119)	24.15 (20.07, N.A.)	77(131)	17.97 (14.00, 24.34)	0.64 (0.45, 0.91)
>= 75	74	19(34)	17.31 (9.43, N.A.)	20(40)	20.27 (16.49, N.A.)	1.23 (0.66, 2.31)
Age Category II						
< 65	497	111(257)	26.71 (21.75, N.A.)	118(240)	19.94 (17.48, N.A.)	0.78 (0.60, 1.01)
>= 65	324	72(153)	23.62 (18.23, N.A.)	97(171)	18.50 (16.43, 21.55)	0.74 (0.55, 1.01)
Gender						
Male	619	135(315)	25.00 (21.91, N.A.)	159(304)	19.75 (17.61, 24.34)	0.73 (0.58, 0.92)
Female	202	48(95)	20.90 (17.08, N.A.)	56(107)	19.09 (16.49, 26.91)	0.84 (0.57, 1.24)
Race						
White	720	159(353)	24.61 (20.80, N.A.)	203(367)	18.69 (16.13, 20.27)	0.71 (0.58, 0.87)
Black or African American	5	1(1)	12.75 (N.A., N.A.)	2(4)	18.43 (13.80, N.A.)	
Asian	74	13(42)	27.37 (23.62, N.A.)	8(32)	N.A.	1.31 (0.54, 3.16)
Other	22	10(14)	16.56 (4.50, 21.91)	2(8)	N.A. (3.61, N.A.)	
Smoking Status						
Current/Former	447	108(240)	24.15 (21.36, N.A.)	106(207)	19.75 (15.87, N.A.)	0.79 (0.60, 1.03)
Never Smoked	355	72(161)	26.71 (18.23, N.A.)	102(194)	19.68 (17.61, 24.34)	0.76 (0.56, 1.03)
Karnofsky Performance Status						
90% - 100%	540	102(276)	N.A. (26.71, N.A.)	105(264)	28.98 (24.34, N.A.)	0.92 (0.70, 1.21)
< 90%	281	81(134)	18.14 (14.32, 22.21)	110(147)	10.05 (7.92, 12.75)	0.55 (0.41, 0.74)
Prior Cytokine in Advanced/Metastatic Setting						
Yes	142	24(68)	27.37 (26.71, N.A.)	34(74)	24.67 (16.03, N.A.)	0.64 (0.38, 1.09)
No	679	159(342)	23.23 (20.70, N.A.)	181(337)	19.09 (17.48, 21.55)	0.77 (0.63, 0.96)
Time from Diagnosis to Start of First Systemic Therapy in Metastatic Regimen						
< 1 Year	461	118(224)	20.70 (17.05, 23.62)	132(237)	17.97 (15.05, 20.04)	0.84 (0.65, 1.07)
>= 1 Year	339	59(174)	N.A.	79(165)	24.74 (19.02, N.A.)	0.63 (0.45, 0.89)
Heng Risk Group						
Favorable	125	13(55)	N.A.	21(70)	28.98 (24.74, N.A.)	0.79 (0.39, 1.58)
Intermediate	483	102(242)	N.A. (21.39, N.A.)	123(241)	19.91 (17.71, 26.22)	0.73 (0.56, 0.95)
Poor	179	61(96)	15.34 (10.64, 20.40)	61(83)	8.38 (5.85, 11.37)	0.60 (0.42, 0.86)



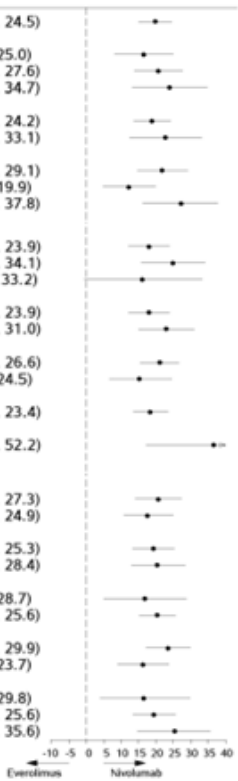
HR is not computed/displayed if a subgroup category has less than 10 subjects per treatment group.
Subgroup categories with less than 5 subjects in total are not displayed.
Source: Figure S.5.2

ORR per subgroups

Subgroup analyses were conducted for the following: baseline MSKCC risk group, number of prior anti-angiogenic regimens in the advanced/metastatic setting; region, age category, gender, race, smoking status, Karnofsky performance status, prior cytokine in the advanced/metastatic setting, time from diagnosis to start of first systemic therapy in metastatic regimen, and Heng risk group.

Figure 13: Forest plot of treatment effect on objective response rate per investigator in pre-defined subsets – all randomized subjects

	N	Nivolumab N of Response (N of subjects)	Nivolumab ORR (95% Exact CI)	Everolimus N of Response (N of subjects)	Everolimus ORR (95% Exact CI)	Unweighted ORR difference (95% CI)
Overall	821	103(410)	25.1% (21.0, 29.6)	22(411)	5.4% (3.4, 8.0)	19.8% (15.0, 24.5)
Baseline MSKCC Risk Group						
Favorable	282	33(137)	24.1% (17.2, 32.1)	11(145)	7.6% (3.8, 13.2)	16.5% (8.1, 25.0)
Intermediate	385	49(193)	25.4% (19.4, 32.1)	9(192)	4.7% (2.2, 8.7)	20.7% (13.8, 27.6)
Poor	153	21(79)	26.6% (17.3, 37.7)	2(74)	2.7% (0.3, 9.4)	23.9% (13.1, 34.7)
Number of Prior Anti-Angiogenic Regimen in the Advanced/Metastatic Setting						
1	629	77(317)	24.3% (19.7, 29.4)	17(312)	5.4% (3.2, 8.6)	18.8% (13.5, 24.2)
2	189	25(90)	27.8% (18.9, 38.2)	5(99)	5.1% (1.7, 11.4)	22.7% (12.4, 33.1)
Region						
US/Canada	346	45(174)	25.9% (19.5, 33.0)	7(172)	4.1% (1.7, 8.2)	21.8% (14.6, 29.1)
Western Europe	281	25(140)	17.9% (11.9, 25.2)	8(141)	5.7% (2.5, 10.9)	12.2% (4.7, 19.9)
Rest of World	194	33(96)	34.4% (25.0, 44.8)	7(98)	7.1% (2.9, 14.2)	27.2% (16.1, 37.8)
Age Category I						
< 65	497	59(257)	23.0% (18.0, 28.6)	12(240)	5.0% (2.6, 8.6)	18.0% (12.1, 23.9)
>= 65 and < 75	250	36(119)	30.3% (22.2, 39.3)	7(131)	5.3% (2.2, 10.7)	24.9% (15.7, 34.1)
>= 75	74	8(34)	23.5% (10.7, 41.2)	3(40)	7.5% (1.6, 20.4)	16.0% (-0.6, 33.2)
Age Category II						
< 65	497	59(257)	23.0% (18.0, 28.6)	12(240)	5.0% (2.6, 8.6)	18.0% (12.1, 23.9)
>= 65	324	44(153)	28.8% (21.7, 36.6)	10(171)	5.8% (2.8, 10.5)	22.9% (14.9, 31.0)
Gender						
Male	619	85(315)	27.0% (22.2, 32.2)	18(304)	5.9% (3.5, 9.2)	21.1% (15.4, 26.6)
Female	202	18(95)	18.9% (11.6, 28.3)	4(107)	3.7% (1.0, 9.3)	15.2% (6.6, 24.5)
Race						
White	720	83(353)	23.5% (19.2, 28.3)	19(367)	5.2% (3.1, 8.0)	18.3% (13.4, 23.4)
Black or African American	5	0(1)	0.0% (0.0, 97.5)	0(4)	0.0% (0.0, 60.2)	
Asian	74	18(42)	42.9% (27.7, 59.0)	2(32)	6.3% (0.8, 20.8)	36.6% (17.1, 52.2)
Other	22	2(14)	14.3% (1.8, 42.8)	1(8)	12.5% (0.3, 52.7)	
Smoking Status						
Current/Former	447	66(240)	27.5% (22.0, 33.6)	14(207)	6.8% (3.7, 11.1)	20.7% (14.0, 27.3)
Never Smoked	355	35(161)	21.7% (15.6, 28.9)	8(194)	4.1% (1.8, 8.0)	17.6% (10.8, 24.9)
Karnofsky Performance Status						
90% - 100%	540	72(276)	26.1% (21.0, 31.7)	18(264)	6.8% (4.1, 10.6)	19.3% (13.2, 25.3)
< 90%	281	31(134)	23.1% (16.3, 31.2)	4(147)	2.7% (0.7, 6.8)	20.4% (12.9, 28.4)
Prior Cytokine in Advanced/Metastatic Setting						
Yes	142	16(68)	23.5% (14.1, 35.4)	5(74)	6.8% (2.2, 15.1)	16.8% (5.0, 28.7)
No	679	87(342)	25.4% (20.9, 30.4)	17(337)	5.0% (3.0, 8.0)	20.4% (15.2, 25.6)
Time from Diagnosis to Start of First Systemic Therapy in Metastatic Regimen						
< 1 Year	461	62(224)	27.7% (21.9, 34.0)	10(237)	4.2% (2.0, 7.6)	23.5% (17.1, 29.9)
>= 1 Year	339	40(174)	23.0% (17.0, 30.0)	11(165)	6.7% (3.4, 11.6)	16.3% (8.9, 23.7)
Heng Risk Group						
Favorable	125	13(55)	23.6% (13.2, 37.0)	5(70)	7.1% (2.4, 15.9)	16.5% (3.9, 29.8)
Intermediate	483	59(242)	24.4% (19.1, 30.3)	12(241)	5.0% (2.6, 8.5)	19.4% (13.3, 25.6)
Poor	179	29(96)	30.2% (21.3, 40.4)	4(83)	4.8% (1.3, 11.9)	25.4% (14.6, 35.6)



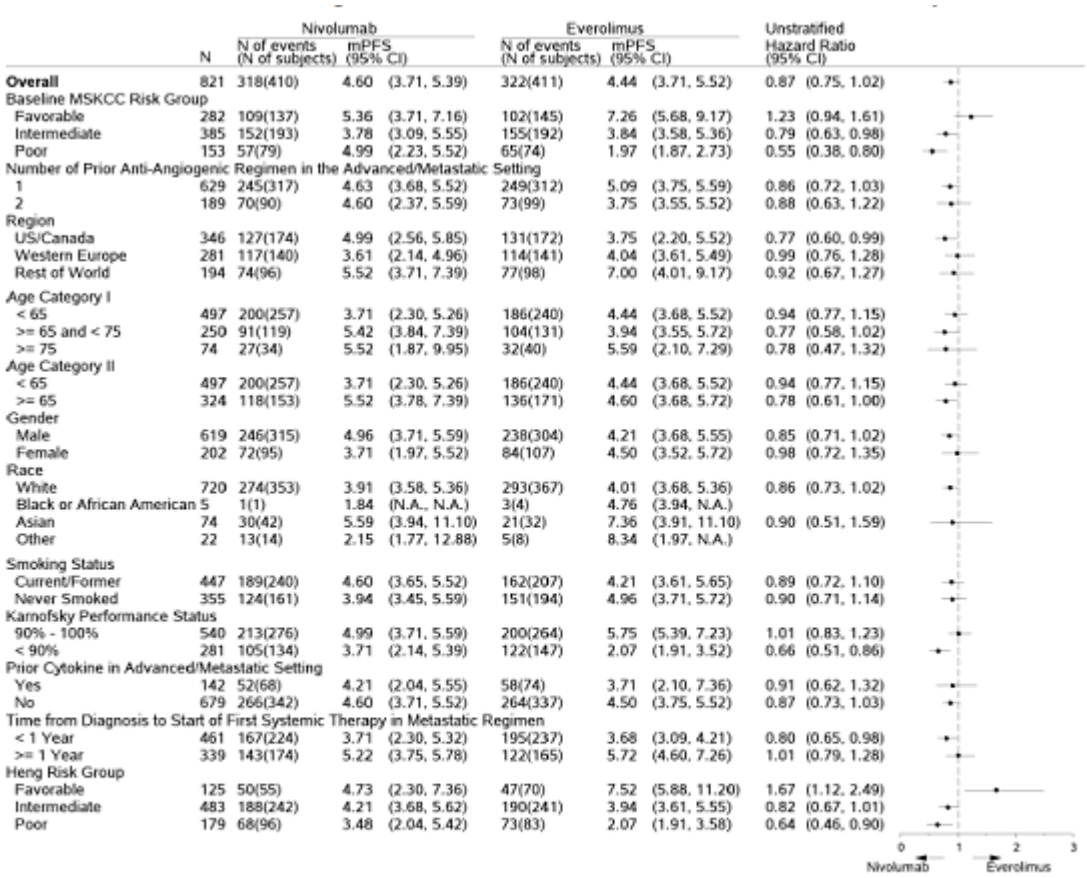
RECIST v1.1 response criteria.
Unweighted ORR difference will not be computed/displayed if a subgroup category has less than 10 subjects per treatment group.
Subgroup categories with less than 5 subjects in total are not displayed. Source: Figure S.5.17

In the sub-population of subjects (N= 46 and 52 in the nivolumab and everolimus treatment groups, respectively) without nephrectomy enrolled in study CA209025, patients on nivolumab had substantially better ORR (15.2% [6.3-28.9] vs 1.9% [0-10.3]) than patients on everolimus.

PFS per subgroups

Subgroup analyses of PFS were conducted for the following: baseline MSKCC risk group, number of prior anti-angiogenic regimens in the advanced/metastatic setting; region, age category, gender, race, smoking status, Karnofsky performance status, prior cytokine in the advanced/metastatic setting, time from diagnosis to start of first systemic therapy in metastatic regimen, and Heng risk group.

Figure 14: Forest plot of treatment effect on progression-free survival per investigator in pre-defined subsets – all randomized subjects



	N	Nivolumab N of events (N of subjects)	Nivolumab mPFS (95% CI)	Everolimus N of events (N of subjects)	Everolimus mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	821	318(410)	4.60 (3.71, 5.39)	322(411)	4.44 (3.71, 5.52)	0.87 (0.75, 1.02)
Baseline MSKCC Risk Group						
Favorable	282	109(137)	5.36 (3.71, 7.16)	102(145)	7.26 (5.68, 9.17)	1.23 (0.94, 1.61)
Intermediate	385	152(193)	3.78 (3.09, 5.55)	155(192)	3.84 (3.58, 5.36)	0.79 (0.63, 0.98)
Poor	153	57(79)	4.99 (2.23, 5.52)	65(74)	1.97 (1.87, 2.73)	0.55 (0.38, 0.80)
Number of Prior Anti-Angiogenic Regimen in the Advanced/Metastatic Setting						
1	629	245(317)	4.63 (3.68, 5.52)	249(312)	5.09 (3.75, 5.59)	0.86 (0.72, 1.03)
2	189	70(90)	4.60 (2.37, 5.59)	73(99)	3.75 (3.55, 5.52)	0.88 (0.63, 1.22)
Region						
US/Canada	346	127(174)	4.99 (2.56, 5.85)	131(172)	3.75 (2.20, 5.52)	0.77 (0.60, 0.99)
Western Europe	281	117(140)	3.61 (2.14, 4.96)	114(141)	4.04 (3.61, 5.49)	0.99 (0.76, 1.28)
Rest of World	194	74(96)	5.52 (3.71, 7.39)	77(98)	7.00 (4.01, 9.17)	0.92 (0.67, 1.27)
Age Category I						
< 65	497	200(257)	3.71 (2.30, 5.26)	186(240)	4.44 (3.68, 5.52)	0.94 (0.77, 1.15)
>= 65 and < 75	250	91(119)	5.42 (3.84, 7.39)	104(131)	3.94 (3.55, 5.72)	0.77 (0.58, 1.02)
>= 75	74	27(34)	5.52 (1.87, 9.95)	32(40)	5.59 (2.10, 7.29)	0.78 (0.47, 1.32)
Age Category II						
< 65	497	200(257)	3.71 (2.30, 5.26)	186(240)	4.44 (3.68, 5.52)	0.94 (0.77, 1.15)
>= 65	324	118(153)	5.52 (3.78, 7.39)	136(171)	4.60 (3.68, 5.72)	0.78 (0.61, 1.00)
Gender						
Male	619	246(315)	4.96 (3.71, 5.59)	238(304)	4.21 (3.68, 5.55)	0.85 (0.71, 1.02)
Female	202	72(95)	3.71 (1.97, 5.52)	84(107)	4.50 (3.52, 5.72)	0.98 (0.72, 1.35)
Race						
White	720	274(353)	3.91 (3.58, 5.36)	293(367)	4.01 (3.68, 5.36)	0.86 (0.73, 1.02)
Black or African American	5	1(1)	1.84 (N.A., N.A.)	3(4)	4.76 (3.94, N.A.)	
Asian	74	30(42)	5.59 (3.94, 11.10)	21(32)	7.36 (3.91, 11.10)	0.90 (0.51, 1.59)
Other	22	13(14)	2.15 (1.77, 12.88)	5(8)	8.34 (1.97, N.A.)	
Smoking Status						
Current/Former	447	189(240)	4.60 (3.65, 5.52)	162(207)	4.21 (3.61, 5.65)	0.89 (0.72, 1.10)
Never Smoked	355	124(161)	3.94 (3.45, 5.59)	151(194)	4.96 (3.71, 5.72)	0.90 (0.71, 1.14)
Karnofsky Performance Status						
90% - 100%	540	213(276)	4.99 (3.71, 5.59)	200(264)	5.75 (5.39, 7.23)	1.01 (0.83, 1.23)
< 90%	281	105(134)	3.71 (2.14, 5.39)	122(147)	2.07 (1.91, 3.52)	0.66 (0.51, 0.86)
Prior Cytokine in Advanced/Metastatic Setting						
Yes	142	52(68)	4.21 (2.04, 5.55)	58(74)	3.71 (2.10, 7.36)	0.91 (0.62, 1.32)
No	679	266(342)	4.60 (3.71, 5.52)	264(337)	4.50 (3.75, 5.52)	0.87 (0.73, 1.03)
Time from Diagnosis to Start of First Systemic Therapy in Metastatic Regimen						
< 1 Year	461	167(224)	3.71 (2.30, 5.32)	195(237)	3.68 (3.09, 4.21)	0.80 (0.65, 0.98)
>= 1 Year	339	143(174)	5.22 (3.75, 5.78)	122(165)	5.72 (4.60, 7.26)	1.01 (0.79, 1.28)
Heng Risk Group						
Favorable	125	50(55)	4.73 (2.30, 7.36)	47(70)	7.52 (5.88, 11.20)	1.67 (1.12, 2.49)
Intermediate	483	188(242)	4.21 (3.68, 5.62)	190(241)	3.94 (3.61, 5.55)	0.82 (0.67, 1.01)
Poor	179	68(96)	3.48 (2.04, 5.42)	73(83)	2.07 (1.91, 3.58)	0.64 (0.46, 0.90)

