26 April 2018
EMA/291536/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yervoy

International non-proprietary name: ipilimumab

Procedure No. EMEA/H/C/002213/II/0055

Note

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

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List of abbreviations

ADA	anti-drug antibody
AE	adverse event
AEs-DC	AEs leading to discontinuation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BOR	best overall response
CI	confidence interval
CL	Clearance
CMH	Cochran Mantel Haenszel
Cmin	minimum serum concentration
CNS	central nervous system
CR	complete response
CSR	clinical study report
CTLA-4	cytotoxic T lymphocyte antigen-4
DC	Discontinuation
DCR	disease control rate
DOR	duration of response
DP	drug product
DS	drug substance
DTIC	dacarbazine
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30
E-R	exposure response
GI	gastrointestinal
HCP	healthcare providers
HR	hazard ratio
HRQoL	health-related quality of life
IgG4	immunoglobulin G4

IL-2	Interleukin-2
Ipi	ipilimumab
IRRC	independent radiology review committee
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary of Regulatory Activities
MTD	maximum tolerated dose
mWHO	modified World Health Organization
NA	not applicable
NAb	neutralizing antibodies
Nivo	nivolumab
NR	not reached
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
Q2W	every two weeks
Q3W	every three weeks
Q12W	every 12 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TIL	tumor infiltrating lymphocytes
TMB	Tumor mutational burden
TTR	time to response

ULN	upper limit of normal
WT	wild type

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 5 January 2018 an application for a variation.

The following variation was requested:

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

Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults in combination with nivolumab for Yervoy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 20.0) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the contact details of the Irish local representative in the Package Leaflet.

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0003/2017 on the agreement of a paediatric investigation plan (PIP) and an EMA decision CW/1/2011 on the granting of a class waiver.

At the time of submission of the application, the PIP (P/0003/2017) was completed.

The PDCO issued an opinion on compliance for the PIP P/0003/2017.

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

Scientific advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Planned dates	Actual dates
Start of procedure:	26 February 2018	26 February 2018
CHMP Rapporteur Assessment Report	26 March 2018	28 March 2018
PRAC Rapporteur Assessment Report	28 March 2018	28 March 2018
PRAC members comments	04 April 2018	04 April 2018
Updated PRAC Rapporteur Assessment Report	05 April 2018	N/A
PRAC Outcome	12 April 2018	12 April 2018
CHMP members comments	16 April 2018	16 April 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 April 2018	N/A
Opinion	26 April 2018	26 April 2018

2. Scientific discussion

2.1. Introduction

Each year in Europe, 62,000 new cases of melanoma are diagnosed[1]. Although estimates suggest that melanoma represents only 4% of all cases of skin cancer, it accounts for 80% of all skin cancer deaths[2]. It is estimated that 20,000 people die of melanoma per year[3].

The outcome of melanoma depends on the stage at presentation. Approximately 85% of patients with melanoma present with localised disease, 10% with regional disease and 5% with distant metastatic disease. The 5-year survival rates in patients who present with localised disease and primary tumours 1.0 mm or less in thickness are very good, with more than 90% of patients surviving. The 5-year survival rates decrease as the tumour spreads: for tumours of more than 1.0mm in thickness, survival rates range from 50% to 90%, with regional node involvement survival rates are around 50%, for within stage III (regional metastatic melanoma) 5-year survival rates range between 20-70%, depending on primary nodal involvement. The long term survival for distant metastatic melanoma, the 5-year survival is less than 10%. Metastatic melanoma can spread to bone, lung, central nervous system (CNS), liver, and skin. It can lead to pain, neurologic sequelae including chord compression and nerve impingement, hemorrhage, and laboratory abnormalities. Generalized effects of metastatic disease also include cachexia, thrombotic and embolic events, and infections.[4]

[1] Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18: 581–592.
[2] Miller AJ, Mihm MC. Melanoma. N Engl J Med 2006; 355:51-65. 77
[3] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Accessed on 11-Aug-2014.
[4] DeVita, VT Jr, Hellman, S and Rosenberg, SA. Cancer: Principles and Available upon Request Practice of Oncology. 7th Edition. 2005. (Chapter 119).

Prior to 2011, approved therapies for the treatment of metastatic melanoma were limited and included chemotherapy (DTIC) and immunotherapy (interleukin-2 [IL-2]). Since then, new therapeutic classes have been added to the treatment armamentarium administered as monotherapy or in combination. These include the B-RAF inhibitors vemurafenib (Zelboraf), dabrafenib (Tafinlar) and MEK inhibitors trametinib (Mekinist) and cobimetinib (Cotellic), which are inhibitors of the serine threonine kinases BRAF and MEK and monoclonal antibodies ipilimumab (Yervoy), an anti-CTLA-4 blocking antibody, and nivolumab (Opdivo) and pembrolizumab (Keytruda) which bind to the programme cell death (PD-1) receptor.

Yervoy (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody and has the following indication:

“for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older (see section 4.4)”.

OPDIVO is indicated for a number of indications, amongst others melanoma which is of interest for the current variation application:

“Opdivo as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).”

The MAH has applied for an extension of indication to the MA of Yervoy with the proposed indication:

“YERVOY in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).”.

The recommended dose is 1 mg/kg nivolumab administered as an intravenous infusion over 60 minutes every 3 weeks for the first 4 doses in combination with 3 mg/kg ipilimumab administered intravenously over 90 minutes. This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 60 minutes every 2 weeks. The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of nivolumab and ipilimumab.

Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The proposed extension of indication is identical to the indication approved for Opdivo. Further, the clinical data in support of the proposed indication are the same as for Opdivo and have been reviewed by the CHMP during the variations EMEA/H/C/003985/II/003 (for final study report of phase 2 CA209069 and interim data from study CA209067) and EMA/H/C/00398/II/0032 (for the final results from study CA209067).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

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

2.2.2. Discussion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, protein containing products as active pharmaceutical ingredient(s) are exempt from ERA studies which is acceptable.

2.2.3. Conclusion on the non-clinical aspects

The lack of non-clinical studies is acceptable. No changes to the SmPC section 5.3 have been proposed. Ipilimumab is not expected to pose a significant risk to the environment, thus the lack of an ERA is 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**

Monotherapy and Combination Studies in Melanoma

Study #/Type	Study Objective	Study Design	Treatment Cohorts	# of Treated Subjects	Study Population
			NIVOLUMAB MONOTHERAPY		
MDX1106-03 (CA209003) Safety, Efficacy, PK	To characterize the safety and tolerability and determine the MTD of multiple doses of nivo	Phase 1 multidose dose escalation study of nivo	Nivo 1, 3, or 10 mg/kg and 0.1 and 0.3 mg/kg Q2W	N=306 Treated	Metastatic NSCLC, CRC, melanoma, RCC (clear cell), or mCRPC
CA209037 Efficacy, Safety	To estimate the ORR in the nivo treatment group and to compare OS of nivo to investigator's choice	Phase 3, randomized (2:1) open-label study of nivo vs investigator's choice (DTIC or PAC/CAR)	Nivo - 3 mg/kg IV Q2W Investigator's choice: DTIC 1000 mg/m2 IV Q3W or CAR (AUC 6) IV and PAC 175mg/m2 Q3W	N=370 Treated (268 nivo and 102 IC) First 120 nivo-treated subjects with 6 months follow-up for ORR analysis	Advanced melanoma s/p anti-CTLA-4 therapy, and if BRAF mutation + s/p BRAF inhibitor
CA209066 Efficacy, Safety	To compare the OS of nivo to DTIC	Phase 3, randomized (1:1) double blind study of nivo vs DTIC	Nivo - 3 mg/kg IV Q2W DTIC- 1000 mg/m2 Q3W	N=411 Treated (206 Nivo)	Previously untreated, BRAF WT unresectable or metastatic melanoma
CA209067 Efficacy, Safety (also included with combo studies below)	To compare the PFS and OS of nivo monotherapy to ipi monotherapy, nivo+ipi to ipi monotherapy	Phase 3, randomized (1:1:1), double-blind study of nivo or nivo+ipi vs ipi	Active dosing regimens: Nivo group: nivo 3 mg/kg IV Q2W Nivo+Ipi group: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses followed by nivo 3 mg/kg Q2W Ipi group: ipi 3 mg/kg Q3W for 4 doses	N= 937 Treated Nivo group: 313 (215 BRAF WT and 98 BRAF mutation+) Nivo+ipi group: 313 (212 BRAF WT and 101 BRAF mutation +) Ipi group:311 (215 BRAF WT and 96 BRAF positive)	Previously untreated, unresectable or metastatic melanoma

Study #/Type	Study Objective	Study Design	Treatment Cohorts	# of Treated Subjects	Study Population
			NIVOLUMAB & IPILIMUMAB COMBINATION THERAPY		
CA209004 Safety, Efficacy, PK	To assess the safety and tolerability of treatment with nivo in combination with ipi when administered concurrently or sequentially after ipi	Open-label, multicenter, multidose, dose-escalation trial of nivo + ipi administered concurrently or sequentially.	Dose Escalation Cohorts 1-3: 8 doses of nivo Q3W + 4 doses of ipi Q3W then 8 doses of both drugs Q12W Cohort 1: 0.3 mg/kg / 3 mg/kg Cohort 2: 1 mg/kg / 3 mg/kg Cohort 2a: 3 mg/kg / 1 mg/kg Cohort 3: 3 mg/kg / 3 mg/kg Sequential Dosing Cohorts 6-7: nivo Q2W for 48 doses after prior ipi Cohort 6: 1 mg/kg Cohort 7: 3 mg/kg Expansion Cohort 8: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses; then nivolumab 3 mg/kg Q2W	127 Treated Cohorts 1-3: 53 Cohort 8: 41 (27 BRAF WT, 12 BRAF mutation +, 2 UNK BRAF) Cohorts 6-7: 33 No subjects were enrolled in Cohorts 4-5.	Unresectable Stage III or IV melanoma (0-3 prior therapies)
CA209069 Efficacy, Safety,	To compare the ORR, as determined by investigators, of nivo+ipi to ipi monotherapy	Phase 2, randomized (2:1) double-blind study of nivo+ipi vs ipi	Active Dosing Regimens: Nivo+Ipi group: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses; then nivo 3 mg/kg Q2W Ipi group: ipi 3 mg/kg Q3W for 4 doses	N= 140 Treated Nivo+ipi group: 94 (71 BRAF WT and 23 BRAF mutation+) Ipi group:46 (37 BRAF WT and 9 BRAF mutation +)	Previously untreated, unresectable or metastatic melanoma
CA209067 Efficacy, Safety *(also included with mono studies above)*	To compare the PFS and OS of nivo monotherapy to ipi monotherapy, nivo+ipi to ipi monotherapy	Phase 3, randomized (1:1:1), double-blind study of nivo or nivo+ipi vs ipi	Active Dosing Regimens: Nivo group: nivo 3 mg/kg IV Q2W. Nivo+Ipi group: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses followed by nivo 3 mg/kg Q2W Ipi group: ipi 3 mg/kg Q3W for 4 doses	N= 937 Treated Nivo group: 313 (215 BRAF WT and 98 BRAF mutation+) Nivo+ipi group: 313 (212 BRAF WT and 101 BRAF mutation +) Ipi group:311 (215 BRAF WT and 96 BRAF positive)	Previously untreated, unresectable or metastatic melanoma

Abbreviations: CAR: carboplatin, CRC: colorectal carcinoma, DTIC: dacarbazine, IV: Intravenous; ipi: ipilimumab, mCRPC: metastatic castrate resistant prostate cancer, MTD: maximum tolerated dose, nivo: nivolumab, NSCLC: non-small cell lung cancer, ORR: objective response rate, OS: overall survival, PAC: paclitaxel, PLA = placebo; PK: pharmacokinetics, PO: by mouth, Q2W: every 2 weeks; Q3W: every 3 weeks, RCC: renal cell carcinoma, s/p: status post, UNK: unknown, WT: wild-type

2.3.2. Pharmacokinetics

The clinical pharmacology program of nivolumab in combination with ipilimumab was based on data from three studies: two primary studies, a Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma (CA209067) and a Phase 2, randomized, double-blinded study of nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) vs ipilimumab alone (3 mg/kg) in subjects with previously untreated, unresectable or metastatic melanoma (CA209069); and a supportive Phase 1b, open-label, multidose, dose- escalation study of nivolumab in

combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma with 0-3 prior therapies (CA209004).

Population PK of the nivolumab+ipilimumab combination was characterised by combining data from studies with data from selected ipilimumab and nivolumab monotherapy trials, which supported previous monotherapy submissions of ipilimumab and nivolumab. The ipilimumab and nivolumab exposures determined by PPK analyses were used to characterise the E-R relationships of efficacy and safety. The immunogenicity of ipilimumab and nivolumab was also assessed in each of the above studies as well as integrated for both the monotherapy and combination regimens.

Absorption

Pharmacokinetic characteristics of ipilimumab and nivolumab as previously described for their respective melanoma monotherapy indications is summarised in Table 1.

Table 1: Summary of pharmacokinetic parameters for ipilimumab and nivolumab monotherapies

	Nivolumab	Ipilimumab
Cl (ml/h)	9.5 (49.7%)	15.3 (38.5%)
Vss (L)	8.0 (30.4%)	7.2 (10.5%)
$T_{1/2}$ (days)	27 (101%)	15 (30.6%)
$C_{trough,ss}$ (µg/ml) 1 mg/kg 3 mg/kg	 19 (38.8%) 57 (35.9%)	 21.8 (51%)

Pharmacokinetic interaction studies

Study CA209004 was a dose-escalating study to assess the safety and tolerability of treatment with nivolumab in combination with ipilimumab when administered concurrently or as sequenced regimens in subjects with unresectable Stage III or Stage IV malignant melanoma. Interaction of pharmacokinetics between ipilimumab and nivolumab was evaluated by peak and trough concentrations of each ipilimumab and nivolumab when given in combination using distinct regimens.

Ipilimumab and nivolumab were administered as an intravenous (IV) infusion at the protocol-specified doses and rates. There were no dose adjustments allowed. After MTD was reached, 2 of the 6 subjects who originally enrolled in Cohort 3 continued on study after de-escalation to Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab).

The following table describes the dosing and duration of treatment for each cohort (Table 2).

Table 2: Dosing and duration of treatment for each cohort

	Cohort						
Study Drug	**1**	**2**	**2a**	**3**	**6**	**7**	**8[a]**
Nivolumab, mg/kg	0.3	1	3	3	1	3	1
Ipilimumab, mg/kg	3	3	1	3	NA	NA	3

[a] Combination treatment followed by 3 mg/kg nivolumab monotherapy Q2W
Abbreviations: NA = not applicable, Q2W: every 2 weeks
Cohort dosing (mg/kg): Cohort 1 = nivo 0.3:ipi 3; Cohort 2 = nivo 1:ipi 3; Cohort 2a = nivo 3:ipi 1; Cohort 3 = nivo 3:ipi 3; Cohort 6 = nivo 1; Cohort 7 = nivo 3; Cohort 8 = nivo 1:ipi 3/nivo 3.

Ipilimumab and nivolumab serum concentration time curves after the first dose for Cohorts 1-3 (Dose Escalation Combination Therapy) and the Expansion Cohort 8 are shown in Figure 1 and Figure 2.

Figure 2: Plot of mean (+SD) ipilimumab serum concentration-time profiles following coadministration of ipilimumab and nivolumab infusions **on day 1**

A dose-related increase in ipilimumab and nivolumab exposure was observed.

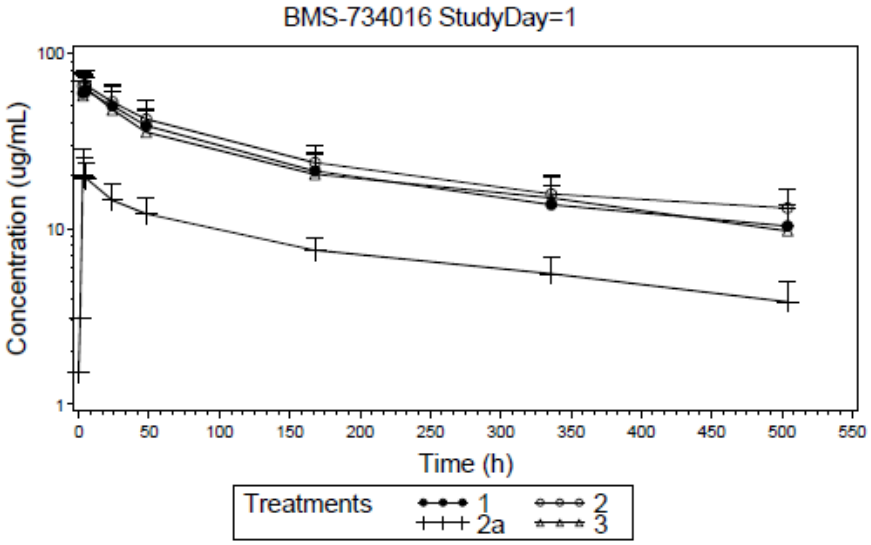


Figure 2: Plot of mean (+SD) ipilimumab serum concentration-time profiles following coadministration of ipilimumab and nivolumab infusions on day 1

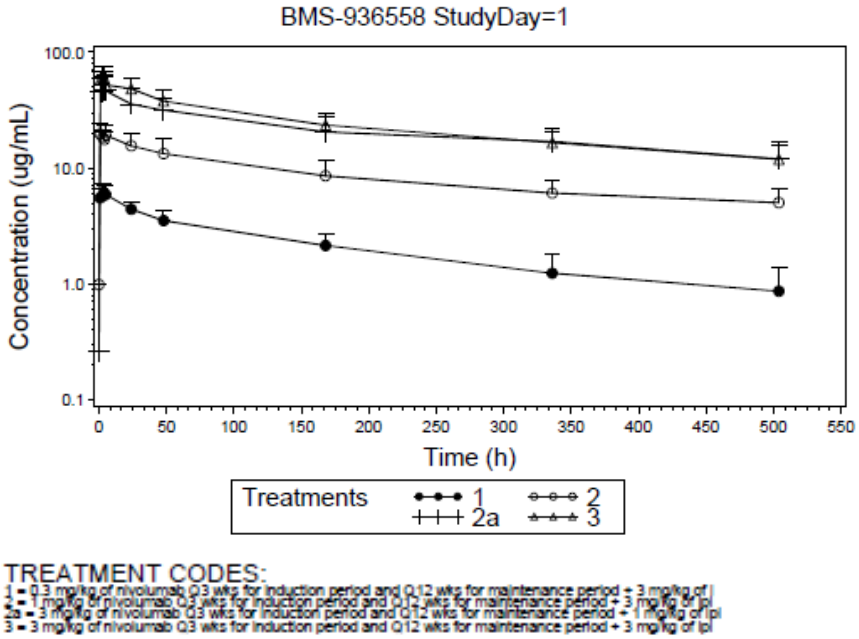


Figure 1: Plot of mean (+SD) nivolumab serum concentration-time profiles following coadministration of ipilimumab and nivolumab infusions on day 1

Ipilimumab peak concentrations at 3 mg/kg in combination with 1 mg/kg nivolumab after the first dose were in the range of 63.5-68.5 µg/mL. Ipilimumab trough concentrations at 3 mg/kg in combination with 1 mg/kg nivolumab after the first dose were in the range of 9.8-11.9 µg/mL. Ipilimumab peak and troughs after Dose 1 were dose proportional between 1 and 3 mg/kg.

Nivolumab peak and trough concentrations after the first dose for 1 mg/kg of nivolumab in combination with 3 mg/kg of ipilimumab Q3W were in the range of 18.1-21.5 µg/mL and 3.2-4.8 µg/mL, respectively. After the fourth dose, peak nivolumab concentrations increased dose proportional.

Interaction between ipilimumab and nivolumab PK was further evaluated in the popPK analysis including sparse PK data from phase 2 study CA209069 and phase 3 study CA209067. The effect of nivolumab coadministration on ipilimumab clearance in the popPK analysis ranged from -7.5% to 11%. Ipilimumab co-administered with nivolumab appears to modestly increase nivolumab clearance. Compared to nivolumab monotherapy, coadministration with ipilimumab 3 mg/kg resulted in a 35% (CI, 27% to 43%) higher nivolumab clearance whereas ipilimumab 1 mg/kg did not appear to have a significant effect with a 2% (CI, -21.4% to 24%) increase in nivolumab clearance. The geometric mean model-predicted dose-normalised nivolumab Cmin, Cavg and Cmax at steady-state were approximately 30.6%, 20.9% and 10.9% lower following nivolumab Q3W in combination with ipilimumab 3 mg/kg compared to nivolumab Q3W without ipilimumab.

PopPK analyses

The final popPK models for ipilimumab and nivolumab monotherapy for melanoma were supplemented with data from studies CA209004, CA209067 and CA209069 where ipilimumab was given in combination with nivolumab.

For ipilimumab, the covariates assessed included ipilimumab antibody status, baseline LDH, baseline BW and nivolumab co-administration on ipilimumab clearance. The magnitude of the effect of continuous covariates, baseline body weight and LDH on clearance and baseline body weight on VC, was outside the ± 20% boundaries and is consistent with results from the previous analysis describing ipilimumab PK for monotherapy, which determined baseline body weight and LDH to be statistically

significant covariates. The typical values of Clearance and VC of 0.0134 L/hr and 4.04 L, respectively, as well as the covariate effects of baseline body weight and LDH on clearance and baseline body weight on VC of 0.692, 1.11, and 0.719, respectively.

The effect of positive anti-ipilimumab antibody status on clearance was assessed as a time-varying covariate in the full model. A positive anti-ipilimumab antibody status from the current drug tolerant assay (drug tolerance = 75 µg/mL), was estimated to have a negligible effect (magnitude of effect was 6%) on ipilimumab clearance in the analysis compared to a negative anti-ipilimumab antibody status.

The individual PK parameter estimates were obtained from the full model and are summarized in Table 3.

Table 3: Summary statistics of individual measures of ipilimumab parameters in ipilimumab combination therapy (Ipi: 3mg/kg Q3W, Nivo: 1mg/kg Q3W)

Exposure Estimate	N	Mean	GeoMean	Median (min, max)	SD	CV%
Baseline CL (BCL) [mL/h]	260	13.9	13.4	13.5(5.67,33.4)	4.11	29.5
CLSS [mL/h]	260	10.6	10.2	10.3(4.39,25.6)	3.19	30.1
VC [L]	260	3.78	3.69	3.74(1.32,6.54)	0.804	21.3
VSS [L]	260	6.67	6.62	6.63(4.21,9.43)	0.804	12.1
T-HALFα [h]	260	32.5	32.3	32.7(17,40.5)	3.22	9.9
T-HALFβ [d]	260	20.6	20	20(10.9,41.4)	4.73	23
EMAXP	260	23.8	23.6	23.5(3.69,38.6)	2.64	11.1

Source: Analysis Directory: /global/pkms/data/CA/209/C20/prd/ipippk-combo2016/final/

For nivolumab, the following covariates were included in the full model: sex, body weight baseline GFR, ECOG status, ipilimumab coadministration, nivolumab immunogenicity. They represent the effects of ipilimumab coadministration and anti-nivolumab antibodies on nivolumab clearance, and the significant covariates from the previous final model.

Compared to the reference of no anti-nivolumab antibody detected (antibody negative), the effect of anti-nivolumab antibodies on nivolumab clearance was 25% (CI, 16% to 34%) higher using the current drug tolerant assay (3rd generation). In subjects with an ECOG performance status of >0, nivolumab clearance was 22% higher (based on median values).

Male subjects had a 12% (CI, 9% to 16%) higher VC than females.

Baseline body weight was identified as a significant covariate for both clearance and VC with the effects of BW at the 5th and 95th percentiles extending outside the ± 20% boundaries, supporting the dosing based on bodyweight.

The individual parameter estimates are obtained from the full popPK model and summarized in Table 4.

Table 4: Summary statistics of nivolumab PK parameters using post-hoc Bayesian estimates of individual parameter from final popPK model

PK Parameter[a]	Mean (SD)	Geometric Mean (CV%)	Median (min, max)
CL [L/h]	0.0108 (0.00532)	0.00983 (49.2)	0.00963 (0.00139, 0.0526)
VC [L]	4.3 (1.1)	4.15 (25.6)	4.22 (0.234, 9.83)
VP [L]	3.57 (1.6)	3.32 (45)	3.33 (0.492, 25)
VSS [L]	7.86 (2.1)	7.62 (26.6)	7.6 (3.19, 28.6)
T-HALFα [h]	40.3 (9.42)	39.2 (23.4)	39.7 (4.73, 90)
T-HALFβ [d]	26.4 (19.3)	24.1 (73.1)	24.3 (5.02, 617)

[a] T1/2β and T1/2α were calculated using formula as below:

KE = CL/VC; K12 = Q/VC; K21 = Q/VP; AA = KE + K12 + K21

$$\beta = \left(\frac{AA - \sqrt{AA^2 - 4 \times KE \times K21}}{2}\right), \text{ and } t_{\beta} = \left(\frac{0.693}{\beta}\right)$$

$$\alpha = \left(\frac{AA + \sqrt{AA^2 - 4 \times KE \times K21}}{2}\right), \text{ and } t_{\alpha} = \left(\frac{0.693}{\alpha}\right)$$

VSS was calculated using formula: VSS=VC+VP. Individual estimate of Q is 0.0297 L/h, as there are no random or covariate effect parameters associated with Q in the full PPK model.

Source: Refer to Table 5.1.3.1-1 of the of the Population Pharmacokinetic and Exposure-Response Report[9]

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Effect of ipilimumab and nivolumab on cytokine expression in human whole blood cells (MDX-1106-010-008R 930036361)

Cytokine release assays of whole blood were performed to examine the potential of ipilimumab and nivolumab alone and in combination to activate cytokine secretion from human peripheral blood cells. Positive control anti-CD3 mAb (UCHT-1) induced cytokine secretion in all donors, while treatment with ipilimumab and nivolumab mAbs alone or in combination did not stimulate cytokine secretion at concentrations up to 100 µg/mL. Addition of the ipilimumab and nivolumab combination did not promote nonspecific activation of lymphocytes.

PD-L1 Expression as a Potential Biomarker

The relevance of baseline PD-L1 expression in tumours as a potential biomarker of nivolumab efficacy is discussed in the clinical efficacy section.

Activated T cells

Pharmacodynamic changes in activated (HLA-DR+) CD4 and CD8 T-cells were measured by flow cytometry in subjects in Cohorts 1-3 and Cohort 8 at baseline and pre-dose at multiple timepoints during treatment (Figure 3). Increases in activated CD4+ and CD8+ T-cells were observed with concurrent dosing, while no increase was observed for nivolumab monotherapy. Following a single dose of the treatment regimen, the mean percentage change from baseline of absolute levels of activated CD4+T-cells and CD8+ T-cells, respectively, reached 106.8%/162.4% and 33.5%/111.9% in

Cohorts 1-3 combined/Cohort 8. There was no consistent effect of the dose of nivolumab or ipilimumab on the observed increases in activated CD4+ and CD8+ T-cells in Cohorts 1-3 and Cohort 8. Associations between response and change in activated CD4+ and CD8+ T-cells were also not evident.