HRs are not computed/displayed if a subgroup category has less than 10 subjects per treatment group.
Subgroup categories with less than 5 subjects in total are not be displayed.
Source: Figure S.5.12

Summary of main study

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

Table 19. Summary of Efficacy for trial CA209025

Title: A Randomized, Open-Label, Phase 3 Study of Nivolumab (BMS-936558) versus Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy (CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation)		
Study identifier	CA209025	
Design	This was a randomized, open-label, phase 3 study of nivolumab vs. everolimus in adults with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy	
	Duration of main phase:	Oct-2012 to 06-May-2015 (last patient last visit for analysis)
	Duration of run-in phase:	not applicable
	Duration of extension phase:	on-going
Hypothesis	Superiority	

Treatment groups	Nivolumab at 3 mg/kg		Nivolumab at 3 mg/kg was administered as an IV infusion over 60 minutes on Day 1 of each 2-week cycle.
	Everolimus 10 mg		Everolimus 10 mg as a daily oral dose.
Endpoints and definitions	Primary endpoint	OS	Defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS was censored on the last date the subject was known to be alive.
	Secondary endpoint	PFS	Defined as the time from randomization to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause.
	Secondary endpoint	ORR	Defined as the number of subjects whose best confirmed objective response (BOR) was either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomized subjects.
Database lock	18-Jun-2015		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Nivolumab at 3 mg/kg	Everolimus 10 mg	
	Number of subjects	410	411	
	OS (months) median	25.00	19.55	
	95% CI	(21.75, NR)	(17.64, 23.06)	
	Investigator-assessed PFS (months) Median	4.60	4.44	
	95% CI	(3.71, 5.39)	(3.71, 5.52)	
	Investigator-assessed ORR n, (%)	103 (25.1)	22 (5.4)	
	95% CI	(21.0, 29.6)	(3.4, 8.0)	
Effect estimate per comparison	Primary endpoint (OS)	Comparison groups	nivolumab vs. everolimus	
		HR	0.73	
		98.52% CI	(0.57, 0.93)	
		P-value	0.0018	

	Secondary endpoint (PFS)	Comparison groups	nivolumab vs. everolimus
		HR	0.88
		95% CI	(0.75, 1.03)
		P-value	0.1135
	<<Co->Primary > <Secondary> <other: specify> endpoint	Comparison groups	nivolumab vs. everolimus
		Odds ratio	5.98
		95% CI	(3.68, 9.72)
		P-value	< 0.0001
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

Non applicable

Clinical studies in special populations

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with nivolumab in all subsets of the paediatric population in the treatment of malignant solid tumours.

Elderly patients

Regarding elderly patients, a relatively large number of patients aged ≥65–<75 years of age was enrolled in the pivotal study, and superiority of nivolumab over everolimus was demonstrated in this population.
A relatively small number of patients aged ≥75 years of age was enrolled, and in this population no clear benefit from treatment with nivolumab relative to everolimus could be established (HR: 1.23, 95%CI: 0.66-2.31, for OS).

Supportive study
See dose-response section of this AR.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies
CA209025 was a randomized, open-label study that included subjects with advanced RCC who had received prior therapy.

The inclusion/exclusion criteria recruited a population in second line of RCC (clear cell) according to the current clinical practice.

However it should be noted that third line patients could be also included into the trial. As per current guidelines (NCCN version 3.2015 Kidney Cancer) cytoreductive nephrectomy (when possible) is recommended in stage IV disease. From the full list of inclusion criteria, it appears that patients that were not amenable to this procedure were also eligible for enrolment in the study. The results in terms of ORR and OS in this sub-group point out the better results for those treated with nivolumab.

Subjects were randomized 1:1 to nivolumab or everolimus and stratified according to the following factors: region, Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups and number of prior anti-angiogenic therapies. These stratification factors were considered acceptable. MSKCC or Heng's model are widely used.

The primary objective was to compare the OS of nivolumab vs everolimus. A single pre-planned interim OS analysis was to be conducted when at least 398 (70%) of the 569 required events for the final analysis had been reported. This formal comparison of OS allowed for early stopping and would become the final analysis if results were statistically significant (P ≤0.0148) and clinically meaningful.

The secondary endpoints of investigator-assessed ORR and PFS (per RECIST v1.1) were tested hierarchically to preserve the experimental-wise type I error rate at 5%. The endpoints were considered acceptable.

Given that OS was the primary endpoint, the open label design was considered acceptable. However, for determination of the secondary endpoints PFS and ORR, investigator-assessed RECIST measurements were used, and no use was made of independent review committee (IRC)-based RECIST measurement. This approach was chosen despite the advice to use IRC-based response evaluation, as previously recommended by the CHMP (scientific advice EMEA/H/SA/2253/2/2011/II). The use of investigator-assessed response determination was not considered adequate in view of the open-label nature of the study, and the consequent high risk of bias influencing determination of PFS. However, this uncertainty is no longer relevant given the magnitude of the effect in terms of OS observed in favour of nivolumab treatment.

Efficacy data and additional analyses

The baseline characteristics were evenly balanced between both arms. The majority of subjects were men and white (75% and 88% respectively) with only 9% > 75 years. The majority of the population included in the study were in the intermediate and poor MSKCC risk group. The disease characteristics and prior treatments are reflecting the current clinical practice. Almost 83% did not receive cytokine agents in previous treatments and the majority of patients received 1 prior anti-angiogenic therapy (76.0%) with 23% receiving two.

Results from study CA209025 are based on a pre-defined interim analysis (clinical database lock of 18-Jun-2015). This interim analysis, according to the protocol and SAP was to be conducted when at least 398 (70%) of the 569 required events for the final analysis had been reported. The independent DMC reviewed the interim OS data on 17-Jul 2015. The DMC confirmed that the pre-specified boundary for significance was crossed (P < 0.0148) and noted that there were no new safety signals that would affect continuation of the study. The last subject was randomized on 11-Mar-2014, and the last patient's last visit date occurred on 06 May 2015, providing a minimum follow-up of approximately 14 months (median of 18.25 months for nivolumab and 17.22 months for everolimus).

The analysis of the primary endpoint (OS) revealed a longer survival for patients treated with nivolumab vs everolimus (HR: 0.73 [98.52% CI: 0.57, 0.93]; stratified log-rank test p value = 0.0018). The median of OS for nivolumab group was 25 months, whereas subjects treated with everolimus achieved a median of OS of 19.55 months. This gain in OS (5.45 months) is considered clinically meaningful. The survival rate at 1 year was higher in the nivolumab group than the everolimus group (76.0% vs 66.7%). The profile of the Kaplan-Meier curves showed a clear separation.

This result seems quite robust, since 3 different sensitivity analyses (unstratified analysis, analysis using stratification factors as determined at baseline [CRF source], and analysis of all treated subjects) demonstrated similar results (HR and 98.5% CI; 0.76 [0.59, 0.97], 0.70 [0.54, 0.90] and 0.72 [0.56, 0.93] respectively). In addition, the results obtained with the multivariate analysis (adjusted for time from diagnosis to start of first systemic therapy in metastatic regimen (< 1 year), baseline ANC > ULN, and baseline platelets > ULN) was also similar with the main analysis (HR: 0.73; stratified Cox model p-value = 0.0030).

Also, the low degree of censoring prior to ~15 months (the minimum follow-up for OS) in both treatment groups substantiate the maturity of the results.

Subsequent systemic anti-cancer therapy was received by 67.3% of nivolumab subjects and 69.1% of everolimus subjects. The most frequently treatments administered were axitinib (24.1% vs 36.3%) and pazopanib (9.0% and 15.6%) for nivolumab subjects and everolimus subjects respectively. Of note, 25.6% of patients previously treated with nivolumab received everolimus after progression, versus 5.6% of the patients in the everolimus arm. However, the OS benefit seen for patients treated with nivolumab in comparison to those treated with everolimus, does not seem to be largely influenced by the use of more or more effective post study treatment by patients treated with nivolumab. More patients in the everolimus arm had post study treatment and the kind of used post study treatments was (apart from anti PDL-1 treatment in the everolimus arm) not different in the two study arms.

The subgroups analysis are consistent with the main study results.

Of note, in the sub-population of subjects (N= 46 and 52 in the nivolumab and everolimus treatment groups, respectively) without nephrectomy enrolled in study CA209025, patients on nivolumab had substantially better survival benefit (mOS: 19.78 [11.3-24.61] vs 8.48 [4.73-13.40]; HR 0.56, p=0.0188) than patients on everolimus.

Regarding the secondary endpoints, there is a lack of difference in PFS between the two treatment arms. This is discordant with the large treatment effect observed on the primary endpoint OS. A potential explanation could be related to the delayed effect of nivolumab. In previous studies with nivolumab it was observed that there is a delay in the effect of nivolumab, for example observed in melanoma patients with rapid disease progression (before 3 months of treatment) where the effect of nivolumab seems to be limited. However, in that case also a delay effect on OS was observed.

Although, the discrepancy between the observed PFS and OS results are not yet completely explained, it is unlikely that the OS benefit seen for nivolumab in comparison to everolimus is caused by subsequent use of different post study treatments in the nivolumab arm.

ORR was superior in the nivolumab group (25.1% vs 5.4%; 21.5% vs 3.9% with a confirmatory scan after at least 4 weeks) even though the medians of the duration of response were identical (11.99 months).

A relatively large proportion of patients were treated beyond progression in both treatment arms: 44.1% (179/406) of treated patients in the nivolumab group and 46.1% (183/397) of patients in the everolimus group were treated beyond progression. Despite a similar proportion of the patients being treated beyond progression, there was a clear and large difference in the treatment duration, demonstrating that patients in the nivolumab arm were treated far longer beyond progression than patients in the everolimus arm.

The analysis of PD-L1 expression did not offer any conclusive data, probably due to the sample size of each subgroup. Overall, no effect on the predictive value of PD-L1 was observed in both treatment arms.

The biomarker analysis presented by the Applicant was not comprehensive, and additional analyses can be envisioned which may lead to improved understanding of predictive biomarkers in patients treated with nivolumab, including: determination of other biomarkers (including but not restricted to PD-L2, PD-L1, mismatch-repair status) and alternative methods for immunohistochemical scoring of PD-L1/PD-L2 (e.g. expression localisation [e.g. tumour center vs. invasive margin], tumour versus immune cell staining).

The impact of different biomarkers on nivolumab treatment will still be further investigated for all approved indications including RCC, post approval. Further investigations on the potential role of PD-L1/2 expression, or any other biomarker, on the efficacy of nivolumab in RCC was considered needed, consistent with

previous requirements for already approved indications. The annex II conditions have been updated to include the exploration of biomarkers in the RCC indication.

In the pivotal study, only patients pretreated with antiangiogenic therapy were enrolled. Some limited data in patients without prior antiangiogenic therapy (9 out of 34 subjects from a phase 1 clinical trial) support that efficacy appears in line to that of patients pretreated with antiangiogenic therapies, but given the limited data available, no definitive conclusions regarding the efficacy of nivolumab in this subgroup of patients can be drawn. However, as nivolumab has a different mode of action than the anti-VEGF and mTOR inhibitor therapies currently indicated for RCC, it is probable to extrapolate the rational that nivolumab would be effective after another treatment other than antiangiogenic therapy. Hence, a restriction to only after prior anti-angiogenic therapy is not deemed adequate. It is noted that antiangiogenic therapies constitute the current standard of care in first line, therefore, it is expected that patients treated without prior antiangiogenic treatment in the clinical practice would be limited. However, physicians should be aware of the existing limitations and appropriate information has been included in Section 5.1.

In addition, no patients with non-clear cell RCC have been treated with nivolumab, but in light of the unique mechanism of action of nivolumab which is independent of any specific mutations such as the Von Hippel-Liday (VHL) mutation, restrictions based on histology subtype are not deemed appropriate. This is consistent with regulatory precedent, taking also into account the rarity of non-clear cell RCC. Additional data will be generated in this subgroup of patients from an ongoing study (study CA209374) at post-approval. The lack of clinical data for nivolumab in patients with non-clear cell RCC has been mentioned in section 5.1 of the SmPC.

2.4.4. Conclusions on the clinical efficacy

The treatment with nivolumab in patients with RCC previously treated has shown a longer survival than everolimus. This result was considered clinically meaningful.

The CHMP considers the following measures necessary to address issues related to efficacy (changes underlined):

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 efficacy. This will be provided for all the approved indications:

- Melanoma: studies CA209038 and CA209066

- RCC: studies CA209025 and CA209009

To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in Study CA209066 and CA209025.

Also, the CHMP recommended that the efficacy results, of study CA209374 (on-going), for the sub-group of patients with non-clear RCC should be submitted post approval.

2.5. Clinical safety

Introduction

The assessment of safety of nivolumab in the proposed indication is based on safety data from the pivotal phase 3 study CA209025 and supportive phase 2 study CA209010.

There are no across study integration analyses in this summary of clinical safety. The rationale for not integrating is due to the large sample size in the primary controlled study (CA209025) using the proposed dosing regimen allows for robust characterization of safety, and second, the supportive study (CA209010) was a 3-arm dose-ranging study which evaluated different dosing from the proposed dosing regimen.

Patient exposure

Study CA209025

An overview of the number of subjects enrolled, randomised, and treated in study CA209057 is presented in the table below.

Table 20: End of Treatment Period Subject Status Summary - All Enrolled, Randomized, and Treated Subjects- CA209025

	Nivolumab N = 406	Everolimus N = 397	Total N = 803
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	67 (16.5)	28 (7.1)	95 (11.8)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	339 (83.5)	369 (92.9)	708 (88.2)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)			
DISEASE PROGRESSION	285 (70.2)	273 (68.8)	558 (69.5)
STUDY DRUG TOXICITY	35 (8.6)	53 (13.4)	88 (11.0)
DEATH	1 (0.2)	1 (0.3)	2 (0.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	9 (2.2)	14 (3.5)	23 (2.9)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	5 (1.2)	18 (4.5)	23 (2.9)
SUBJECT WITHDREW CONSENT	2 (0.5)	3 (0.8)	5 (0.6)
MAXIMUM CLINICAL BENEFIT	2 (0.5)	3 (0.8)	5 (0.6)
OTHER	0	4 (1.0)	4 (0.5)
SUBJECTS CONTINUING IN THE STUDY (%)	217 (53.4)	176 (44.3)	393 (48.9)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	189 (46.6)	221 (55.7)	410 (51.1)

The last subject was randomized on 11-Mar-2014, and the last patient's last visit date for this CSR occurred on 06-May-2015, providing a minimum follow-up of approximately 14 months.

At the time of the database lock for this CSR (18-Jun-2015), there were 708 subjects (88%) who discontinued study therapy (339 subjects [83.5%] in the nivolumab group and 369 subjects [92.9%] in the everolimus group). The most common reason for discontinuation of study therapy between the 2 treatment groups was disease progression: 285 subjects (70.2%) and 273 subjects (68.8%) in the nivolumab and everolimus groups, respectively.

Subjects were able to receive a higher dose of nivolumab than everolimus (82.0% vs 68.5% received ≥ 90% of the planned dose intensity), an observation consistent with the observed safety profile of both agents, and with protocol-defined dose reductions for everolimus toxicity as per the approved product labeling (Table 21).