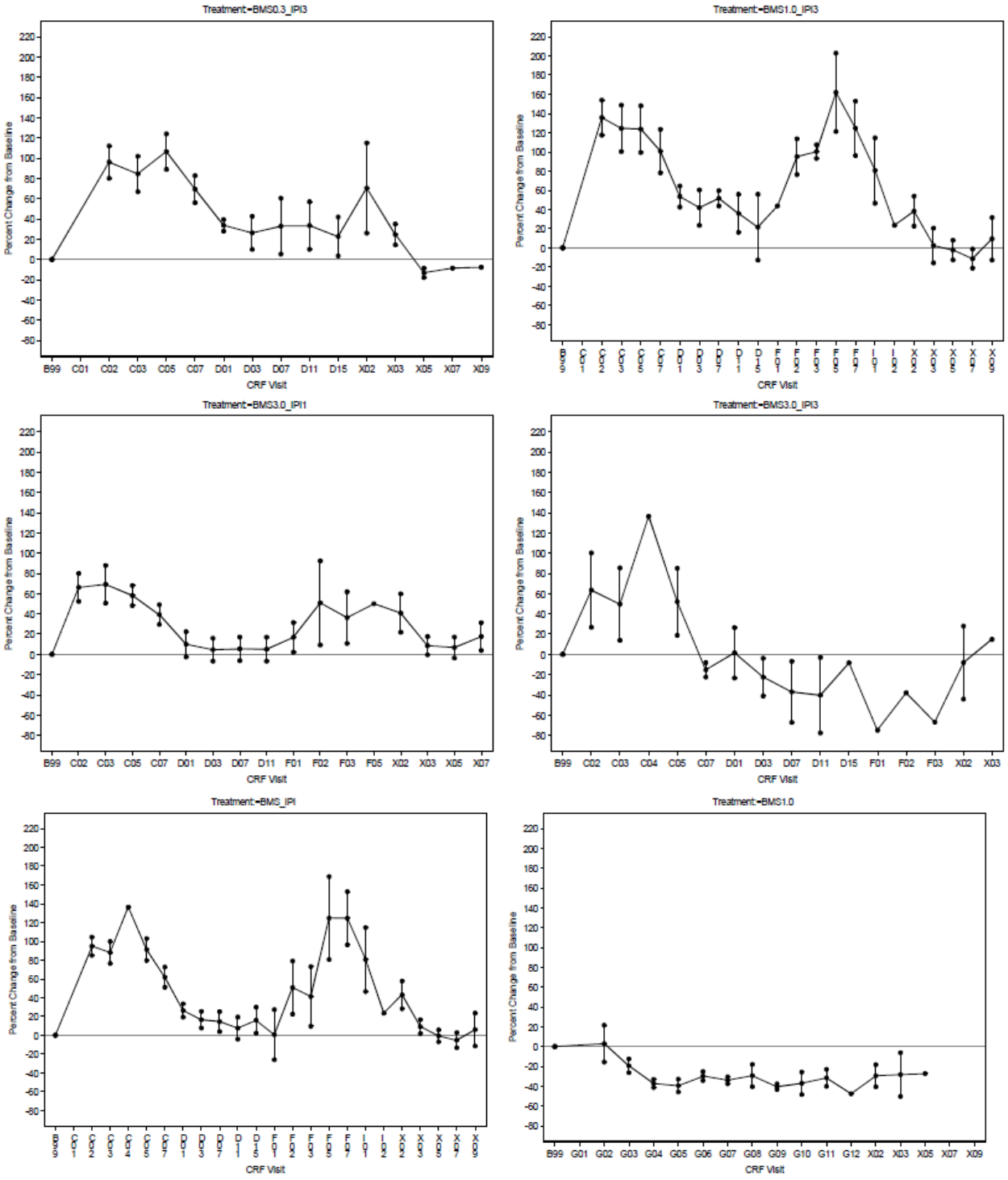


Figure 2: Activated CD4+ T cells Mean Percent Change from Baseline by Treatment (from top left to bottom right: cohort 1 0.3 nivolumab+3 ipilimumab, cohort 2: 1 nivolumab+3 ipilimumab, cohort 2a: 3 nivolumab +1 ipilimumab, cohort 3: 3 nivolumab + 3 ipilimumab, 3 ipilimumab alone, 1 nivolumab alone) - Study CA209004

Absolute lymphocyte counts (ALC) were measured from whole blood samples at pre-treatment and during treatment. The maximum mean increase in absolute levels was 0.25 (x10*9 cells/liter) during the first 12 weeks of the induction period in Cohorts 1-3 combined, and was 0.26 (x10*9 cells/liter) during the combination period of Cohort 8.

Of the 12 serum cytokines included in the analyses (IFN-G, MIG, IP-10, IL-1a, IL-1b, IL-2ra, IL-6, IL-10, TNFa, IL-12p40, IL-12p70 and IL-23), 6 had values that were measurable above the lower limits of quantitation of the assay in >15 of the serum samples tested: MIG, IP-10, IL-2ra, IL-6, IL-10 and IL-12p40. MIG, IP-10, IL-2ra and IL-10 were changed over time with treatment in Cohorts 1-3 (Dose Escalation Combination Therapy) and Expansion Cohort 8.

2.3.4. PK/PD modelling

The E-R relationship of efficacy for PFS was developed using data from Study CA209067 in 927 subjects. The relationship between ipilimumab and nivolumab exposure (Cavg1) and time to PFS was described by a semi-parametric Cox Proportional-Hazards (CPH) model. The model performance was evaluated by comparing the cumulative probability of PFS predicted by the full model with that determined by Kaplan-Meier analyses.

A graphical presentation of all of the estimated effects in the full model, showing the hazard ratios of disease progression across the predictor ranges and the associated 95% confidence intervals is presented in Figure 4.

The predictor variables with a significant effect on the PFS were PD-L1 expression status, gender, body weight, and baseline LDH (95% CI of effect did not include 1). Nivolumab Cavg1 was also significant predictor of PFS. Cavg1 of nivolumab produced from nivolumab 1 mg/kg+ ipilimumab 3 mg/kg had improved PFS relative to Cavg1 from nivolumab 3 mg/kg monotherapy. The 95% CI of all the other predictor variables (M-stage, BRAF, ECOG status, age and baseline tumour size) evaluated did not have a statistical significant effect on PFS.

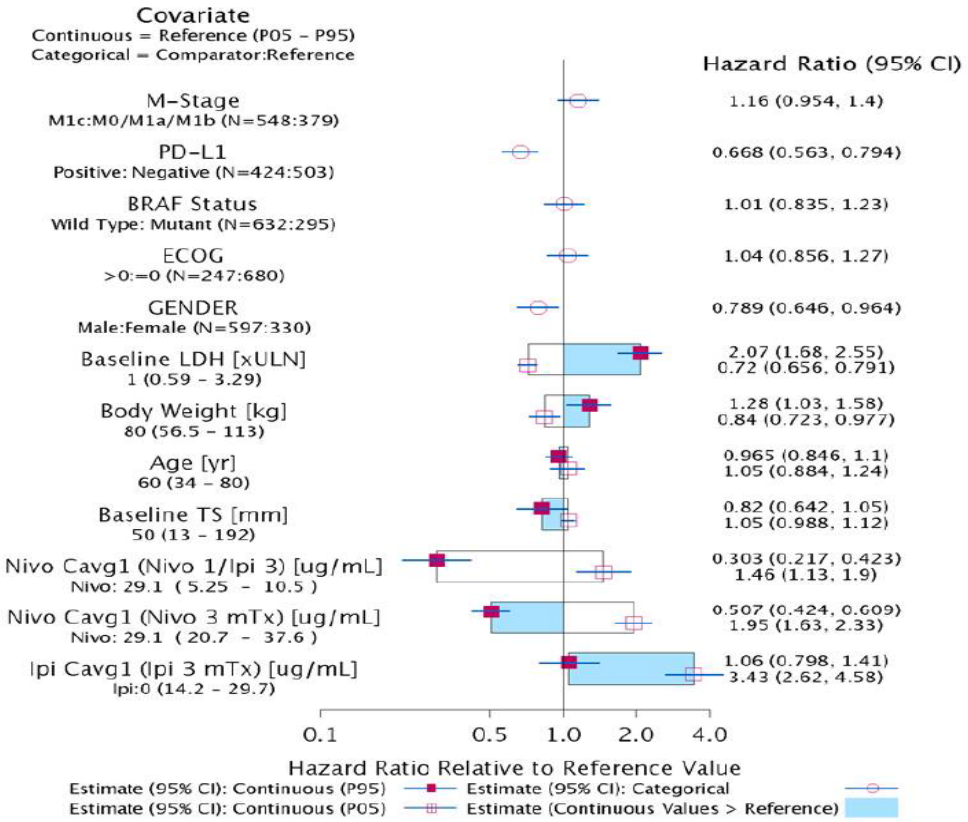


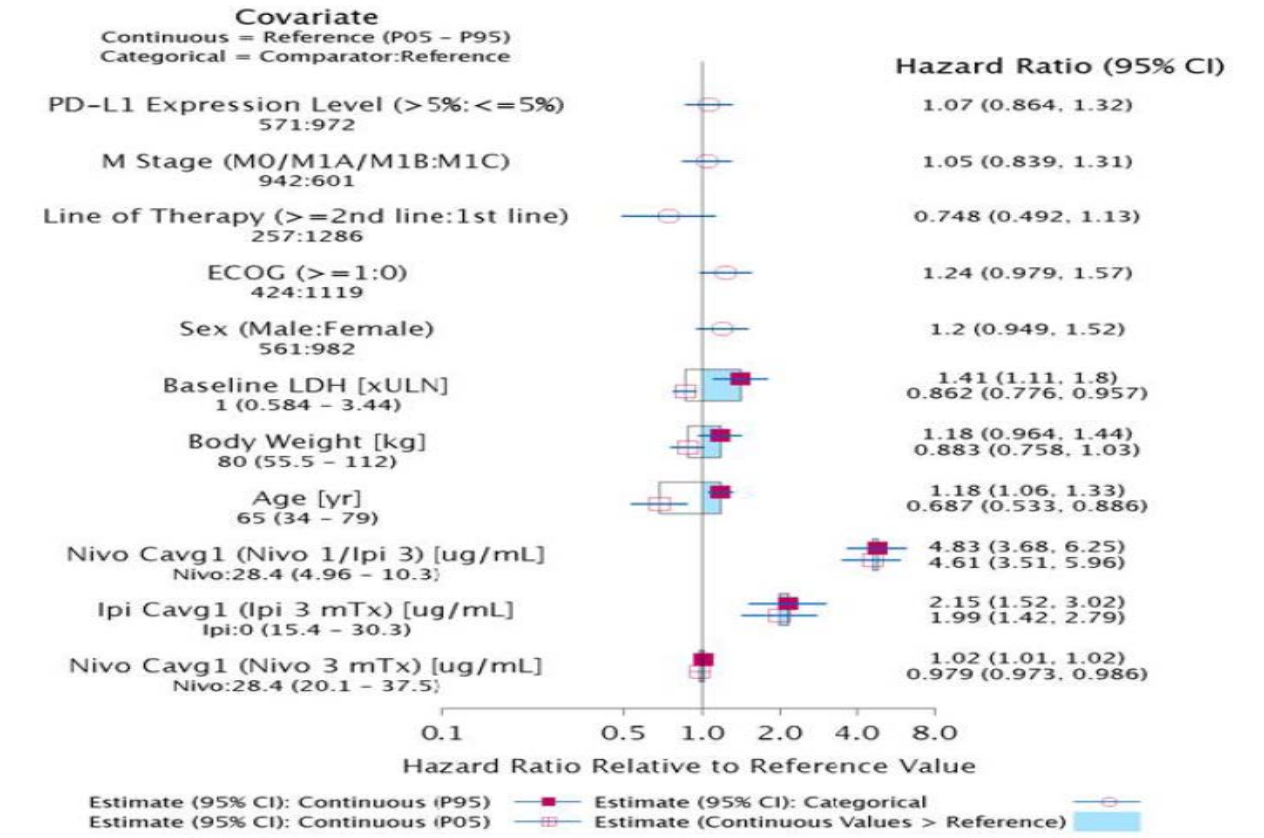
Figure 3: Estimated covariate effects of exposure-PFS by Cox Proportional-Hazards Analysis

The hazard ratio (HR) of PFS was predicted from the full model at various values of Cavg1, in order to understand the impact of ipilimumab and nivolumab regimens on the risk of disease progression. The median Cavg1 at nivolumab 3 mg/kg monotherapy was used as the reference. The estimated hazard ratios indicated a decreased risk of disease progression in the combination regimens (HR: 0.68) compared with nivolumab 3 mg/kg monotherapy, while the risk was higher (HR: 1.87) in the ipilimumab monotherapy group.

Exposure-Response Relationship for Safety

The E-R relationship of safety Adverse Events leading to dose discontinuation or death (AE-DC/D) was developed using the data pooled from various regimens of ipilimumab and nivolumab in CA209004, CA209037, CA209069, CA209066 and CA209067 in 1543 subjects. The popPK model predicted Cavg1 was used as the measure of exposure of both ipilimumab and nivolumab and the relationship between ipilimumab and nivolumab exposure (Cavg1) and time to AE-DC/D was described by a semi-parametric Cox Proportional Hazard model, and included assessments of the modulatory effect of covariates as well as the potential interaction between ipilimumab and nivolumab Cavg1. The covariates for the full model included age, BW, gender, baseline LDH, ECOG status, M stage, line of therapy and PD-L1 expression level.

The estimated covariate effects of E-R for safety are shown in **Figure 5**. The exposure effect was represented by hazard ratios of ipilimumab 3 mg/kg and nivolumab 1 mg/kg + ipilimumab 3 mg/kg compared with that of nivolumab 3 mg/kg (median Cavg1). It shows an increased hazard in both ipilimumab monotherapy and combination therapy, with the combination therapy having a greater increase.



Note: hazard ratio at nivolumab 1 + ipilimumab 3 mg/kg was calculated by using median ipilimumab Cavg1 and varying nivolumab Cavg1

Figure 4: Estimated covariate effects of exposure-safety (adverse events leading to dose discontinuation or death) by Cox Proportional-Hazards analysis

Immunogenicity

Anti-ipilimumab antibodies

Of the 391 ipilimumab antibody evaluable subjects in the nivolumab+ipilimumab group, 24 (6.1%) subjects were ipilimumab antibody positive at baseline and 33 (8.4%) subjects were ipilimumab antibody positive after treatment. None of the subjects were considered persistent positive and only one subject was considered neutralizing positive. The incidence of ipilimumab antibody in combination was comparable to that reported for ipilimumab monotherapy.

Anti-nivolumab antibodies

Of the 394 subjects who were treated with nivolumab + ipilimumab in combination and evaluable for the presence of anti-nivolumab antibodies, 149 (37.8%) subjects tested positive for anti-product antibodies by an ECL assay. Twenty-five subjects were nivolumab antibody persistent positive (N=18, 4.6%) and/or NAb positive (N=18, 4.6%) in the combination group. The nivolumab antibody titers appear to decrease after Week 12, corresponding to the beginning of the maintenance phase when ipilimumab treatment was discontinued as per the schedule. The overall incidence of anti-nivolumab antibodies in the assessed population was higher as compared to nivolumab monotherapy (12.3%). Nivolumab clearance increased by 25% in the presence of anti-nivolumab antibodies.

Immunogenicity – efficacy

Of the 25 subjects that were nivolumab antibody persistent positive and/or Nab positive in the combination group, 5 (20%) subjects had a BOR of CR and 11 (44%) had a BOR of PR. Three (12%) subjects had a BOR of SD and 6 (24%) had a BOR of PD. The 1 (4%) subject in the nivolumab + ipilimumab combination group who was ipilimumab NAb positive had a BOR of PR. The one subject in the nivolumab monotherapy group that was NAb positive had a BOR of CR.

An additional exposure-response (E-R) analysis of efficacy was conducted evaluating the effect of anti-drug antibodies (ADA, positive-negative) with respect to progression free survival (PFS). The E-R analysis of PFS was conducted using a full Cox proportional-hazards (CPH) model with data from 731 subjects who received either nivolumab monotherapy or 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab. The estimated HR of the occurrence of ADA on the risk of PFS was 1.03, and the 95% confidence interval (CI) of HR included unity.

Immunogenicity – safety

The effect of immunogenicity on safety was assessed in studies CA209004, CA209069, and CA209067. In studies CA209004 and CA209069, the safety profiles of the 4 persistent positive subjects and 1 NAb positive subject were similar to those observed in nivolumab antibody negative subjects. There were no hypersensitivity, acute infusion reactions, and new AEs observed in persistent or NAb positive subjects compared to antibody negative subjects.

In Study CA209067 the number of subjects with hypersensitivity/infusion related reactions was similar between the nivolumab+ipilimumab combination (n=14) and nivolumab monotherapy groups (n=16), while slightly lower in the ipilimumab monotherapy group (n=9). In addition, in the nivolumab and ipilimumab monotherapy groups, hypersensitivity/infusion related reactions were observed in antibody negative subjects, whereas hypersensitivity and infusion related reactions were not observed in any antibody positive subject.

2.3.5. Discussion on clinical pharmacology

Ipilimumab pharmacokinetics was similar when administered in combination with 1 mg/kg nivolumab or as monotherapy. Nivolumab coadministration with ipilimumab 3 mg/kg resulted in a modest 35% increase in nivolumab clearance, relative to the nivolumab clearance when given as monotherapy. The modest effect of ipilimumab on nivolumab clearance is unlikely to be clinically relevant, because no dose response of nivolumab in melanoma has been observed (range 0.1 – 10 mg/kg).

A dose finding study was conducted to evaluate safety and efficacy of the combination of nivolumab and ipilimumab in patients with advanced melanoma. Treatment with 3 mg/kg nivolumab and 3 mg/kg ipilimumab, the doses approved for monotherapy, resulted in dose-limiting toxicities that exceeded the MTD. Treatment with 1 mg/kg nivolumab + 3 mg/kg ipilimumab or 3 mg/kg nivolumab + 1 mg/kg ipilimumab were tolerable, establishing both dose combinations as the maximum tolerated dose. Efficacy seemed comparable in both arms. The dose and exposure response evaluations for monotherapy nivolumab suggested that increasing doses of nivolumab above 1 mg/kg did not change the likelihood of response, while in monotherapy ipilimumab studies, increasing doses of ipilimumab (0.3 mg/kg vs 3 mg/kg vs 10 mg/kg) increased the likelihood of clinical response. Therefore, the selection of 1 mg/kg nivolumab + 3 mg/kg ipilimumab for the extension study and the clinical phase 2 & 3 study has been sufficiently substantiated.

The incidence of nivolumab antibodies was higher when nivolumab was combined with ipilimumab relative to nivolumab monotherapy (37.8% vs. 12.3%). Neutralising antibodies were observed in 4.6% of subjects treated with the combination and nivolumab clearance increased by 25% in the presence of

nivolumab antibodies. The immunogenicity of ipilimumab when given in combination with nivolumab was low (approximately 8.4% antibody positive), and had no impact on ipilimumab PK.

The risk of disease progression was lower for the combination of nivolumab and ipilimumab compared to nivolumab monotherapy and ipilimumab monotherapy. The risk of disease progression was evaluated in sensitivity analyses investigating further covariates. The risk of disease progression appeared to increase with lower ipilimumab and nivolumab exposure, higher LDH and body weight, PD-L1 positivity and in male melanoma subjects. Patients with ECOG status>0, high LDH, low albumin, and poor appetite/low bodyweight tend to have lower antibody exposure. The risk of disease progression decreased with increased tumour shrinkage data at Week 12 and in patients with positive PD-L1 expression. The relevance of baseline PD-L1 expression as a potential biomarker of nivolumab efficacy is discussed in the clinical efficacy section.

No association between baseline values or change from baseline of serum cytokines with response was observed, nor was an association with dose of ipilimumab and/or nivolumab.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics, pharmacodynamics and exposure-response relationships for the combination of nivolumab with ipilimumab for treatment of advanced melanoma have been adequately investigated. The SmPC has been updated in section 5.2 with PK data from the combination treatment.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Dose selection

The dose of ipilimumab 3 mg/kg and nivolumab 1 mg/kg was based on the totality of available data including anti-tumour activity and safety data in study CA209004.

Study CA209004

This was a Phase 1b, open-label, multi-center, multi-dose, dose-escalation study of nivolumab in combination with ipilimumab. Study drugs were administered either concurrently (Cohorts 1 through 5 and Cohort 8) or in a sequenced regimen (Cohorts 6 and 7) (See Table 5).

For subjects enrolled in the concurrent dose cohorts, or dose-escalation cohorts (Cohorts 1 through 5), the study consisted of Screening (up to 4 weeks), Treatment (induction for up to 24 weeks and maintenance for up to 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years). During the treatment period, subjects were scheduled to receive nivolumab and ipilimumab in combination for 4 doses, then nivolumab for 4 additional doses, followed by nivolumab and ipilimumab in combination for 8 doses. The Cohort 3 dose regimen exceeded the maximum tolerated dose, thus no subjects were enrolled in Cohorts 4 and 5.

For subjects enrolled in the sequenced regimen cohorts (Cohorts 6 and 7), the study consisted of 4 periods: Screening (up to 4 weeks), Study Treatment (up to 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years).

For subjects enrolled in the nivolumab/ipilimumab combination expansion cohort (Cohort 8), the study

consisted of the screening period (up to 4 weeks), Treatment period (combination treatment for 12 weeks then nivolumab monotherapy for 96 weeks), Follow-up (minimum of 12 weeks), and Survival Follow up (up to 3 years). During the treatment period, subjects were scheduled to receive nivolumab and ipilimumab in combination for 4 doses Q3W, followed by nivolumab alone Q2W.

Table 5: Treatment regimen for cohorts 1 – 8 for combination of nivolumab and ipilimumab – Study CA209004

	Cohort						
Study Drug	**1**	**2**	**2a**	**3**	**6**	**7**	**8**[a]
Nivolumab, mg/kg	0.3	1	3	3	1	3	1
Ipilimumab, mg/kg	3	3	1	3	NA	NA	3

[a] Combination treatment followed by 3 mg/kg nivolumab monotherapy Q2W
Abbreviations: NA = not applicable, Q2W: every 2 weeks
Cohort dosing (mg/kg): Cohort 1 = nivo 0.3:ipi 3; Cohort 2 = nivo 1:ipi 3; Cohort 2a = nivo 3:ipi 1; Cohort 3 = nivo 3:ipi 3; Cohort 6 = nivo 1; Cohort 7 = nivo 3; Cohort 8 = nivo 1:ipi 3/nivo 3.

Outcomes

The results of the various cohorts are presented in the Tables below (Table 6, Table 7 and Table 8).

Table 6: Subjects in cohorts 1-3 (Dose Escalation Combination Therapy) – Study CA209004

	Number (%) of Subjects				
	Cohort 1 N = 14	Cohort 2 N = 17	Cohort 2a N = 16	Cohort 3 N = 6	Total, Cohorts 1-3 N = 53
Response by mWHO criteria:					
Best Overall Response					
Complete Response (CR)	2(14)	3(18)	4(25)	0	9(17)
Partial Response (PR)	1(7)	5(29)	4(25)	3(50)	13(25)
Progressive Disease	8(57)	7(41)	5(31)	1(17)	21(40)
Stable Disease	2(14)	1(6)	3(19)	2(33)	8(15)
(SD >=24 weeks)	2(14)	0	3(19)	0	5(9)
Unable to Determine	1(7)	1(6)	0	0	2(4)
Objective Response Rate	3(21)	8(47)	8(50)	3(50)	22(42)
95% CI	(4.7,50.8)	(23.0,72.2)	(24.7,75.3)	(11.8,88.2)	(28.1,55.9)
Disease Control Rate	5(36)	8(47)	11(69)	3(50)	27(51)
95% CI	(12.8,64.9)	(23.0,72.2)	(41.3,89.0)	(11.8,88.2)	(36.8,64.9)
Aggregate Response (CR,PR,uCR, uPR,irCR,irPR) Rate	5(36)	9(53)	11(69)	5(83)	30(57)
95% CI	(12.8,64.9)	(27.8,77.0)	(41.3,89.0)	(35.9,99.6)	(42.3,70.2)

Abbreviations: CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
Cohort dosing (mg/kg): Cohort 1 = nivo 0.3:ipi 3; Cohort 2 = nivo 1:ipi 3; Cohort 2a = nivo 3:ipi 1; Cohort 3 = nivo 3:ipi 3.
Note: Objective Response Rate (ORR) will be defined as the total number of subjects whose BOR is CR, PR divided by the total number of subjects in the population of interest. Aggregate response rate is essentially immune-related overall response rate (irORR), as there was no uPR or uCR in this study. Disease Control Rate is the total number of subjects whose best overall response is CR, PR, or SD ≥24 weeks divided by the total number of treated subjects.

Table 7: Overall response summary including mWHO and Immune-Related Criteria (all treated subjects, Cohort 8) – Study CA209004

	Number (%) of Subjects
Response by mWHO criteria:	**Cohort 8 (N=41)**
Best overall response	
Complete response (CR)	3 (7)
Partial Response (PR)	15 (37)
Progressive disease (PD)	14 (34)
Stable disease	6 (15)
Stable disease ≥24 weeks	2 (5)
Unable to determine	3 (7)
Objective response rate	18 (44)
95% CI	28.5, 60.3
Disease control rate	20 (49)
95% CI	32.9, 64.9
Aggregate response (CR, PR, uCR, uPR, irCR, irPR)	20 (49)
95% CI	32.9, 64.9

Abbreviations: CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
Cohort dosing (mg/kg): Cohort 8 = nivo 1:ipi 3/nivo 3.
Note: Objective Response Rate (ORR) will be defined as the total number of subjects whose BOR is CR, PR divided by the total number of subjects in the population of interest. Aggregate response rate is essentially immune-related overall response rate (irORR), as there was no uPR or uCR in this study. Disease Control Rate is the total number of subjects whose best overall response is CR, PR, or SD ≥24 weeks divided by the total number of treated subjects.

Table 8: Summary of efficacy in all subjects treated with nivolumab sequential therapy (Cohorts 6-7) - Study CA209004

	Number (%) of Subjects		
Response by mWHO criteria:	Cohort 6 N = 16	Cohort 7 N = 17	Total, Cohort 6-7 N=33
Best Overall Response			
Complete Response (CR)	2 (12)	0	2 (6)
Partial Response (PR)	7 (41)	3 (19)	10 (30)
Progressive Disease	5 (29)	8 (50)	13 (39)
Stable Disease	2 (12)	5 (31)	7 (21)
(SD ≥24 weeks)	0	1 (6)	1 (3)[a]
Unable to Determine	1 (6)	0	1 (3)
Objective Response Rate	9 (53)	3 (19)	12 (36)
95% CI	(27.8,77.0)	(4.0,45.6)	(20.4,54.9)
Disease Control Rate	9 (53)	4 (25)	13 (39)
95% CI	(27.8,77.0)	(7.3,52.4)	(22.9,57.9)

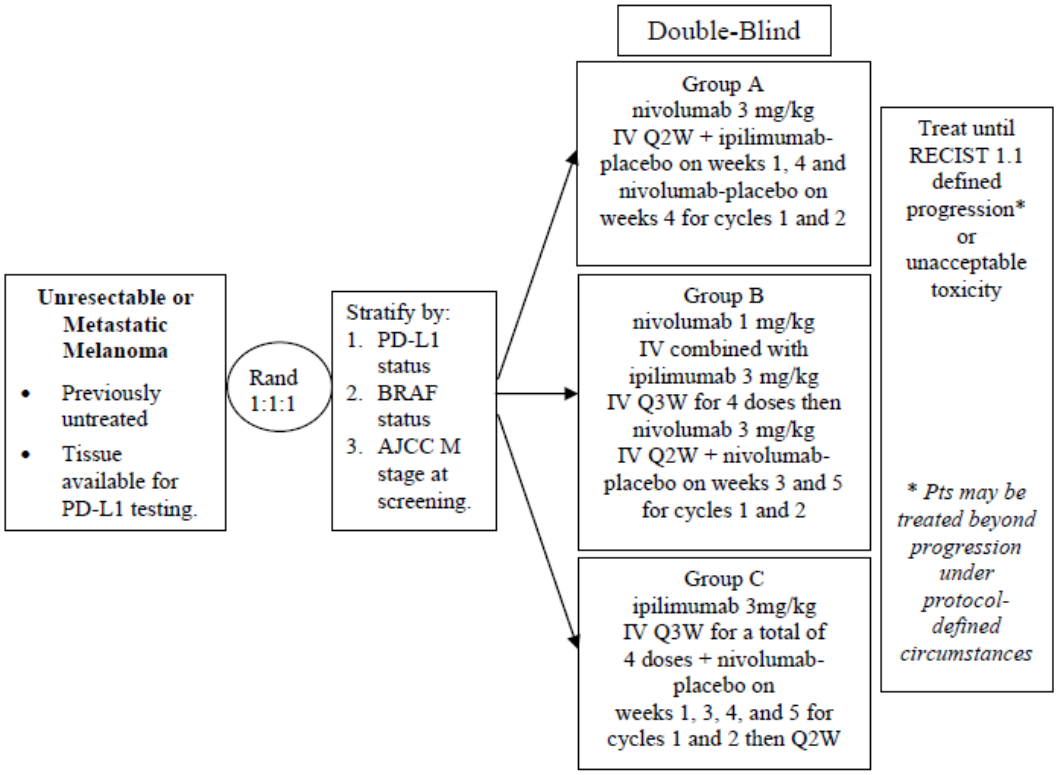
Abbreviations: CI: confidence interval.
[a] One subject in Cohort 7 achieved stable disease ≥24 weeks.
Note: + indicates assessment of response is ongoing.
Cohort dosing (mg/kg): Cohort 6 = nivo 1; Cohort 7 = nivo 3.

2.4.2. Main study(ies)

Title of Study CA209067: A Phase 3, Randomized, Double-blind Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab Versus Ipilimumab Monotherapy in Subjects With Previously Untreated Unresectable or Metastatic Melanoma

Methods

Figure 5 Study design schematic - CA209067



Study participants

Key inclusion criteria were as follows:

- ECOG performance status 0 or 1.
- Histologically confirmed Stage III (unresectable) or Stage IV melanoma, as per AJCC staging system.
- Treatment naïve patients (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Prior adjuvant or neoadjuvant melanoma therapy was permitted if it was completed at least 6 weeks prior to randomisation, and all related adverse events had either returned to baseline or stabilised.
- Measurable disease by computer tomography or magnetic resonance imaging (MRI) per RECIST 1.1 criteria.
- Known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period.
- Tumour tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomised, a subject must have been classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumour tissue from an unresectable or metastatic site was available prior to the start of the screening phase subjects must have consented to allow the acquisition of additional tumour tissue for performance of biomarker analyses.

Key exclusion criteria were as follows:

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases were eligible if these had been treated and there was no MRI evidence of progression for at least8 weeks after treatment was complete and within 28 days prior to first dose of study drug administration.
- Ocular melanoma.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

Treatments

This study consisted of 3 phases: screening, treatment, and follow-up.

One cycle of treatment was defined as 6 weeks. On-study tumour assessments began 12 weeks (± 1 week) from randomisation and continued every 6 weeks (± 1 week) for the first 12 months up to week 49 from randomisation and every 12 weeks (± 1 week) thereafter until disease progression. Subjects continued to have tumour assessments in the follow up period if they discontinued treatment for reasons other than progression (eg, toxicity). Treatment beyond initial investigator-assessed Response Evaluation Criteria In Solid Tumours (RECIST) 1.1-defined progression was permitted if the subject had investigator-assessed clinical benefit and tolerated the study drug.

Nivolumab at 3 mg/kg (nivolumab group), 1 mg/kg (nivolumab+ipilimumab group), or nivolumab placebo (ipilimumab group) was administered IV over 60 minutes followed by ipilimumab at 3 mg/kg (nivolumab+ipilimumab group and ipilimumab group) or ipilimumab placebo (nivolumab group) administered IV over 90 minutes. Dosing schedule for the different cycles is shown in Table 9 and Table 10 below.

Table 9: Dosing schedule for cycle 1 and cycle 2 – Study CA209067

1 Cycle = 6 weeks				
	Day 1 Week 1	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**
Group A Nivolumab Monotherapy 3mg/kg + Placebo	3mg/kg Nivolumab 3 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	1 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab
Group B Nivolumab 1mg/kg + Ipilimumab 3 mg/kg	1 mg/kg Nivolumab [a] 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	1 mg/kg Nivolumab[a,] 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo
Group C Ipilimumab Monotherapy 3mg/kg+ Placebo	3 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	1 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo

[a] Group B - In order to protect the blind, the 1mg/kg nivolumab administered on D1W1 and D1W4 in cycles 1 and 2 was to be diluted to the same volume as 3 mg/kg nivolumab-placebo prepared on D1W3, D1W5 and treatment visits after Cycle 2.

Table 10: Dosing schedule cycle 3 and beyond – Study CA209067

1 Cycle = 6 weeks			
	Day 1 Week 1	**Day 1 Week 3**	**Day 1 Week 5**
Arm A (Nivolumab Monotherapy + Placebo)	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab
Arm B (Nivolumab + Ipilimumab)	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab
Arm C (Ipilimumab Monotherapy + Placebo)	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo

Source: Protocol (Appendix 1.1)

Dose escalation or reduction was not permitted.

The protocol allowed for administration of study drugs to be delayed based on drug-related AEs attributed to nivolumab, ipilimumab, or both.

The following medications were prohibited during the study:

- Immunosuppressive agents, except to treat a drug-related adverse event.
- Systemic corticosteroids > 10 mg daily prednisone equivalent, except to treat a drug-related adverse event.
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy or standard or investigational agents for treatment of cancer).

Supportive care for disease-related symptoms was allowed for all subjects in the trial.

Objectives

Primary Objective

To compare PFS and OS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma.

Secondary Objective(s)

- To compare objective response rate (ORR) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma.
- evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for OS
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30

Outcomes / endpoints

Co-Primary Endpoints: The co-primary endpoints were PFS and OS

- PFS was defined as the time from randomisation to the date of first documented disease progression, as assessed by the investigator per RECIST 1.1, or death due to any cause, whichever occurs first.
- OS was defined as the time between the date of randomisation and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive.

Secondary endpoints

- ORR, defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomised subjects for each treatment group;
- Differences in OS, PFS and ORR between the groups;
- PD-L1 expression as a predictive biomarker for OS;
- Health-related quality of life (HRQoL) was assessed from European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 responses.

PD-L1 Results

PD-L1 expression was based on two different assays: Verified DAKO PD-L1 IHC assay and Validated DAKO PD-L1 IHC assay. At study initiation, the validated assay was not available. Analytical comparison of the verified and validated assays by DAKO using 104 melanoma tissue samples demonstrated an overall agreement in PD-L1 status between the assays of 97.1% using both 1% and 5% cut-off.

PD-L1 expression was defined as the percent of tumour cells demonstrating plasma membrane PD-L1 staining in a minimum of 100 evaluable tumour cells per a DAKO PD-L1 IHC assay (this is referred to as quantifiable PD-L1 expression). If the PD-L1 staining could not be quantified, it was further classified as:

- Indeterminate: Tumour cell membrane staining hampered for pre-specified reasons attributed to the biology of the tumour tissue sample, such as high melanin content or high cytoplasmic staining, and not because of improper sample preparation or handling.
- Not evaluable: Tumour tissue sample was not optimally collected or prepared.
- Missing: Tumour tissue sample not available for evaluation.

For stratification purposes with the verified assay, quantifiable PD-L1 expression was dichotomized by a 5% cut-off. PD-L1 positive status was defined as a tumour specimen with 5% tumour cell membrane staining, and subjects were stratified based on a PD-L1 positive status or PD-L1 negative /indeterminate status. Using this cut-off, the MAH determined in tumour biopsy specimens from Study MDX1106-034, that 45% of melanoma subjects were defined as PD-L1 positive. Conversely, PD-L1 negative status was defined as a tumour specimen with <5% tumour cell membrane staining.

Exploratory endpoints included Duration of objective response (DOR), Time to objective response (TTR), safety and tolerability, pharmacokinetics, immunogenicity, potential association between biomarker (eg, PD-L1) expression and efficacy endpoints, potential association between natural genetic variation and efficacy endpoints, and change in health status (EuroQoL EQ-5D).

Sample size

Approximately 915 subjects were planned to be randomised to 3 treatment groups in a 1:1:1ratio. The sample size of the study accounted for the co-primary endpoints of PFS and OS, with an alpha allocation of 0.01 for PFS and 0.04 for OS. Formal analyses of PFS and OS were planned to be conducted at different time points.

- The PFS analysis was targeted to occur after all subjects had 9 months follow-up per sample size and power considerations. However, the required minimum follow-up for analysis of PFS was 6 months.

For each PFS comparison, the number of events projected to be observed at 9 months follow-up provide approximately 83% power to detect an average hazard ratio (HR) of 0.71 with a Type I error of 0.005 (two-sided).

- The OS analysis was targeted to occur after all subjects had 28 months follow-up per sample size and power considerations. However, the required minimum follow-up for analysis of OS was 22 months.

For each OS comparison, the number of events projected to be observed at 28 months of follow up provide approximately 99% power to detect an average HR of 0.65 with a Type I error of 0.02 (two-sided).

Approximately 9 months was required to enroll the required number of subjects.

Randomisation

Subjects who met all eligibility criteria were randomized in a 1:1:1 ratio to Arm A: nivolumab+ placebo, Arm B: nivolumab + ipilimumab, or Arm C: ipilimumab + placebo, stratified byPD-L1 status (positive or negative as determined by the verified assay), M Stage at screening (M0/M1a/M1b vs M1c), and BRAF V600 mutation status (wildtype [WT] vs mutation positive).

Blinding (masking)

The study was a double blinded study where the subjects and the investigator were blinded to the study drug administered (nivolumab plus placebo, ipilimumab plus placebo, or nivolumab plus ipilimumab). Upon progression of disease and treatment discontinuation, the investigator and subject were unblinded to each subject's treatment assignment through the IVRS.

Statistical methods

Analyses were conducted in following populations:

Formal analyses of PFS and OS were conducted at different time points with PFS being analysed first (PFS analysis time point) followed by analysis of OS (OS analysis time point). Except where otherwise noted, analyses were conducted at both time points.

Time to event distributions (i.e. PFS, OS, time to response, and duration of response) were estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI was estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (e.g. OS at 12 months) were derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals. Confidence intervals for binomial proportions were derived using the Clopper-Pearson method.

The difference in ORRs between the 2 treatment groups along with their two-sided 95% CI was estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the stratification factors PD-L1 status, M stage, and BRAF status.

Primary Endpoint

a) PFS analyses were conducted on data from subjects classified as PD-L1 positive, PD-L1negative, or PD-L1 indeterminate and regardless of BRAF status. These analyses were done using a 2-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in randomised subjects to compare each of the 2 experimental treatments to the control group. Hazard ratios (HRs) and corresponding two-sided 99.5% CIs were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

b) OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in all randomised subjects using Hochberg's procedure to address multiplicity.

Results

Nivolumab as monotherapy or in combination with ipilimumab was approved for the treatment of advanced (unresectable or metastatic) melanoma in adults was approved on the submission of efficacy and safety data from Study CA209067 for the first co-primary endpoint of PFS, based on a 17-Feb-2015 DBL with a minimum follow-up of 9 months after first dose of study therapy, were provided. In addition, reports providing descriptive OS results and PFS and ORR updates based on the 13-Nov-2015

DBL with a minimum follow-up of at least 18 months after first dose of study therapy were submitted during the procedure (EMA/H/C/003985/II/003, refer to EPAR Opdivo). Additional efficacy, including the co-primary endpoint of overall survival (OS), and safety data were based on the CA209067 Final CSR based on a database lock (DBL) of 13-Sep-2016 and provides at least 28 months of follow-up for all subjects. Additional OS data based on 36 months of follow-up (DBL 24 May 2017) were provided as well and discussed in the CHMP (EMA/H/C/003985/II/032). The current description of results is primarily derived from the latter procedure.

Participant flow

Of the 945 subjects randomized (316 to NIVO, 314 to NIVO+IPI, and 315 to IPI), 937 (99.2%) were treated (NIVO: 313, NIVO+IPI: 313, and IPI: 311). As of the DBL for the CA209067 Final CSR, the proportion of subjects continuing in the treatment period in the NIVO, NIVO+IPI, and IPI groups was 20.4% (64/313), 14.1% (44/313), and 5.1% (16/311), respectively (see **Table 11**).

Table 11: Subject Status Summary - End of Treatment Period, Treated Subjects

	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	Total
SUBJECTS	313	313	311	937
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	64 (20.4)	44 (14.1)	16 (5.1)	124 (13.2)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	249 (79.6)	269 (85.9)	295 (94.9)	813 (86.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)				
DISEASE PROGRESSION	170 (54.3)	88 (28.1)	224 (72.0)	482 (51.4)
STUDY DRUG TOXICITY	40 (12.8)	131 (41.9)	50 (16.1)	221 (23.6)
DEATH	1 (0.3)	3 (1.0)	1 (0.3)	5 (0.5)
ADVERSE EVENT UNRELATED TO STUDY DRUG	7 (2.2)	15 (4.8)	6 (1.9)	28 (3.0)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	17 (5.4)	14 (4.5)	8 (2.6)	39 (4.2)
SUBJECT WITHDREW CONSENT	0	3 (1.0)	0	3 (0.3)
LOST TO FOLLOW-UP	1 (0.3)	0	0	1 (0.1)
MAXIMUM CLINICAL BENEFIT	8 (2.6)	11 (3.5)	2 (0.6)	21 (2.2)
POOR/NON-COMPLIANCE	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)
PREGNANCY	0	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.3)	0	1 (0.1)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	0
OTHER	4 (1.3)	2 (0.6)	2 (0.6)	8 (0.9)
NOT REPORTED	0	0	1 (0.3)	1 (0.1)
SUBJECTS CONTINUING IN THE STUDY (%)	167 (53.4)	181 (57.8)	106 (34.1)	454 (48.5)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	146 (46.6)	132 (42.2)	205 (65.9)	483 (51.5)

Percentages based on subjects entering period.
Program Source: /projects/bms217228/stats/primary/prog/tables/rt-ds-off.sas 13APR2015:20:13:48

Recruitment

The enrolment period lasted approximately 10 months (Jun-2013 to Mar-2014). The last subject was randomized on 31-Mar-2014 and the last subject first treatment was on 01-Apr-2014. Study CA209067 completed its primary and secondary objectives; the clinical cut-off date for CA209067 was 01-Aug-2016 with a clinical DBL on 13-Sep-2016. Although the co-primary analysis of OS is completed, the study is ongoing and additional survival follow-up may continue for up to 5 years from this final analysis.

The study will end when survival follow-up is completed. 945 subjects were randomized at 137 sites in 21 countries (Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom, and United States of America.

Conduct of the study

Relevant protocol deviations (significant protocol deviations that could potentially affect the interpretability of study results) were reported in 0.7% of subjects (NIVO 1.6%, NIVO+IPI 0.3%, and IPI 0.3%). No relevant protocol deviation at study entry was reported in > 1 subject.

The most common relevant protocol deviation during the treatment period was receipt of concurrent anti-cancer therapy, affecting 1.3% of subjects in the NIVO group, no subjects in the NIVO+IPI group, and 0.3% of subjects in the IPI group (see Table 12).

Table 12: Relevant Protocol Deviations Summary (all randomised subjects) – Study CA209067

	Number of Subjects (%)			
	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315	Total N = 945
SUBJECTS WITH AT LEAST ONE DEVIATION	5 (1.6)	1 (0.3)	1 (0.3)	7 (0.7)
AT ENTRANCE				
SUBJECT WITH BASELINE ECOG PERFORMANCE STATUS > 1	1 (0.3)	0	0	1 (0.1)
PRIOR SYSTEMIC ANTI-CANCER TREATMENT IN THE METASTATIC SETTING	0	1 (0.3)	0	1 (0.1)
NO HISTOLOGICALLY DOCUMENTED STAGE III OR STAGE IV MELANOMA, AS PER AJCC STAGING SYSTEM	0	0	0	0
UNKNOWN BRAF V600 STATUS (CRF)	0	0	0	0
ON-TREATMENT DEVIATIONS				
SUBJECT RECEIVING CONCURRENT ANTI-CANCER THERAPY	4 (1.3)	0	1 (0.3)	5 (0.5)
SUBJECTS TREATED DIFFERENTLY AS RANDOMIZED	0	0	0	0

An additional Amendment to protocol (only applicable in DE sites) was introduced on 15-Jul-2015: At the request of the local health authority, the contraception method of “Male Condom with Spermicide” was reclassified under the “Less Effective Methods of Contraception” category.

Baseline data

Baseline demographic and disease characteristics are presented in Table 13, Table 14, Table 15 and Table 16.

Table 13: Demographic characteristics summary (all randomised subjects) – Study CA209067

	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315	Total N = 945
AGE (YEARS)				
N	316	314	315	945
MEAN	58.7	59.3	60.8	59.6
MEDIAN	60.0	61.0	62.0	61.0
MIN , MAX	25 , 90	18 , 88	18 , 89	18 , 90
STANDARD DEVIATION	13.92	13.86	13.23	13.69
AGE CATEGORIZATION I (%)				
< 65	198 (62.7)	185 (58.9)	182 (57.8)	565 (59.8)
>= 65	118 (37.3)	129 (41.1)	133 (42.2)	380 (40.2)
AGE CATEGORIZATION II (%)				
< 65	198 (62.7)	185 (58.9)	182 (57.8)	565 (59.8)
>= 65 AND < 75	79 (25.0)	94 (29.9)	89 (28.3)	262 (27.7)
>= 75	39 (12.3)	35 (11.1)	44 (14.0)	118 (12.5)
GENDER (%)				
MALE	202 (63.9)	206 (65.6)	202 (64.1)	610 (64.6)
FEMALE	114 (36.1)	108 (34.4)	113 (35.9)	335 (35.4)
RACE (%)				
WHITE	308 (97.5)	310 (98.7)	303 (96.2)	921 (97.5)
BLACK OR AFRICAN AMERICAN	0	0	0	0
ASIAN	2 (0.6)	2 (0.6)	6 (1.9)	10 (1.1)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.3)	0	0	1 (0.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.3)	0	0	1 (0.1)
OTHER	4 (1.3)	2 (0.6)	5 (1.6)	11 (1.2)
NOT REPORTED	0	0	1 (0.3)	1 (0.1)

Table 14: Baseline PD-L1, M Stage, AJCC Stage, and BRAF Status summary (all randomised subjects) – Study CA209067

	Number of Subjects (%)			
	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315	Total N = 945
PD-L1 STATUS (IVRS)				
POSITIVE	143 (45.3)	144 (45.9)	144 (45.7)	431 (45.6)
NEGATIVE/INDETERMINATE	173 (54.7)	170 (54.1)	171 (54.3)	514 (54.4)
M STAGE AT STUDY ENTRY (IVRS)				
M0/M1A/M1B	132 (41.8)	133 (42.4)	132 (41.9)	397 (42.0)
M1C	184 (58.2)	181 (57.6)	183 (58.1)	548 (58.0)
M STAGE AT STUDY ENTRY (CRF)				
M0/M1A/M1B	131 (41.5)	129 (41.1)	126 (40.0)	386 (40.8)
M1C	185 (58.5)	185 (58.9)	189 (60.0)	559 (59.2)
AJCC STAGE AT STUDY ENTRY				
STAGE III	25 (7.9)	17 (5.4)	22 (7.0)	64 (6.8)
STAGE IV	291 (92.1)	297 (94.6)	293 (93.0)	881 (93.2)
BRAF STATUS (IVRS)				
MUTANT	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
WILDTYPE	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)
BRAF STATUS (CRF)				
MUTANT	98 (31.0)	102 (32.5)	100 (31.7)	300 (31.7)
WILDTYPE	218 (69.0)	212 (67.5)	215 (68.3)	645 (68.3)
BRAF MUTATION TEST				
COBAS+THXID	85 (26.9)	89 (28.3)	96 (30.5)	270 (28.6)
OTHER	182 (57.6)	151 (48.1)	164 (52.1)	497 (52.6)
UNKNOWN	49 (15.5)	74 (23.6)	55 (17.5)	178 (18.8)

Table 15: Other baseline characteristics summary (all randomised subjects) – Study CA209067

	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315	Total N = 945
REGION				
US	68 (21.5)	64 (20.4)	75 (23.8)	207 (21.9)
EU	170 (53.8)	177 (56.4)	170 (54.0)	517 (54.7)
AUSTRALIA	38 (12.0)	40 (12.7)	37 (11.7)	115 (12.2)
REST OF WORLD	40 (12.7)	33 (10.5)	33 (10.5)	106 (11.2)
BASELINE LDH				
<= ULN	196 (62.0)	199 (63.4)	194 (61.6)	589 (62.3)
> ULN	112 (35.4)	114 (36.3)	115 (36.5)	341 (36.1)
<= 2*ULN	271 (85.8)	276 (87.9)	279 (88.6)	826 (87.4)
> 2*ULN	37 (11.7)	37 (11.8)	30 (9.5)	104 (11.0)
NOT REPORTED	8 (2.5)	1 (0.3)	6 (1.9)	15 (1.6)
HISTORY OF BRAIN METASTASES				
YES	8 (2.5)	11 (3.5)	15 (4.8)	34 (3.6)
NO	308 (97.5)	303 (96.5)	300 (95.2)	911 (96.4)
SMOKING STATUS				
YES	133 (42.1)	138 (43.9)	139 (44.1)	410 (43.4)
NO	170 (53.8)	161 (51.3)	167 (53.0)	498 (52.7)
UNKNOWN	13 (4.1)	15 (4.8)	9 (2.9)	37 (3.9)

	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315	Total N = 945
SUBJECTS WITH AT LEAST ONE LESION (B) (%)	315 (99.7)	314 (100.0)	315 (100.0)	944 (99.9)
SITE OF LESION (A) (B) (%)				
BONE	29 (9.2)	30 (9.6)	37 (11.7)	96 (10.2)
CENTRAL NERVOUS SYSTEM	0	3 (1.0)	7 (2.2)	10 (1.1)
INTESTINE	12 (3.8)	11 (3.5)	16 (5.1)	39 (4.1)
LIVER	89 (28.2)	93 (29.6)	92 (29.2)	274 (29.0)
LUNG	183 (57.9)	184 (58.6)	184 (58.4)	551 (58.3)
LYMPH NODE	180 (57.0)	174 (55.4)	196 (62.2)	550 (58.2)
OTHER	24 (7.6)	27 (8.6)	25 (7.9)	76 (8.0)
SKIN	57 (18.0)	43 (13.7)	36 (11.4)	136 (14.4)
SOFT TISSUE	102 (32.3)	105 (33.4)	98 (31.1)	305 (32.3)
VISCERAL, OTHER	75 (23.7)	71 (22.6)	75 (23.8)	221 (23.4)
NUMBER OF SITES WITH AT LEAST ONE LESION (B) (%)				
1	83 (26.3)	90 (28.7)	83 (26.3)	256 (27.1)
2	107 (33.9)	101 (32.2)	96 (30.5)	304 (32.2)
3	69 (21.8)	64 (20.4)	75 (23.8)	208 (22.0)
4	38 (12.0)	40 (12.7)	46 (14.6)	124 (13.1)
>=5	18 (5.7)	19 (6.1)	15 (4.8)	52 (5.5)

Table 16: Prior cancer therapy summary (all randomised subjects) – Study CA209067

	Number of Subjects (%)			
	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315	Total N = 945
PRIOR NEO-ADJUVANT THERAPY				
YES	1 (0.3)	3 (1.0)	2 (0.6)	6 (0.6)
NO	315 (99.7)	311 (99.0)	313 (99.4)	939 (99.4)
PRIOR ADJUVANT THERAPY				
YES	73 (23.1)	68 (21.7)	64 (20.3)	205 (21.7)
NO	243 (76.9)	246 (78.3)	251 (79.7)	740 (78.3)
TIME FROM COMPLETION OF PRIOR ADJUVANT THERAPY TO RANDOMIZATION (A)				
< 6 MONTHS	21 (28.8)	25 (36.8)	21 (32.8)	67 (32.7)
>= 6 MONTHS	51 (69.9)	43 (63.2)	42 (65.6)	136 (66.3)
NOT REPORTED	1 (1.4)	0	1 (1.6)	2 (1.0)
PRIOR SURGERY RELATED TO CANCER				
YES	312 (98.7)	307 (97.8)	306 (97.1)	925 (97.9)
NO	4 (1.3)	7 (2.2)	9 (2.9)	20 (2.1)
PRIOR RADIOTHERAPY				
YES	79 (25.0)	73 (23.2)	59 (18.7)	211 (22.3)
NO	237 (75.0)	241 (76.8)	256 (81.3)	734 (77.7)

For All Randomized subjects:

- The majority of the subjects were male (64.6%) and white (97.5%).
- Mean age was 59.6 years, with 12.5% of subjects aged 75 years or older.
- The percentage of subjects who were BRAF mutation positive was 31.7% as recorded in the CSRs.
- The proportion of evaluable subjects with PD-L1 positive expression (≥ 5%) was 26.5% (223/843) based on the validated assay.
- At trial entry, the majority of subjects (93.2%) were AJCC Stage IV and 58.0% of subjects had tumours characterized as M1c.
- The percentage of subjects who received adjuvant therapy was 21.7%. The most frequently received adjuvant therapy was interferon.

87.9% of treated subjects in the NIVO group received ≥ 90% of the planned dose intensity, which was similar to ipilimumab in the IPI group (88.4%) and greater than nivolumab and ipilimumab in the NIVO+IPI group (69.0% and 70.6%, respectively).

The median duration of therapy was 6.60 months in the NIVO group, 2.83 months in the NIVO+IPI group, and 3.02 months in the IPI group. A greater proportion of subjects were continuing in the study at the time of analysis in the NIVO+IPI group (57.8%), as compared to the NIVO group and IPI group (53.4% and 34.1%, respectively).

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 used for safety analyses (Table 17 and Table 18).

Table 17: Analysis populations – Study CA209067

Population	NIVO Group N	NIVO+IPI Group N	IPI Group N	Total N
All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS. This is the population for pre-treatment disposition.	NA	NA	NA	1296
All Randomized Subjects: All subjects who were randomized to any treatment group. This is the primary dataset for analyses of study conduct, study population, and efficacy analyses.	316	314	315	945
All Treated Subjects: All subjects who received at least one dose of any study medication. This is the primary dataset for analyses of exposure and safety.	313	313	311	937
Biomarker Subjects: All randomized subjects with available biomarker data. *All randomized subjects with quantifiable tumor PD-L1 expression at baseline.* See definitions of baseline and quantifiable tumor PD-L1 expression in Table 3.5-1.	316	314	315	945
PD-L1 Evaluable Subjects, validated assay	305	297	296	898
Immunogenicity (ADA-evaluable) Subjects: All treated subjects with baseline and at least 1 post-baseline assessment for ADA.	292	291 nivolumab 290 ipilimumab	296	879

Table 18: Summary of PD-L1 positive status in PD-L1 evaluable subjects – Study CA209067

Assay Type		Number of subjects, n(%)		
		Nivolumab	Nivolumab+ipilimumab	Ipilimumab
Verified	PD-L1 evaluable subjects[a]	316	314	315
	PD-L1 Indeterminate	8 (2.5)	15 (4.8)	9 (2.9)
	PD-L1 positive expression:			
	≥5%	143 (45.3)	144 (45.9)	144 (45.7)
Validated	PD-L1 evaluable subjects[a]	305	297	296
	PD-L1 Indeterminate	17 (5.6)	19 (6.4)	19 (6.4)
	PD-L1 quantifiable subjects[b]	288	278	277
	PD-L1 expression level:			
	≥1%	171 (59.4)	155 (55.8)	164 (59.2)
	≥5%	80 (27.8)	68 (24.5)	75 (27.1)
	≥10%	59 (20.5)	46 (16.5)	54 (19.5)

[a] Number of quantifiable PD-L1 results plus the number of indeterminate PD-L1 results

[b] Number of quantifiable PD-L1 results only; does not include the number indeterminate PD-L1 results (Table 4-1)

Abbreviations: PD-L1 = programmed cell death ligand 1

The PD-L1 subgroups represent nested populations defined by the PD-L1 expression levels (Figure 7). The difference in patient numbers between the ⩾1% vs the ⩾5% subgroup was 267 subjects (490 vs 223, respectively), and between the ⩾5% vs the ⩾10% subgroup was 64 subjects (223 vs 159, respectively).

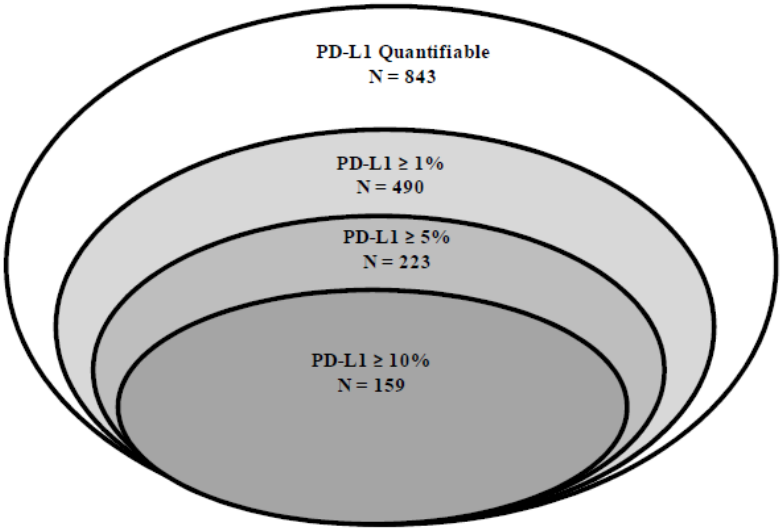


Figure 6: Frequency of pre-study (Baseline) PD-L1 expression at the 1%, 5%, and 10% expression levels - All PD-L1 quantifiable subjects

Outcomes and estimation

Outcomes were submitted with various DBL as part of the extension of the indication for OPDIVO (EMA/H/C/003985/II/003) and submission of the post-authorisation measure (EMA/H/C/003985/II/032) to fulfil the condition in Annex II to submit the final report for study CA209067.