Table 21: Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects - CA209025

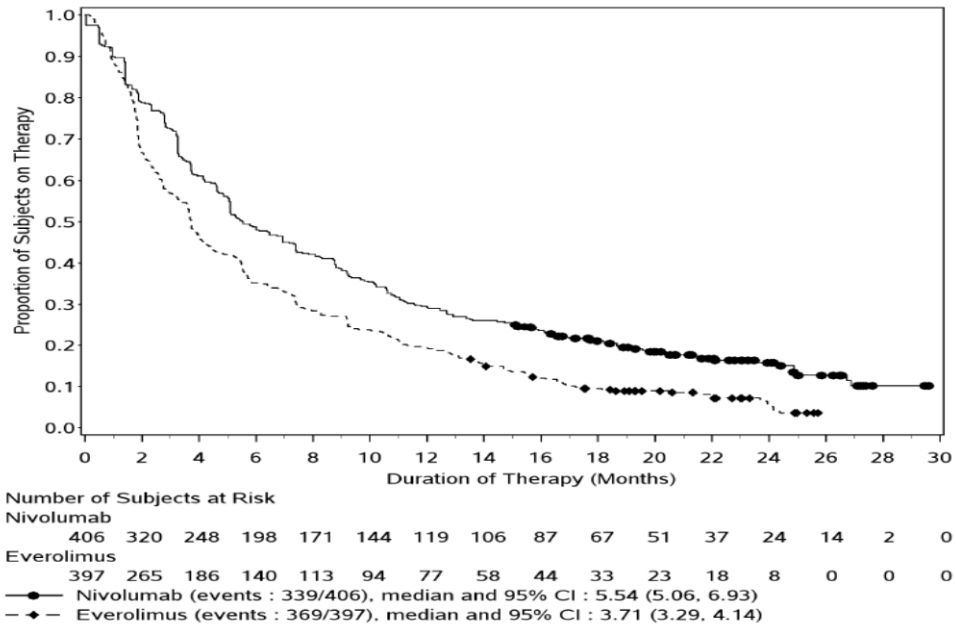
	Nivolumab N = 406	Everolimus N = 397
RELATIVE DOSE INTENSITY		
>= 110%	3 (0.7)	0
90% TO < 110%	330 (81.3)	272 (68.5)
70% TO < 90%	64 (15.8)	49 (12.3)
50% TO < 70%	8 (2.0)	50 (12.6)
< 50%	1 (0.2)	26 (6.5)
AVERAGE DAILY DOSE (MG/DAY)		
MEAN (SD)	N.A.	8.80 (1.851)
MEDIAN (MIN - MAX)	N.A.	9.94 (2.1 - 10.0)
NUMBER OF DOSES RECEIVED		
MEAN (SD)	19.2 (16.25)	N.A.
MEDIAN (MIN - MAX)	12.0 (1 - 65)	N.A.
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	57.72 (49.025)	N.A.
MEDIAN (MIN - MAX)	36.03 (0.5 - 195.1)	N.A.

Abbreviations: MAX: maximum; MIN: minimum; N.A.: not applicable; SD: standard deviation.

In CA209025, nivolumab was administered at 3 mg/kg monotherapy as an IV infusion every 2 weeks. The majority of nivolumab-treated subjects received the intended nivolumab dosing regimen on-study.

The median duration of nivolumab treatment was 5.54 months (range: 0.0 to 29.6+ months) with a median of 12.0 doses received (range: 1 to 65 doses), which was higher than the median duration of everolimus treatment of 3.71 months (range: 0.2 to 25.7+ months) (Figure 15).

Figure 15: Kaplan-Meier Plot of Duration of Study Therapy Subjects -



A substantially higher proportion of subjects in the nivolumab group had a duration of therapy lasting > 6 months than in the everolimus group, and this trend persisted for duration of therapy > 12 months. Accordingly, at the time of analysis, a greater number of subjects were continuing nivolumab treatment than everolimus treatment (67 vs 28 subjects).

A lower frequency of discontinuation for study drug toxicity regardless of causality was observed in the nivolumab group compared with the everolimus group (8.6% vs. 13.4%, respectively). In addition, there were fewer subjects who requested to discontinue study treatment in the nivolumab group compared with the everolimus group (1.2% vs. 4.5%). Nine subjects (2.2%) in the nivolumab group and 14 subjects

(3.5%) in the everolimus group discontinued study treatment due to AEs unrelated to study drug; none of these subjects had disease progression as an additional reason for discontinuation. No subject discontinued nivolumab in the treatment period for a reason listed as “other”. However, 4 subjects in the everolimus group discontinued treatment for a reason listed as “other”: one subjects for PI discretion, other subject for CT report suggested radiological progression and investigator used this instead of RECIST to determine that patient had progressed and took them off trial treatment, in other subject the investigator has determined that the patient should receive radiotherapy for cutaneous metastasis and other required interruption of everolimus for greater than 6 weeks.

Reasons for withdrawal of consent, when given, were: subject refusal to continue treatment, study procedures and survival follow-up (nivolumab group); subject admitted on oncological network and accessing on-market everolimus (everolimus group); subject decided to stop the medication and not accept follow-up contact (everolimus group); subject refused further treatment under the protocol and refused surveillance in the site (everolimus group); and subject will see doctor closer to home (everolimus group).

A total of 5 subjects (2 in the nivolumab group and 3 in the everolimus group) discontinued the study treatment for maximum clinical benefit.

Dose Delay, Dose Reduction, Infusion Interruption, and Reduction of Infusion Rate

Most subjects received all doses of study medication without an infusion interruption (96.6 in the nivolumab group), rate reduction, or delay (Table 22). Dose reductions were not permitted with nivolumab treatment.

Dose Delays and Interruptions

In the nivolumab group, 51.0% of subjects had at least 1 dose delayed, with 42.4% of subjects in the nivolumab group experiencing an AE leading to dose delay (Table 23). Of subjects who experienced dose delays, most experienced only 1 delay, and the majority of cycle delays were ≤14 days.

Table 22: Nivolumab Infusion Interruption, Infusion Rate Reduction, and Dose Delays of Study Therapy - All Treated Subjects- CA209025

	Nivolumab N = 406
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	26 (6.4)
NUMBER OF INFUSION INTERRUPTED PER SUBJECT	
0	380 (93.6)
1	23 (5.7)
2	2 (0.5)
>=3	1 (0.2)
TOTAL NUMBER INFUSION INTERRUPTED/TOTAL NUMBER INFUSION RECEIVED	33/7796 (0.4)
REASON FOR INFUSION INTERRUPTION (A)	
HYPERSENSITIVITY REACTION	19 (57.6)
INFUSION ADMIN ISSUES	10 (30.3)
OTHER	4 (12.1)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	17 (4.2)
NUMBER OF INFUSION WITH IV RATE REDUCED PER SUBJECT	
0	389 (95.8)
1	14 (3.4)
2	0
>=3	3 (0.7)
TOTAL NUMBER INFUSION WITH IV RATE REDUCED/TOTAL NUMBER INFUSION RECEIVED	32/7796 (0.4)
REASON FOR INFUSION IV RATE REDUCTION (B)	
HYPERSENSITIVITY REACTION	16 (50.0)
INFUSION ADMIN ISSUES	9 (28.1)
OTHER	7 (21.9)
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	207 (51.0)
NUMBER OF DOSE DELAYED PER SUBJECT	
0	199 (49.0)
1	120 (29.6)
2	34 (8.4)
>=3	53 (13.1)
TOTAL NUMBER DOSE DELAYED/TOTAL NUMBER DOSE RECEIVED (C)	406/7390 (5.5)
LENGTH OF DELAY (D)	
ON TIME	6984 (94.5)
3 - 7 DAYS	174 (2.4)
8 - 14 DAYS	130 (1.8)
15 - 42 DAYS	93 (1.3)
> 42 DAYS	9 (0.1)
REASON FOR DOSE DELAY (E)	
ADVERSE EVENT	172 (42.4)
OTHER	184 (45.3)
NOT REPORTED	50 (12.3)

Abbreviations: IV: intravenous.
A dose was considered as actually delayed if the delay is exceeding 2 days.
(A) Percentages are computed out of the total number of infusions interrupted
(B) Percentages are computed out of the total number of infusions with IV rate reduced
(C) TOTAL NUMBER DOSE RECEIVED is excluding first dose.
(D) Percentages are computed out of the total number of doses received excluding first dose.
(E) Percentages are computed out of the total number of Dose Delayed.

In the everolimus group, 25.7% of subjects had at least 1 dose reduction and 66.0% of subjects had at least 1 dose interruption.

Table 23: Everolimus Dose Reduction and Dose Delay/Omission/Interruption Summary - All Treated subjects

	Everolimus N = 397
SUBJECTS WITH AT LEAST ONE DOSE REDUCTION (%)	102 (25.7)
REASON FOR DOSE REDUCTION (A)	
ADVERSE EVENT	96
OTHER	20
NOT REPORTED	190
SUBJECTS WITH AT LEAST ONE DOSE DELAY/OMISSION/INTERRUPTION (%)	262 (66.0)
REASON FOR DOSE DELAY/OMISSION/INTERRUPTION (B)	
ADVERSE EVENT	467
OTHER	154
NOT REPORTED	204

(A) Subject may have more than one reason for dose reduction.
(B) Subject may have more than one reason for drug delay/omission/interruption.

A safety update for CA209025 with a database lock (DBL) of 21-Aug-2015, 15.8% of subjects on the nivolumab arm and 6.5% of subjects on the everolimus arm remained on study treatment, and all subjects have had a minimum of 16 months of follow-up. No new safety signals were identified in CA209025 with the longer follow-up. The database lock point of the safety profile for CA209025 is for 18-Jun-2015.

Adverse events

The primary analyses of AEs, SAEs, and AEs leading to discontinuation are based on all treated subjects using a safety window of 30 days after last dose. The 30-day safety window was intended to provide a characterization of the safety experience of nivolumab monotherapy without influence of AEs associated with subsequent therapies. Additional analyses with extended safety follow-up (using a 100-day window), although potentially confounded by subsequent therapies, were conducted to assess differences in safety potentially due to late occurring AEs.

Safety with Extended Follow-up

Overall, similar frequencies were observed for all-causality, any-grade AEs reported within 100 days of the last dose (extended follow up) compared to those reported within 30 days for the nivolumab group.

- With extended follow-up, the frequencies of all-causality, all-grade SAEs, and Grade 5 SAEs/AEs increased compared to the frequencies reported within 30 days. This increase was observed for subjects in both treatment groups and was primarily due to disease-related deaths as would be expected.
- The frequencies of AEs leading to discontinuation, drug-related AEs and drug-related SAEs reported within 100 days of last dose were consistent with those reported within 30 days of the last dose.

A summary of the safety results in all treated subjects in study CA209025 is provided in the table below.

Table 24: Summary of Safety Results - All Treated Subjects - CA209025

	Number (%) Subjects	
	Nivolumab (N = 406)	Everolimus (N = 397)
DEATHS	181 (44.6)	213 (53.7)
WITHIN 30 DAYS OF LAST DOSE	19 (4.7)	34 (8.6)
WITHIN 100 DAYS OF LAST DOSE	56 (13.8)	80 (20.2)
DUE TO STUDY DRUG TOXICITY	0	2 (0.5)

	Number (%) Subjects					
	Nivolumab (N = 406)			Everolimus (N = 397)		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL AEs	397 (97.8)	216 (53.2)	14 (3.4)	386 (97.2)	224 (56.4)	27 (6.8)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)						
FATIGUE	195 (48.0)	18 (4.4)	0	178 (44.8)	19 (4.8)	0
COUGH	129 (31.8)	0	0	141 (35.5)	2 (0.5)	0
NAUSEA	115 (28.3)	2 (0.5)	0	114 (28.7)	5 (1.3)	0
DIARRHOEA	96 (23.6)	5 (1.2)	0	124 (31.2)	6 (1.5)	0
DYSPNOEA	94 (23.2)	11 (2.7)	0	106 (26.7)	8 (2.0)	0
DECREASED APPETITE	93 (22.9)	5 (1.2)	0	121 (30.5)	6 (1.5)	0
CONSTIPATION	92 (22.7)	2 (0.5)	0	73 (18.4)	2 (0.5)	0
BACK PAIN	87 (21.4)	14 (3.4)	0	62 (15.6)	11 (2.8)	0
ANAEMIA	78 (19.2)	24 (5.9)	0	139 (35.0)	52 (13.1)	0
PYREXIA	67 (16.5)	3 (0.7)	0	80 (20.2)	3 (0.8)	0
RASH	64 (15.8)	3 (0.7)	0	92 (23.2)	3 (0.8)	0
OEDEMA PERIPHERAL	58 (14.3)	2 (0.5)	0	102 (25.7)	4 (1.0)	0
STOMATITIS	20 (4.9)	0	0	126 (31.7)	18 (4.5)	0
MUCOSAL INFLAMMATION	15 (3.7)	0	0	82 (20.7)	14 (3.5)	0
DRUG-RELATED AEs	319 (78.6)	76 (18.7)	0	349 (87.9)	145 (36.5)	2 (0.5)
Most Frequent AEs (≥15% of Any Grade in either treatment group)						
FATIGUE	134 (33.0)	10 (2.5)	0	134 (33.8)	11 (2.8)	0
NAUSEA	57 (14.0)	1 (0.2)	0	66 (16.6)	3 (0.8)	0
DIARRHOEA	50 (12.3)	5 (1.2)	0	84 (21.2)	5 (1.3)	0
DECREASED APPETITE	48 (11.8)	2 (0.5)	0	82 (20.7)	4 (1.0)	0
RASH	41 (10.1)	2 (0.5)	0	79 (19.9)	3 (0.8)	0
COUGH	36 (8.9)	0	0	77 (19.4)	0	0
ANAEMIA	32 (7.9)	7 (1.7)	0	94 (23.7)	31 (7.8)	0
MUCOSAL INFLAMMATION	11 (2.7)	0	0	75 (18.9)	12 (3.0)	0
STOMATITIS	8 (2.0)	0	0	117 (29.5)	17 (4.3)	0
HYPERTRIGLYCERIDAEMIA	5 (1.2)	0	0	64 (16.1)	20 (5.0)	0
ALL SAEs	194 (47.8)	148 (36.5)	14 (3.4)	173 (43.6)	116 (29.2)	27 (6.8)
DRUG-RELATED SAEs	47 (11.6)	32 (7.9)	0	53 (13.4)	37 (9.3)	2 (0.5)
ALL AEs LEADING TO DISCONTINUATION	72 (17.7)	45 (11.1)	7 (1.7)	82 (20.7)	45 (11.3)	6 (1.5)
DRUG-RELATED AEs LEADING TO DISCONTINUATION	31 (7.6)	19 (4.7)	0	52 (13.1)	28 (7.1)	2 (0.5)

Abbreviations: AE: adverse event; SAE: serious adverse event.
All events are within 30 days of the last dose of study drug, unless otherwise indicated.

The overall frequencies of all-causality AEs of any grade and Grade 3-4 AEs were similar between the nivolumab and everolimus groups; table 25 (5% cutoff).

Table 25: Summary of Any Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 5% Cutoff - All Treated Subjects - CA209025