Final results at the time of the planned OS analysis after 28 months of follow-up (DBL 13-Sep-2016) were submitted. During the procedure data, from an updated analysis from 36 months of follow-up were also presented (DBL 24 May 2017). The results for the co-primary and secondary endpoints are presented in Table 19.

Table 19: CA209067 Summary of Efficacy results – All randomised subjects

	NIVO N = 316	NIVO+IPI N = 314	IPI N = 315
CO-PRIMARY ENDPOINTS			
Overall Survival			
Events, n (%)	142 (44.9)	128 (40.8)	197 (62.5)
Stratified log-rank test p-value[a]	<0.0001	<0.0001	
HR (98% confidence interval [CI])	0.63 (0.48, 0.81)[b]	0.55 (0.42, 0.72)[c]	
Median OS (95% CI), months[d]	NA (29.08, NA)	NA	19.98 (17.08, 24.61)
Rate at 6 months (95% CI), %	0.85 (0.81, 0.89)	0.86 (0.81, 0.89)	0.82 (0.78, 0.86)
Rate at 12 months (95% CI), %	0.74 (0.69, 0.79)	0.73 (0.68, 0.78)	0.67 (0.61, 0.72)
Rate at 24 months (95% CI), %	0.59 (0.53, 0.64)	0.64 (0.59, 0.69)	0.45 (0.39, 0.50)
Progression-free Survival			
Events, n (%)	195 (61.7)	169 (53.8)	253 (80.3)
HR (95% CI)	0.54 (0.45, 0.66)[b]	0.42 (0.34, 0.51)[c]	
Median PFS (95% CI), months[e]	6.87 (4.34, 9.46)	11.73 (8.90, 21.88)	2.86 (2.79, 3.15)
Rate at 6 months (95% CI), %	0.52 (0.46, 0.58)	0.63 (0.57, 0.68)	0.28 (0.23, 0.33)
Rate at 12 months (95% CI), %	0.43 (0.37, 0.49)	0.50 (0.44, 0.55)	0.18 (0.14, 0.22)
Rate at 24 months (95% CI), %	0.37 (0.31, 0.43)	0.43 (0.37, 0.48)	0.12 (0.09, 0.17)
SECONDARY ENDPOINTS			
Complete Response Rate (CR)[f]	47 (14.9%)	54 (17.2%)	14 (4.4%)
Objective Response Rate (CR+PR)[g]			
N responders (%)	141 (44.6%)	185 (58.9%)	60 (19.0%)
95% CI	39.1, 50.3	53.3, 64.4	14.9, 23.8
Difference of ORRs (95% CI)[h]	25.7%[i] (18.9, 32.5)	39.7%[j] (32.8, 46.5)	
Odds ratio estimate (99.5% CI)[k]	3.54[l] (2.10, 5.95)	6.50[m] (3.81, 11.08)	
Difference of ORRs (95% CI)[h]		14.1%[n] (6.7, 21.6)	
Odds ratio estimate (95% CI)[k]		1.82[m] (1.32, 2.52)	

EXPLORATORY ENDPOINTS Randomized Subjects with a Response	NIVO N = 141	NIVO+IPI N = 185	IPI N = 60
Time to Objective Response			
Median (Min, Max), months	2.79 (2.3, 32.9)	2.76 (1.1, 28.8)	2.79 (2.5, 17.3)
Duration of Objective Response			
Ongoing responder (as of the last available tumor assessment), n/N (%)	94/141 (66.7)	124/185 (67.0)	30/60 (50.0)
Median (95% CI), months[o]	31.11 (31.11, NA)	NA	18.20 (8.34, NA)
Min, Max	0.0[p], 32.3[p]	0.0, 33.3[p]	0.0[p], 31.5[p]
Proportion with DOR ≥12 months, n (%)	98 (69.5)	118 (63.8)	32 (53.3)
Proportion with DOR ≥24 months, n (%)	69 (48.9)	93 (50.3)	19 (31.7)
Randomized Subjects with Confirmed Response[q]	**N = 130**	**N = 157**	**N = 46**
Proportion with DOR ≥12 months, n (%)	98 (75.4)	113 (72.0)	28 (60.9)
Proportion with DOR ≥24 months, n (%)	73 (56.2)	87 (55.4)	18 (39.1)

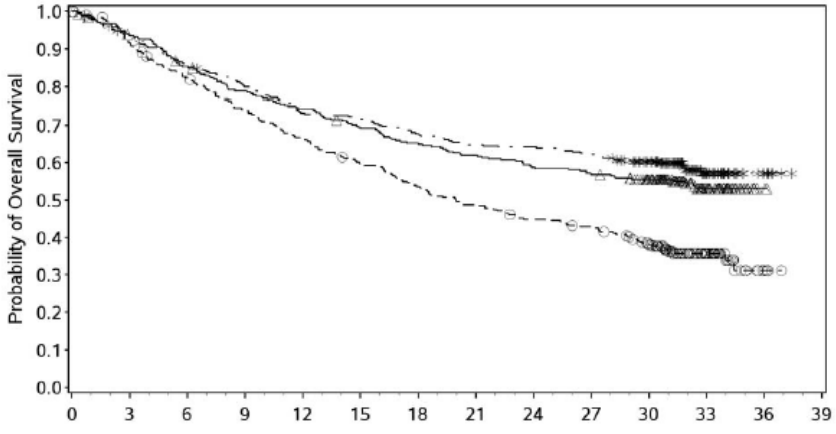
a Log-rank Test stratified by PD-L1 status, BRAF status, and M stage at screening as entered into the IVRS.
b Stratified Cox proportional hazard model. Ratio of NIVO over IPI.
c Stratified Cox proportional hazard model. Ratio of NIVO+IPI over IPI.
d Kaplan-Meier estimate. NA - not available/not estimable
e Kaplan-Meier estimate.
f Per RECIST 1.1, unconfirmed response.
g Confidence interval based on the Clopper and Pearson method.
h The estimate of the difference in ORR and corresponding 95% CI is based on Cochran-Mantel-Haenszel method of weighting, adjusting for PD-L1 Status, BRAF Mutation Status and M-stage at screening as entered into the IVRS.
i Difference of NIVO - IPI.
j Difference of NIVO+IPI - IPI.
k Cochran-Mantel-Haenszel method stratified by PD-L1 Status, BRAF Status and M stage at screening as entered into the IVRS.
l Ratio of NIVO over IPI.
m Ratio of NIVO+IPI over IPI.
n Difference of NIVO+IPI - NIVO.
o Median computed using Kaplan-Meier product-limit method.
p Censored observation.
q Confirmed response is derived programmatically based on tumour assessments per investigator using RECIST 1.1 criteria.

Overall Survival (Co-primary Endpoint)

A statistically significant improvement in OS was observed in NIVO versus IPI monotherapy (HR = 0.63 [98% CI: 0.48, 0.81]; stratified log-rank test p-value = <0.0001) and NIVO+IPI versus IPI monotherapy (HR = 0.55 [98% CI: 0.42, 0.72]; stratified log-rank test p-value = <0.0001); Figure 8. OS rates at 6, 9, 12, 18, and 24 months are presented below in Table 20.Median OS for All Randomized subjects was not reached in the NIVO group and NIVO+IPI group as compared to 19.98 months in the IPI group. The number of events observed at the time of the DBL (467 total deaths) was lower than projected (644 deaths) for this time-based analysis at 28 months of follow-up for all subjects.

- Based on descriptive analyses, NIVO+IPI relative to NIVO demonstrated a numeric difference in OS favouring the combination of NIVO+IPI (24-month OS rate: NIVO+IPI 0.64, NIVO 0.59; Table 20). Separation between the Kaplan-Meier curves, once present, for the NIVO+IPI group relative to the NIVO group relative to the IPI group is maintained over time. (Figure 8).

- At the time of the DBL (13-Sep-2016), 174 (55.1%), 186 (59.2%), and 118 (37.5%) subjects were censored in the NIVO, NIVO+IPI, and IPI groups, respectively. Among those censored, a higher proportion of subjects in the NIVO and NIVO+IPI groups relative to the IPI group were still on treatment (20.3% and 14.0% relative to 5.1%, respectively), and a greater proportion in the NIVO and NIVO+IPI groups were in follow-up (32.6% and 43.6% relative to 28.6%, respectively). The proportion of subjects censored who were off study was similarly low in all 3 groups (NIVO 2.2%, NIVO+IPI 1.6%, and IPI 3.8%).



Number of Subjects at Risk

Nivolumab	316	292	265	244	230	213	201	191	181	175	157	55	3	0
Nivolumab + Ipilimumab	314	292	265	247	226	221	209	200	198	192	170	49	7	0
Ipilimumab	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Nivolumab (events: 142/316), median and 95% CI: N.A. (29.08, N.A.)
Nivolumab + Ipilimumab (events: 128/314), median and 95% CI: N.A.
Ipilimumab (events: 197/315), median and 95% CI: 19.98 (17.08, 24.61)

Nivolumab vs Ipilimumab - hazard ratio and 98% CI: 0.63 (0.48, 0.81); p-value: <0.0001
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 98% CI: 0.55 (0.42, 0.72); p-value: <0.0001
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.88 (0.69, 1.12)

Symbols represent censored observations.

Hazard ratios are estimated using Cox proportional hazard model with treatment group as a single covariate, stratified by PD-L1 status, BRAF status and M stage at screening as entered into the Interactive Voice Response System (IVRS) and p-values are from log-rank test stratified by the same factors.

Figure 7: Kaplan-Meier Plot of Overall Survival - All Randomized Subjects

Table 20: Overall Survival Rates - All Randomized Subjects

Survival Rate (95% CI)	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315
6 MONTH	0.85 (0.81, 0.89)	0.86 (0.81, 0.89)	0.82 (0.78, 0.86)
9 MONTH	0.79 (0.74, 0.83)	0.80 (0.75, 0.84)	0.74 (0.69, 0.79)
12 MONTH	0.74 (0.69, 0.79)	0.73 (0.68, 0.78)	0.67 (0.61, 0.72)
18 MONTH	0.65 (0.60, 0.70)	0.68 (0.62, 0.73)	0.54 (0.48, 0.59)
24 MONTH	0.59 (0.53, 0.64)	0.64 (0.59, 0.69)	0.45 (0.39, 0.50)

Based on Kaplan-Meier Estimates.

The OS analysis was not adjusted to account for subsequent therapies received.

Subsequent systemic therapy was received by 100 (31.8%), 140 (44.3%), and 196 (62.2%) subjects in the combination, nivolumab monotherapy, and ipilimumab arms, respectively (Table 21). Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 46 (14.6%), 92 (29.1%), and 139 (44.1%) subjects in the combination, nivolumab monotherapy, and ipilimumab arms. (Table 21).

Table 21: Summary of Subsequent Therapies - All Randomized Subjects

	NIVO N = 316	NIVO+IPI N = 314	IPI N = 315
Any subsequent therapy, n (%)[a]	169 (53.5)	129 (41.1)	225 (71.4)
Systemic therapy, %	44.3	31.8	62.2
Anti-PD-1 agents	10.1	9.6	41.9
Anti-CTLA-4	26.3	6.1	3.8
BRAF inhibitors	18.0	12.7	21.6
MEK/NRAS Inhibitors	12.0	9.6	12.4
Investigational agents	1.9	2.5	4.8
Median time to subsequent systemic therapy (months)[b]	26.8	NR	8.5
Free of subsequent therapy rate at 12 months, %	60.7	76.6	37.9
Free of subsequent therapy rate at 24 months, %	53.8	65.8	24.7

[a] Subjects may have received more than 1 subsequent therapy (e.g. radiation, surgery and systemic therapies)

[b] Median computed using Kaplan-Meier method.

A sensitivity analysis of OS censored for first subsequent systemic cancer therapy is presented in Table 22.

Table 22: Overall Survival - Sensitivity Analysis: Subjects Censored at First Subsequent Systemic Cancer Therapy - All Randomized Subjects in CA209067

	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315
# EVENTS / # SUBJECTS (%)	54/316 (17.1)	66/314 (21.0)	64/315 (20.3)
MEDIAN OS (MONTHS) (95% CI) (1)	N.A.	N.A.	N.A.
HR (95% CI)	0.69 (0.48, 0.99) (A)	0.80 (0.57, 1.13) (B)	
HR (95% CI)		1.17 (0.81, 1.67) (C)	
OS RATE AT 6 MONTH (95% CI)	0.89 (0.84, 0.92)	0.86 (0.81, 0.89)	0.82 (0.77, 0.86)
OS RATE AT 9 MONTH (95% CI)	0.84 (0.79, 0.88)	0.84 (0.79, 0.87)	0.80 (0.74, 0.85)
OS RATE AT 12 MONTH (95% CI)	0.83 (0.78, 0.87)	0.80 (0.75, 0.84)	0.75 (0.69, 0.81)
OS RATE AT 18 MONTH (95% CI)	0.80 (0.75, 0.85)	0.78 (0.72, 0.82)	0.71 (0.64, 0.77)
OS RATE AT 24 MONTH (95% CI)	0.78 (0.72, 0.83)	0.77 (0.71, 0.81)	0.69 (0.61, 0.75)

(1) Based on Kaplan-Meier Estimates.
(A) Cox proportional hazard model stratified by PD-L1 status, BRAF status and M stage at screening as entered into the IVRS. Hazard Ratio is Nivolumab over Ipilimumab.
(B) Cox proportional hazard model stratified by PD-L1 status, BRAF status and M stage at screening as entered into the IVRS. Hazard Ratio is Nivolumab + Ipilimumab over Ipilimumab.
(C) Cox proportional hazard model stratified by PD-L1 status, BRAF status and M stage at screening as entered into the IVRS. Hazard Ratio is Nivolumab + Ipilimumab over Nivolumab.
Program Source: /projects/bms217228/stats/FA2/prog/tables/rt-ef-ossens.sas 20JAN2017:06:09:27

Follow-up for Overall Survival

Median follow-up for OS (time between randomization date and last known date alive or date of death) was 29.95 months (range: 0.0 to 36.1 months) in the NIVO group, 30.41 months (range: 0.1 to 37.4 months) in the NIVO+IPI group, and 18.63 months (range: 0.0 to 36.9 months) in the IPI group.

Minimum follow-up for OS (the time between last subject randomized [31-Mar-2014] and clinical cut-off date [01-Aug-2016]) was 28 months for all subjects.

Follow-up for OS was current for the majority of randomized subjects; 96.8%, 95.5%, and 94.0% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively, either died or had a last known alive date on or after the data cut-off date.

Multivariate Analysis of Overall Survival

Exploratory multivariate analyses identified subject and tumour characteristics of ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status (tumour PD-L1 expression level <1%, ≥1%, indeterminate or not evaluable), and gender which might contribute to the survival outcome. The modeling showed that ECOG performance status, M Stage, baseline LDH, BRAF status, PD-L1 expression, and gender were significantly associated with OS at a 5% significance level irrespective of treatment group, and treatment-by-region was the only significant interaction term at a 20% significance level (p = 0.0858) (Table 23).

Table 23: Overall Survival Multivariate Analysis-All Randomized subjects

	HR (95% CI)	P-value (1)	AIC (2)
			3108.03
TREATMENT NIVOLUMAB + IPILIMUMAB VS NIVOLUMAB	N.A.	0.0730	
BRAF MUTATION STATUS MUTANT VS WILDTYPE	0.65 (0.49, 0.86)	0.0025	
M STAGE AT STUDY ENTRY M1C VS M0/M1A/M1B	1.88 (1.41, 2.51)	<0.0001	
GENDER MALE VS FEMALE	0.74 (0.58, 0.95)	0.0186	
REGION	N.A.	0.1407	
BASELINE ECOG PERFORMANCE STATUS >= 1 VS 0	2.05 (1.57, 2.68)	<0.0001	
BASELINE LDH > ULN VS <= ULN	1.83 (1.40, 2.40)	<0.0001	
PD-L1 EXPRESSION LEVEL		0.0495	
>= 1% VS < 1%	0.72 (0.55, 0.94)		
INDETERMINATE OR NOT EVALUABLE VS < 1%	0.88 (0.59, 1.32)		
TREATMENT * REGION		0.0858	
TREATMENT NIVOLUMAB + IPILIMUMAB VS NIVOLUMAB AT REGION=EU	0.89 (0.65, 1.22)		
TREATMENT NIVOLUMAB + IPILIMUMAB VS NIVOLUMAB AT REGION=AUSTRALIA	0.78 (0.35, 1.72)		
TREATMENT NIVOLUMAB + IPILIMUMAB VS NIVOLUMAB AT REGION=REST OF WORLD	1.80 (0.94, 3.46)		
TREATMENT NIVOLUMAB + IPILIMUMAB VS NIVOLUMAB AT REGION=US	0.57 (0.31, 1.05)		

Progression-free Survival (Co-primary Endpoint)

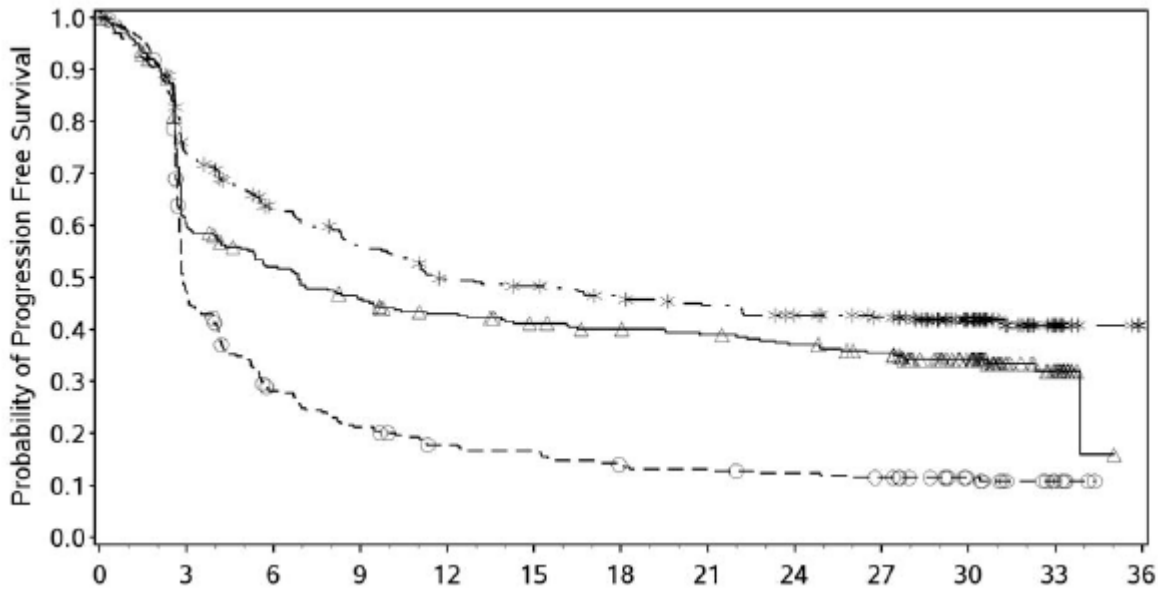
The formal analysis of the PFS co-primary endpoint occurred at an earlier time point (9-month follow-up, DBL 17-Feb-2015). An additional analysis of PFS was performed following the 13-Nov-2015 DBL and was submitted. The results of a descriptive update to the PFS endpoint based on the 13-Sep-2016 DBL are provided in Table 24 (reference to summary table) and below, and are consistent with the previous analysis.

Figure 9 provides the PFS Kaplan-Meier curves.

Based on the data from DBL 13-Sep-2016, at 24 months follow-up, the PFS rate was 0.43 in the NIVO+IPI group, 0.37 in the NIVO group, and 0.12 in the IPI group. The median PFS was 6.9 months in the NIVO group and 11.7 months in the NIVO+IPI group as compared with 2.9 months in the IPI group, All Randomized population (HR = 0.54, 95% CI: 0.45, 0.66) and (HR = 0.42, 95% CI: 0.34, 0.51), respectively. At both 9 months and at 18 months, median PFS was 6.87, 11.50, and 2.89 months for the NIVO, NIVO+IPI, and IPI groups, respectively.

Figure 9 provides the PFS Kaplan-Meier curves.

121 (38.3%) subjects in the NIVO group, 145 (46.2%) subjects in the NIVO+IPI group, and 62 (19.7%) subjects in the IPI group were censored in the PFS analysis. 34.5%, 43.0%, and 13.3% of randomized subjects in the NIVO, NIVO+IPI, and IPI groups, respectively, had their PFS time censored on the date of last on-study tumour assessment. The most common reasons for censoring among these subjects was 'still on treatment' in the NIVO group and 'in follow-up' in the NIVO+IPI and IPI groups (Table 24).



Number of Subjects at Risk

Nivolumab	316	178	151	132	120	112	107	103	97	88	62	16	0
Nivolumab + Ipilimumab	314	218	176	156	137	132	125	118	110	104	71	16	0
Ipilimumab	315	136	77	58	46	43	35	33	30	27	16	5	0

Nivolumab (events: 195/316), median and 95% CI: 6.87 (4.34, 9.46)
Nivolumab + Ipilimumab (events: 169/314), median and 95% CI: 11.73 (8.90, 21.88)
Ipilimumab (events: 253/315), median and 95% CI: 2.86 (2.79, 3.15)

Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.54 (0.45, 0.66)
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.42 (0.34, 0.51)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.76 (0.62, 0.94)

Symbols represent censored observations.

Hazard ratios are estimated using Cox proportional hazard model with treatment group as a single covariate, stratified by PD-L1 status, BRAF status and M stage at screening as entered into the IVRS.

Figure 8: Kaplan-Meier Plot of Progression-free Survival - All Randomized Subjects

Table 24: Status of Censored Subjects, Progression Free Survival per Investigator (all randomised subjects)

	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315
NUMBER OF EVENTS (%)	195 (61.7)	169 (53.8)	253 (80.3)
TYPE OF EVENTS (%)			
PROGRESSION (1)	176 (55.7)	146 (46.5)	227 (72.1)
DEATH	19 (6.0)	23 (7.3)	26 (8.3)
NUMBER OF SUBJECTS CENSORED (%)	121 (38.3)	145 (46.2)	62 (19.7)
CENSORED ON DATE OF RANDOMIZATION	12 (3.8)	10 (3.2)	20 (6.3)
NO BASELINE TUMOR ASSESSMENT AND NO DEATH (2)	1 (0.3)	0	0
NEVER TREATED	1 (0.3)	0	0
OTHER	0	0	0
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	11 (3.5)	10 (3.2)	20 (6.3)
NEVER TREATED	2 (0.6)	1 (0.3)	4 (1.3)
OTHER	9 (2.8)	9 (2.9)	16 (5.1)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	109 (34.5)	135 (43.0)	42 (13.3)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (3)	24 (7.6)	20 (6.4)	14 (4.4)
STILL ON-TREATMENT	52 (16.5)	39 (12.4)	10 (3.2)
IN FOLLOW-UP	33 (10.4)	74 (23.6)	17 (5.4)
OFF STUDY	0	2 (0.6)	1 (0.3)
LOST TO FOLLOW-UP	0	0	0
SUBJECT WITHDREW CONSENT	0	2 (0.6)	1 (0.3)
OTHER	0	0	0

(1) RECIST 1.1 criteria.
(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.
(3) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy.
Program Source: /projects/bms217228/stats/FA2/prog/tables/rt-ef-pfs-inv-reasons.sas 18OCT2016:12:13:18

Objective Response Rate - Secondary Endpoint

The formal analysis of the ORR secondary endpoint occurred at an earlier time point and were reported in the CA209067 Interim CSR (DBL 17-Feb-2015) at the time of the initial variation application for Opdivo. An updated descriptive analysis of ORR at 18-months follow-up (DBL 13-Nov-2015) was submitted. At both the 9-month (DBL 17-Feb-2015) and 18-month (DBL 13-Nov-2015) analyses, ORR rates per Investigator were NIVO 43.7%, NIVO+IPI 57.6%, and IPI 19.0%. The 9-month [DBL 17-Feb-2015] CR rates were: NIVO 8.9%, NIVO+IPI 11.5%, IPI 2.2% and 18-month [DBL 13-Nov-2015] CR rates were: NIVO 9.8%, NIVO+IPI 12.1%, and IPI 2.2%.

The results of a descriptive update to the ORR endpoint (DBL 13-Sep-2016) are provided in Table 25. ORR results for this updated analyses were 44.6%, 58.9%, and 19.0% in the NIVO, NIVO+IPI, and IPI groups, respectively and consistent with those previously reported.

Table 25: Best Overall Response - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315
BEST OVERALL RESPONSE (A):			
COMPLETE RESPONSE (CR)	47 (14.9)	54 (17.2)	14 (4.4)
PARTIAL RESPONSE (PR)	94 (29.7)	131 (41.7)	46 (14.6)
STABLE DISEASE (SD)	31 (9.8)	36 (11.5)	67 (21.3)
PROGRESSIVE DISEASE (PD)	122 (38.6)	74 (23.6)	161 (51.1)
UNABLE TO DETERMINE (UTD)	22 (7.0)	19 (6.1)	27 (8.6)
OBJECTIVE RESPONSE RATE (1) (95% CI)	141/316 (44.6%) (39.1, 50.3)	185/314 (58.9%) (53.3, 64.4)	60/315 (19.0%) (14.9, 23.8)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2) (95% CI)	25.7% (B) (18.9, 32.5)	39.7% (C) (32.8, 46.5)	
ESTIMATE OF ODDS RATIO (3) (99.5% CI)	3.54 (D) (2.10, 5.95)	6.50 (E) (3.81, 11.08)	
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2) (95% CI)		14.1% (F) (6.7, 21.6)	
ESTIMATE OF ODDS RATIO (3) (95% CI)		1.82 (G) (1.32, 2.52)	

(A) Per RECIST 1.1.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) The estimate of the difference in ORR and corresponding 95% CI is based on Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for PD-L1 Status, BRAF Mutation Status and M-stage at screening as entered into the IVRS.
(3) Cochran-Mantel-Haenszel Test Stratified by PD-L1 Status, BRAF Status and M stage at screening as entered into the IVRS.
(B) Difference of Nivolumab - Ipilimumab. (C) Difference of Nivolumab + Ipilimumab - Ipilimumab.
(D) Ratio of Nivolumab over Ipilimumab. (E) Ratio of Nivolumab + Ipilimumab over Ipilimumab.
(F) Difference of Nivolumab + Ipilimumab - Nivolumab. (G) Ratio of Nivolumab + Ipilimumab over Nivolumab.
Program Source: /projects/bms217228/stats/FA2/prog/tables/rt-ef-bor.sas 27SEP2016:08:31:52

OS by response status from Month 6 showed that a BOR of CR correlated to improved OS in the NIVO (Figure 10) and NIVO+IPI (Figure 11) groups.

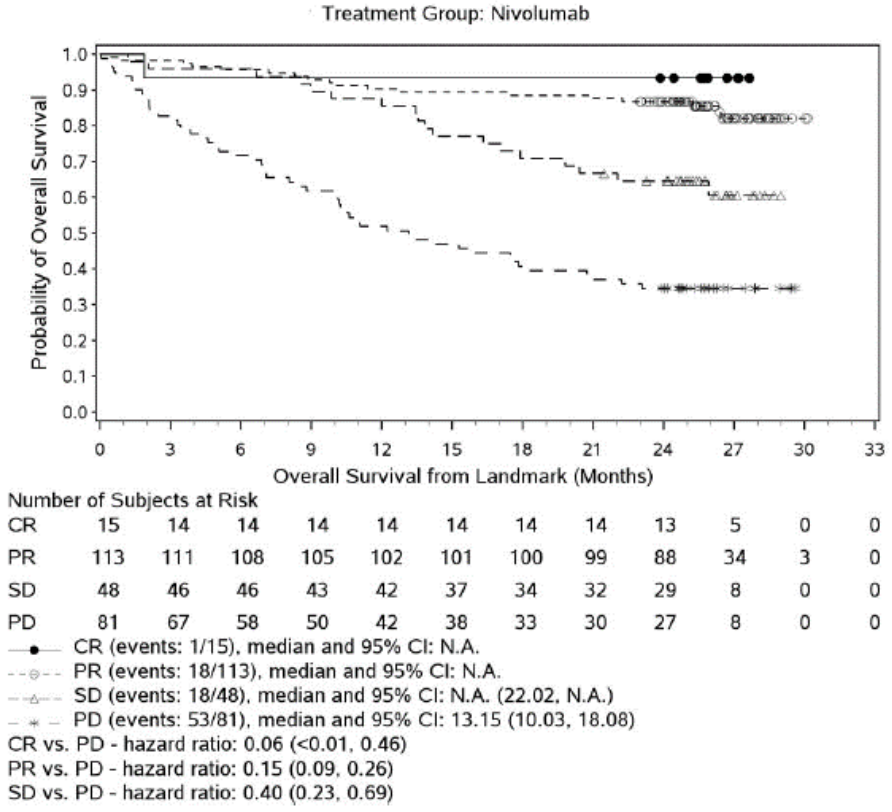


Figure 9: Landmark Analysis Overall Survival from Month 6 by Response Status - All Randomized Subjects (Nivolumab group)

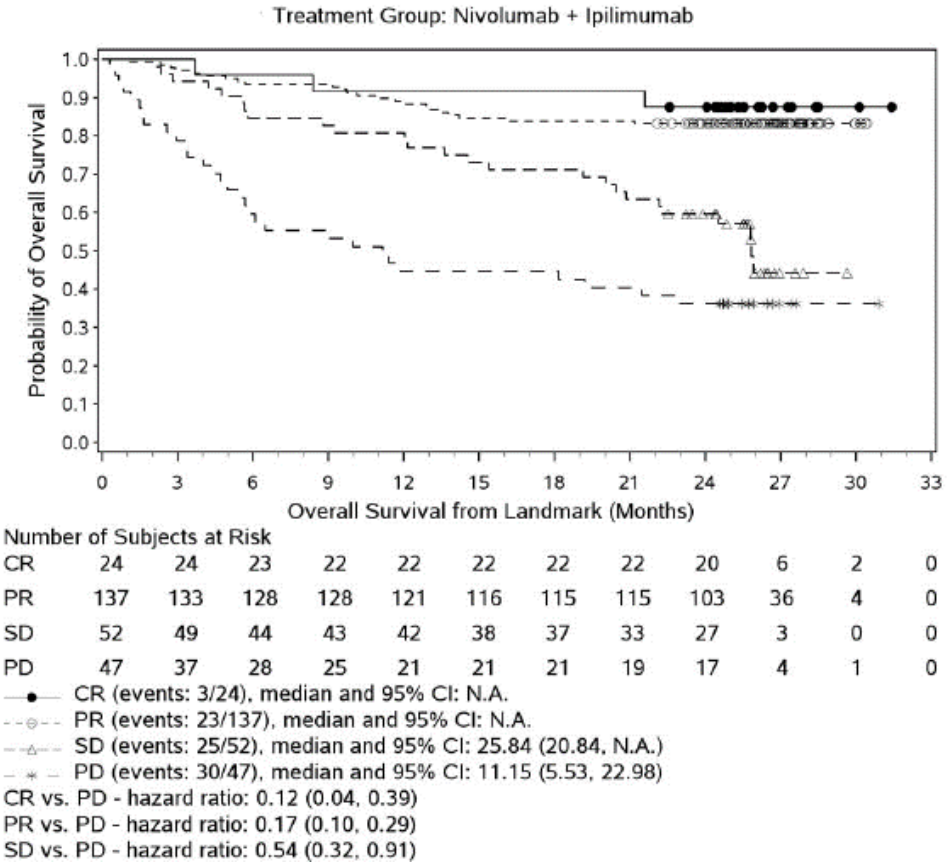


Figure 10: Landmark Analysis Overall Survival from Month 6 by Response Status - All Randomized Subjects (Nivolumab+Ipilumimab group)

Time to Response and Duration of Response - Exploratory Endpoints

Median TTR was 2.8 months in all treatment groups. The median DOR was not reached in the NIVO+IPI group and was 31.1 months (95% CI: 31.11, NR) and 18.2 months (95% CI: 8.34, NR) in the NIVO group and IPI group, respectively, in all randomized subjects with a response (Table 26 Figure 12 below).

At the time of DBL, there was a greater proportion of responders with an ongoing response (as of the last available tumour assessment) in the NIVO and NIVO+IPI groups than in the IPI group (94/141 [66.7%] subjects, 124/185 [67.0%] subjects, and 30/60 [50.0%] subjects, respectively, derived by subtracting the number of subjects with an event [progression] from the number of responders).

Table 26: Time to Objective Response and Duration of Objective Response - All Randomized Subjects with Response

	Nivolumab N = 141	Nivolumab + Ipilimumab N = 185	Ipilimumab N = 60
TIME TO OBJECTIVE RESPONSE (MONTHS)			
NUMBER OF RESPONDERS	141	185	60
MEAN	4.45	3.92	4.38
MEDIAN	2.79	2.76	2.79
MIN, MAX	2.3, 32.9	1.1, 28.8	2.5, 17.3
STANDARD DEVIATION	4.844	3.407	2.913
DURATION OF OBJECTIVE RESPONSE (MONTHS)			
MIN, MAX	0.0 (A), 32.3 (A)	0.0, 33.3 (A)	0.0 (A), 31.5 (A)
MEDIAN (95% CI) (B)	31.11 (31.11, N.A.)	N.A.	18.20 (8.34, N.A.)
N EVENT/N RESP (%)	47/141 (33.3)	61/185 (33.0)	30/60 (50.0)
PROPORTION >=12 MONTHS IN DURATION	98 (69.5)	118 (63.8)	32 (53.3)
PROPORTION >=24 MONTHS IN DURATION	69 (48.9)	93 (50.3)	19 (31.7)
RANDOMIZED SUBJECTS WITH CONFIRMED RESPONSE (C)	N = 130	N = 157	N = 46
PROPORTION >=12 MONTHS IN DURATION	98 (75.4)	113 (72.0)	28 (60.9)
PROPORTION >=24 MONTHS IN DURATION	73 (56.2)	87 (55.4)	18 (39.1)

RECIST 1.1 Response Criteria.
(A) Censored observation.
(B) Median computed using Kaplan-Meier product-limit method.
(C) Confirmed response is derived programmatically based on tumor assessments per investigator using RECIST 1.1 criteria.

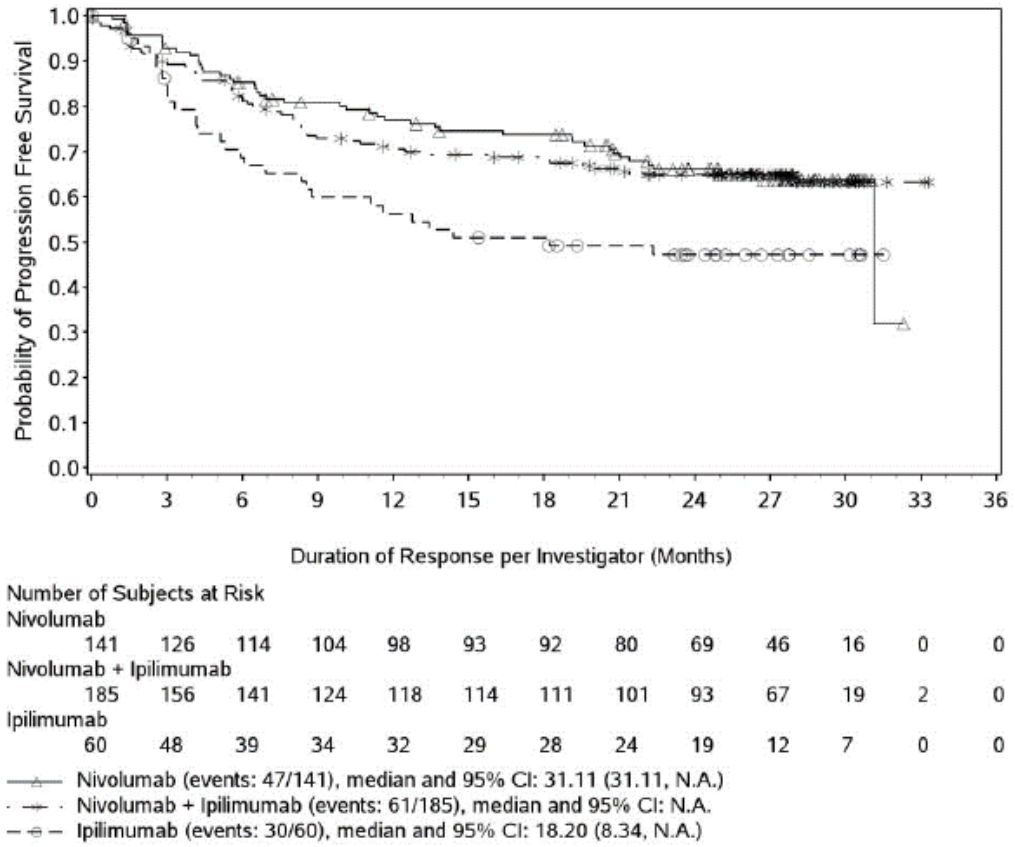


Figure 11: Kaplan-Meier Plot of Duration of Response per Investigator – All Randomized Subjects with Response

Efficacy by Baseline Tumour PD-L1 Expression - Secondary Endpoint

Tumour Tissue Disposition and Frequency of Tumour PD-L1 Expression

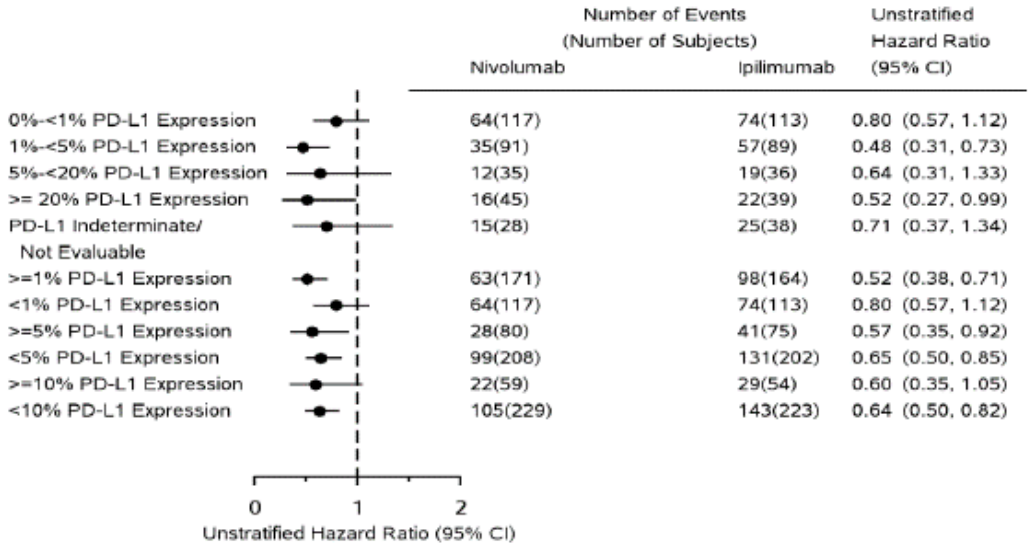
Subjects were randomized 1:1:1 with stratification by tumour PD-L1 expression (Dako PD-L1 IHC assay) status at a 5% expression level (along with BRAF status and AJCC M stage) to one of the 3 treatment groups. The majority (96.8%) of randomized subjects had tumour tissue samples that were retrospectively assessed for tumour PD-L1 expression using the validated Dako assay.

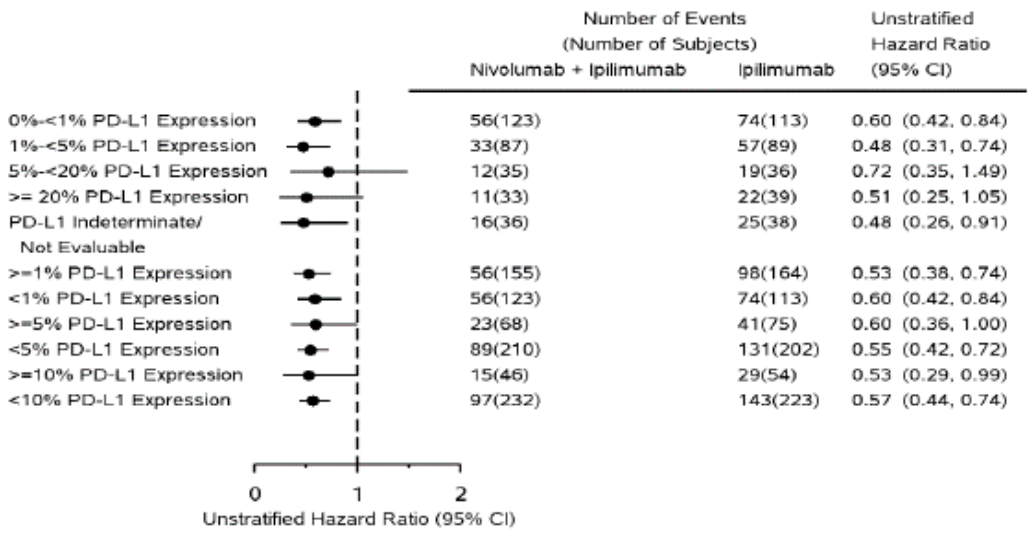
Tumour PD-L1 Expression and Efficacy

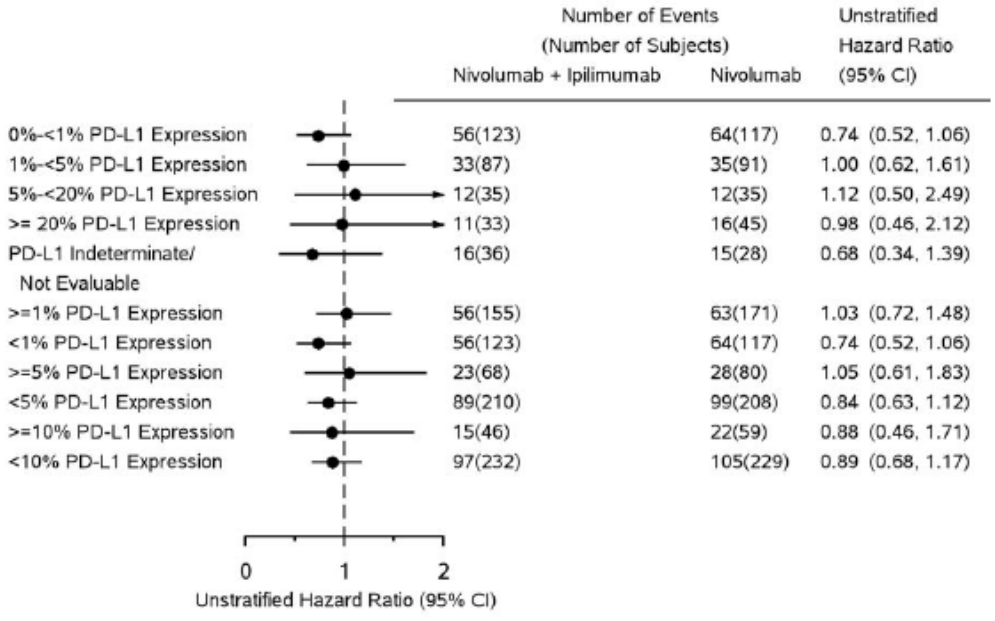
There was a lower risk of death for NIVO +IPI combination therapy vs IPI monotherapy and for NIVO monotherapy vs IPI monotherapy at all predefined levels of tumour PD-L1 expression. Descriptive comparisons between the two NIVO-containing arms, suggest improved OS in the lower tumour PD-L1 expression groups (<1% and <5%) with combination therapy. OS was similar between NIVO and NIVO+IPI in the ≥ 1% and ≥ 5% PD-L1 subgroups. Similar results were observed in the Kaplan-Meier plots of OS by PD-L1 status and treatment at both the 1% and 5% tumour PD-L1 expression levels (Figure 13, Figure 14). The combination of NIVO + IPI also demonstrated improved PFS compared to IPI monotherapy across all PD-L1 expression groups (data not shown).

A receiver operating characteristic (ROC) curve for PD-L1 expression based on OS was constructed (Figure 16). As indicated by the shape of the curve and area under the curve (AUC) of 0.6 for NIVO and 0.5 for NIVO+IPI, ROC analysis does not clearly define an optimal PD-L1 cut-off that maximizes sensitivity and specificity.

For subjects with tumours having ≥ 5% tumour PD-L1 expression, the updated ORRs (CR +PR) for NIVO monotherapy and NIVO+IPI combination therapy were 58.8% and 73.5%, respectively. In those subjects with tumours that had < 5% tumour PD-L1 expression, the ORRs for NIVO monotherapy and NIVO+IPI combination therapy were 42.3% and 56.2%, respectively (Table 27).







PD-L1 expression results from validated assay.

Figure 12: Forest Plots of OS Hazard Ratios by Tumour PD-L1 Expression Result Subgroup and PD-L1 Status Subgroup, All PD-L1 Tested Subjects

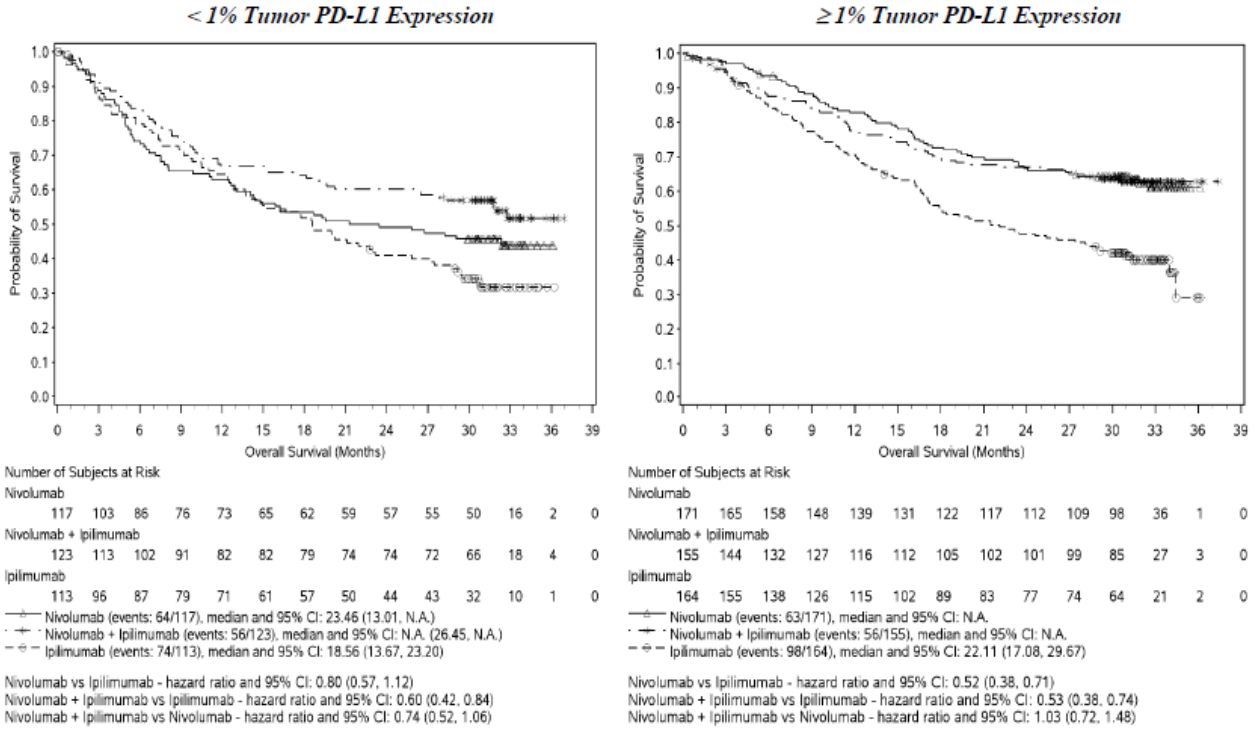


Figure 13: Kaplan-Meier Plot of OS by PD-L1 Status and Treatment (1% and 5% Expression Levels) < 1% Tumour PD-L1 Expression

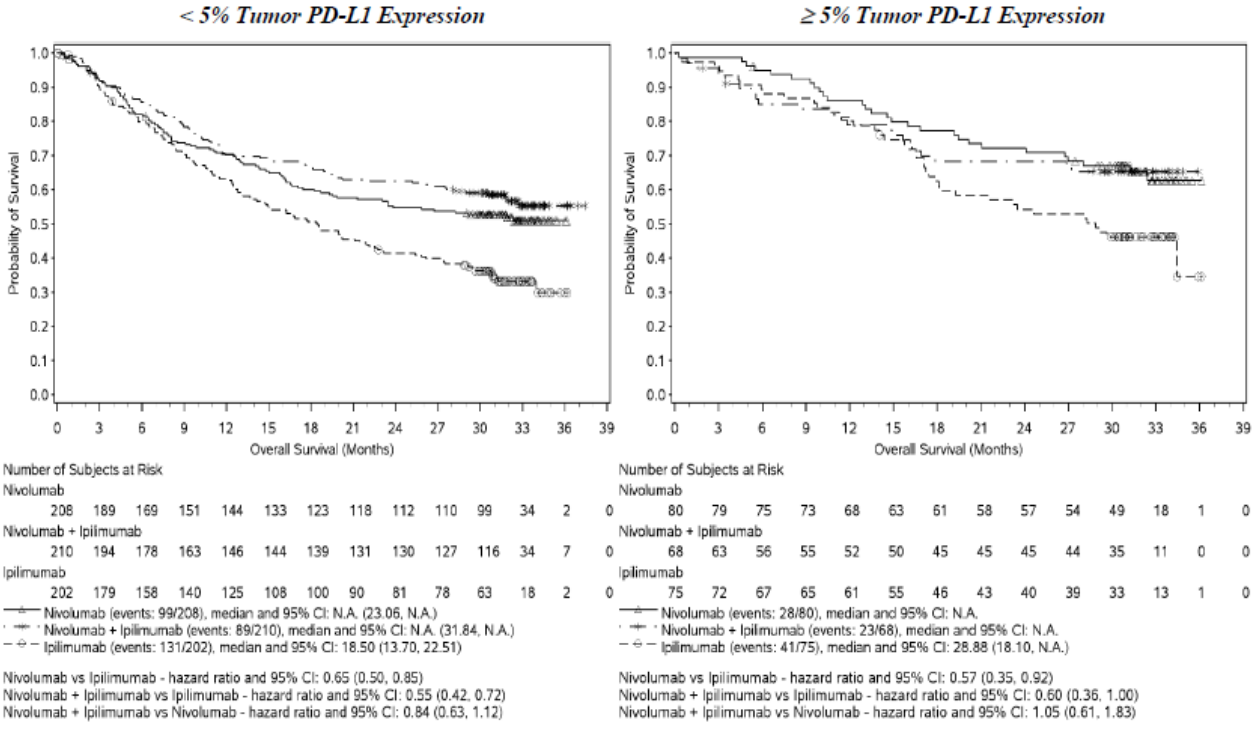
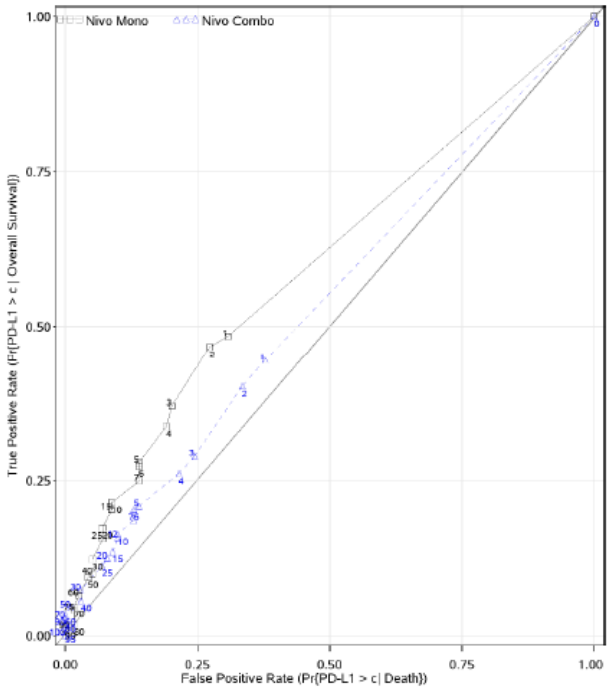


Figure 14: Kaplan-Meier Plot of OS by PD-L1 Status and Treatment (1% and 5% Expression Levels) < 5% Tumour PD-L1 Expression



NIVOLUMAB N = 288, NIVOLUMAB+IPILIMUMAB N = 278
Area Under the Curve:(Nivo Mono) = 0.6004 95% CI=(0.55, 0.65), (Nivo Combo) = 0.5412 95% CI=(0.49, 0.59)

Figure 15: Receiver Operating Characteristic (ROC) Curve Based on 2-Year OS per Investigator -- All Randomized Subjects with Nivolumab Mono and Nivolumab + Ipilimumab Combo

Table 27: Investigator-assessed ORR and DOR by PD-L1 Expression Level (Validated Assay) - PD-L1 Tested Subjects - CA209067

Nivolumab Group N=316					
PD-L1 expression	**< 1%**	**≥ 1%**	**< 5%**	**≥ 5%**	**Indeterminate or Not Evaluable[a]**
ORR (%)[a]	41/117 (35.0)	94/171 (55.0)	88/208 (42.3)	47/80 (58.8)	6/28 (21.4%)
Exact 95% CI	26.5, 44.4	47.2, 62.6	35.5, 49.3	47.2, 69.6	8.3, 41.0
CR rate (%)	15/117 (12.8)	32/171 (18.7)	32/208 (15.4)	15/80 (18.8)	0
Median DOR (95% CI)[b]	N.A. (26.68, N.A.)	N.A.	N.A.	N.A. (21.39, N.A.)	NR
Nivolumab + Ipilimumab Group N=314					
PD-L1 expression	**< 1%**	**≥ 1%**	**< 5%**	**≥ 5%**	**Indeterminate or Not Evaluable[a]**
ORR (%)[c]	67/123 (54.5)	101/155 (65.2)	118/210 (56.2)	50/68 (73.5)	17/36 (47.2%)
Exact 95% CI	45.2, 63.5	57.1, 72.6	49.2, 63.0	61.4, 83.5	30.4, 64.5
CR rate (%)	21/123 (17.1)	28/155 (18.1)	36/210 (17.1)	13/68 (19.1)	5/36 (13.9)
Median DOR (95% CI)[d]	N.A. (28.02, N.A.)	N.A.	N.A.	N.A. (18.07, N.A.)	NR
Ipilimumab Group N=315					
PD-L1 expression	**< 1%**	**≥ 1%**	**< 5%**	**≥ 5%**	**Indeterminate or Not Evaluable[a]**
ORR (%)	21/113 (18.6)	31/164 (18.9)	36/202 (17.8)	16/75 (21.3)	8/38 (21.1%)
Exact 95% CI	11.9, 27.0	13.2, 25.7	12.8, 23.8	12.7, 32.3	9.6, 37.3
CR rate (%)	6/113 (5.3)	7/164 (4.3)	9/202 (4.5)	4/75 (5.3)	1/38 (2.6%)
Median DOR (95% CI)[e]	11.60 (4.17, N.A.)	N.A. (8.34, N.A.)	18.20 (5.32, N.A.)	N.A. (6.08, N.A.)	NR

[a] CR+PR, CI based on the Clopper and Pearson method.

[b] Median computed using Kaplan-Meier product-limit method.

NA - not available/not estimable: NR - not reached

Health-related Quality of Life - QLQ-C30 Secondary Endpoint

Quality of life measured by the EORTC QLQ-C30 Global Health Status remained stable in all treatment groups, with no mean change in score from baseline reaching the minimal important difference for the patient (i.e., mean change ≥ 10 points) at any time point for any of the three treatment arms.

Ancillary analyses

Overall Survival in Subpopulations

Survival effect for most subgroups was consistent with that of the All Randomized subjects, including BRAF[V600] mutation-positive and BRAF wild-type subjects and favoured the NIVO-containing arms compared to IPI monotherapy (Figure 18 and figure 19).