System Organ Class (%) Preferred Term (%)	Nivolumab N = 406			Everolimus N = 397		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	397 (97.8)	216 (53.2)	14 (3.4)	386 (97.2)	224 (56.4)	27 (6.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	288 (70.9)	37 (9.1)	1 (0.2)	297 (74.8)	57 (14.4)	0
FATIGUE	195 (48.0)	18 (4.4)	0	178 (44.8)	19 (4.8)	0
PYREXIA	67 (16.5)	3 (0.7)	0	80 (20.2)	3 (0.8)	0
OEDEMA PERIPHERAL	58 (14.3)	2 (0.5)	0	102 (25.7)	4 (1.0)	0
ASTHENIA	36 (8.9)	6 (1.5)	0	65 (16.4)	11 (2.8)	0
CHILLS	29 (7.1)	0	0	23 (5.8)	0	0
PAIN	23 (5.7)	7 (1.7)	0	19 (4.8)	2 (0.5)	0
MUCOSAL INFLAMMATION	15 (3.7)	0	0	82 (20.7)	14 (3.5)	0
GASTROINTESTINAL DISORDERS	263 (64.8)	27 (6.7)	0	291 (73.3)	44 (11.1)	1 (0.3)
NAUSEA	115 (28.3)	2 (0.5)	0	114 (28.7)	5 (1.3)	0
DIARRHOEA	96 (23.6)	5 (1.2)	0	124 (31.2)	6 (1.5)	0
CONSTIPATION	92 (22.7)	2 (0.5)	0	73 (18.4)	2 (0.5)	0
VOMITING	66 (16.3)	2 (0.5)	0	63 (15.9)	2 (0.5)	0
ABDOMINAL PAIN	36 (8.9)	4 (1.0)	0	32 (8.1)	1 (0.3)	0
DRY MOUTH	26 (6.4)	0	0	18 (4.5)	0	0
ABDOMINAL PAIN UPPER	25 (6.2)	2 (0.5)	0	15 (3.8)	1 (0.3)	0
STOMATITIS	20 (4.9)	0	0	126 (31.7)	18 (4.5)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	240 (59.1)	38 (9.4)	0	186 (46.9)	20 (5.0)	0
BACK PAIN	87 (21.4)	14 (3.4)	0	62 (15.6)	11 (2.8)	0
ARTHRALGIA	80 (19.7)	4 (1.0)	0	57 (14.4)	2 (0.5)	0
PAIN IN EXTREMITY	49 (12.1)	5 (1.2)	0	35 (8.8)	0	0
MUSCULOSKELETAL PAIN	41 (10.1)	4 (1.0)	0	21 (5.3)	1 (0.3)	0
MYALGIA	39 (9.6)	0	0	14 (3.5)	0	0
MUSCULOSKELETAL CHEST PAIN	25 (6.2)	0	0	18 (4.5)	0	0
FLANK PAIN	21 (5.2)	0	0	15 (3.8)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	232 (57.1)	34 (8.4)	0	260 (65.5)	48 (12.1)	0
COUGH	129 (31.8)	0	0	141 (35.5)	2 (0.5)	0
DYSPNOEA	94 (23.2)	11 (2.7)	0	106 (26.7)	8 (2.0)	0
DYSPHONIA	25 (6.2)	0	0	18 (4.5)	1 (0.3)	0
HAEMOPTYSIS	23 (5.7)	1 (0.2)	0	13 (3.3)	1 (0.3)	0
NASAL CONGESTION	23 (5.7)	0	0	12 (3.0)	0	0
PLEURAL EFFUSION	20 (4.9)	11 (2.7)	0	26 (6.5)	14 (3.5)	0
DYSPNOEA EXERTIONAL	19 (4.7)	1 (0.2)	0	22 (5.5)	0	0
PNEUMONITIS	19 (4.7)	6 (1.5)	0	61 (15.4)	12 (3.0)	0
OROPHARYNGEAL PAIN	12 (3.0)	0	0	24 (6.0)	0	0
EPISTAXIS	10 (2.5)	0	0	56 (14.1)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	194 (47.8)	8 (2.0)	0	219 (55.2)	7 (1.8)	0
PRURITUS	75 (18.5)	0	0	50 (12.6)	0	0
RASH	64 (15.8)	3 (0.7)	0	92 (23.2)	3 (0.8)	0
DRY SKIN	41 (10.1)	1 (0.2)	0	44 (11.1)	0	0
RASH MACULO-PAPULAR	19 (4.7)	2 (0.5)	0	20 (5.0)	0	0
DERMATITIS ACNEIFORM	12 (3.0)	0	0	21 (5.3)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	10 (2.5)	0	0	25 (6.3)	0	0
INVESTIGATIONS	182 (44.8)	49 (12.1)	0	171 (43.1)	17 (4.3)	0
BLOOD CREATININE INCREASED	56 (13.8)	4 (1.0)	0	50 (12.6)	1 (0.3)	0
WEIGHT DECREASED	45 (11.1)	2 (0.5)	0	58 (14.6)	3 (0.8)	0
ASPARTATE AMINOTRANSFERASE INCREASED	31 (7.6)	11 (2.7)	0	25 (6.3)	3 (0.8)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	27 (6.7)	1 (0.2)	0	14 (3.5)	1 (0.3)	0
ALANINE AMINOTRANSFERASE INCREASED	26 (6.4)	12 (3.0)	0	23 (5.8)	1 (0.3)	0
BLOOD CHOLESTEROL INCREASED	7 (1.7)	1 (0.2)	0	31 (7.8)	1 (0.3)	0
METABOLISM AND NUTRITION DISORDERS	172 (42.4)	48 (11.8)	0	239 (60.2)	72 (18.1)	0
DECREASED APPETITE	93 (22.9)	5 (1.2)	0	121 (30.5)	6 (1.5)	0
HYPERGLYCAEMIA	34 (8.4)	14 (3.4)	0	62 (15.6)	25 (6.3)	0
HYPERCALCAEMIA	29 (7.1)	12 (3.0)	0	12 (3.0)	2 (0.5)	0
HYPERKALAEMIA	24 (5.9)	4 (1.0)	0	15 (3.8)	3 (0.8)	0
HYPONATRAEMIA	22 (5.4)	10 (2.5)	0	18 (4.5)	12 (3.0)	0
HYPERTRIGLYCERIDAEMIA	21 (5.2)	3 (0.7)	0	75 (18.9)	24 (6.0)	0
HYPERCHOLESTEROLAEMIA	2 (0.5)	0	0	37 (9.3)	0	0
INFECTIONS AND INFESTATIONS	167 (41.1)	37 (9.1)	1 (0.2)	187 (47.1)	40 (10.1)	1 (0.3)
NASOPHARYNGITIS	37 (9.1)	0	0	18 (4.5)	0	0
UPPER RESPIRATORY TRACT INFECTION	30 (7.4)	0	0	22 (5.5)	0	0
URINARY TRACT INFECTION	21 (5.2)	4 (1.0)	0	21 (5.3)	5 (1.3)	0
PNEUMONIA	15 (3.7)	8 (2.0)	1 (0.2)	28 (7.1)	15 (3.8)	1 (0.3)

System Organ Class (%) Preferred Term (%)	Nivolumab N = 406			Everolimus N = 397		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
NERVOUS SYSTEM DISORDERS	147 (36.2)	20 (4.9)	1 (0.2)	140 (35.3)	6 (1.5)	2 (0.5)
HEADACHE	57 (14.0)	1 (0.2)	0	55 (13.9)	1 (0.3)	0
DIZZINESS	35 (8.6)	0	0	31 (7.8)	0	0
DYSGEUSIA	14 (3.4)	0	0	53 (13.4)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	90 (22.2)	24 (5.9)	0	154 (38.8)	58 (14.6)	0
ANAEMIA	78 (19.2)	24 (5.9)	0	139 (35.0)	52 (13.1)	0
VASCULAR DISORDERS	79 (19.5)	13 (3.2)	0	57 (14.4)	14 (3.5)	0
HYPERTENSION	35 (8.6)	9 (2.2)	0	28 (7.1)	12 (3.0)	0
HYPOTENSION	22 (5.4)	1 (0.2)	0	6 (1.5)	1 (0.3)	0
PSYCHIATRIC DISORDERS	78 (19.2)	2 (0.5)	1 (0.2)	68 (17.1)	2 (0.5)	1 (0.3)
INSOMNIA	28 (6.9)	0	0	26 (6.5)	0	0
ANXIETY	27 (6.7)	0	0	20 (5.0)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	63 (15.5)	35 (8.6)	8 (2.0)	40 (10.1)	13 (3.3)	20 (5.0)
MALIGNANT NEOPLASM PROGRESSION	22 (5.4)	12 (3.0)	8 (2.0)	24 (6.0)	4 (1.0)	20 (5.0)
ENDOCRINE DISORDERS	40 (9.9)	4 (1.0)	0	9 (2.3)	1 (0.3)	0
HYPOTHYROIDISM	28 (6.9)	1 (0.2)	0	6 (1.5)	0	0

MedDRA Version: 18.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program Source: /projects/bms211241/stats/primary/prog/tables/rt-ae-aecat.sas 06AUG2015:06:35:44

Study CA209010:

In CA209010 the safety profile was generally similar across treatment groups and the types of events reported were as expected based on the mechanism of action of nivolumab and previous experience in earlier studies (Table 26).

Table 26: Summary of Safety Results - All Treated Subjects - CA209010

		Nivolumab (N = 167)		
		0.3 mg/kg (N = 59)	2 mg/kg (N = 54)	10 mg/kg (N = 54)
		n (%)		
Deaths		40 (67.8)	35 (64.8)	37 (68.5)
Drug-Related Deaths		0	0	0
Any SAEs	Any Grade	28 (47.5)	35 (64.8)	22 (40.7)
	Grade 3	11 (18.6)	22 (40.7)	13 (24.1)
	Grade 4	6 (10.2)	6 (11.1)	4 (7.4)
	Grade 5	6 (10.2)	5 (9.3)	3 (5.6)
Drug-Related SAEs	Any Grade	3 (5.1)	6 (11.1)	3 (5.6)
	Grade 3	0	5 (9.3)	2 (3.7)
	Grade 4	0	0	0
	Grade 5	0	0	0
Any AEs Leading to Discontinuation	Any Grade	4 (6.8)	12 (22.2)	8 (14.8)
	Grade 3	2 (3.4)	8 (14.8)	2 (3.7)
	Grade 4	1 (1.7)	0	1 (1.9)
	Grade 5	0	1 (1.9)	1 (1.9)
Drug-Related AEs Leading to Discontinuation	Any Grade	2 (3.4)	7 (13.0)	4 (7.4)
	Grade 3	1 (1.7)	4 (7.4)	0
	Grade 4	0	0	0
	Grade 5	0	0	0
Any AEs	Any Grade	58 (98.3)	54 (100)	53 (98.1)
	Grade 3	19 (32.2)	27 (50.0)	22 (40.7)
	Grade 4	6 (10.2)	6 (11.1)	4 (7.4)
	Grade 5	6 (10.2)	5 (9.3)	3 (5.6)
Drug-Related AEs	Any Grade	45 (76.3)	36 (66.7)	41 (75.9)
	Grade 3	4 (6.8)	9 (16.7)	9 (16.7)
	Grade 4	0	0	0
	Grade 5	0	0	0

Abbreviations: AE: adverse event; n: number; SAE: serious adverse event.

Selected AEs - CA209025

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, diarrhea/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.

Analysis of AEs belonging to select AE categories were not performed on an individual term level, but instead include all terms in each select AE category. The composite group of MedDRA PTs belonging to each select AE category was included in each individual select AE section below. Events of special clinical interest that do not benefit from pooling of multiple terms were analyzed outside of the context of the select AE categories.

Hypersensitivity/infusion reactions were analyzed along with the select AE categories because multiple event terms may be used to describe such events and pooling of terms was therefore necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs.

Among nivolumab-treated subjects, skin, GI, renal and hepatic were the most frequently reported select AE categories (≥ 15% of subjects), regardless of causality. The majority of select AEs reported were Grade 1-2, and most were considered drug-related by the investigator.

The most frequently reported (> 10% of subjects) any grade drug-related select AE category with nivolumab treatment was skin (24.9%), followed by GI (12.6%), and hepatic (11.3%). The most frequently reported (≥ 1% of subjects) Grade 3-4 drug-related select AE categories with nivolumab treatment were hepatic (2.7%), GI (2.0%), pulmonary (1.5%); endocrine, renal and skin were each reported by 1.0% of subjects.

The median time to onset varied among the select AE categories. Drug-related hypersensitivity/infusion reaction select AEs (any grade) had a median time to onset < 6 weeks after initiation of nivolumab treatment whereas all other categories had a median time to onset > 6 weeks.

The time to resolution also varied among the select AE categories. Most drug-related select AEs (any grade) in the GI, pulmonary, and hypersensitivity/infusion reaction categories had a median time to resolution < 6 weeks after onset. Those in the hepatic category had a median time to resolution 8.00 weeks; while renal and skin categories had a median time to resolution of 31.14 and 20.14 weeks, respectively. Most AEs belonging to the endocrine select AE category had not yet resolved due to the continuing need for replacement therapy.

Endocrine Events - CA209025

The endocrine select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders. These terms were selected to encompass those considered most likely to be reported in a subject with an endocrinopathy belonging to the subcategories above.

Endocrine select AEs (all-causality, any grade) were reported in 12.3% of subjects in the nivolumab group and 4.8% of subjects in the everolimus group. The majority of endocrine select AEs in the nivolumab group were considered to be drug-related by the investigator.

In the nivolumab group:

- Drug-related endocrine select AEs were reported in 39 subjects (9.6%) and the majority of the events reported were hypothyroidism (24 subjects [5.9%]).
- There were 4 subjects (1.0%) with Grade 3-4 drug-related events. Three of these events were considered serious drug-related events (Grade 3-4): 2 subjects (0.5%) had adrenal insufficiency drug-related SAEs, and 1 subject (0.2%) had a diabetic ketoacidosis drug-related SAE.
- One subject (0.2%) reported drug-related events of adrenal insufficiency and hypophysitis that led to treatment discontinuation.
- The median time to onset for any grade drug-related endocrine select AE was 16.00 weeks
- Eight subjects with a drug-related event were treated with immune-modulating medication, 3 subjects received high-dose corticosteroids.
- Overall, 14 (35.9%) of the 39 subjects with drug-related endocrine AEs had resolution of their events.
- A similar incidence was observed for AEs belonging to the endocrine select AE category reported within 100 days of last dose compared to those reported within 30 days of the last dose.

Gastrointestinal Events - CA209025

The GI select AE category included the following terms: autoimmune colitis, colitis ulcerative, diarrhea, enteritis, enterocolitis, frequent bowel movements, and GI perforation. These terms were selected to encompass those most likely to be reported in a subject with diarrhea or colitis.

The frequency of GI select AEs (all-causality, any grade) was lower in the nivolumab group than in the everolimus group (24.4% vs 31.2%, respectively). The frequency of drug-related GI select AEs (any grade) was also lower in the nivolumab group than in the everolimus group (12.6% vs 21.2%, respectively).

In the nivolumab group:

- All drug-related events reported were diarrhea (12.3%) or colitis (1.7%), and the majority of drug-related GI select AEs were Grade 1-2. Seven drug-related GI select AEs were reported as SAEs; for 4 subjects, the AEs led to discontinuation of study therapy.
    - There were 5 subjects with Grade 3 diarrhea events reported: 2 subjects had SAEs of diarrhea; 2 subjects had 2 AEs of diarrhea; 1 subject had 4 events of diarrhea reported (2 AEs and 2 SAEs). There were no Grade 4 or 5 events reported.
    - There were 3 subjects with Grade 3 colitis events reported, each subject had 1 event. For 2 of the 3 subjects, the events of colitis were SAEs and drug was withdrawn. There were no Grade 4 or 5 events reported.
- The median time to onset for any grade drug-related GI select AE was 8.29 weeks. The median time to onset of the Grade 3 drug-related events was 20.71 weeks.
- Eleven subjects received immune-modulating medication (high-dose corticosteroids in 10 of the 11 cases) for drug-related GI select AEs.
- The majority of subjects (44 subjects [86.3%]) with drug-related GI AEs (any grade) had resolution of their event. All but 1 subject with Grade 3 drug-related GI select AEs had resolution of their events. The median time to resolution for any grade drug-related GI select AEs was 5.57 weeks.
- A similar incidence was observed for AEs belonging to the GI select AE category reported within 100 days of last dose compared to those reported within 30 days of the last dose. One additional drug-related Grade 3 SAE of diarrhea was reported during the extended follow-up period (between 30 and 100 days after last dose).

Hepatic Events- CA209025

The hepatic select AE category included the following terms: acute hepatic failure, ALT increased, AST increased, autoimmune hepatitis, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, drug-induced liver injury, GGT increased, hepatic enzyme increased, hepatic failure, hepatitis, hepatitis acute, hepatotoxicity, hyperbilirubinemia, liver disorder, liver function test abnormal, liver injury, and transaminases increased. These terms were selected to encompass those most likely to be reported in a subject with hepatitis.

Hepatic select AEs (all-causality, any-grade) were reported in 16.0% of subjects in the nivolumab and 11.3% of subjects in the everolimus groups.

In the nivolumab group:

- Drug-related hepatic select AEs were reported in 46 (11.3%) subjects, and increased ALT, increased blood ALP, and increased AST were the most frequently reported drug-related hepatic select AEs.
- The majority of drug-related hepatic select AEs were Grade 1-2.
- Eleven subjects (2.7%) reported Grade 3-4 drug-related hepatic select events, and most of the AEs were laboratory abnormalities. One of these subjects reported a serious drug-related hepatic select event for autoimmune hepatitis (and increased transaminase) (Grade 3) that led to study medication discontinuation. In addition, the following subjects discontinued study medication (all grades): 4 subjects (1.0%) discontinued due to increased ALT, and 3 subjects (0.7%) discontinued due to increased AST.
- The median time to onset of any grade drug-related hepatic AE was 7.21 weeks. The median time to onset of the Grade 3-4 drug-related events (in 11 subjects) was 4.14 weeks.
- Five subjects received immune-modulating medication (high-dose corticosteroids in all cases) for drug-related hepatic select AEs.
- The majority of the subjects (37 subjects [82.2%]) with drug-related hepatic select AEs had resolution of their event. Ten of the 11 Grade 3-4 drug-related events resolved, and all of the subjects with Grade 3-4 drug-related events who received immune-modulating medication had resolution of their event. The median time to resolution for any grade drug-related hepatic select AE was 8.00 weeks.
- A similar incidence was observed for AEs belonging to the hepatic select AE category reported within 100 days of last dose compared to those reported within 30 days of the last dose.

Pulmonary Events - CA209025

The pulmonary select AE category included the following terms: acute respiratory distress syndrome, acute respiratory failure, interstitial lung disease, lung infiltration, and pneumonitis. These terms were selected to encompass those most likely to be reported in a subject with pneumonitis. Although hypoxia and dyspnea are not included as terms in this category, all events of hypoxia and clinically important events of dyspnea (Grade 1-2 requiring dose modification, Grade 2 requiring treatment, or Grade 3-4) occurring on or after the first day of dosing, were systematically queried by the Sponsor to confirm that an underlying diagnosis such as pneumonitis, rather than a sign or symptom related to another etiology, was reported if available.

Pneumonia was not included as a term in the pulmonary select AE category because of the high frequency with which it was expected to be reported, especially to describe infectious etiologies rather than non-infectious pneumonitis. The inclusion of pneumonia as a select AE term would hinder characterization of the true frequency of pneumonitis.

Pulmonary select AEs (all-causality, any-grade) were reported in fewer subjects in the nivolumab group compared with the everolimus group (5.7% vs 18.6%). The majority of pulmonary select AEs in the nivolumab group were considered to be drug-related by the investigator.

In the nivolumab group:

- Drug-related pulmonary select AEs were reported in 18 subjects (4.4%).
- Pneumonitis (3.9%) and interstitial lung disease (0.5%) were the only drug-related pulmonary select AEs reported.
- The majority of drug-related AEs were Grade 1-2. Drug-related Grade 3-4 events of pneumonitis were reported in 6 subjects (5 subjects with Grade 3 and 1 subject with Grade 4 events). There were no Grade 3-4 interstitial lung disease events reported.
- All 6 drug-related Grade 3-4 pulmonary AEs were considered SAEs; all but 1 event led to treatment discontinuation.
- The median time to onset of any-grade drug-related pulmonary select AE was 16.57 weeks. The median time to onset of the Grade 3-4 drug-related events (in 6 subjects) was 15.79 weeks.
- Fourteen of the 18 subjects with drug-related pulmonary select AEs received immunemodulating medication (12 were high-dose corticosteroids); all 5 subjects with Grade 3-4 events were treated with high-dose corticosteroids.
- Fifteen of the 18 subjects (83.3%) with events (any grade) had resolution of their events. Five of the Grade 3-4 pulmonary events resolved; 1 event of pneumonitis was ongoing at the time of database lock. The median time to resolution for any grade drug-related pulmonary select AE was 5.57 weeks.

A similar incidence was observed for AEs belonging to the pulmonary select AE category reported within 100 days of last dose compared to those reported within 30 days of the last dose. No additional drug-related events were reported during the extended follow-up period (between 30 and 100 days after last dose).

Renal Events - CA209025

The renal select AE category included the following terms: acute kidney injury, blood creatinine increased, blood urea increased, creatinine renal clearance decreased, hypercreatinemia, nephritis, nephritis allergic, nephritis autoimmune, renal failure, renal tubular necrosis, tubulointerstitial nephritis, and urine output decreased. These terms were selected to encompass those most likely to be reported in a subject with nephritis.

Renal select AEs (all-causality, any-grade) were reported in 17.5% of subjects in the nivolumab group and 14.1% of subjects in the everolimus group. Drug-related renal select AEs were similar between the 2 groups: 6.9% and 8.8% in nivolumab and everolimus groups, respectively.

In the nivolumab group:

- Grade 3-4 drug-related renal select AEs included: increased blood creatinine (0.2%), acute kidney injury (0.7%), and tubulointerstitial nephritis (0.2%). Three subjects (0.7%) reported drug-related renal select SAEs.
    - 1 subject had 4-Grade 3 and 1-Grade 4 increased blood creatinine events, and this subject also had a SAE reported of acute kidney injury (Grade 4), which led to study medication discontinuation.
    - 1 subject had a SAE of tubulointerstitial nephritis (Grade 3), and study medication was discontinued due to this SAE.
    - 1 subject had a SAE of acute kidney injury (Grade 3), and 1 subject had an AE of acute kidney injury (Grade 3).
- The median time to onset of any grade drug-related renal AE in the nivolumab group was 10.64 weeks.
- Seven subjects with drug-related renal select AEs received immune-modulating medication (all high dose corticosteroids).
- Sixteen (59.3%) of the 27 subjects in the nivolumab group with drug-related renal select AEs had resolution of their event. Two subjects with Grade 3-4 events who received immune-modulating

medication had resolution of their event in 1.57 weeks. The median time to resolution for any grade drug-related renal select AE was 31.14 weeks.

A similar incidence was observed for AEs belonging to the renal select AE category reported up to 100 days after last dose compared to those reported up to 30 days after last dose.

Skin Events - CA209025

The skin select AE category included the following terms: autoimmune dermatitis, blister, dermatitis, dermatitis exfoliative, drug eruption, eczema, erythema, erythema multiform, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, pruritus, pruritus allergic, pruritus generalized, psoriasis, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, skin exfoliation, skin hypopigmentation, skin irritation, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, and vitiligo. These terms were selected to encompass those most likely to be reported in a subject with rash.

Skin select AEs (all-causality, any-grade) were reported in fewer subjects in the nivolumab group (37.2%) compared with the everolimus group (44.6%). Most of the skin select AEs were considered to be drug-related by the investigator in both treatment groups.

In the nivolumab group:

- Drug-related skin select AEs were reported in 101 (24.9%) subjects.
- The most frequently reported drug-related terms (> 1% of subjects) were pruritus, rash, rash maculo-papular, and erythema.
- There was no event of toxic epidermal necrolysis reported.
- The majority of drug-related select skin AEs were Grade 1-2; there were 4-Grade 3 drug-related events reported (rash, rash macular, and rash maculo-papular). There were no Grade 4 or 5 events.
- One subject (0.2%) had a drug-related skin select SAE (erythema multiforme), and 1 subject (0.2%) reported an AE of rash maculo-papular, which led to study medication discontinuation.
- The median time to onset of any grade drug-related skin AE was 8.29 weeks.
- Thirty-one subjects (30.7%) with drug-related events received immune-modulating medication (2 subjects received high dose corticosteroids).
- Seventy-five (75.8%) of the 99 subjects with drug-related skin select AEs had resolution of their event, including 21 of the subjects treated with immune-modulating medication. All 4 subjects with Grade 3 drug-related skin select AEs had resolution of their events. The median time to resolution of any grade drug-related skin select AE was 20.14 weeks.

A similar incidence was observed for AEs belonging to the skin select AE category reported up to 100 days after last dose compared to those reported up to 30 days after last dose.

Hypersensitivity/Infusion Reactions - CA209025

Hypersensitivity/infusion reactions were analyzed along with the select AE categories because multiple event terms may be used to describe such events and pooling of terms is therefore necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered a select AE. Hypersensitivity/infusion reactions included the following terms: anaphylactic reaction, anaphylactic shock, bronchospasm, hypersensitivity, and infusionrelated reaction.

Hypersensitivity/infusion related reactions (all-causality, any-grade) were reported in 6.2% of subjects in the nivolumab group and 1.0% in the everolimus group. Most of the hypersensitivity/infusion reactions were considered to be drug-related by investigators.

In the nivolumab group:

- Drug-related hypersensitivity and infusion reactions were reported in 21 subjects (5.2%).
- There was 1 SAE reported of anaphylactic reaction, Grade 4, which led to study medication discontinuation. One subject also discontinued study medication due to an AE of an infusion-related reaction (Grade 2).
- The median time to onset of any grade drug-related hypersensitivity/infusion reaction was 2.00 weeks.
- Seven subjects with drug-related events received immune-modulating medication; 3 received high dose corticosteroids.
- All subjects with drug-related hypersensitivity/infusion reactions had resolution of their event. The median time to resolution of any grade drug-related hypersensitivity/infusion reaction was 0.14 weeks.

No new Grade 3-4 hypersensitivity/infusion reactions were reported in the extended follow-up period between 30 and 100 days after last dose.

Select AEs – CA209010

Select Adverse Events in all treated subjects for study CA209010 are summarized in the table below.

Table 27: Summary of Select Adverse Events - All Treated Subjects - CA209010

		Nivolumab (N = 167)		
		0.3 mg/kg (N = 59)	2 mg/kg (N = 54)	10 mg/kg (N = 54)
Category	Worst Grade	n (%)		
Endocrine AEs				
Any Causality	Any Grade	5 (8.5)	7 (13.0)	9 (16.7)
	Grade 3-4	0	2 (3.7)	0
	Grade 5	0	0	0
Drug-Related	Any Grade	4 (6.8)	7 (13.0)	7 (13.0)
	Grade 3-4	0	2 (3.7)	0
	Grade 5	0	0	0
Gastrointestinal AEs				
Any Causality	Any Grade	8 (13.6)	10 (18.5)	17 (31.5)
	Grade 3-4	0	1 (1.9)	2 (3.7)
	Grade 5	0	0	0
Drug-Related	Any Grade	4 (6.8)	7 (13.0)	9 (16.7)
	Grade 3-4	0	1 (1.9)	1 (1.9)
	Grade 5	0	0	0
Hepatic AEs				
Any Causality	Any Grade	4 (6.8)	7 (13.0)	8 (14.8)
	Grade 3-4	1 (1.7)	3 (5.6)	1 (1.9)
	Grade 5	0	0	0
Drug-Related	Any Grade	2 (3.4)	5 (9.3)	3 (5.6)
	Grade 3-4	1 (1.7)	2 (3.7)	0
	Grade 5	0	0	0
Hypersensitivity Infusion Reaction				
Any Causality	Any Grade	3 (5.1)	2 (3.7)	11 (20.4)
	Grade 3-4	0	0	0
	Grade 5	0	0	0
Drug-Related	Any Grade	1 (1.7)	2 (3.7)	11 (20.4)
	Grade 3-4	0	0	0
	Grade 5	0	0	0
Pulmonary AEs				
Any Causality	Any Grade	3 (5.1)	3 (5.6)	5 (9.3)
	Grade 3-4	0	0	0
	Grade 5	0	0	0
Drug-Related	Any Grade	3 (5.1)	3 (5.6)	5 (9.3)
	Grade 3-4	0	0	0
	Grade 5	0	0	0
Renal AEs				
Any Causality	Any Grade	7 (11.9)	7 (13.0)	3 (5.6)
	Grade 3-4	2 (3.4)	2 (3.7)	0
	Grade 5	0	0	0
Drug-Related	Any Grade	1 (1.7)	0	1 (1.9)
	Grade 3-4	0	0	0
	Grade 5	0	0	0
Skin AEs				
Any Causality	Any Grade	16 (27.1)	18 (33.3)	21 (38.9)
	Grade 3-4	0	2 (3.7)	1 (1.9)
	Grade 5	0	0	0
Drug-Related	Any Grade	13 (22.0)	12 (22.2)	16 (29.6)
	Grade 3-4	0	2 (3.7)	0
	Grade 5	0	0	0

Adverse drug reactions

Safety data to support Section 4.8 of the SmPC were pooled across completed studies in multiple indications using the intended dose and regimen for nivolumab monotherapy. The studies included in the analyses for nivolumab monotherapy (3 mg/kg Q2W) were as follows: three studies in NSCLC (CA209057, CA209017, and CA209063), three studies in melanoma (CA209037, CA209066, and CA209067 [monotherapy arm]) and one study in renal cell carcinoma (CA209025).

The general safety profile in the pooled monotherapy data across indications is consistent with the safety reported for each indication.

The studies used for the pooling of safety data are summarized in the table below.

Table 28: Overview of Nivolumab 3 mg/kg monotherapy phase 2/3 studies in NSCLC, Melanoma and RCC

	RCC	Melanoma	NSCLC
Study (no. subjects treated with nivolumab 3 mg/kg monotherapy)	CA209025 (406)	CA209067 (313) CA209066 (206) CA209037 (268)	CA209057 (287) CA209017 (131) CA209063 (117)
Total no. subjects treated with nivolumab 3 mg/kg monotherapy per tumor type	406	787	535
Total exposure, patient years	328.3	500.2	277.8
Mean duration of nivolumab treatment, months[a]	9.7	7.6	6.2
Mean number of nivolumab doses received	19.2	15.4	12.0

Abbreviations: NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

[a] Mean duration of study therapy was calculated as total exposure (years) * 12/number of treated subjects.

All studies are Phase 3, with the exception of Phase 2 Study CA209063.

Overall, the safety profile of nivolumab monotherapy in the different indications is consistent.

In general, the type, frequency, and severity of AEs were consistent across tumour types.

Exposure-adjusted AE incidence rates (events per 100 person-years of exposure) were 1648.7 in RCC, 1747.7 in melanoma, and 1795.6 in NSCLC.

The table below summarises all ADRs listed in section 4.8 together with frequency based on the pooled safety dataset.

Table 29: Adverse drug reactions as reported in the pooled safety data (melanoma, NSCLC and RCC)

		ADR frequency
Infections and infestations		
Common	Upper respiratory tract infection	1.2
Uncommon	Pneumonia	0.5
Uncommon	Bronchitis	0.2
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Rare	Histocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	<0.1
Blood and lymphatic system disorders		
Uncommon	Eosinophilia	0.2
Immune system disorders		
Common	Infusion related reaction	2.4
Uncommon	Anaphylactic reaction	0.1
Common	Hypersensitivity	1.8
Endocrine disorders		
Common	Hypothyroidism	6.1
Common	Hyperthyroidism	2.1
Common	Hyperglycaemia	1.0
Uncommon	Adrenal insufficiency	0.6
Uncommon	Hypopituitarism	0.2
Uncommon	Hypophysitis	0.3
Uncommon	Thyroiditis	0.5

Uncommon	Diabetic ketoacidosis	0.1
Rare	Diabetes mellitus	<0.1
Metabolism and nutrition disorders		
Very common	Decreased appetite	10.2
Uncommon	Dehydration	0.6
Uncommon	Metabolic acidosis	0.2
Hepatobiliary disorders		
Uncommon	Hepatitis	0.2
Uncommon	Hyperbilirubinaemia	0.2
Rare	Cholestasis	<0.1
Nervous system disorders		
Common	Peripheral neuropathy	2.1
Common	Headache	4.3
Common	Dizziness	2.5
Uncommon	Polyneuropathy	0.1
Rare	Guillain-Barré syndrome,	<0.1
Rare	Demyelination	<0.1
Rare	Myasthenic syndrome	<0.1
Rare	Autoimmune neuropthy (including facial and abducens nerve paresis)	<0.1
Eye disorders		
Common	Vision blurred	0.9
Common	Dry eye	1.0
Uncommon	Uveitis	0.4
Cardiac disorders		
Uncommon	Tachycardia	0.5
Rare	Arrhythmia (including ventricular arrhythmia)[c]	<0.1
Rare	Atrial fibrillation	<0.1
Vascular disorders		
Common	Hypertension	1.2
Uncommon	Vasculitis	0.1
Respiratory, thoracic and mediastinal disorders		
Common	Pneumonitis	3.2
Common	Dyspnoea	5.3
Common	Cough	5.3
Uncommon	Pleural effusion	0.2
Rare	Lung infiltration	<0.1
Gastrointestinal disorders		
Very common	Diarrhoea	13.3
Very common	Nausea	13.3
Common	Colitis	1.1
Common	Stomatitis	2.9
Common	Vomiting	5.5
Common	Abdominal pain	4.0
Common	Constipation	5.6
Common	Dry mouth	3.1
Uncommon	Pancreatitis	0.3
Rare	Gastritis	<0.1
Rare	Duodenal ulcer	<0.1

Skin and subcutaneous tissue disorders		
Very common	Rash	18.5
Very common	Pruritus	13.7
Common	Vitiligo	4.0
Common	Dry skin	4.5
Common	Erythema	2.1
Common	Alopecia	1.2
Uncommon	Erythema multiforme	0.2
Uncommon	Psoriasis	0.2
Uncommon	Rosacea	0.2
Uncommon	Urticaria	0.4
Musculoskeletal and connective tissue disorders		
Common	Musculoskeletal pain	8.1
Common	Arthralgia	6.1
Uncommon	Polymyalgia rheumatica	0.2
Uncommon	Arthritis	0.9
Rare	Myopathy	<0.1
Renal and urinary disorders		
Uncommon	Tubulointerstitial nephritis	0.2
Uncommon	Renal failure	0.3
General disorders and administration site conditions		
Very common	Fatigue	33.8
Common	Pyrexia	5.8
Common	Oedema (including peripheral oedema)	3.5
Uncommon	Pain	0.8
Uncommon	Chest pain	0.9
Investigations		
Very common	Increased AST	27.7
Very common	Increased ALT	21.2
Very common	Increased alkaline phosphatase	25.5
Very common	Increased lipase	26.6
Very common	Increased amylase	16.4
Very common	Increased creatinine	22.7
Very common	Lymphopaenia (*lymphocyte absolute)*	43.0
Very common	Leukopaenia (*leukocyte absolute)*	12.3
Very common	Thrombocytopaenia *(platelet count)*	10.9
Very common	Anaemia (*haemoglobin (B))*	37.1
Very common	Hypercalcaemia	11.4
Very common	Hypocalcaemia	18.3
Very common	Hyperkalaemia	20.3
Very common	Hypokalaemia	10.4
Very common	Hypomagnesaemia	14.8
Very common	Hyponatraemia	28.1
Common	Increased total bilirubin	8.5
Common	Neutropaenia (*absolute neutrophil count)*	9.1
Common	Hypermagnesaemia	5.0
Common	Hypernatraemia	5.9
Common	Weight decreased	2.6

In addition, Toxic epidermal necrolysis (TEN) has been included in the SmPC as ADR following the report of 3 cases of fatal TEN during on-going routine pharmacovigilance (EMEA/H/C/003985/II/0004).

Safety of nivolumab monotherapy across tumour types

The safety profile of nivolumab 3 mg/kg monotherapy in RCC was compared to the recently submitted pooled safety profiles of nivolumab monotherapy in melanoma and NSCLC.

Studies submitted in support of approval used for comparison of safety of nivolumab 3 mg/kg monotherapy in RCC versus other tumour types (melanoma and NSCLC) are summarized in Table 30. The mean duration of nivolumab therapy and the number of nivolumab doses received was higher in RCC than melanoma and NSCLC.

Table 30: Overview of Nivolumab 3 mg/kg Monotherapy Phase 2/3 Registrational Studies in RCC, Melanoma, and NSCLC

	RCC	Melanoma	NSCLC
Study (no. subjects treated with nivolumab 3 mg/kg monotherapy)	CA209025 (406)	CA209067 (313) CA209066 (206) CA209037 (268)	CA209057 (287) CA209017 (131) CA209063 (117)
Total no. subjects treated with nivolumab 3 mg/kg monotherapy per tumor type	406	787	535
Total exposure, patient years	328.3	500.2	277.8
Mean duration of nivolumab treatment, months[a]	9.7	7.6	6.2
Mean number of nivolumab doses received	19.2	15.4	12.0

Abbreviations: NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

[a] Mean duration of study therapy was calculated as total exposure (years) * 12/number of treated subjects.