	N	Nivolumab N of events (N of subjects)	mOS (95% CI)	Ipilimumab N of events (N of subjects)	mOS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	142(316)	N.A. (29.08, N.A.)	197(315)	19.98 (17.08, 24.61)	0.63 (0.51, 0.78)
BRAF Mutation Status						
Mutant	300	40(98)	N.A. (26.41, N.A.)	60(100)	24.61 (17.91, 30.98)	0.60 (0.40, 0.89)
Wildtype	645	102(218)	N.A. (25.82, N.A.)	137(215)	18.50 (14.78, 23.03)	0.64 (0.49, 0.83)
M Stage at Study Entry						
M0/M1A/M1B	388	40(132)	N.A.	65(127)	30.82 (26.15, N.A.)	0.54 (0.36, 0.80)
M1C	557	102(184)	23.43 (16.53, 32.33)	132(188)	14.95 (11.47, 17.74)	0.66 (0.51, 0.86)
Age Category I						
< 65	565	89(198)	N.A. (28.02, N.A.)	117(182)	18.10 (14.98, 23.20)	0.59 (0.45, 0.77)
>= 65	380	53(118)	N.A. (21.06, N.A.)	80(133)	22.51 (17.22, 30.78)	0.69 (0.49, 0.98)
Age Category II						
< 65	565	89(198)	N.A. (28.02, N.A.)	117(182)	18.10 (14.98, 23.20)	0.59 (0.45, 0.77)
>= 65 and < 75	262	32(79)	N.A. (26.97, N.A.)	52(89)	23.49 (17.12, 33.97)	0.62 (0.40, 0.96)
>= 75	118	21(39)	20.24 (7.20, N.A.)	28(44)	21.09 (7.33, 30.98)	0.85 (0.48, 1.49)
Gender						
Male	610	84(202)	N.A. (32.43, N.A.)	126(202)	18.40 (15.08, 23.20)	0.55 (0.42, 0.73)
Female	335	58(114)	28.22 (19.45, N.A.)	71(113)	22.70 (16.66, 29.14)	0.79 (0.56, 1.11)
Race						
White	921	136(308)	N.A. (31.24, N.A.)	186(303)	20.17 (16.79, 25.56)	0.63 (0.50, 0.78)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	2(2)	10.07 (5.59, 14.55)	6(6)	18.43 (15.97, 27.40)	
Other	13	4(6)	23.93 (4.96, 31.90)	4(5)	10.87 (3.25, N.A.)	
Region						
US	207	28(68)	N.A. (24.08, N.A.)	43(75)	27.47 (19.91, 34.43)	0.69 (0.43, 1.12)
EU	517	79(170)	N.A. (23.46, N.A.)	113(170)	16.16 (11.53, 20.21)	0.58 (0.44, 0.78)
Australia	115	14(38)	N.A. (31.90, N.A.)	21(37)	21.91 (12.12, N.A.)	0.48 (0.24, 0.95)
Rest of World	106	21(40)	24.92 (16.13, N.A.)	20(33)	23.20 (17.91, N.A.)	0.89 (0.48, 1.64)
Baseline ECOG Performance Status						
0	691	91(237)	N.A.	128(224)	25.40 (18.73, 29.50)	0.58 (0.44, 0.76)
1	252	50(78)	14.16 (8.05, 25.82)	69(91)	12.45 (7.49, 17.91)	0.77 (0.54, 1.11)
History of Brain Metastases						
Yes	33	3(7)	N.A. (0.82, N.A.)	10(15)	14.98 (5.65, N.A.)	
No	912	139(309)	N.A. (28.25, N.A.)	187(300)	20.14 (17.12, 25.40)	0.63 (0.51, 0.79)
Smoking Status						
Yes	410	59(133)	N.A. (24.08, N.A.)	88(139)	21.91 (16.56, 28.12)	0.63 (0.45, 0.87)
No	498	79(170)	N.A. (23.89, N.A.)	104(167)	18.56 (14.95, 25.56)	0.64 (0.48, 0.86)
Baseline LDH 1						
<= ULN	590	70(197)	N.A.	107(194)	28.81 (22.70, 33.97)	0.57 (0.42, 0.77)
> ULN	341	70(112)	14.98 (11.66, 23.43)	86(115)	10.87 (8.41, 13.14)	0.72 (0.52, 0.99)
Baseline LDH 2						
<= 2*ULN	827	110(272)	N.A.	165(279)	23.20 (19.29, 29.08)	0.59 (0.46, 0.75)
> 2*ULN	104	30(37)	6.31 (4.07, 14.55)	28(30)	4.57 (2.76, 8.38)	0.66 (0.39, 1.12)
AJCC Stage at Study Entry						
Stage III	63	7(25)	N.A. (31.24, N.A.)	13(22)	25.72 (13.70, N.A.)	0.43 (0.17, 1.09)
Stage IV	882	135(291)	N.A. (26.74, N.A.)	184(293)	19.91 (16.66, 23.20)	0.64 (0.51, 0.80)

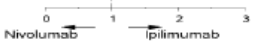


Figure 16: Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - All Randomized Subjects, NIVO Relative to IPI

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mOS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mOS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	128(314)	N.A.	197(315)	19.98 (17.08, 24.61)	0.56 (0.44, 0.69)
BRAF Mutation Status						
Mutant	300	32(102)	N.A.	60(100)	24.61 (17.91, 30.98)	0.43 (0.28, 0.66)
Wildtype	645	96(212)	N.A. (27.60, N.A.)	137(215)	18.50 (14.78, 23.03)	0.62 (0.48, 0.80)
M Stage at Study Entry						
M0/M1A/M1B	388	34(129)	N.A.	65(127)	30.82 (26.15, N.A.)	0.45 (0.30, 0.69)
M1C	557	94(185)	30.52 (19.35, N.A.)	132(188)	14.95 (11.47, 17.74)	0.60 (0.46, 0.78)
Age Category I						
< 65	565	70(185)	N.A.	117(182)	18.10 (14.98, 23.20)	0.48 (0.36, 0.65)
>= 65	380	58(129)	N.A. (26.45, N.A.)	80(133)	22.51 (17.22, 30.78)	0.68 (0.48, 0.95)
Age Category II						
< 65	565	70(185)	N.A.	117(182)	18.10 (14.98, 23.20)	0.48 (0.36, 0.65)
>= 65 and < 75	262	40(94)	N.A. (26.45, N.A.)	52(89)	23.49 (17.12, 33.97)	0.67 (0.45, 1.02)
>= 75	118	18(35)	32.72 (11.66, N.A.)	28(44)	21.09 (7.33, 30.98)	0.72 (0.40, 1.31)
Gender						
Male	610	78(206)	N.A.	126(202)	18.40 (15.08, 23.20)	0.49 (0.37, 0.65)
Female	335	50(108)	N.A. (19.78, N.A.)	71(113)	22.70 (16.66, 29.14)	0.69 (0.48, 1.00)
Race						
White	921	126(310)	N.A.	186(303)	20.17 (16.79, 25.56)	0.57 (0.45, 0.71)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	1(2)	N.A. (19.78, N.A.)	6(6)	18.43 (15.97, 27.40)	
Other	13	1(2)	N.A. (3.81, N.A.)	4(5)	10.87 (3.25, N.A.)	
Region						
US	207	18(64)	N.A.	43(75)	27.47 (19.91, 34.43)	0.40 (0.23, 0.70)
EU	517	81(177)	N.A. (26.84, N.A.)	113(170)	16.16 (11.53, 20.21)	0.56 (0.42, 0.74)
Australia	115	11(40)	N.A.	21(37)	21.91 (12.12, N.A.)	0.43 (0.21, 0.89)
Rest of World	106	18(33)	18.14 (10.91, N.A.)	20(33)	23.20 (17.91, N.A.)	1.00 (0.53, 1.90)
Baseline ECOG Performance Status						
0	691	82(230)	N.A.	128(224)	25.40 (18.73, 29.50)	0.53 (0.40, 0.70)
1	252	45(83)	19.78 (10.02, N.A.)	69(91)	12.45 (7.49, 17.91)	0.63 (0.43, 0.91)
History of Brain Metastases						
Yes	33	5(11)	31.90 (2.76, N.A.)	10(15)	14.98 (5.65, N.A.)	0.51 (0.17, 1.52)
No	912	123(303)	N.A.	187(300)	20.14 (17.12, 25.40)	0.56 (0.44, 0.70)
Smoking Status						
Yes	410	58(138)	N.A. (30.52, N.A.)	88(139)	21.91 (16.56, 28.12)	0.57 (0.41, 0.80)
No	498	60(161)	N.A.	104(167)	18.56 (14.95, 25.56)	0.49 (0.35, 0.67)
Baseline LDH 1						
<= ULN	590	64(199)	N.A.	107(194)	28.81 (22.70, 33.97)	0.50 (0.37, 0.68)
> ULN	341	63(114)	17.41 (10.71, N.A.)	86(115)	10.87 (8.41, 13.14)	0.63 (0.46, 0.87)
Baseline LDH 2						
<= 2*ULN	827	102(276)	N.A.	165(279)	23.20 (19.29, 29.08)	0.54 (0.42, 0.69)
> 2*ULN	104	25(37)	8.31 (4.60, 11.70)	28(30)	4.57 (2.76, 8.38)	0.50 (0.29, 0.87)
AJCC Stage at Study Entry						
Stage III	63	4(16)	N.A. (31.90, N.A.)	13(22)	25.72 (13.70, N.A.)	0.32 (0.10, 0.97)
Stage IV	882	124(298)	N.A.	184(293)	19.91 (16.66, 23.20)	0.57 (0.45, 0.71)

Figure 17: Forest Plot of Treatment Effect on Overall Survival in Pre-defined Subsets - All Randomized Subjects, NIVO+IPI Relative to IPI

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mOS (95% CI)	Nivolumab N of events (N of subjects)	Nivolumab mOS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	128(314)	N.A.	142(316)	N.A. (29.08, N.A.)	0.89 (0.70, 1.13)
BRAF Mutation Status						
Mutant	300	32(102)	N.A.	40(98)	N.A. (26.41, N.A.)	0.71 (0.45, 1.13)
Wildtype	645	96(212)	N.A. (27.60, N.A.)	102(218)	N.A. (25.82, N.A.)	0.97 (0.74, 1.28)
M Stage at Study Entry						
M0/M1A/M1B	388	34(129)	N.A.	40(132)	N.A.	0.84 (0.53, 1.33)
M1C	557	94(185)	30.52 (19.35, N.A.)	102(184)	23.43 (16.53, 32.33)	0.90 (0.68, 1.19)
Age Category I						
< 65	565	70(185)	N.A.	89(198)	N.A. (28.02, N.A.)	0.81 (0.59, 1.11)
>= 65	380	58(129)	N.A. (26.45, N.A.)	53(118)	N.A. (21.06, N.A.)	0.99 (0.68, 1.44)
Age Category II						
< 65	565	70(185)	N.A.	89(198)	N.A. (28.02, N.A.)	0.81 (0.59, 1.11)
>= 65 and < 75	262	40(94)	N.A. (26.45, N.A.)	32(79)	N.A. (26.97, N.A.)	1.09 (0.69, 1.74)
>= 75	118	18(35)	32.72 (11.66, N.A.)	21(39)	20.24 (7.20, N.A.)	0.86 (0.46, 1.63)
Gender						
Male	610	78(206)	N.A.	84(202)	N.A. (32.43, N.A.)	0.89 (0.66, 1.21)
Female	335	50(108)	N.A. (19.78, N.A.)	58(114)	28.22 (19.45, N.A.)	0.89 (0.61, 1.30)
Race						
White	921	126(310)	N.A.	136(308)	N.A. (31.24, N.A.)	0.90 (0.71, 1.15)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	1(2)	N.A. (19.78, N.A.)	2(2)	10.07 (5.59, 14.55)	
Other	13	1(2)	N.A. (3.81, N.A.)	4(6)	23.93 (4.96, 31.90)	
Region						
US	207	18(64)	N.A.	28(68)	N.A. (24.08, N.A.)	0.59 (0.33, 1.08)
EU	517	81(177)	N.A. (26.84, N.A.)	79(170)	N.A. (23.46, N.A.)	0.96 (0.71, 1.31)
Australia	115	11(40)	N.A.	14(38)	N.A. (31.90, N.A.)	0.83 (0.38, 1.82)
Rest of World	106	18(33)	18.14 (10.91, N.A.)	21(40)	24.92 (16.13, N.A.)	1.14 (0.60, 2.14)
Baseline ECOG Performance Status						
0	691	82(230)	N.A.	91(237)	N.A.	0.91 (0.68, 1.23)
1	252	45(83)	19.78 (10.02, N.A.)	50(78)	14.16 (8.05, 25.82)	0.82 (0.55, 1.23)
History of Brain Metastases						
Yes	33	5(11)	31.90 (2.76, N.A.)	3(7)	N.A. (0.82, N.A.)	
No	912	123(303)	N.A.	139(309)	N.A. (28.25, N.A.)	0.88 (0.69, 1.12)
Smoking Status						
Yes	410	58(138)	N.A. (30.52, N.A.)	59(133)	N.A. (24.08, N.A.)	0.91 (0.64, 1.31)
No	498	60(161)	N.A.	79(170)	N.A. (23.89, N.A.)	0.76 (0.54, 1.06)
Baseline LDH 1						
<= ULN	590	64(199)	N.A.	70(197)	N.A.	0.89 (0.64, 1.25)
> ULN	341	63(114)	17.41 (10.71, N.A.)	70(112)	14.98 (11.66, 23.43)	0.86 (0.61, 1.21)
Baseline LDH 2						
<= 2*ULN	827	102(276)	N.A.	110(272)	N.A.	0.91 (0.70, 1.19)
> 2*ULN	104	25(37)	8.31 (4.60, 11.70)	30(37)	6.31 (4.07, 14.55)	0.71 (0.41, 1.20)
AJCC Stage at Study Entry						
Stage III	63	4(16)	N.A. (31.90, N.A.)	7(25)	N.A. (31.24, N.A.)	0.76 (0.22, 2.59)
Stage IV	882	124(298)	N.A.	135(291)	N.A. (26.74, N.A.)	0.88 (0.69, 1.12)

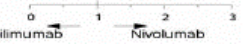


Figure 18: Forest Plot of Treatment Effect on Overall Survival in Pre-defined Subsets - All Randomized Subjects, NIVO+IPI Relative to NIVO

PFS in Subpopulations

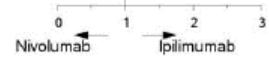
Results in are presented in Figure 20.

Figure 21 and Figure 22.

Forest Plots of Treatment Effect on Progression Free Survival per Investigator in Pre-Defined Subsets at 18 Month Minimum Follow-up Analysis - All Randomized Subjects

	N	Nivolumab N of events (N of subjects)	Nivolumab mPFS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	183(316)	6.87 (4.34, 9.46)	245(315)	2.89 (2.79, 3.42)	0.55 (0.46, 0.67)
BRAF Mutation Status						
Mutant	300	63(98)	5.62 (2.79, 9.30)	71(100)	4.04 (2.79, 5.52)	0.76 (0.54, 1.07)
Wildtype	645	120(218)	7.13 (4.86, 14.29)	174(215)	2.83 (2.76, 3.09)	0.48 (0.38, 0.61)
M Stage at Study Entry						
M0/M1A/M1B	387	65(132)	9.46 (5.62, N.A.)	99(126)	4.17 (2.96, 5.52)	0.49 (0.36, 0.67)
M1C	558	118(184)	5.32 (2.83, 7.13)	146(189)	2.79 (2.73, 2.83)	0.60 (0.47, 0.76)
Age Category I						
< 65	565	118(198)	5.49 (2.96, 7.06)	136(182)	2.83 (2.79, 3.06)	0.60 (0.47, 0.78)
>= 65	380	65(118)	10.18 (5.39, 24.87)	109(133)	3.09 (2.79, 4.14)	0.49 (0.36, 0.66)
Age Category II						
< 65	565	118(198)	5.49 (2.96, 7.06)	136(182)	2.83 (2.79, 3.06)	0.60 (0.47, 0.78)
>= 65 and < 75	262	41(79)	16.13 (6.74, 24.87)	76(89)	2.89 (2.69, 3.94)	0.38 (0.26, 0.56)
>= 75	118	24(39)	5.26 (2.63, N.A.)	33(44)	4.14 (2.79, 6.90)	0.77 (0.45, 1.30)

	N	Nivolumab N of events (N of subjects)	Nivolumab mPFS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Gender						
Male	610	112(202)	8.87 (5.62, 16.49)	154(202)	2.86 (2.79, 3.38)	0.48 (0.37, 0.61)
Female	335	71(114)	2.99 (2.76, 6.67)	91(113)	2.89 (2.76, 4.27)	0.72 (0.53, 0.99)
Race						
White	921	178(308)	6.87 (4.34, 9.46)	233(303)	2.92 (2.79, 3.94)	0.57 (0.47, 0.69)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	1(2)	2.60 (N.A., N.A.)	6(6)	2.84 (2.60, 6.97)	
Other	13	4(6)	13.22 (2.56, 19.52)	5(5)	2.60 (1.61, 2.63)	
Region						
US	207	37(68)	6.87 (2.96, 14.29)	57(75)	4.70 (2.89, 6.97)	0.69 (0.45, 1.04)
EU	517	107(170)	5.13 (2.83, 7.89)	132(170)	2.79 (2.76, 3.06)	0.56 (0.43, 0.73)
Australia	115	18(38)	21.95 (6.93, N.A.)	30(37)	2.79 (2.63, 4.14)	0.33 (0.18, 0.60)
Rest of World	106	21(40)	7.06 (2.76, N.A.)	26(33)	3.09 (2.63, 5.72)	0.56 (0.32, 1.00)
Baseline ECOG Performance Status						
0	691	135(237)	7.06 (5.32, 14.00)	172(224)	3.09 (2.83, 4.14)	0.54 (0.43, 0.68)
1	252	47(78)	4.34 (2.63, 7.13)	73(91)	2.76 (2.63, 2.89)	0.61 (0.42, 0.88)



	N	Nivolumab N of events (N of subjects)	Nivolumab mPFS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
History of Brain Metastases						
Yes	33	4(7)	9.69 (0.62, N.A.)	9(15)	2.89 (2.07, N.A.)	
No	912	179(309)	6.87 (4.34, 9.30)	236(300)	2.86 (2.79, 3.42)	0.54 (0.45, 0.66)
Smoking Status						
Yes	410	77(133)	8.18 (3.15, 16.49)	106(139)	3.48 (2.83, 4.17)	0.57 (0.42, 0.77)
No	498	101(170)	5.49 (3.02, 8.11)	132(167)	2.83 (2.76, 3.09)	0.57 (0.44, 0.74)
Baseline LDH 1						
<= ULN	589	106(196)	9.69 (6.87, 21.95)	148(194)	4.04 (3.02, 5.19)	0.54 (0.42, 0.69)
> ULN	341	76(112)	2.79 (2.63, 4.04)	96(115)	2.63 (2.60, 2.76)	0.59 (0.43, 0.80)
Baseline LDH 2						
<= 2*ULN	826	152(271)	8.11 (5.49, 14.29)	219(279)	3.09 (2.83, 4.11)	0.53 (0.43, 0.65)
> 2*ULN	104	30(37)	2.56 (1.71, 2.76)	25(30)	2.33 (1.77, 2.66)	0.61 (0.34, 1.07)
AJCC Stage at Study Entry						
Stage III	63	12(25)	7.38 (2.83, N.A.)	17(22)	2.89 (2.60, 9.46)	0.50 (0.24, 1.04)
Stage IV	882	171(291)	6.87 (4.21, 9.46)	228(293)	2.86 (2.79, 3.48)	0.56 (0.46, 0.68)

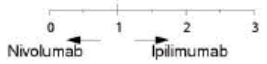
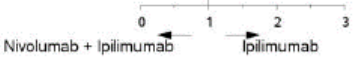
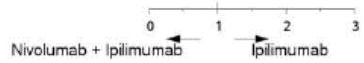


Figure 19: NIVO Relative to IPI

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mPFS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	161(314)	11.50 (8.90, 22.18)	245(315)	2.89 (2.79, 3.42)	0.41 (0.33, 0.50)
BRAF Mutation Status						
Mutant	300	51(102)	15.54 (8.02, N.A.)	71(100)	4.04 (2.79, 5.52)	0.43 (0.30, 0.62)
Wildtype	645	110(212)	11.27 (8.34, 22.18)	174(215)	2.83 (2.76, 3.09)	0.40 (0.31, 0.51)
M Stage at Study Entry						
M0/M1A/M1B	387	53(129)	N.A. (11.17, N.A.)	99(126)	4.17 (2.96, 5.52)	0.31 (0.22, 0.44)
M1C	558	108(185)	8.51 (5.52, 13.21)	146(189)	2.79 (2.73, 2.83)	0.48 (0.37, 0.61)
Age Category I						
< 65	565	93(185)	11.73 (7.00, N.A.)	136(182)	2.83 (2.79, 3.06)	0.40 (0.30, 0.52)
>= 65	380	68(129)	11.17 (8.51, 23.03)	109(133)	3.09 (2.79, 4.14)	0.43 (0.31, 0.58)
Age Category II						
< 65	565	93(185)	11.73 (7.00, N.A.)	136(182)	2.83 (2.79, 3.06)	0.40 (0.30, 0.52)
>= 65 and < 75	262	51(94)	11.10 (8.34, N.A.)	76(89)	2.89 (2.69, 3.94)	0.37 (0.26, 0.54)
>= 75	118	17(35)	22.18 (4.44, N.A.)	33(44)	4.14 (2.79, 6.90)	0.52 (0.29, 0.93)



	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mPFS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Gender						
Male	610	101(206)	16.76 (10.84, N.A.)	154(202)	2.86 (2.79, 3.38)	0.36 (0.28, 0.47)
Female	335	60(108)	7.98 (4.67, 15.54)	91(113)	2.89 (2.76, 4.27)	0.51 (0.37, 0.71)
Race						
White	921	158(310)	11.73 (8.90, 22.18)	233(303)	2.92 (2.79, 3.94)	0.41 (0.34, 0.51)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	2(2)	6.70 (2.66, 10.74)	6(6)	2.84 (2.60, 6.97)	
Other	13	1(2)	N.A. (2.60, N.A.)	5(5)	2.60 (1.61, 2.63)	
Region						
US	207	27(64)	N.A. (5.52, N.A.)	57(75)	4.70 (2.89, 6.97)	0.42 (0.27, 0.67)
EU	517	100(177)	10.15 (6.93, 16.53)	132(170)	2.79 (2.76, 3.06)	0.41 (0.31, 0.53)
Australia	115	14(40)	N.A. (13.96, N.A.)	30(37)	2.79 (2.63, 4.14)	0.24 (0.12, 0.46)
Rest of World	106	20(33)	8.51 (5.26, 18.14)	26(33)	3.09 (2.63, 5.72)	0.56 (0.31, 1.01)
Baseline ECOG Performance Status						
0	691	116(230)	15.54 (9.92, N.A.)	172(224)	3.09 (2.83, 4.14)	0.40 (0.31, 0.50)
1	252	45(83)	8.41 (3.38, N.A.)	73(91)	2.76 (2.63, 2.89)	0.45 (0.31, 0.66)



	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mPFS (95% CI)	Ipilimumab N of events (N of subjects)	Ipilimumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
History of Brain Metastases						
Yes	33	2(11)	N.A. (0.07, N.A.)	9(15)	2.89 (2.07, N.A.)	0.24 (0.05, 1.13)
No	912	159(303)	11.24 (8.51, 19.32)	236(300)	2.86 (2.79, 3.42)	0.41 (0.33, 0.50)
Smoking Status						
Yes	410	69(138)	11.07 (5.88, N.A.)	106(139)	3.48 (2.83, 4.17)	0.43 (0.32, 0.59)
No	498	80(161)	15.54 (10.74, N.A.)	132(167)	2.83 (2.76, 3.09)	0.37 (0.28, 0.49)
Baseline LDH 1						
<= ULN	589	87(199)	N.A. (11.50, N.A.)	148(194)	4.04 (3.02, 5.19)	0.36 (0.27, 0.47)
> ULN	341	74(114)	4.21 (2.79, 9.26)	96(115)	2.63 (2.60, 2.76)	0.45 (0.33, 0.61)
Baseline LDH 2						
<= 2*ULN	826	132(276)	18.14 (11.07, N.A.)	219(279)	3.09 (2.83, 4.11)	0.38 (0.30, 0.47)
> 2*ULN	104	29(37)	2.79 (2.17, 4.40)	25(30)	2.33 (1.77, 2.66)	0.39 (0.22, 0.71)
AJCC Stage at Study Entry						
Stage III	63	7(16)	N.A. (4.17, N.A.)	17(22)	2.89 (2.60, 9.46)	0.33 (0.13, 0.79)
Stage IV	882	154(298)	11.27 (8.51, 22.18)	228(293)	2.86 (2.79, 3.48)	0.41 (0.33, 0.51)

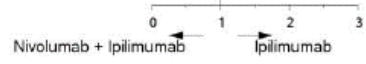


Figure 20: NIVO+IPI Relative to IPI

	N	Nivolumab + Ipilimumab N of events (N of subjects)	Nivolumab + Ipilimumab mPFS (95% CI)	Nivolumab N of events (N of subjects)	Nivolumab mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	161(314)	11.50 (8.90, 22.18)	183(316)	6.87 (4.34, 9.46)	0.78 (0.63, 0.96)
BRAF Mutation Status						
Mutant	300	51(102)	15.54 (8.02, N.A.)	63(98)	5.62 (2.79, 9.30)	0.59 (0.40, 0.85)
Wildtype	645	110(212)	11.27 (8.34, 22.18)	120(218)	7.13 (4.86, 14.29)	0.88 (0.68, 1.14)
M Stage at Study Entry						
M0/M1A/M1B	387	53(129)	N.A. (11.17, N.A.)	65(132)	9.46 (5.62, N.A.)	0.69 (0.48, 0.99)
M1C	558	108(185)	8.51 (5.52, 13.21)	118(184)	5.32 (2.83, 7.13)	0.82 (0.63, 1.07)
Age Category I						
< 65	565	93(185)	11.73 (7.00, N.A.)	118(198)	5.49 (2.96, 7.06)	0.69 (0.53, 0.91)
>= 65	380	68(129)	11.17 (8.51, 23.03)	65(118)	10.18 (5.39, 24.87)	0.93 (0.66, 1.31)
Age Category II						
< 65	565	93(185)	11.73 (7.00, N.A.)	118(198)	5.49 (2.96, 7.06)	0.69 (0.53, 0.91)
>= 65 and < 75	262	51(94)	11.10 (8.34, N.A.)	41(79)	16.13 (6.74, 24.87)	1.07 (0.71, 1.61)
>= 75	118	17(35)	22.18 (4.44, N.A.)	24(39)	5.26 (2.63, N.A.)	0.69 (0.37, 1.28)
Gender						
Male	610	101(206)	16.76 (10.84, N.A.)	112(202)	8.87 (5.62, 16.49)	0.79 (0.60, 1.04)
Female	335	60(108)	7.98 (4.67, 15.54)	71(114)	2.99 (2.76, 6.67)	0.75 (0.53, 1.06)
Race						
White	921	158(310)	11.73 (8.90, 22.18)	178(308)	6.87 (4.34, 9.46)	0.77 (0.62, 0.96)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	2(2)	6.70 (2.66, 10.74)	1(2)	2.60 (N.A., N.A.)	
Other	13	1(2)	N.A. (2.60, N.A.)	4(6)	13.22 (2.56, 19.52)	
Region						
US	207	27(64)	N.A. (5.52, N.A.)	37(68)	6.87 (2.96, 14.29)	0.63 (0.39, 1.04)
EU	517	100(177)	10.15 (6.93, 16.53)	107(170)	5.13 (2.83, 7.89)	0.79 (0.60, 1.04)
Australia	115	14(40)	N.A. (13.96, N.A.)	18(38)	21.95 (6.93, N.A.)	0.69 (0.34, 1.39)
Rest of World	106	20(33)	8.51 (5.26, 18.14)	21(40)	7.06 (2.76, N.A.)	1.03 (0.56, 1.90)
Baseline ECOG Performance Status						
0	691	116(230)	15.54 (9.92, N.A.)	135(237)	7.06 (5.32, 14.00)	0.77 (0.60, 0.99)
1	252	45(83)	8.41 (3.38, N.A.)	47(78)	4.34 (2.63, 7.13)	0.79 (0.52, 1.18)
History of Brain Metastases						
Yes	33	2(11)	N.A. (0.07, N.A.)	4(7)	9.69 (0.62, N.A.)	
No	912	159(303)	11.24 (8.51, 19.32)	179(309)	6.87 (4.34, 9.30)	0.79 (0.64, 0.98)
Smoking Status						
Yes	410	69(138)	11.07 (5.88, N.A.)	77(133)	8.18 (3.15, 16.49)	0.78 (0.57, 1.09)
No	498	80(161)	15.54 (10.74, N.A.)	101(170)	5.49 (3.02, 8.11)	0.69 (0.51, 0.92)
Baseline LDH 1						
<= ULN	589	87(199)	N.A. (11.50, N.A.)	106(196)	9.69 (6.87, 21.95)	0.71 (0.54, 0.95)
> ULN	341	74(114)	4.21 (2.79, 9.26)	76(112)	2.79 (2.63, 4.04)	0.80 (0.58, 1.11)
Baseline LDH 2						
<= 2*ULN	826	132(276)	18.14 (11.07, N.A.)	152(271)	8.11 (5.49, 14.29)	0.75 (0.60, 0.95)
> 2*ULN	104	29(37)	2.79 (2.17, 4.40)	30(37)	2.56 (1.71, 2.76)	0.68 (0.41, 1.14)
AJCC Stage at Study Entry						
Stage III	63	7(16)	N.A. (4.17, N.A.)	12(25)	7.38 (2.83, N.A.)	0.70 (0.28, 1.78)
Stage IV	882	154(298)	11.27 (8.51, 22.18)	171(291)	6.87 (4.21, 9.46)	0.78 (0.62, 0.97)