All studies are Phase 3, with the exception of Phase 2 Study CA209063.

Serious adverse event/deaths/other significant events

Serious Adverse Events - CA209025

The overall frequencies of all-causality SAEs (any grade) were similar between the treatment groups (Table 31). The SAE rates represent those for any causality (i.e. reported as related or not related by the investigator).

Pleural effusion was considered related to study therapy in each arm. All cases of spinal cord compression in both arms were considered not related to study therapy and most often related to metastatic disease. There were two cases of Grade 3-4 acute kidney injury that were considered related to study therapy in each arm.

All reported cases of malignant neoplasm progression were indicated as not related to study therapy on both arms. Other neoplasms unrelated to RCC were reported on both arms and were not categorized as “Malignant neoplasm progression.” These included cases of skin cancers (basal, squamous, melanoma). Nivolumab subjects had reports of basal cell and squamous cell (3 each) and malignant melanoma (1). For everolimus there was one report of basal cell. In addition, other types of potentially new neoplasms reported included; neoplasm (1), neoplasm malignant (1) and lung adenocarcinoma (1) for the nivolumab arm, and

duodenal neoplasm, lymphangiosis carcinomatosa, peritoneal neoplasm, neoplasm and oesophageal adenocarcinoma (1 each) for the everolimus arm.

Table 31: Summary of Serious Adverse Events by Worst CTC Grade - (Any Grade, Grade 3-4, Grade 5) with 1% Cutoff - All Treated Subjects - CA209025

System Organ Class (%) Preferred Term (%)	Nivolumab (N = 406)			Everolimus (N = 397)		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	194 (47.8)	148 (36.5)	14 (3.4)	173 (43.6)	116 (29.2)	27 (6.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	50 (12.3)	33 (8.1)	8 (2.0)	34 (8.6)	12 (3.0)	20 (5.0)
MALIGNANT NEOPLASM PROGRESSION	22 (5.4)	12 (3.0)	8 (2.0)	24 (6.0)	4 (1.0)	20 (5.0)
METASTASES TO CENTRAL NERVOUS SYSTEM	6 (1.5)	5 (1.2)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	40 (9.9)	27 (6.7)	0	46 (11.6)	33 (8.3)	0
PLEURAL EFFUSION	14 (3.4)	11 (2.7)	0	13 (3.3)	11 (2.8)	0
PNEUMONITIS	8 (2.0)	6 (1.5)	0	12 (3.0)	8 (2.0)	0
DYSPNOEA	6 (1.5)	5 (1.2)	0	4 (1.0)	1 (0.3)	0
PULMONARY EMBOLISM	4 (1.0)	3 (0.7)	0	7 (1.8)	5 (1.3)	0
INFECTIONS AND INFESTATIONS	38 (9.4)	32 (7.9)	1 (0.2)	34 (8.6)	28 (7.1)	1 (0.3)
PNEUMONIA	11 (2.7)	7 (1.7)	1 (0.2)	15 (3.8)	14 (3.5)	1 (0.3)
SEPSIS	5 (1.2)	5 (1.2)	0	3 (0.8)	3 (0.8)	0
GASTROINTESTINAL DISORDERS	26 (6.4)	20 (4.9)	0	22 (5.5)	17 (4.3)	1 (0.3)
DIARRHOEA	6 (1.5)	4 (1.0)	0	2 (0.5)	2 (0.5)	0
CONSTIPATION	5 (1.2)	1 (0.2)	0	2 (0.5)	1 (0.3)	0
SMALL INTESTINAL OBSTRUCTION	1 (0.2)	1 (0.2)	0	5 (1.3)	5 (1.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	26 (6.4)	21 (5.2)	0	15 (3.8)	9 (2.3)	0
BACK PAIN	7 (1.7)	7 (1.7)	0	5 (1.3)	4 (1.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	18 (4.4)	9 (2.2)	1 (0.2)	19 (4.8)	13 (3.3)	0
PYREXIA	4 (1.0)	1 (0.2)	0	5 (1.3)	3 (0.8)	0
GENERAL PHYSICAL HEALTH DETERIORATION	2 (0.5)	2 (0.5)	0	5 (1.3)	5 (1.3)	0
METABOLISM AND NUTRITION DISORDERS	18 (4.4)	16 (3.9)	0	13 (3.3)	12 (3.0)	0
HYPERCALCAEMIA	10 (2.5)	9 (2.2)	0	2 (0.5)	2 (0.5)	0
HYPERGLYCAEMIA	4 (1.0)	4 (1.0)	0	5 (1.3)	5 (1.3)	0
NERVOUS SYSTEM DISORDERS	18 (4.4)	12 (3.0)	1 (0.2)	8 (2.0)	3 (0.8)	2 (0.5)
SPINAL CORD COMPRESSION	8 (2.0)	8 (2.0)	0	2 (0.5)	2 (0.5)	0
RENAL AND URINARY DISORDERS	18 (4.4)	12 (3.0)	0	12 (3.0)	11 (2.8)	1 (0.3)
ACUTE KIDNEY INJURY	8 (2.0)	5 (1.2)	0	5 (1.3)	4 (1.0)	1 (0.3)
RENAL FAILURE	5 (1.2)	3 (0.7)	0	0	0	0
CARDIAC DISORDERS	16 (3.9)	12 (3.0)	2 (0.5)	12 (3.0)	11 (2.8)	1 (0.3)
MYOCARDIAL INFARCTION	6 (1.5)	5 (1.2)	1 (0.2)	1 (0.3)	1 (0.3)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (1.7)	3 (0.7)	0	12 (3.0)	12 (3.0)	0
ANAEMIA	7 (1.7)	3 (0.7)	0	12 (3.0)	12 (3.0)	0

MedDRA Version: 18.0; CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Study CA209010

The CA209010 CSR included narratives for all nivolumab-treated subjects who experienced a related serious adverse event (SAE, "related" or "missing" relationship per investigator's assessment), discontinued study therapy due to an AE, died due to reason other than progressive disease, or had other significant medical events, within 100 days of last dose as defined by the old narrative criteria. In addition, narratives for all nivolumab subjects who experienced any Grade 2 related select AE requiring systemic immunosuppressants to treat the AE were also provided.

Other Events of Special Interest - CA209025

Other events of special interest are events that do not fulfill 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, but do not benefit from pooling of multiple AE terms for full characterization and are therefore presented as unique events rather than using select AE methodology. Other select event categories included myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, and uveitis.

No events of myasthenic syndrome, demyelination, Guillain-Barré syndrome, and encephalitis were reported in either the nivolumab or everolimus treatment groups.

The only event of special interest requiring treatment with immune-modulating medication was 1 case of uveitis in the nivolumab treatment group (extended follow-up):

- Immune-mediated uveitis where immune modulating mediation was initiated occurred in 1 (0.2%) subject in the nivolumab group and no subjects in the everolimus group.
    - The nivolumab-treated subject experienced Grade 2 iridocyclitis that was not considered an SAE.
    - This event did not lead to treatment discontinuation or dose delay. The subject was continuing nivolumab at the time of database lock.
    - The time to onset was 34.71 weeks.
    - The subject received a topical corticosteroid (intraocular administration) for treatment of the event.
    - The event resolved (per investigator assessment) in 3.14 weeks. The subject had complete resolution (i.e., resolution with completion of immune-modulating medication).
    - The subject was re-challenged with nivolumab treatment and had a successful/negative re-challenge (i.e., no recurrence with re-treatment).

In addition events of special interest not requiring treatment with immune-modulating medication were reported (extended follow-up) in 2 nivolumab-treated subjects.

- Immune-mediated pancreatitis (not treated with immune-modulating medication) occurred in 2 (0.5%) subjects in the nivolumab group and no subjects in the everolimus group. In the nivolumab group:
    - There was 1 subject with Grade 2 pancreatitis that was not considered an SAE and was not drug-related and 1 subject with Grade 3 pancreatitis that was considered an SAE and was not drug related.
    - Neither event led to treatment discontinuation and the Grade 3 event resulted in dose delay.
    - The median time to onset was 20.29 weeks (range: 16.6 to 24.0 weeks).
    - As stated above, neither event was treated with immune-modulating concomitant medication.
    - Both pancreatitis events resolved (per investigator assessment), with a median time to resolution of 16.29 weeks (range 9.1 to 23.4 weeks).

Another event of special interest observed in CA209025 was systemic inflammatory response syndrome. One subject (CA209025-29-988) had 2 Grade 3 drug-related SAEs of systemic inflammatory response syndrome reported during the extended follow-up period (start/stop: 22-Dec-2014 to 24-Dec-2014 and 20-Jan-2015 to 29-Jan-2015). The subject was treated with systemic corticosteroids from 07-Jan-2015 to 17-Jan-2015 and 21-Jan-2015 to 23-Jan-2015, and both events resolved.

There were no events of toxic epidermal necrolysis reported in CA209025.

Deaths - CA209025

Prior to the database lock point, fewer subjects had died in the nivolumab group (181 subjects [44.6%]) compared with the everolimus group (213 subjects [53.7%]); see Table 32.

- Disease progression was the most common cause of death for both groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose.
- No deaths were attributed to study drug toxicity with nivolumab, and 2 deaths (0.5%) in the everolimus group were assessed as study drug toxicity: 1 of the subjects died due to septic shock

(Subject CA209025-118-160) and 1 of the subjects died due to acute bowel ischaemia (Subject CA209025-97-286).

- A reason for death of "other" was reported by the investigator for 14 subjects in the nivolumab group (none were assessed as related to nivolumab) and 10 subjects in the everolimus group, and "unknown" for 4 subjects in the nivolumab group, and 8 subjects in the everolimus group. These verbatim terms were consistent with events expected in the population under study.

Table 32: Death Summary - All Treated Subjects - CA209025

	Number (%) Subjects	
	Nivolumab (N = 406)	Everolimus (N = 397)
DEATHS	181 (44.6)	213 (53.7)
WITHIN 30 DAYS OF LAST DOSE	19 (4.7)	34 (8.6)
WITHIN 100 DAYS OF LAST DOSE	56 (13.8)	80 (20.2)
DUE TO STUDY DRUG TOXICITY	0	2 (0.5)

	Nivolumab N = 406	Everolimus N = 397
NUMBER OF SUBJECTS WHO DIED (%)	181 (44.6)	213 (53.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	162 (39.9)	192 (48.4)
STUDY DRUG TOXICITY	0	2 (0.5)
UNKNOWN	5 (1.2)	9 (2.3)
OTHER	14 (3.4)	10 (2.5)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	19 (4.7)	34 (8.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	15 (3.7)	27 (6.8)
STUDY DRUG TOXICITY	0	2 (0.5)
UNKNOWN	0	0
OTHER	4 (1.0)	5 (1.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	56 (13.8)	80 (20.2)
PRIMARY REASON FOR DEATH (%)		
DISEASE	49 (12.1)	71 (17.9)
STUDY DRUG TOXICITY	0	2 (0.5)
UNKNOWN	0	1 (0.3)
OTHER	7 (1.7)	6 (1.5)

Laboratory findings

Haematology

Haematology was assessed through laboratory evaluation of haemoglobin, platelet count, leukocytes, lymphocytes, and absolute neutrophils.

In CA209025, the majority of subjects in the nivolumab group did not have on-study worsening in haematology. Any-grade abnormalities in haematology laboratory results relative to baseline were reported less frequently in the nivolumab group than the everolimus group (Table 33).

- The majority of haematology laboratory abnormalities reported in the nivolumab group were Grade 1-2.
- The only Grade 3-4 haematologic abnormalities reported in ≥5% of subjects in the nivolumab group was haemoglobin decrease (8.4%) and absolute lymphocyte count decrease (6.4%). In the everolimus group, Grade 3-4 haemoglobin decrease (15.7%) and absolute lymphocyte count decrease (11.2%) were also reported in ≥5% of subjects.

- No haematology laboratory abnormalities occurred in ≥10% of subjects in the nivolumab group and at a higher frequency than in the everolimus group (between-group difference of ≥5% [all grades] or ≥2% [Grades 3-4]).

A low number of nivolumab and everolimus treated subjects experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality.

Table 33: Summary of On-Treatment Worst CTC Grade Haematology Tests that Worsened Relative to Baseline - Reported Within 30 Days of Last Dose for All Treated Subjects (SI Units) - CA209025

	Number (%) of Subjects					
	Nivolumab			Everolimus		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	395	153 (38.7)	33 (8.4)	383	264 (68.9)	60 (15.7)
PLATELET COUNT	391	39 (10.0)	1 (0.3)	379	104 (27.4)	7 (1.8)
LEUKOCYTES	393	38 (9.7)	1 (0.3)	380	98 (25.8)	1 (0.3)
LYMPHOCYTES (ABSOLUTE)	390	163 (41.8)	25 (6.4)	376	198 (52.7)	42 (11.2)
ABSOLUTE NEUTROPHIL COUNT	391	28 (7.2)	0	377	56 (14.9)	3 (0.8)

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

Serum Chemistry - CA209025

Liver parameters

Liver function was assessed through serum chemistry laboratories (AST, ALT, ALP, and total bilirubin) and review of AEs related to hepatic function abnormalities.

The majority of subjects in both treatment groups did not have on-study worsening in liver function tests. Most abnormalities in liver function were Grade 1-2 in both treatment groups (Table 34).

Table 34: Summary of On-Treatment Worst CTC Grade Liver Function Test Results that Worsened Relative to Baseline - Reported Within 30 Days of Last Dose (SI Units) - All Treated Subjects - CA209025

	Number (%) of Subjects					
	Nivolumab			Everolimus		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
ALKALINE PHOSPHATASE	400	127 (31.8)	9 (2.3)	374	119 (31.8)	3 (0.8)
ASPARTATE AMINOTRANSFERASE	399	131 (32.8)	11 (2.8)	374	146 (39.0)	6 (1.6)
ALANINE AMINOTRANSFERASE	401	87 (21.7)	13 (3.2)	376	115 (30.6)	3 (0.8)
BILIRUBIN, TOTAL	401	37 (9.2)	2 (0.5)	376	13 (3.5)	2 (0.5)

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

Grade 3-4 ALT increases occurred at a higher frequency (≥2% difference) in the nivolumab group than in the everolimus group (3.2% vs 0.8%).

The number of subjects who experienced a ≥2-grade shift from baseline to a Grade 3-4 laboratory abnormality in either treatment group was low.

In the nivolumab group, 3 (0.7%) subjects had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 1 day of last dose of study therapy, and 4 (1.0%) subjects had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy (Table 35).

Table 35: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects - CA209025

	Nivolumab N = 406	Everolimus N = 397	Total N = 803
	N = 401	N = 377	N = 778
ALT OR AST > 3ULN	28 (7.0)	14 (3.7)	42 (5.4)
ALT OR AST > 5ULN	16 (4.0)	6 (1.6)	22 (2.8)
ALT OR AST > 10ULN	7 (1.7)	1 (0.3)	8 (1.0)
ALT OR AST > 20ULN	2 (0.5)	0	2 (0.3)
	N = 401	N = 376	N = 777
TOTAL BILIRUBIN > 2ULN	6 (1.5)	2 (0.5)	8 (1.0)
	N = 401	N = 376	N = 777
CONCURRENT ALT OR AST ELEVATION > 3ULN WITH TOTAL BILIRUBIN > 2ULN WITHIN ONE DAY	3 (0.7)	0	3 (0.4)
CONCURRENT ALT OR AST ELEVATION > 3ULN WITH TOTAL BILIRUBIN > 2ULN WITHIN 30 DAYS	4 (1.0)	1 (0.3)	5 (0.6)

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.

Renal parameters

Serum creatinine that worsened relative to baseline (any grade) was reported in 42.2% of subjects in the nivolumab group and 44.9% of subjects in the everolimus group. Changes in serum creatinine during the study were similar between the two treatment groups. Grade 3-4 abnormalities in serum creatinine were reported in 2.0% of subjects in the nivolumab group and 1.6% of subjects in the everolimus group.

It was acknowledged that GFR was not a significant covariate on nivolumab CL and had no meaningful clinical relevance on nivolumab CL (<20% effect on CL). As renal impairment does not affect pharmacokinetics of nivolumab, it is not expected to have an impact on the safety profile. No nivolumab dose adjustment is recommended in patients with renal impairment.

Thyroid function tests

The majority of subjects in both groups had normal TSH levels at baseline and throughout the treatment period (Table 36).

- The proportion of subjects with elevated TSH > ULN who had TSH ≤ULN at baseline was higher in the nivolumab group than the everolimus group (19.6% and 10.5%, respectively). The proportion of subjects with TSH > ULN and at least 1 FT3/FT4 value < LLN was higher in the nivolumab group (13.4%) than the everolimus group (5.0%).
- The proportion of subjects with TSH < LLN with at least 1 FT3/FT4 test value > ULN was higher in the nivolumab group (5.0%) than the everolimus group (2.5%).
- No meaningful differences were noted between treatment groups for subjects with on treatment TSH < LLN who had TSH ≥LLN at baseline.

Table 36: Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) – Treated Subjects With at Least 1 On-Treatment TSH - CA209025

	Nivolumab N = 382	Everolimus N = 361	Total N = 743
TSH > ULN	**148 (38.7)**	**70 (19.4)**	**218 (29.3)**
TSH > ULN WITH TSH <= ULN AT BASELINE	75 (19.6)	38 (10.5)	113 (15.2)
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	51 (13.4)	18 (5.0)	69 (9.3)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	38 (9.9)	18 (5.0)	56 (7.5)
WITH FT3/FT4 TEST MISSING (A) (B)	59 (15.4)	34 (9.4)	93 (12.5)
TSH < LLN	**59 (15.4)**	**55 (15.2)**	**114 (15.3)**
TSH < LLN WITH TSH >= LLN AT BASELINE	45 (11.8)	42 (11.6)	87 (11.7)
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	19 (5.0)	9 (2.5)	28 (3.8)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	19 (5.0)	15 (4.2)	34 (4.6)
WITH FT3/FT4 TEST MISSING (A) (B)	21 (5.5)	31 (8.6)	52 (7.0)

Abbreviations: LLN: lower limit of normal; TSH: thyroid stimulating hormone; ULN: upper limit of normal.
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.

Electrolytes

Most subjects in both treatment groups had normal electrolyte levels during the treatment reporting period (Table 37). Abnormalities in electrolytes were primarily Grade 1 to 2 in severity. Hypercalcaemia, hyperkalaemia, and hyponatraemia occurred in ≥10% of subjects in the nivolumab group and at a higher frequency than in the everolimus group (between-group difference of ≥5% [all grades] or ≥2% [Grades 3-4]).

Table 37: Summary of On-Treatment Worst CTC Grade Electrolyte Levels that Worsened Relative to Baseline - Reported Within 30 Days of Last Dose (SI Units) - All Treated Subjects - CA209025

	Number (%) of Subjects					
	Nivolumab			Everolimus		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
CALCIUM						
HYPERCALCEMIA	339	65 (19.2)	11 (3.2)	315	18 (5.7)	1 (0.3)
HYPOCALCEMIA	339	77 (22.7)	3 (0.9)	315	81 (25.7)	4 (1.3)
POTASSIUM						
HYPERKALEMIA	352	107 (30.4)	14 (4.0)	332	65 (19.6)	7 (2.1)
HYPOKALEMIA	352	18 (5.1)	5 (1.4)	332	31 (9.3)	3 (0.9)
MAGNESIUM						
HYPERMAGNESEMIA	190	9 (4.7)	3 (1.6)	162	7 (4.3)	0
HYPOMAGNESEMIA	190	27 (14.2)	1 (0.5)	162	22 (13.6)	0
SODIUM						
HYPERNATREMIA	353	23 (6.5)	0	331	13 (3.9)	0
HYPONATREMIA	353	114 (32.3)	26 (7.4)	331	85 (25.7)	21 (6.3)

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

Immunogenicity - CA209025

A summary of the anti-drug antibody (ADA) assessments for nivolumab subjects in CA209025 who had evaluable ADA data at baseline and on treatment is presented in Table 38.

Overall, there were 27 (7.3%) subjects who were ADA positive, of which only 1 (0.3%) subject was considered persistent positive (CA209025-31-317) and no subjects were neutralizing ADA positive. The highest titer value observed in ADA positive subjects was 256, which occurred in only 1 subject. This subject had only one ADA positive sample observed at 2 weeks after initiation of nivolumab dosing and no other ADA positive samples (subject included in the Other positive category). All other ADA positive subjects had titer values less than 16.

Table 38: Summary of Anti Drug Antibody Assessments, Based on 16-week Definition for Persistent Positive - All Nivolumab-treated Subjects with Baseline and at Least One Post-Baseline Assessment - CA209025

	Number of Subjects (%)
	Nivolumab N = 371
BASELINE ADA POSITIVE	10 (2.7)
ADA POSITIVE	27 (7.3)
PERSISTENT POSITIVE[a]	1 (0.3)
ONLY AT LAST SAMPLE POSITIVE	7 (1.9)
OTHER POSITIVE	19 (5.1)
NEUTRALIZING ADA POSITIVE	0
ADA NEGATIVE	344 (92.7)

Abbreviations: ADA: anti-drug antibody; CSR: clinical study report.
[a] Refer to the ADA narrative for Subject CA209025-31-317 in Appendix 7.4A of the CA209025 Final CSR.
Source: Refer to Table S.7.10 of the CA209025 Final CSR

Effect of Immunogenicity on Safety - CA209025

In CA209025, a total of 26 subjects experienced hypersensitivity/infusion reaction events within 100 days of last dose (extended follow-up), and all were ADA negative (Table 39). Thus, the presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion related reactions. Overall, the incidence of nivolumab ADA was low and did not appear to have an effect on the safety of nivolumab.

Table 39: Summary of Select Adverse Events by ADA Status (Positive, Negative) - All Nivolumab Treated Subjects With ADA Positive or ADA Negative Select Adverse Events Category - Hypersensitivity / Infusion Reaction - CA209025

	Nivolumab	
	Nivolumab ADA	
Preferred Term	Positive N = 27	Negative N = 344
TOTAL SUBJECTS WITH AN EVENT	0	26 (7.6)
ANAPHYLACTIC REACTION	0	1 (0.3)
BRONCHOSPASM	0	1 (0.3)
HYPERSENSITIVITY	0	12 (3.5)
INFUSION RELATED REACTION	0	13 (3.8)

MedDRA Version: 18.0
CTC Version 4.0
Includes events reported between first dose and 100 days after last dose of therapy.
Program Source: /projects/bms211241/stats/primary/prog/tables/rt-ae-im.sas

Integrated Immunogenicity Summary

Collectively to date, of 1408 subjects with solid tumors including RCC, NSCLC, and melanoma, who were treated with nivolumab 3 mg/kg every 2 weeks and evaluable for the presence of ADA, 155 subjects (11.0%) tested positive for treatment-emergent ADA (Table 40). Of those who were ADA positive, only 2 subjects (0.1% of the total) were persistent positive, and neutralizing antibodies were detected in only 9 subjects (0.6% of the total).

Table 40: Summary of Nivolumab Antibody Assessments Using Method ICDIM 140 V1.00/V2.02 Following Nivolumab 3 mg/kg Every 2 weeks - 16-week Definition for Persistent Positive

	Number of Subjects (%)							
	CA209063 (N=101)	CA209037 (N=181)	CA209066 (N=107)	CA209017 (N=109)	CA209057 (N=251)	CA209067 (N=288)	CA209025 (N=371)	Pooled Summary (N=1408)
Baseline ADA Positive	11 (10.9)	9 (5.0)	3 (2.8)	8 (7.3)	18 (7.2)	10 (3.5)	10 (2.7)	69 (4.9)
ADA Positive	12 (11.9)	13 (7.2)	6 (5.6)	21 (19.3)	43 (17.1)	33 (11.5)	27 (7.3)	155 (11.0)
Persistent Positive	0	0	0	1 (0.9)	0	0	1 (0.3)	2 (0.1)
Only Last Sample Positive	8 (7.9)	9 (5.0)	2 (1.9)	4 (3.7)	12 (4.8)	10 (3.5)	7 (1.9)	52 (3.7)
Other Positive	4 (4.0)	4 (2.2)	4 (3.7)	16 (14.7)	31 (12.4%)	23 (8.0)	19 (5.1)	101 (7.2)
Neutralizing ADA Positive	0	2 (1.1)	0	3 (2.8)	3 (1.2%)	1 (0.3)	0	9 (0.6)
ADA Negative	89 (88.1)	168 (92.8)	101 (94.4)	88 (80.7)	208 (82.9)	255 (88.5)	344 (92.7)	1253 (89.0)

Abbreviations: ADA: anti-drug antibody; NAb: neutralizing antibody.
Method ICDIM 140 V1.00/V2.02 had a sensitivity of 6.25 ng/mL to 12.5 ng/mL and drug tolerance up to 800 µg/mL nivolumab.
Baseline ADA Positive Subject: a subject with Baseline ADA Positive Sample
ADA positive: a subject with 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 timepoints, where the first and last ADA positive samples at least 16 weeks apart.
Only Last Sample Positive: Not persistent but ADA positive sample in the last sampling timepoint.
Other Positive: Not persistent but some ADA positive samples with the last sample being negative.
Neutralizing ADA positive: At least one ADA positive sample with neutralizing antibodies detected post baseline. A NAb assay was only used in confirmed ADA positive samples
ADA Negative: A subject with no ADA positive sample after the initiation of treatment. Post-baseline are assessments reported after initiation of treatment.

Immunogenicity Results - CA209010

Of the 133 nivolumab-treated subjects who had evaluable ADA data at baseline and postbaseline, 15 (11.3%) subjects were ADA positive at baseline. During treatment with nivolumab, ADA were detected in 21 (15.8%) subjects, of whom 3 (2.3%) subjects were considered as persistent positive; and 112 (84.2%) subjects were ADA negative. A higher percentage of subjects were ADA positive in the 0.3 mg/kg treatment group than in the 2 mg/kg treatment group, and no subjects were ADA positive in the 10 mg/kg treatment group. The decrease in immunogenicity with increasing dose level could be due to drug tolerance of the ADA assay used. The safety profile of the 3 persistent positive subjects (CA209010-18-89, CA209010-52-198, and CA209010-54-150) was no different from those seen in the general population; no new or additional AEs were reported in these subjects. The limited number of persistent positive subjects precludes any interpretation or definitive conclusion regarding the safety and efficacy of nivolumab in these subjects compared to ADA-negative subjects.

Safety in special populations

Intrinsic and Extrinsic Factors - CA209025

The frequencies of all-causality and drug-related AEs in the nivolumab group for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population. Small numerical differences in frequencies of all-causality AEs of any grade and Grade 3-4 AEs were observed in nivolumab-treated subjects in the following subgroups: for Black/African American (n = 1) and "other" races (n = 13), age (≥75 and < 85 [n = 30], ≥85 years [n = 4]), and in the "rest of world" regions (n = 95). These differences are of limited interpretability due to low sample sizes and event rates, and do not alter the overall safety profile of nivolumab in these subgroups.

Age

The frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/ Standardized MedDRA Queries (SMQ)/SOC appear similar for subjects < 75 years vs ≥ 75 years; however, interpretation is limited by small numbers of subjects in the older subgroups, particularly for the ≥ 85 years age group (Table 41).

Table 41: Summary of On-treatment AEs by Age Group - All Treated Subjects- Pooled Nivolumab Monotherapy Data Across Indications

	Number of Subjects (%)			
	Pooled Monotherapy Data Across Indications[a]			
MedDRA Terms	Age < 65 years (N = 1045)	Age 65-74 years (N = 497)	Age 75-84 years (N = 165)	Age 85+ years (N = 21)
Total AEs	1021 (97.7)	485 (97.6)	162 (98.2)	21 (100.0)
Serious AEs -Total	446 (42.7)	236 (47.5)	82 (49.7)	12 (57.1)
- Fatal	100 (9.6)	45 (9.1)	21 (12.7)	3 (14.3)
- Hospitalization/prolong existing hospitalization	393 (37.6)	209 (42.1)	73 (44.2)	8 (38.1)
- Life-threatening	19 (1.8)	7 (1.4)	2 (1.2)	0
- Cancer	13 (1.2)	11 (2.2)	9 (5.5)	1 (4.8)
- Disability/incapacity	1 (< 0.1)	1 (0.2)	0	0
AEs leading to drop-out	143 (13.7)	76 (15.3)	38 (23.0)	5 (23.8)
Psychiatric disorders	201 (19.2)	78 (15.7)	26 (15.8)	6 (28.6)
Nervous system disorders	380 (36.4)	177 (35.6)	57 (34.5)	13 (61.9)
Accidents and Injuries	79 (7.6)	46 (9.3)	14 (8.5)	3 (14.3)
Cardiac disorders	100 (9.6)	51 (10.3)	13 (7.9)	5 (23.8)
Vascular disorders	174 (16.7)	90 (18.1)	26 (15.8)	9 (42.9)
Cerebrovascular disorders	9 (0.9)	9 (1.8)	1 (0.6)	1 (4.8)
Infections and infestations	378 (36.2)	213 (42.9)	62 (37.6)	10 (47.6)
Anticholinergic syndrome	353 (33.8)	160 (32.2)	56 (33.9)	9 (42.9)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	119 (11.4)	68 (13.7)	24 (14.5)	4 (19.0)

[a] Includes data from studies CA209025, CA209063, CA209017, CA209057, CA209037, CA209066, and CA209067 (monotherapy arm only).
MedDRA Version: 18.0; CTC version 4.0 (except for Study CA209004: CTC version 3.0).
Includes events reported between first dose and 30 days after last dose of study therapy.
Abbreviations: AE: adverse event; HLGT: MedDRA High-Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Queries; SAE: serious adverse event; SOC: System Organ Class.

Safety related to drug-drug interactions and other interactions

No new information was provided regarding this application.

Discontinuation due to adverse events

In CA209025, the overall frequency of all-causality, any grade AEs leading to discontinuation of study therapy (any grade and Grade 3-4) were similar between the nivolumab and everolimus groups (Table 42).

Table 42: Summary of Adverse Events (≥1) Leading to Discontinuation by Worst CTC Grade - (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects - CA209025

System Organ Class (%) Preferred Term (%)	Nivolumab N = 406			Everolimus N = 397		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	72 (17.7)	45 (11.1)	7 (1.7)	82 (20.7)	45 (11.3)	6 (1.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	20 (4.9)	13 (3.2)	4 (1.0)	7 (1.8)	4 (1.0)	2 (0.5)
MALIGNANT NEOPLASM PROGRESSION	16 (3.9)	10 (2.5)	4 (1.0)	4 (1.0)	2 (0.5)	2 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13 (3.2)	8 (2.0)	0	24 (6.0)	10 (2.5)	0
PNEUMONITIS	6 (1.5)	5 (1.2)	0	13 (3.3)	5 (1.3)	0
COUGH	0	0	0	4 (1.0)	0	0
INVESTIGATIONS	7 (1.7)	6 (1.5)	0	3 (0.8)	2 (0.5)	0
ALANINE AMINOTRANSFERASE INCREASED	5 (1.2)	4 (1.0)	0	0	0	0
INFECTIONS AND INFESTATIONS	2 (0.5)	1 (0.2)	1 (0.2)	10 (2.5)	7 (1.8)	1 (0.3)
PNEUMONIA	1 (0.2)	0	1 (0.2)	5 (1.3)	4 (1.0)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.2)	1 (0.2)	0	9 (2.3)	3 (0.8)	0
FATIGUE	0	0	0	5 (1.3)	0	0

MedDRA Version: 18.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.117 of the CA209025 Final CSR

Overall frequencies of drug-related AEs leading to discontinuation of study therapy (any grade and Grade 3-4) were lower in the nivolumab group than the everolimus group.

Any-grade drug-related AEs leading to discontinuation of study therapy were reported at a lower frequency in the nivolumab group (7.6%) than the everolimus group (13.1%). In the nivolumab group, the most frequently reported all-grade drug-related AEs leading to discontinuation (≥1% of subjects) were pneumonitis (1.2%) and ALT increased (1.0%). In the everolimus group, the most frequently reported all-grade drug-related AEs leading to discontinuation (≥1% of subjects) were: pneumonitis (3.0%), cough (1.0%), and fatigue (1.0%).

Grade 3-4 drug-related AEs leading to discontinuation of study therapy were reported at a lower frequency in the nivolumab group (4.7%) than the everolimus group (7.1%). In the nivolumab group, pneumonitis (1.2%) was the only Grade 3-4 drug-related AE leading to discontinuation reported by ≥1% of subjects. In the everolimus group, pneumonitis (1.3%) was the only Grade 3-4 drug-related AE leading to discontinuation reported by ≥1% of subjects.

Post marketing experience

No new significant safety concerns were identified based on the postmarketing reports.

2.5.1. Discussion on clinical safety

For the purpose of this application, the population from study CA209025 was considered the main safety dataset. Supportive data from CA209010, dose-ranging study was included.

Baseline demographic and disease characteristics in study CA209025 were well balanced between the nivolumab and everolimus groups, except for the gender (male 75.4%). The patient population and baseline characteristics in CA209010 were comparable to that in CA209025.

The median duration of therapy in the nivolumab treatment group was longer at 5.54 months compared with the everolimus group at 3.71 months.

At the time of the database lock point (18-Jun-2015), 88% of subjects had discontinued study therapy (83.5% in the nivolumab group and 92.9% in the everolimus group). Across treatment groups, the most

common reason for discontinuation of study therapy was disease progression (70.2% and 68.8% in the nivolumab and everolimus groups, respectively). In the nivolumab group, 51.0% of subjects had at least one dose delayed, with 43.6% of subjects in the nivolumab group experiencing an AE leading to dose delay. A lower proportion of subjects discontinued study therapy due to study drug toxicity in the nivolumab group compared with the everolimus group (8.6% vs. 13.4%).

Any-grade AEs were reported in 97.8% of subjects in the nivolumab group and 97.2% of subjects in the everolimus group.

Grade 3-4 AEs were reported in 53.2% of subjects in the nivolumab group and 56.4% of subjects in the everolimus group. In the nivolumab group, the only Grade 3-4 AE reported in ≥5% of subjects was anemia (5.9%).

Any-grade drug-related AEs were reported less frequently in the nivolumab group than in the everolimus group (78.6% vs 87.9%). In the nivolumab group, fatigue (33.0%) was the only any-grade drug-related AE that occurred in ≥20% of subjects. Grade 3-4 drug-related AEs were also reported less frequently in the nivolumab group than the everolimus group (18.7% vs 36.5%). In the nivolumab group, fatigue (2.5%) was the only Grade 3-4 drug-related AE that occurred in ≥2% of subjects.