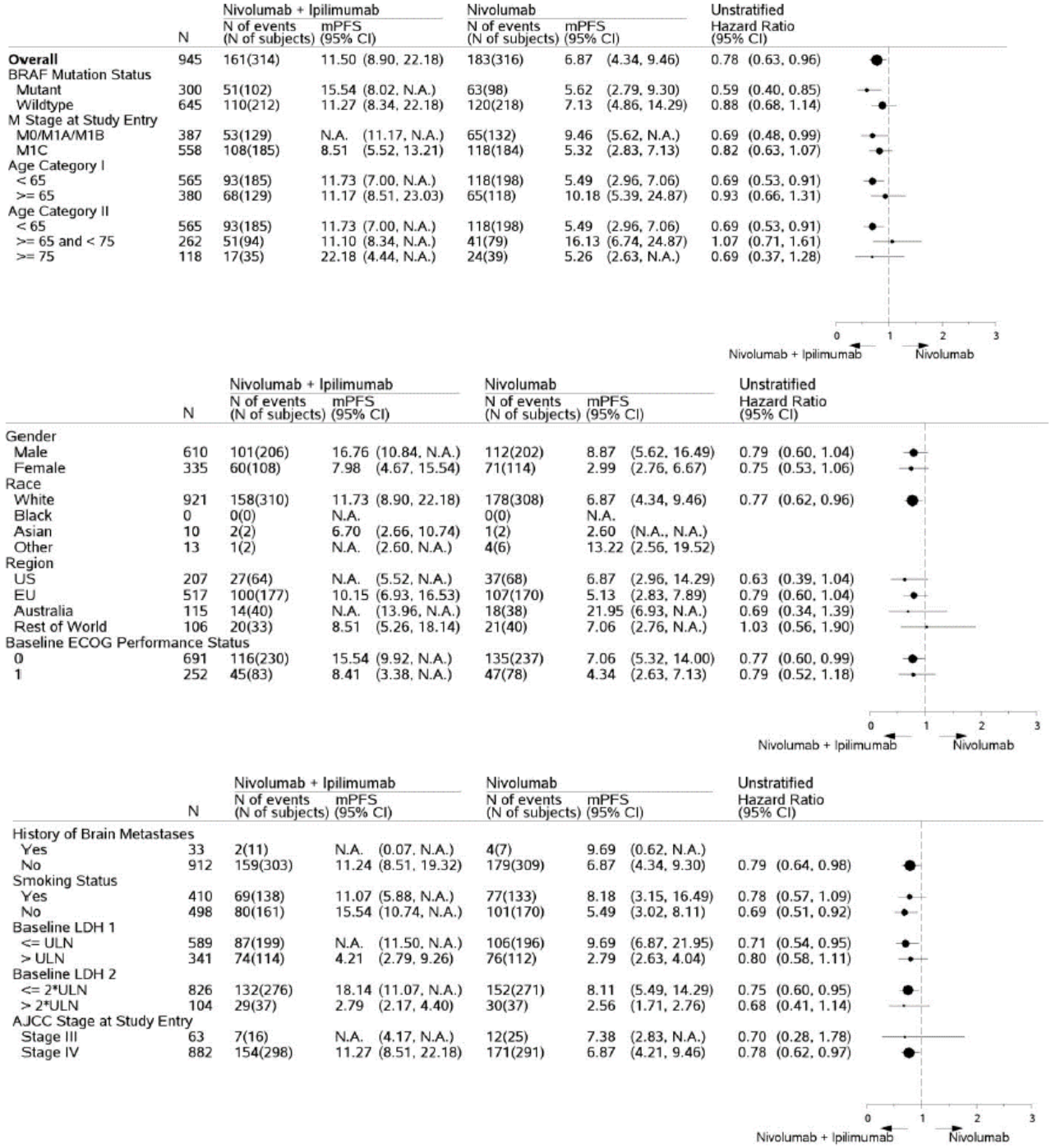


Figure 21: NIVO+IPI Relative to NIVO

ORR in Subpopulations

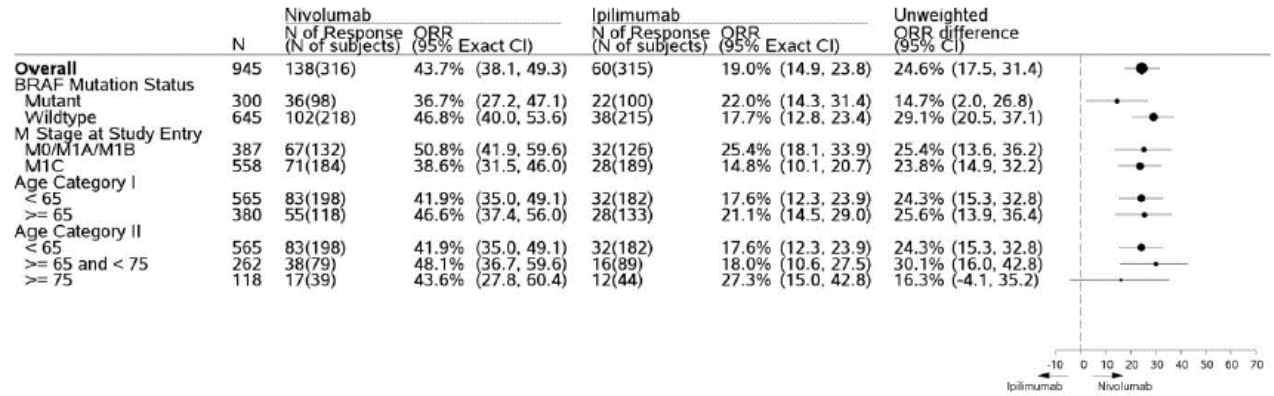
Results in are presented in

Figure 23,

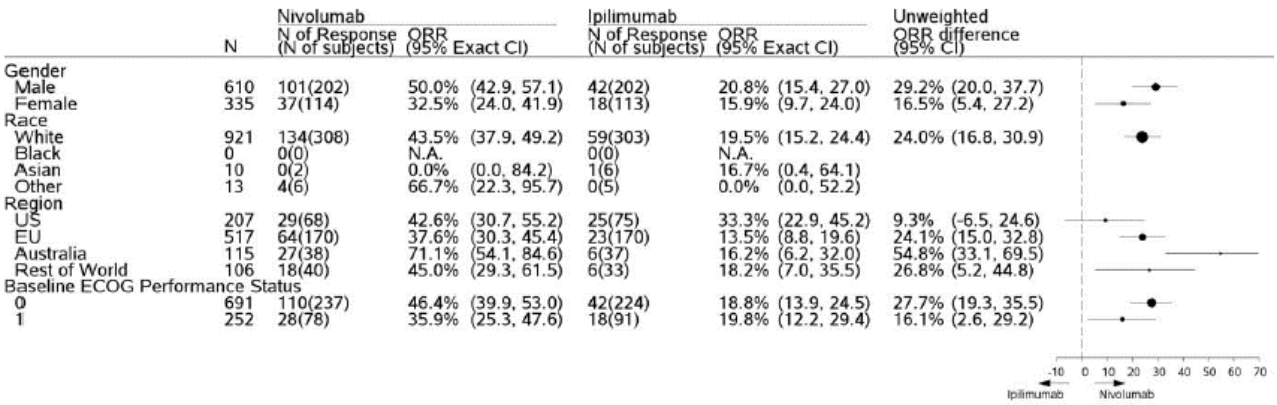
Figure 24 and

Figure 25.

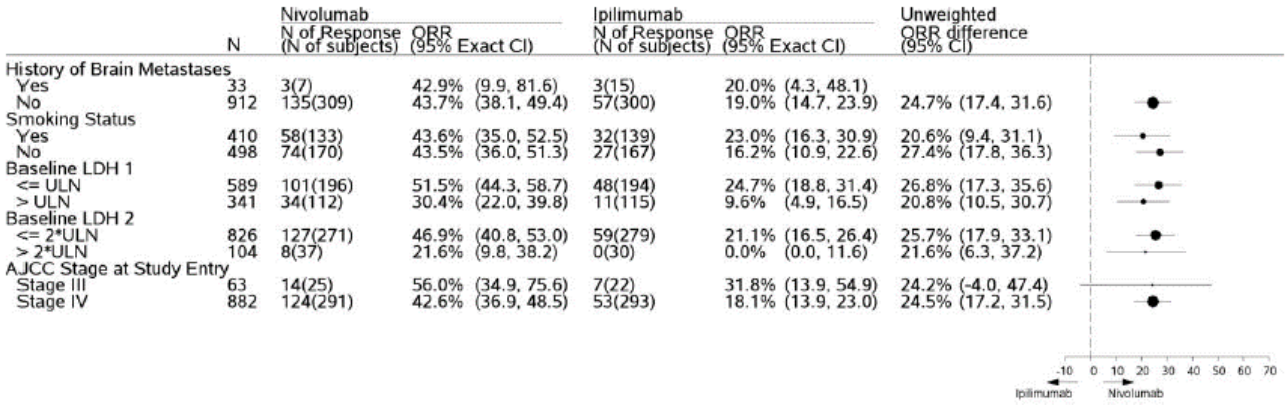
Forest Plot of Treatment Effect on Objective Response Rate per Investigator in Pre-Defined Subsets at 18 Month Minimum Follow-up Analysis - All Randomized Subjects



	N	Nivolumab N of Response (N of subjects)	Nivolumab ORR (95% Exact CI)	Ipilimumab N of Response (N of subjects)	Ipilimumab ORR (95% Exact CI)	Unweighted ORR difference (95% CI)
Overall	945	138(316)	43.7% (38.1, 49.3)	60(315)	19.0% (14.9, 23.8)	24.6% (17.5, 31.4)
BRAF Mutation Status						
Mutant	300	36(98)	36.7% (27.2, 47.1)	22(100)	22.0% (14.3, 31.4)	14.7% (2.0, 26.8)
Wildtype	645	102(218)	46.8% (40.0, 53.6)	38(215)	17.7% (12.8, 23.4)	29.1% (20.5, 37.1)
M Stage at Study Entry						
M0/M1A/M1B	387	67(132)	50.8% (41.9, 59.6)	32(126)	25.4% (18.1, 33.9)	25.4% (13.6, 36.2)
M1C	558	71(184)	38.6% (31.5, 46.0)	28(189)	14.8% (10.1, 20.7)	23.8% (14.9, 32.2)
Age Category I						
< 65	565	83(198)	41.9% (35.0, 49.1)	32(182)	17.6% (12.3, 23.9)	24.3% (15.3, 32.8)
>= 65	380	55(118)	46.6% (37.4, 56.0)	28(133)	21.1% (14.5, 29.0)	25.6% (13.9, 36.4)
Age Category II						
< 65	565	83(198)	41.9% (35.0, 49.1)	32(182)	17.6% (12.3, 23.9)	24.3% (15.3, 32.8)
>= 65 and < 75	262	38(79)	48.1% (36.7, 59.6)	16(89)	18.0% (10.6, 27.5)	30.1% (16.0, 42.8)
>= 75	118	17(39)	43.6% (27.8, 60.4)	12(44)	27.3% (15.0, 42.8)	16.3% (-4.1, 35.2)

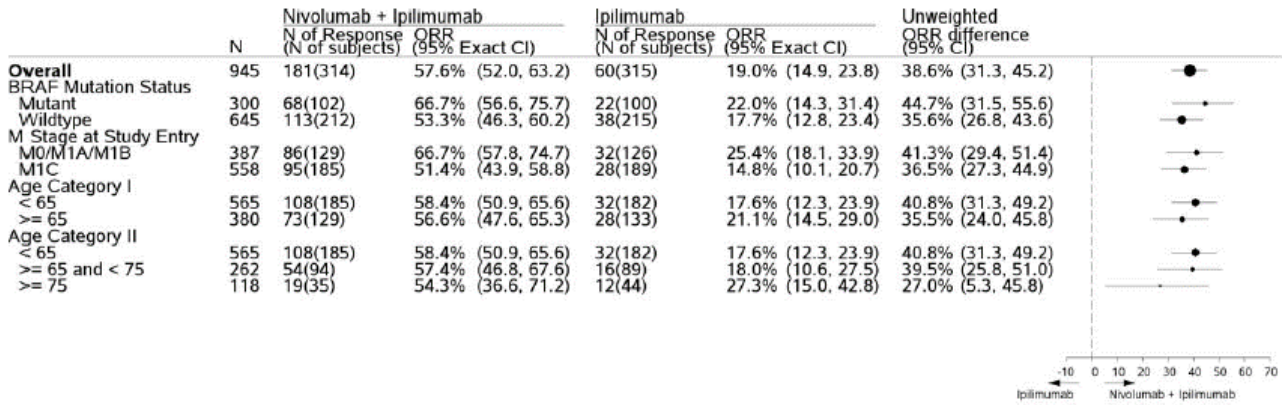


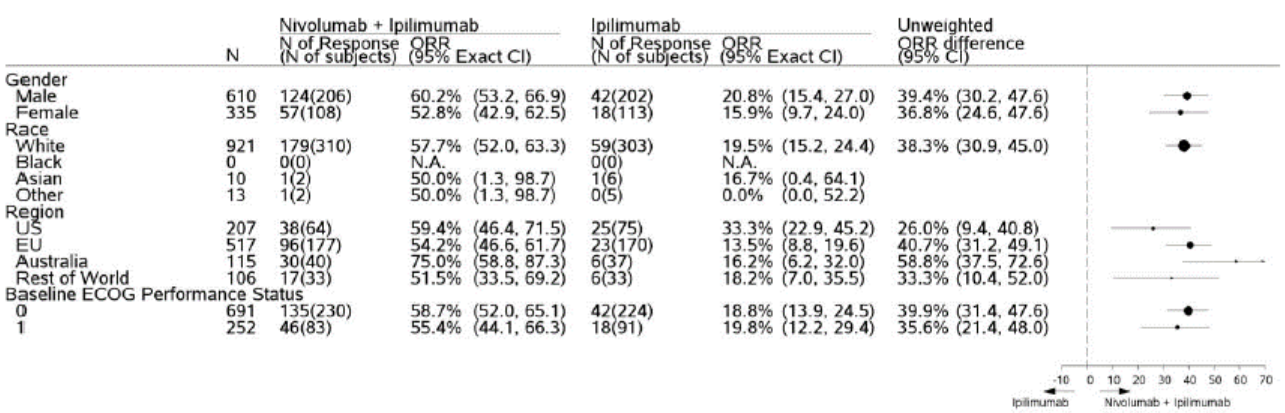
	N	Nivolumab N of Response (N of subjects)	Nivolumab ORR (95% Exact CI)	Ipilimumab N of Response (N of subjects)	Ipilimumab ORR (95% Exact CI)	Unweighted ORR difference (95% CI)
Gender						
Male	610	101(202)	50.0% (42.9, 57.1)	42(202)	20.8% (15.4, 27.0)	29.2% (20.0, 37.7)
Female	335	37(114)	32.5% (24.0, 41.9)	18(113)	15.9% (9.7, 24.0)	16.5% (5.4, 27.2)
Race						
White	921	134(308)	43.5% (37.9, 49.2)	59(303)	19.5% (15.2, 24.4)	24.0% (16.8, 30.9)
Black	0	0(0)	N.A.	0(0)	N.A.	
Asian	10	0(2)	0.0% (0.0, 84.2)	1(6)	16.7% (0.4, 64.1)	
Other	13	4(6)	66.7% (22.3, 95.7)	0(5)	0.0% (0.0, 52.2)	
Region						
US	207	29(68)	42.6% (30.7, 55.2)	25(75)	33.3% (22.9, 45.2)	9.3% (-6.5, 24.6)
EU	517	64(170)	37.6% (30.3, 45.4)	23(170)	13.5% (8.8, 19.6)	24.1% (15.0, 32.8)
Australia	115	27(38)	71.1% (54.1, 84.6)	6(37)	16.2% (6.2, 32.0)	54.8% (33.1, 69.5)
Rest of World	106	18(40)	45.0% (29.3, 61.5)	6(33)	18.2% (7.0, 35.5)	26.8% (5.2, 44.8)
Baseline ECOG Performance Status						
0	691	110(237)	46.4% (39.9, 53.0)	42(224)	18.8% (13.9, 24.5)	27.7% (19.3, 35.5)
1	252	28(78)	35.9% (25.3, 47.6)	18(91)	19.8% (12.2, 29.4)	16.1% (2.6, 29.2)



	N	Nivolumab N of Response (N of subjects)	Nivolumab ORR (95% Exact CI)	Ipilimumab N of Response (N of subjects)	Ipilimumab ORR (95% Exact CI)	Unweighted ORR difference (95% CI)
History of Brain Metastases						
Yes	33	3(7)	42.9% (9.9, 81.6)	3(15)	20.0% (4.3, 48.1)	
No	912	135(309)	43.7% (38.1, 49.4)	57(300)	19.0% (14.7, 23.9)	24.7% (17.4, 31.6)
Smoking Status						
Yes	410	58(133)	43.6% (35.0, 52.5)	32(139)	23.0% (16.3, 30.9)	20.6% (9.4, 31.1)
No	498	74(170)	43.5% (36.0, 51.3)	27(167)	16.2% (10.9, 22.6)	27.4% (17.8, 36.3)
Baseline LDH 1						
<= ULN	589	101(196)	51.5% (44.3, 58.7)	48(194)	24.7% (18.8, 31.4)	26.8% (17.3, 35.6)
> ULN	341	34(112)	30.4% (22.0, 39.8)	11(115)	9.6% (4.9, 16.5)	20.8% (10.5, 30.7)
Baseline LDH 2						
<= 2*ULN	826	127(271)	46.9% (40.8, 53.0)	59(279)	21.1% (16.5, 26.4)	25.7% (17.9, 33.1)
> 2*ULN	104	8(37)	21.6% (9.8, 38.2)	0(30)	0.0% (0.0, 11.6)	21.6% (6.3, 37.2)
AJCC Stage at Study Entry						
Stage III	63	14(25)	56.0% (34.9, 75.6)	7(22)	31.8% (13.9, 54.9)	24.2% (-4.0, 47.4)
Stage IV	882	124(291)	42.6% (36.9, 48.5)	53(293)	18.1% (13.9, 23.0)	24.5% (17.2, 31.5)

Figure 22: NIVO Relative to IPI





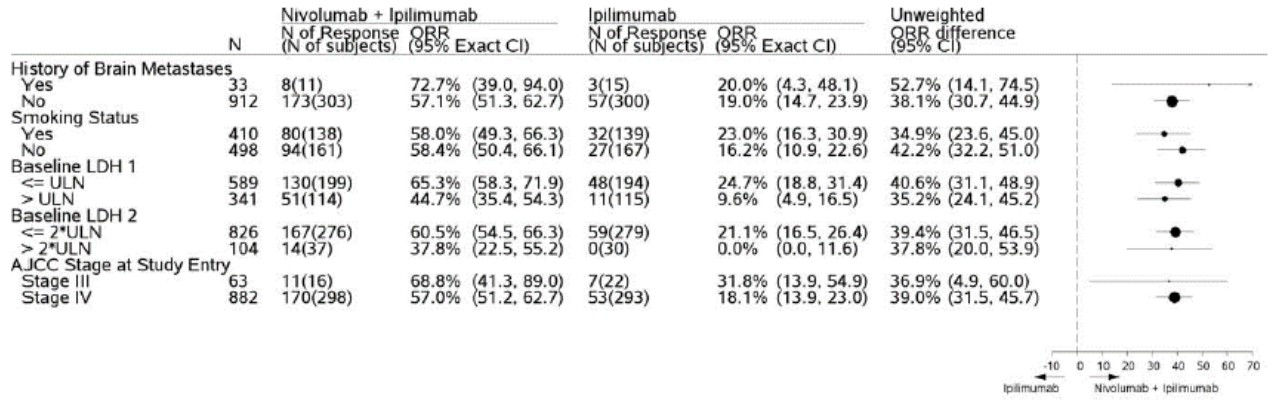
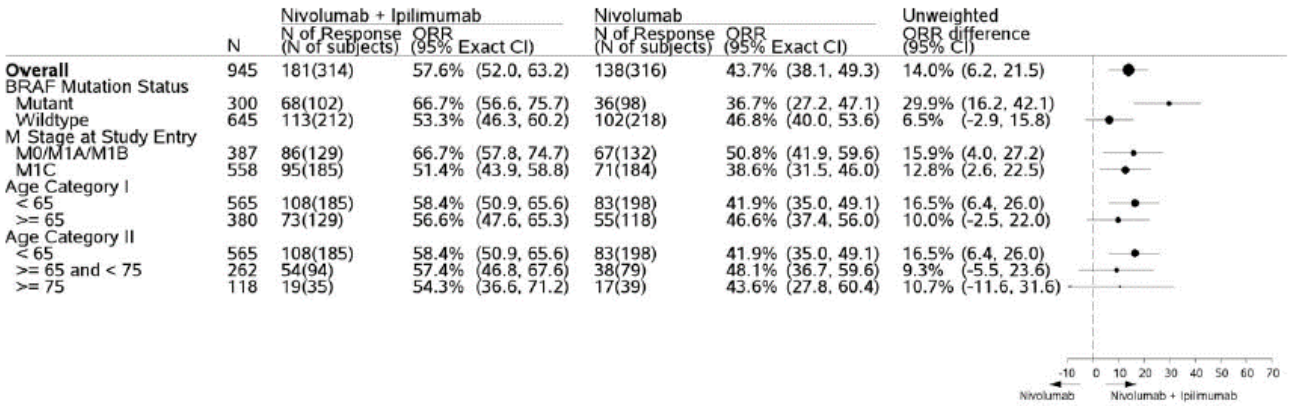


Figure 23: NIVO+IPI Relative to IPI



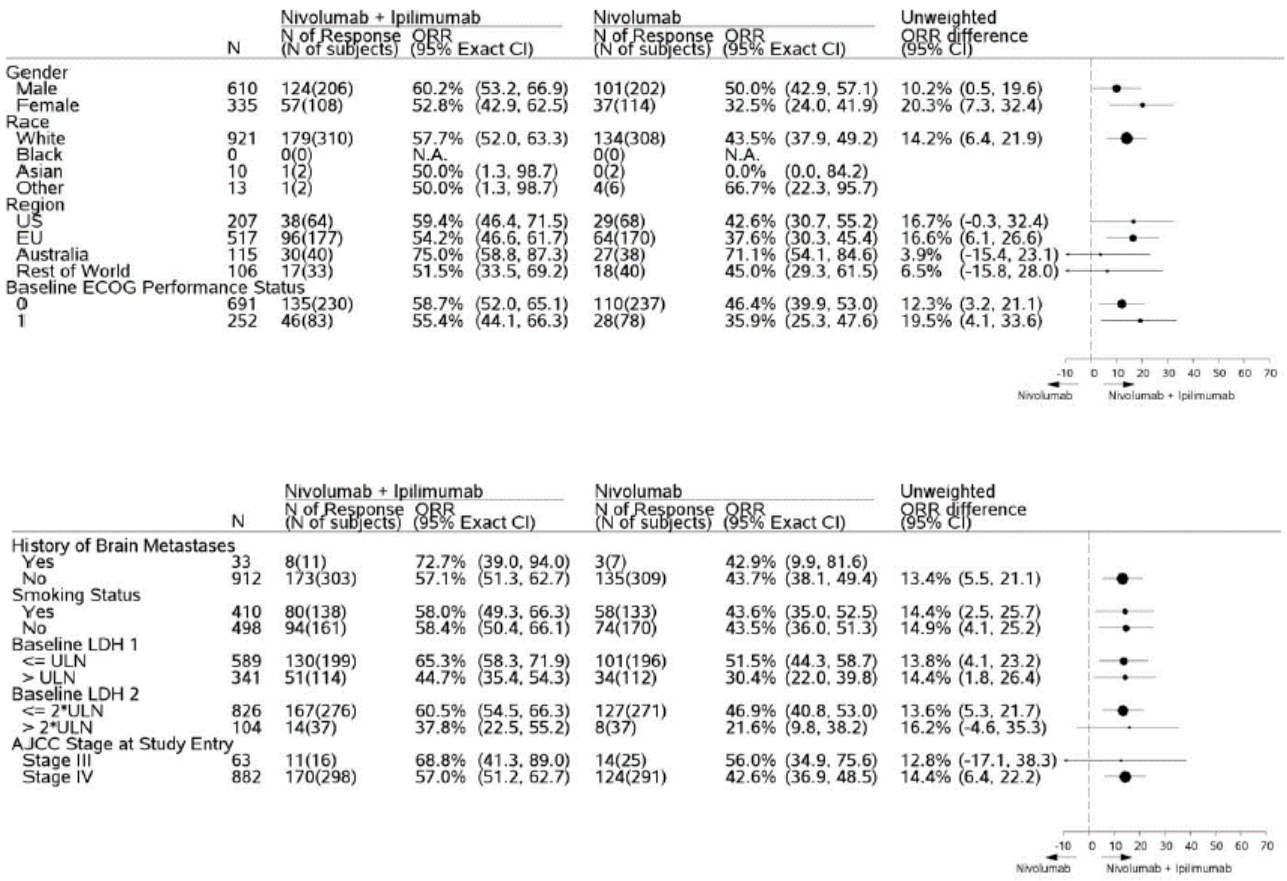


Figure 24: NIVO+IPI Relative to NIVO

<u>Updated data</u> <u>following a database lock in 24-May-2017 (OS data at 3-years follow-up)</u>

Slightly more mature results with the updated efficacy results at the data cut-off of May 2017, with +9 months additional follow up (OS data at 3-years available) in all randomized subjects show a statistically significant improvement in OS for NIVO monotherapy vs IPI monotherapy (HR = 0.65 [98% CI: 0.53, 0.80]; stratified log-rank test p-value = < 0.0001) and the combination (NIVO+IPI) vs IPI monotherapy (HR = 0.55 [98% CI: 0.45, 0.69]; stratified log-rank test p-value = < 0.0001). Based on descriptive analyses, the combination of NIVO+IPI showed a numeric difference in OS vs NIVO (HR = 0.85, 95% CI: 0.68, 1.07) not reaching statistical significance. Median OS for all randomized subjects was not reached in the NIVO+IPI group whereas it was 37.59 months (95% CI: 29.08, NA) for the NIVO group as compared to 19.94 months (95% CI: 16.85, 24.61) in the IPI group. 3-year OS rates were 58% for the NIVO+IPI, 52% for NIVO, and 34% for IPI groups.

OS rates at 6, 9, 12, 18, 24, and 36 months are presented below in Table 28. Kaplan-Meier plot of OS at 3-year follow-up is provided in Figure 26.