Any-grade SAEs were reported in 47.8% of subjects in the nivolumab group and 43.6% of subjects in the everolimus group. In the nivolumab group, the most frequently reported SAEs (≥ 2% of subjects) were malignant neoplasm progression (5.4%), pleural effusion (3.4%), pneumonia (2.7%), hypercalcemia (2.5%), pneumonitis (2.0%), spinal cord compression (2.0%), and acute kidney injury (2.0%).

Grade 3-4 SAEs were reported in 36.5% of subjects in the nivolumab group and 29.2% of subjects in the everolimus group.

Any-grade drug-related SAEs were reported in 11.6% of subjects in the nivolumab group and 13.4% of subjects in the everolimus group.

The overall frequency of drug-related AEs leading to discontinuation was lower in the nivolumab group than the everolimus group for all-grade events (7.6% vs 13.1%) and Grade 3-4 events (4.7% vs 7.1%). The overall frequency of drug-related AEs was lower in the nivolumab group than the everolimus group for all-grade events (78.6% vs 87.9%) and Grade 3-4 events (18.7% vs 36.5%).

The overall frequencies of all-causality SAEs (any grade) were similar between the treatment groups.

Across select AE categories, the majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered. Some endocrine select AEs, though well-controlled with hormone replacement therapy, were not considered resolved due to the continuing need for hormone replacement therapy.

Drug-related renal select AEs were similar between the 2 groups: 6.9% and 8.8% in nivolumab and everolimus groups, respectively.

The most frequently reported (> 10% of subjects) any grade drug-related select AE category with nivolumab treatment was skin (24.9%), followed by GI (12.6%), and hepatic (11.3%). The most frequently reported (≥ 1% of subjects) Grade 3-4 drug-related select AE categories with nivolumab treatment were hepatic (2.7%), GI (2.0%), pulmonary (1.5%); endocrine, renal and skin were each reported by 1.0% of subjects.

In the nivolumab group:

* Drug-related endocrine select AEs were reported in 9.6% subjects and the majority of the events reported were hypothyroidism (5.9%). There were 1.0% subjects with Grade 3-4 drug-related events (0.5% had adrenal insufficiency and 0.2% had a diabetic ketoacidosis drug-related SAE). One subject (0.2%) reported drug-related events of adrenal insufficiency and hypophysitis that led to treatment discontinuation.

* All drug-related GI events reported were diarrhea (12.3%) or colitis (1.7%), 7 drug-related GI select AEs were reported as SAEs; for 4 subjects, the AEs led to discontinuation of study therapy.

* Drug-related hepatic select AEs were reported in 11.3% subjects, 2.7% reported Grade 3-4 drug. One of these subjects reported a serious drug-related hepatic select event for autoimmune hepatitis, 1.0% discontinued due to increased ALT, and 0.7% discontinued due to increased AST.

* Drug-related pulmonary select AEs were reported in 4.4% subjects. Pneumonitis (3.9%) and interstitial lung disease (0.5%) were the only drug-related pulmonary select AEs reported.

*Grade 3-4 drug-related renal select AEs included: increased blood creatinine (0.2%), acute kidney injury (0.7%), and tubulointerstitial nephritis (0.2%). 0.7% reported drug-related renal select SAEs.

* Drug-related skin select AEs were reported in 24.9% subjects. There was no event of toxic epidermal necrolysis reported, 0.2% had a drug-related skin select SAE (erythema multiforme), 0.2% reported an AE of rash maculo-papular, which led to study medication discontinuation. Thirty-one subjects (30.7%) with drug-related events received immune-modulating medication (2 subjects received high dose corticosteroids.

Disease progression was the most common cause of death for both groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose. In CA209025, there were fewer deaths in nivolumab group (44.6%, 181/406 subjects) compared with the everolimus group (53.7%, 213/397 subjects) with the majority due to disease progression in both groups. No deaths were attributed to study drug toxicity with nivolumab.

44.6% subjects treated with nivolumab died compared with 53.7% treated with everolimus.

The frequencies of all-causality and drug-related AEs in the nivolumab group for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population.

The majority of subjects in the nivolumab group did not have on-study worsening in haematology laboratory parameters. Any-grade abnormalities in haematology laboratory results worsened relative to baseline were reported less frequently in the nivolumab group than the everolimus group. The majority of subjects in both treatment groups did not have on-study worsening in liver function tests. Most abnormalities in liver function were Grade 1-2 in both treatment groups. Serum creatinine that worsened relative to baseline (any grade) was reported in 42.2% of subjects in the nivolumab group and 44.9% of subjects in the everolimus group. Grade 3-4 abnormalities in serum creatinine were reported in 2.0% of subjects in the nivolumab group and 1.6% of subjects in the everolimus group. The majority of subjects in both groups had normal TSH levels at baseline and throughout the treatment period. Most subjects in both treatment groups had normal electrolyte levels during the treatment reporting period; abnormalities in electrolytes were primarily Grade 1 to 2 in severity.

A lower frequency of discontinuation for study drug toxicity regardless of causality was observed in the nivolumab group compared with the everolimus group (8.6% vs. 13.4%, respectively). In addition, there were fewer subjects who requested to discontinue study treatment in the nivolumab group compared with the everolimus group (1.2% vs. 4.5%).

All-grade AEs leading to discontinuation of study therapy were reported in 17.7% of subjects in the nivolumab group and 20.7% of subjects in the everolimus group.

Grade 3-4 AEs leading to discontinuation of study therapy were reported in 11.1% of subjects in the nivolumab group and 11.3% of subjects in the everolimus group.

The incidence of nivolumab-treated subjects with RCC who were positive for nivolumab ADA was 7.3%, and only 1 (0.3%) subject was considered persistent positive. No subjects were positive for neutralizing antibodies. In CA209025, a total of 26 nivolumab treated subjects experienced select AEs in the

hypersensitivity/infusion reaction category (within 100 days of last dose) and all subjects were ADA negative. Thus, the presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions. Overall, the incidence of nivolumab ADA was low and did not appear to have an effect on the safety of nivolumab. These findings were consistent with those from previous analyses of melanoma and NSCLC studies.

Comparative safety data from CA209025 demonstrate that nivolumab monotherapy has an acceptable safety profile as compared to everolimus, as evidenced by the lower rates of drug-related AEs (all grades and Grade 3-4) and drug-related AEs leading to discontinuation (all grades and Grade 3-4) in the nivolumab group.

There were no deaths attributed to nivolumab during the study.

In CA209010 the safety profile was generally similar across treatment groups and the types of events reported were as expected based on the mechanism of action of nivolumab and previous experience in earlier studies.

In general, the type, frequency, and severity of AEs were consistent between RCC and other tumor types (melanoma and NSCLC). Overall, the safety profile of nivolumab monotherapy in RCC was consistent with previously submitted pooled data of nivolumab monotherapy in melanoma and NSCLC.

2.5.2. Conclusions on clinical safety

The safety profile of nivolumab monotherapy in RCC was consistent with previously submitted pooled data of nivolumab monotherapy in melanoma and NSCLC. No new safety concerns with nivolumab monotherapy treatment were identified in RCC. Based on safety data from Phase 3 Study CA209025, the safety profile of nivolumab in advanced RCC is manageable using routine risk minimisation measures and the recommendations as stated in the SmPC.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The RMP version 4.1 (dated 23 February 2016) is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the RMP version 4.1 with the following content:

Safety concerns

Table 43 – Summary of the Safety Concerns

Important identified risks	Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis or renal dysfunction Immune-related endocrinopathies

	Immune-related rash Other immune-related ARs Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Cardiac arrhythmias (previously treated melanoma indication, only)
Missing information	Pediatric patients <18 years of age Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Table 44: Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
CA209234: Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice. Category 3	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	Post-marketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome), and infusion reactions	Planned	Final CSR submission: 4Q2024

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations.

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The planned study in melanoma (CA209172) and the planned study in NSCLC (CA209171), both are considered Category 4 (i.e. stated additional PV activities).

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Table 45: Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis or renal dysfunction Immune-related endocrinopathies Immune related rash Other immune-related ARs	The SmPC warns the risks of immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies, immune-related rash, and other immune-related adverse reactions in Section 4.4 (Special warnings and precautions for use), and provides specific guidance on their monitoring and management, including treatment delay or discontinuation and intervention with corticosteroids in Sections 4.2, 4.4 and 4.8, as appropriate. Further ADRs are included in Section 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important safety information in the language suitable for patients.	To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan. The Plan comprising 2 tools to be distributed to potential prescribers at launch by BMS: Adverse Reaction Management Guide Patient Alert Card
Severe infusion reactions	The SmPC warns the risk of severe infusion reactions in Section 4.4 and ADR in Section 4.8.	None
Important Potential Risks		
Embryofetal Toxicity	SmPC includes Embryofetal Toxicity in Section 4.6 Fertility, pregnancy and lactation, Section 5.3 Preclinical safety data The package leaflet also includes specific description on the safety information in the language suitable for patients.	None
Immunogenicity	SmPC Section 4.8 Immunogenicity	None
Cardiac arrhythmias (previously treated melanoma indication, only)	SmPC Section 4.8 Undesirable effects	None
Missing Information		
Pediatric patients	SmPC Section 4.2 Posology and method of administration, subsection on Pediatric population	None
Severe hepatic and/or renal impairment	SmPC Section 4.2 Posology and method of administration: Patients with hepatic or renal impairment; SmPC Section 5.2 Pharmacokinetic properties: Hepatic or renal impairment	None
Patients with autoimmune	SmPC Section 4.4 provides warning and cautionary information for patients with a history of autoimmune	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
disease	disease	
Patients already receiving systemic immunosuppressants before starting nivolumab	SmPC Sections 4.4 Special populations and 4.5 Systemic Immunosuppressants	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC have been updated and the Package Leaflet and the descriptions and timelines of the 'obligations to conduct post-authorisation measures' in the Annex II have been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet and to update the contact details of the local representative in France in the Package Leaflet.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed accepted by the CHMP.

The full PI, as a relevant example with all changes highlighted is provided as an attachment.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Since the submitted type II variation to extend the current approved therapeutic indication for OPDIVO to include "treatment of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults" does not involve a relevant impact on the PIL.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Results of the predefined interim analysis from study CA209025 revealed a longer survival for patients treated with nivolumab vs everolimus (HR: 0.73 [98.52% CI: 0.57, 0.93]; stratified log-rank test p value = 0.0018). The median of OS for nivolumab group was 25 months, whereas subjects treated with everolimus achieved a median of OS of 19.55 months. This gain in OS (5.45 months) is considered clinically meaningful. The survival rate at 1 year was higher in the nivolumab group than the everolimus group (76.0% vs 66.7%). The Kaplan Meier curves were convincing, showing a clear separation between the two treatments.

The gain in OS seems to be independent of PD-L1 expression and consistent across sensitivity analyses and adjusted analyses.

Regarding the secondary endpoints, ORR was superior in the nivolumab group (25.1% vs 5.4%; 21.5% vs 3.9% with a confirmatory scan after at least 4 weeks).

Uncertainty in the knowledge about the beneficial effects

No benefit in terms of PFS has been shown (HR: 0.88 [95%CI: 0.75 to 1.03]). Reasons, when it comes to explaining this finding, are not totally clear. Treatment beyond progression, could have contributed to the observed discrepancy (non-conventional responders). The OS results are considered convincing and the lack of an effect on PFS does not have an impact on the robustness of the effect observed in terms of OS.

Only patients pretreated with antiangiogenic therapy were included in the pivotal study. However, given the available data and current knowledge, there is no reason to suspect that the efficacy of nivolumab will be different in patients treated with other prior therapies. As such, restriction of the indication was not deemed necessary. The limitations of the patient population included in the main clinical study (pivotal study only includes patients with prior antiangiogenic) are mentioned in section 5.1 of the SmPC.

Only patients with clear-cell histology were included in the pivotal study. The lack of clinical data for nivolumab in patients with non-clear cell RCC is mentioned in section 5.1 of the SmPC.

Risks

Unfavourable effects

Grade 3-4 AEs were reported in 53.2% of subjects in the nivolumab group and 56.4% of subjects in the everolimus group. In the nivolumab group, the only Grade 3-4 AE reported in ≥5% of subjects was anaemia (5.9%).

Any-grade drug-related AEs were reported less frequently in the nivolumab group than in the everolimus group (78.6% vs 87.9%). In the nivolumab group, fatigue (33.0%) was the only any-grade drug-related AE that occurred in ≥20% of subjects. Grade 3-4 drug-related AEs were also reported less frequently in the nivolumab group than the everolimus group (18.7% vs 36.5%). In the nivolumab group, fatigue (2.5%) was the only Grade 3-4 drug-related AE that occurred in ≥2% of subjects.

Any-grade SAEs were reported in 47.8% of subjects in the nivolumab group and 43.6% of subjects in the everolimus group. In the nivolumab group, the most frequently reported SAEs (≥ 2% of subjects) were malignant neoplasm progression (5.4%), pleural effusion (3.4%), pneumonia (2.7%), hypercalcaemia (2.5%), pneumonitis (2.0%), spinal cord compression (2.0%), and acute kidney injury (2.0%).

Disease progression was the most common cause of death for both groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose. In CA209025, there were fewer deaths in nivolumab group (44.6%, 181/406 subjects) compared with the everolimus group (53.7%, 213/397 subjects) with the majority due to disease progression in both groups. No deaths were attributed to study drug toxicity with nivolumab

Uncertainty in the knowledge about the unfavourable effects

See RMP.

Effects Table

Table 46: Effects Table for nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in adults (data cut-off: 18-Jun-2015[CJ1])

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
OS	Gain in survival	Median (months)	25	19.55	Consistency among sensitivity analysis and different subgroups
ORR	Antitumor activity (CR+PR)	% of patients with ORR	25.1	5.4	The subgroups analysed did not show any discordant result
PFS	Patients alive and free of progression	Median (months)	4.60	4.4	
All AEs	Adverse events regardless causality	%	97.8	97.2	No new safety concerns with nivolumab monotherapy treatment were identified in RCC
Fatigue	Most frequent drug-related AE	%	33	33.8	
Nausea	Most frequent drug-related AE	%	14	16.6	
Diarrhoea	Most frequent drug-related AE	%	12.3	21.2	
Decreased appetite	Most frequent drug	%	11.8	20.7	
Rash	Most frequent drug	%	10.1	19.9	
SAEs	Serious Adverse Events regardless causality	%	47.8	43.6	

Abbreviations: AEs (adverse events), AR (assessment report), ORR (objective response rate), OS (overall survival), PFS (progression free survival), RCC (renal cell carcinoma)

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Treatment with nivolumab in patients with RCC previously treated with antiangiogenic therapy has shown a longer survival than everolimus. This result is considered clinically meaningful. The uncertainties related to PFS do not decrease the value of the clinical benefit offered by nivolumab. From a safety point of view, the toxicity and tolerability of nivolumab was consistent with previously submitted pooled data of nivolumab monotherapy in melanoma and NSCLC. No new safety concerns with nivolumab monotherapy treatment were identified in RCC. There were no deaths attributed to nivolumab during the study. Furthermore, comparative safety data from CA209025 demonstrate that nivolumab monotherapy has a acceptable safety

profile as compared to everolimus, as evidenced by the lower rates of drug-related AEs (all grades and Grade 3-4) and drug-related AEs leading to discontinuation (all grades and Grade 3-4) in the nivolumab group.

Benefit-risk balance

The benefit risk balance for nivolumab in the applied indication is positive.

The CHMP considers the following measures necessary to address issues related to efficacy (changes underlined):

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 efficacy. This will be provided for all the approved indications:

- Melanoma: studies CA209038 and CA209066

- RCC: studies CA209025 and CA209009

To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in Study CA209066 and CA209025.

Also, the CHMP recommended that the efficacy results, of study CA209374 (on-going), for the sub-group of patients with non-clear RCC should be submitted post approval.

4. Recommendations

Outcome

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

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

Extension of Indication to add treatment as monotherapy of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults, based on Study CA209025; a phase 3 study of nivolumab vs. everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy, and the CA209010 addendum study report; phase 2 dose-ranging study of nivolumab in subjects with progressive advanced/metastatic clear-cell RCC who have received prior anti-angiogenic therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated, and the Package Leaflet and the descriptions and timelines of the 'obligations to conduct post-authorisation measures' in the Annex II have been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet and to update the contact details of the local representative in France in the Package Leaflet. An updated RMP version 4.1 was agreed during the procedure.

Similarity with authorised orphan medicinal products

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

This CHMP recommendation is subject to the following amended conditions:

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
4. The value of biomarkers to predict the efficacy of nivolumab should be further explored, specifically:	
1. To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy. These analyses will be conducted in studies CA209037 and CA209066 in patients with advanced melanoma.	30th September 2015
2. 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 efficacy. This will be provided for all the approved indications:	
- Melanoma: studies CA209038 and CA209066	30th September 2017
- NSCLC: studies CA209017, CA209057 and CA209026	31st March 2018
- RCC: studies CA209025 and CA209009	31st March 2018
3. To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies (CA209009, CA209038 and CA209064).	31st March 2017
4. To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in studies CA209066, CA209057 and CA209025.	30th June 2018
5. To further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in studies CA209009, CA209038 and CA209064.	30th September 2017