Table 28: Summary of OS at 3-year Follow-up - All Randomized Subjects

	NIVO N = 316	NIVO+IPI N = 314	IPI N = 315
Overall Survival			
Events, n (%)	158 (50.0)	139 (44.3)	206 (65.4)
Median OS (95% CI), months[a]	37.59 (29.08, NA)	NA (38.18, NA)	19.94 (16.85, 24.61)
HR (95% CI)	0.65 (0.53, 0.80)[b]	0.55 (0.45, 0.69)[c]	
Stratified log-rank test p-value[d]	<0.0001	<0.0001	
HR (95% CI)		0.85 (0.68, 1.07)[e]	
OS Rate at 6 months (95% CI)	0.85 (0.81, 0.89)	0.86 (0.81, 0.89)	0.82 (0.78, 0.86)
OS Rate at 12 months (95% CI)	0.74 (0.69, 0.79)	0.73 (0.68, 0.78)	0.67 (0.61, 0.72)
OS Rate at 24 months (95% CI)	0.59 (0.53, 0.64)	0.64 (0.59, 0.69)	0.45 (0.39, 0.50)
OS Rate at 36 months (95% CI)	0.52 (0.46, 0.57)	0.58 (0.52, 0.63)	0.34 (0.29, 0.39)

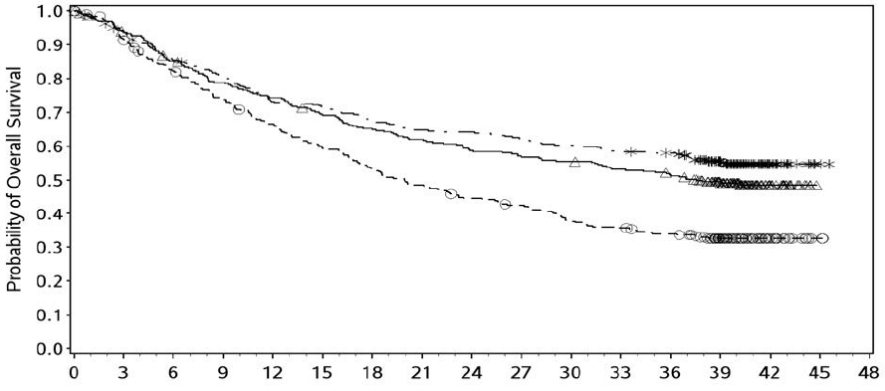
[a] Based on Kaplan-Meier estimate. NA - not available/not estimable

[b] Stratified Cox proportional hazard model. Ratio of NIVO over IPI.

[c] Stratified Cox proportional hazard model. Ratio of NIVO+IPI over IPI.

[d] Log-rank Test stratified by PD-L1 status, BRAF status, and M stage at screening as entered into the IVRS.

[e] Stratified Cox proportional hazard model. Hazard Ratio is NIVO+IPI over NIVO.



Number of Subjects at Risk

Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Nivolumab + Ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	68	20	2	0

Nivolumab (events: 158/316), median and 95% CI: 37.59 (29.08, N.A.)
Nivolumab + Ipilimumab (events: 139/314), median and 95% CI: N.A. (38.18, N.A.)
Ipilimumab (events: 206/315), median and 95% CI: 19.94 (16.85, 24.61)

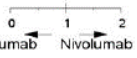
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.65 (0.53, 0.80)
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.55 (0.45, 0.69)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.85 (0.68, 1.07)
Symbols represent censored observations.
Hazard ratios are estimated using Cox proportional hazard model with treatment group as a single covariate, stratified by PD-L1 status, BRAF status and M stage at screening as entered into the IVRS.

Figure 25: Kaplan-Meier Plot of Overall Survival - All Randomized Subjects

Updated OS data (cut-off of May 2017) in patients with PD-L1 status below 1% vs PD-L1 above 1% (HR = 0.70, 95% CI: 0.49, 0.99 vs HR = 1.02, 95% CI: 0.73, 1.43; NIVO+IPI vs NIVO) show that patients with PD-L1 status above 1% would obtain a similar benefit than those treated with the monotherapy with nivolumab. A trend for greater benefit is observed with the combination vs nivo monotherapy in thise subjects BRAF mutated vs WT (Figure 27).

Figure 26: Forest Plot of Treatment Effect on Overall Survival in Pre-defined Subsets - All Randomized Subjects CA209067 (NIVO+IPI relative to NIVO)

		Nivolumab + Ipilimumab			Nivolumab			Unstratified
	N	N of events (N of subjects)	mOS (95% CI)	3 Years OS	N of events (N of subjects)	mOS (95% CI)	3 Years OS	Hazard Ratio (95% CI)
Overall	945	139 (314)	N.A. (38.18, N.A.)	0.58	158 (316)	37.59 (29.08, N.A.)	0.52	0.85 (0.68, 1.07)
BRAF Mutation Status								
Mutant	300	35 (102)	N.A.	0.68	44 (98)	N.A. (26.41, N.A.)	0.56	0.69 (0.44, 1.07)
Wildtype	645	104 (212)	39.06 (27.60, N.A.)	0.53	114 (218)	35.75 (25.82, N.A.)	0.50	0.94 (0.72, 1.22)
M Stage at Study Entry								
M0/M1A/M1B	388	41 (129)	N.A.	0.72	50 (132)	N.A.	0.64	0.79 (0.53, 1.20)
M1C	557	98 (185)	30.52 (19.35, N.A.)	0.48	108 (184)	23.43 (16.53, 35.06)	0.42	0.88 (0.67, 1.16)
Age Category I								
< 65	565	76 (185)	N.A.	0.61	99 (198)	37.95 (28.02, N.A.)	0.51	0.78 (0.58, 1.05)
>= 65	380	63 (129)	N.A. (26.45, N.A.)	0.54	59 (118)	37.59 (21.06, N.A.)	0.52	0.96 (0.68, 1.38)
Age Category II								
< 65	565	76 (185)	N.A.	0.61	99 (198)	37.95 (28.02, N.A.)	0.51	0.78 (0.58, 1.05)
>= 65 and < 75	262	44 (94)	N.A. (26.45, N.A.)	0.57	38 (79)	N.A. (26.97, N.A.)	0.56	1.01 (0.65, 1.56)
>= 75	118	19 (35)	31.54 (11.66, N.A.)	0.44	21 (39)	20.24 (7.20, N.A.)	0.45	0.90 (0.48, 1.68)
Gender								
Male	610	88 (206)	N.A. (39.06, N.A.)	0.60	92 (202)	N.A. (32.13, N.A.)	0.55	0.91 (0.68, 1.22)
Female	335	51 (108)	N.A. (19.78, N.A.)	0.53	66 (114)	28.22 (19.45, 37.95)	0.45	0.78 (0.54, 1.13)
White	921	137 (310)	N.A. (38.18, N.A.)	0.58	152 (308)	39.00 (31.24, N.A.)	0.52	0.87 (0.69, 1.09)
Non-White	23	2 (4)	N.A. (3.81, N.A.)	0.50	6 (8)	15.26 (4.96, N.A.)	0.25	
Region								
US	207	21 (64)	N.A.	0.70	32 (68)	N.A. (24.08, N.A.)	0.57	0.59 (0.34, 1.02)
EU	517	87 (177)	38.18 (26.84, N.A.)	0.53	89 (170)	35.06 (23.46, N.A.)	0.49	0.91 (0.68, 1.23)
Australia	115	11 (40)	N.A.	0.72	14 (38)	N.A. (31.90, N.A.)	0.63	0.82 (0.37, 1.81)
Rest of World	106	20 (33)	18.14 (10.91, N.A.)	0.45	23 (40)	24.92 (16.13, N.A.)	0.42	1.13 (0.62, 2.06)
Baseline ECOG Performance Status								
0	691	90 (230)	N.A.	0.64	105 (237)	N.A. (36.93, N.A.)	0.58	0.85 (0.64, 1.13)
>= 1	253	48 (83)	19.78 (10.02, N.A.)	0.43	53 (79)	13.47 (8.05, 23.89)	0.32	0.81 (0.55, 1.20)
History of Brain Metastases								
Yes	33	5 (11)	N.A. (2.76, N.A.)	0.55	4 (7)	35.06 (0.82, N.A.)	0.43	
No	912	134 (303)	N.A. (38.18, N.A.)	0.58	154 (309)	37.95 (28.25, N.A.)	0.52	0.86 (0.68, 1.08)
Smoking Status								
Yes	410	63 (138)	N.A. (30.52, N.A.)	0.56	64 (133)	N.A. (24.08, N.A.)	0.53	0.90 (0.64, 1.28)
No	498	65 (161)	N.A.	0.62	89 (170)	35.75 (23.89, N.A.)	0.49	0.72 (0.52, 0.99)
Baseline LDH								
<= ULN	590	74 (199)	N.A.	0.66	83 (197)	N.A. (40.21, N.A.)	0.61	0.86 (0.63, 1.18)
> ULN	341	64 (114)	17.41 (10.71, N.A.)	0.44	73 (112)	14.98 (11.66, 23.43)	0.34	0.83 (0.59, 1.16)
Baseline LDH								
<= 2*ULN	827	112 (276)	N.A.	0.62	126 (272)	N.A. (36.01, N.A.)	0.56	0.86 (0.67, 1.11)
> 2*ULN	104	26 (37)	8.31 (4.60, 11.70)	0.31	30 (37)	6.31 (4.07, 14.55)	0.14	0.73 (0.43, 1.23)
AJCC Stage at Study Entry								
Stage III	63	5 (16)	N.A. (31.90, N.A.)	0.69	8 (25)	N.A. (31.24, N.A.)	0.65	0.83 (0.27, 2.53)
Stage IV	882	134 (298)	N.A. (37.36, N.A.)	0.57	150 (291)	36.53 (26.74, N.A.)	0.50	0.85 (0.67, 1.07)
PD-L1 expression								
< 1%	353	59 (123)	N.A. (26.45, N.A.)	0.54	71 (117)	23.46 (13.01, 36.53)	0.42	0.70 (0.49, 0.99)
>= 1%	490	63 (155)	N.A. (39.06, N.A.)	0.62	71 (171)	N.A. (40.21, N.A.)	0.60	1.02 (0.73, 1.43)
PD-L1 expression								
< 5%	620	97 (210)	N.A. (32.72, N.A.)	0.56	110 (208)	35.94 (23.06, N.A.)	0.50	0.82 (0.62, 1.08)
>= 5%	223	25 (68)	N.A. (39.06, N.A.)	0.65	32 (80)	N.A. (35.75, N.A.)	0.61	0.99 (0.59, 1.67)
PD-L1 expression								
< 10%	684	106 (232)	N.A. (34.83, N.A.)	0.57	117 (229)	36.93 (23.46, N.A.)	0.51	0.87 (0.67, 1.13)
>= 10%	159	16 (46)	N.A. (39.06, N.A.)	0.67	25 (59)	N.A. (31.41, N.A.)	0.58	0.82 (0.44, 1.54)
<= Q1(31 mm)	242	23 (78)	N.A.	0.72	27 (85)	N.A.	0.69	0.96 (0.55, 1.68)
> Q1(31 mm) and <= Q3(97 mm)	471	68 (154)	N.A. (37.06, N.A.)	0.59	82 (150)	32.13 (19.84, N.A.)	0.48	0.74 (0.54, 1.02)
> Q3(97 mm)	231	48 (82)	17.64 (10.74, N.A.)	0.41	49 (80)	16.53 (9.10, 35.94)	0.39	0.92 (0.62, 1.37)
Number of Lesion Sites								
1	253	28 (89)	N.A.	0.70	28 (80)	N.A.	0.65	0.88 (0.52, 1.49)
2-3	512	77 (166)	N.A. (32.72, N.A.)	0.57	94 (176)	32.43 (21.65, N.A.)	0.48	0.80 (0.59, 1.08)
> 3	179	34 (59)	18.14 (7.49, N.A.)	0.42	36 (59)	20.17 (12.88, N.A.)	0.44	1.06 (0.66, 1.69)



Summary of main study(ies)

The following table (Table 29) 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 29: Summary of the main study CA209067

Title: A Phase 3, Randomized, Double-blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma		
Study Identifier	CA209067	
Design	Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with Ipilimumab versus Ipilimumab monotherapy in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma (independent of BRAF status). Subjects had unresectable or metastatic Stage III or Stage IV melanoma, as per the American Joint Committee on Cancer (AJCC) staging system, and had not received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy was allowed in the setting of completely resectable disease. PD-L1 status was obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization.	
	Duration: FPFV 11-Jun-2013; Clinical cutoff date for Final CSR 01-Aug-2016; the study is ongoing in follow-up. The study consists of 3 phases: screening, treatment, and follow-up.	
	Duration: Duration of Run-in phase: Duration of Extension phase:	FPFV: 11-Jun-2013; LPLV for the Sep 2016 database lock: 01-Aug-2016 Not Applicable Ongoing
Hypothesis	Treatment with nivolumab combined with ipilimumab will lead to clinical benefit, as demonstrated by an improved clinically meaningful PFS compared to nivolumab monotherapy and Ipilimumab monotherapy, including durable responses with substantial magnitude of tumor reduction.	
Treatment Groups	Nivolumab	Nivolumab 3 mg/kg IV once every other week (Q2W) +ipilimumab-placebo on weeks 1, 4 and nivolumab on weeks 4 for cycles 1 and 2. One cycle of treatment was defined as 6 weeks. Dose reductions were not allowed.
	Nivolumab + Ipilimumab	Nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3mg/kg IV Q2W + nivolumab placebo on weeks 3 and 5 for cycles 1 and 2. Dose reductions were not allowed.
	Ipilimumab	Ipilimumab 3 mg/kg IV Q3W for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4 and 5 for cycle 1 and 2 then Q2W. Dose reductions were not allowed.

Treatment Group	Nivolumab + Ipilimumab	Nivolumab	Ipilimumab
Number of Subjects	N = 314	N = 316	N = 315
Time from Completion of Prior Adjuvant Therapy to Randomization[a](%)			
< 6 Months	25 (36.8)	21 (28.8)	21 (32.8)
≥ 6 Months	43 (63.2)	51 (69.9)	42 (65.6)
Not Reported	0	1 (1.4)	1 (1.6)
Prior Surgery Related to Cancer (%)			
Yes	307 (97.8)	312 (98.7)	306 (97.1)
No	7 (2.2)	4 (1.3)	9 (2.9)
Prior Radiotherapy (%)			
Yes	73 (23.2)	79 (25.0)	59 (18.7)
No	241 (76.8)	237 (75.0)	256 (81.3)
Efficacy Results			
CO-PRIMARY ENDPOINTS			
Overall Survival			
Events, n (%)	128 (40.8)	142 (44.9)	197 (62.5)
Stratified log-rank test p-value[b]	<0.0001	<0.0001	
HR (98% confidence interval [CI])	0.55 (0.42, 0.72)[c]	0.63 (0.48, 0.81)[d]	
Median OS (95% CI), months[e]	NA (29.08, NA)	NA	19.98 (17.08, 24.61)
Rate at 6 months, % (95% CI)	0.86 (0.81, 0.89)	0.85 (0.81, 0.89)	0.82 (0.78, 0.86)
Rate at 12 months, % (95% CI)	0.73 (0.68, 0.78)	0.74 (0.69, 0.79)	0.67 (0.61, 0.72)
Rate at 18 months, % (95% CI)	0.68 (0.62, 0.73)	0.65 (0.60, 0.70)	0.54 (0.48, 0.59)
Rate at 24 months, % (95% CI)	0.64 (0.59, 0.69)	0.59 (0.53, 0.64)	0.45 (0.39, 0.50)
Progression-free Survival			
Events, n (%)	169 (53.8)	195 (61.7)	253 (80.3)
HR (95% CI)	0.42 (0.34, 0.51)[c]	0.54 (0.45, 0.66)[d]	
Median PFS (95% CI), months[e]	11.73 (8.90, 21.88)	6.87 (4.34, 9.46)	2.86 (2.79, 3.15)
Rate at 6 months (95% CI), %	0.63 (0.57, 0.68)	0.52 (0.46, 0.58)	0.28 (0.23, 0.33)
Rate at 12 months (95% CI), %	0.50 (0.44, 0.55)	0.43 (0.37, 0.49)	0.18 (0.14, 0.22)
Rate at 24 months (95% CI), %	0.43 (0.37, 0.48)	0.37 (0.31, 0.43)	0.12 (0.09, 0.17)

Treatment Group	Nivolumab + Ipilimumab		Nivolumab		Ipilimumab
Number of Subjects	N = 314		N = 316		N = 315
SECONDARY ENDPOINTS					
Complete Response Rate (CR)[f]	54 (17.2%)		47 (14.9%)		14 (4.4%)
Objective Response Rate (CR+PR)[g]					
N responders (%)	185 (58.9%)		141 (44.6%)		60 (19.0%)
95% CI	53.3, 64.4		39.1, 50.3		14.9, 23.8
Difference of ORRs (95% CI)[h]	39.7%[i] (32.8, 46.5)		25.7%[j] (18.9, 32.5)		
Odds ratio estimate (99.5% CI)[k]	6.50[l] (3.81, 11.08)		3.54[m] (2.10, 5.95)		
Difference of ORRs (95% CI)[h]	14.1%[n] (6.7, 21.6)				
Odds ratio estimate (95% CI)[k]	1.82[o] (1.32, 2.52)				
Overall Survival Tumor PD-L1 Expression Level	**N**	**Nivolumab Median OS (95% CI)**	**N**	**Ipilimumab Median OS (95% CI)**	**Hazard Ratio (95% CI)**
≥1%	171	NR (NR, NR)	164	22.11 (17.08, 29.67)	0.52 (0.38, 0.71)
<1%	117	23.46 (13.01, NR)	113	18.56 (13.67, 23.20)	0.80 (0.57, 1.12)
≥5%	80	NR (NR, NR)	75	28.88 (18.10, NR)	0.57 (0.35, 0.92)
<5%	208	NR (23.06, NR)	202	18.50 (13.70, 22.51)	0.65 (0.50, 0.85)
Overall Survival Tumor PD-L1 Expression Level	**N**	**Nivolumab + Ipilimumab Median OS (95% CI)**	**N**	**Ipilimumab Median OS (95% CI)**	**Hazard Ratio (95% CI)**
≥1%	155	NR (NR, NR)	164	22.11 (17.08, 29.67)	0.53 (0.38, 0.74)
<1%	123	NR (26.45, NR)	113	18.56 (13.67, 23.20)	0.60 (0.42, 0.84)
≥5%	68	NR (NR, NR)	75	28.88 (18.10, NR)	0.60 (0.36, 1.00)
<5%	210	NR (31.84, NR)	202	18.50 (13.70, 22.51)	0.55 (0.42, 0.72)

Overall Survival Tumor PD-L1 Expression Level	N	Nivolumab + Ipilimumab Median OS (95% CI)	N	Nivolumab Median OS (95% CI)	Hazard Ratio (95% CI)
≥1%	155	NR (NR, NR)	171	NR (NR, NR)	1.03 (0.72, 1.48)
<1%	123	NR (26.45, NR)	117	23.46 (13.01, NR)	0.74 (0.52, 1.06)
≥5%	68	NR (NR, NR)	80	NR (NR, NR)	1.05 (0.61, 1.83)
<5%	210	NR (31.84, NR)	208	NR (23.06, NR)	0.84 (0.63, 1.12)
Treatment Group	**Nivolumab + Ipilimumab**		**Nivolumab**		**Ipilimumab**
Number of Subjects	**N = 314**		**N = 316**		**N = 315**
EXPLORATORY ENDPOINTS					
Randomized Subjects with a Response	**Nivolumab + Ipilimumab N = 185**		**Nivolumab N = 141**		**Ipilimumab N = 60**
Time to Objective Response					
Median (Min, Max), months	2.76 (1.1, 28.8)		2.79 (2.3, 32.9)		2.79 (2.5, 17.3)
Duration of Objective Response					
Ongoing responder (as of the last available tumor assessment), n/N (%)	124/185 (67.0)		94/141 (66.7)		30/60 (50.0)
Median (95% CI), months[p]	NR		31.11 (31.11, NR)		18.20 (8.34, NR)
Min, Max	0.0, 33.3[q]		0.0[q], 32.3[q]		0.0[q], 31.5[q]
Proportion with DOR ≥12 months, n (%)	118 (63.8)		98 (69.5)		32 (53.3)
Proportion with DOR ≥24 months, n (%)	93 (50.3)		69 (48.9)		19 (31.7)

Efficacy Conclusions: Based on both the final PFS and OS results, CA209067 was a positive study that met both of its co-primary endpoints. The treatment difference for both NIVO and NIVO+IPI combination relative to IPI were clinically and statistically significant for OS and PFS and in addition, both nivolumab-containing arms demonstrated higher response rates and longer durability of response compared to IPI alone. At the time of this final OS analysis (DBL 13-Sep-2017), the PFS and ORR benefits of NIVO and the combination of NIVO+IPI were maintained versus IPI monotherapy and results were consistent with the 9 month (DBL 17-Feb-2015) and 18 month (DBL 13-Nov-2015) analyses. In descriptive analyses, NIVO+IPI resulted in numerically higher OS, PFS, and ORR, with a reduction in the risk of death of 12% relative to NIVO. It should be noted that the CR rates have increased in all 3 treatment arms with longer follow up.

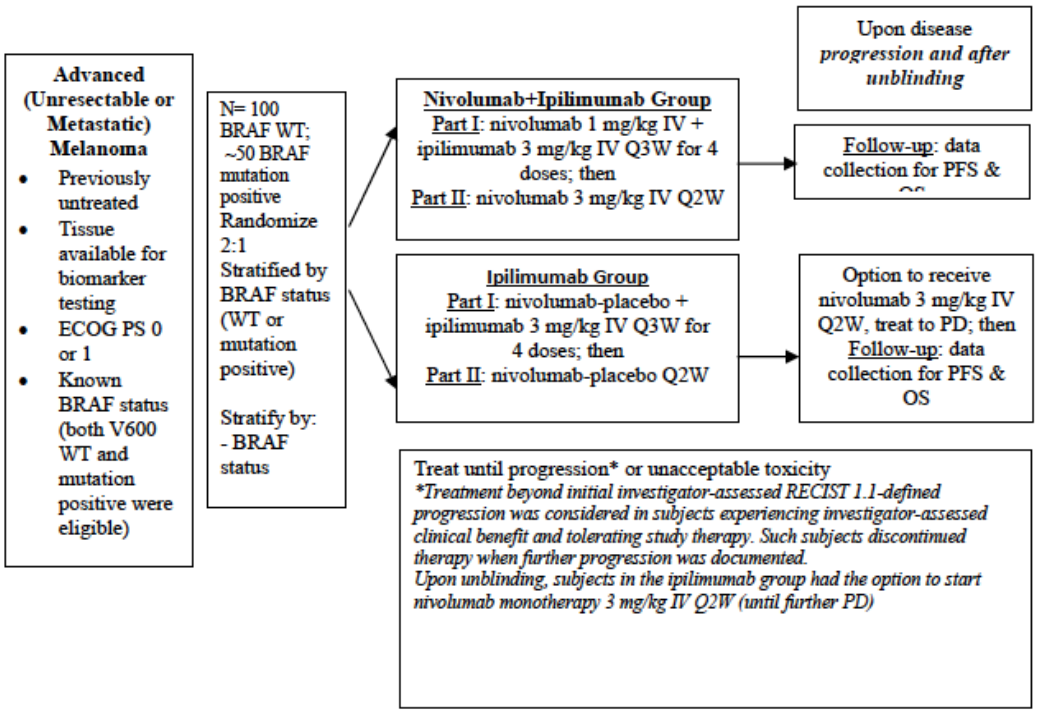
Efficacy Endpoints and Definitions	Primary Endpoint	Co-primary endpoints of PFS and OS in all randomized subjects	PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the Investigator, or death due to any cause, whichever occurred first.
	Secondary Endpoint	ORR	The ORR was defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group.
	Secondary Endpoint	OS, PFS, and ORR	See ORR and PFS definitions above. OS: Time between the date of randomization and the date of death.
	Exploratory Endpoint	Duration of objective response (DOR) and time to objective response	DOR was defined as the time between the date of first documented response (CR or PR) to the date of the first disease progression, as assessed by the Investigator per RECIST 1.1 or death due to any cause, whichever occurred first. TTR was defined as the time from randomization to the date of the first documented response (CR or PR). TTR was evaluated in all randomized subjects and for responders (i.e. subjects with a BOR of CR or PR).
Database Lock	13-Sep-2016		
Analysis Description	**OS**		

RESULTS AND ANALYSIS			
Analysis Population	**All Randomized Subjects:** nivolumab 316, nivolumab+ipilimumab 314, ipilimumab 315, Total 945 **PD-L1-evaluable Subjects:** nivolumab 305, nivolumab+ipilimumab 297, ipilimumab 296, Total 898		
Baseline Demographic Characteristics			
Treatment Group	**Nivolumab + Ipilimumab**	**Nivolumab**	**Ipilimumab**
Number of Subjects	**N = 314**	**N = 316**	**N = 315**
Age (years)			
Mean	59.3	58.7	60.8
Median	61.0	60.0	62.0
Min, Max	18, 88	25, 90	18, 89
Standard Deviation	13.86	13.92	13.23
Age Categorization (%)			
< 65	185 (58.9)	198 (62.7)	182 (57.8)
≥ 65 and < 75	94 (29.9)	79 (25.0)	89 (28.3)
≥ 75	35 (11.1)	39 (12.3)	44 (14.0)
Gender (%)			
Male	206 (65.6)	202 (63.9)	202 (64.1)
Female	108 (34.4)	114 (36.1)	113 (35.9)
Race (%)			
White	310 (98.7)	308 (97.5)	303 (96.2)
Black or African American	0	0	0
Asian	2 (0.6)	2 (0.6)	6 (1.9)
American Indian or Alaska Native	0	1 (0.3)	0
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	0
Other	2 (0.6)	4 (1.3)	5 (1.6)
Not Reported	0	0	1 (0.3)
Baseline Disease Characteristics and Tumor Assessments			
ECOG Performance Status (%)			
0	230 (73.2)	238 (75.3)	224 (71.1)
1	83 (26.4)	77 (24.4)	91 (28.9)
2	0	1 (0.3)	0
Not Reported	1 (0.3)	0	0

Supportive study(ies)

Study CA209069: Phase 2, randomised, double blinded study of nivolumab in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic

Study CA209069 was a randomized, double-blind Phase 2 study of nivolumab+ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma. The primary objective was to compare the ORR, as determined by investigators, of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with BRAF WT unresectable or metastatic melanoma (See Figure 28 below).



Abbreviations: IV = intravenous; OS = overall survival; PD = progressive disease; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; WT = wild type.

Figure 27: Design of study *CA209069*

Design

Enrolment continued until at least 100 BRAF WT subjects were randomized. Subjects were treated in a blinded fashion until progression or unacceptable toxicity.

Tumour assessments using RECIST v1.1 criteria were performed at Week 12 and every 6 weeks for the first year, and then every 12 weeks until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons.

The primary endpoint of CA209069 was confirmed ORR as assessed by the investigator using RECIST v1.1 criteria in BRAF WT subjects. Analysis of the ORR was to occur at least 24 weeks after the last subject's first dose of study treatment. The primary analysis population of CA209069 was BRAF WT subjects.

Key secondary efficacy endpoints were: PFS as assessed by the investigator in the BRAF WT population and ORR and PFS in the BRAF Mutation-Positive population. PFS and ORR were also evaluated in the All Randomized population (BRAF WT and BRAF mutation-positive subjects). Overall survival and the association between ORR and PFS and PD-L1 status were exploratory efficacy endpoints.

A blinded Independent Radiology Review Committee (IRRC) reviewed all available tumour assessment scans to determine response using RECIST v1.1 criteria. IRRC-determined response was used in sensitivity analyses of ORR and PFS.

In order to preserve an experimental-wise type I error rate of 5%, a hierarchical testing approach was applied to key secondary endpoints following analysis of the primary endpoint of ORR in BRAF WT subjects. The hierarchical ordering of key secondary endpoints was as follows:

1) ORR in All Randomized subjects

2) PFS in BRAFWT subjects

3) PFS in All Randomized subjects

Conduct of the study

Study CA209069 was conducted at 21 sites in 2 countries (US, France). All sites treated at least 1 subject. Of the 142 randomized subjects, 126 (88.7%) were from the US and 16 (11.3%) were from France.

At the time of analysis, the minimum follow-up was approximately 24 weeks (~6 months) (from 06-Feb-2014 [date last subject was randomized] to 24-Jul-2014 [clinical cut-off date for ORR]).

Subject disposition for all treated subjects (N = 140) is summarized below:

- At the time of analysis, 26.6% of subjects in the nivolumab+ipilimumab group and 41.3% of subjects in the ipilimumab group were continuing in the treatment period.
- The proportion of subjects who discontinued in the treatment period due to study drug toxicity was 45.7% in the nivolumab+ipilimumab group and 15.2% in the ipilimumab group.
- The proportion of subjects who discontinued in the treatment period due to disease progression was 16.0% in the nivolumab+ipilimumab group and 37.0% in the ipilimumab group.
- The disposition of all treated subjects and all treated BRAF WT subjects was similar.

Baseline characteristics

Overall, baseline demographic and disease characteristics in CA209069 were representative of an unresectable or metastatic melanoma population and were balanced between the nivolumab+ipilimumab and ipilimumab groups for both the BRAF WT and All Randomized populations. In the All Randomized population (N = 142):

- The majority of subjects (76.8%) were BRAF WT and 23.2% of subjects were BRAF mutation positive (BRAF V600 mutation status as determined by an FDA-approved test).
- The majority of subjects were male (66.9%) and white (97.9%), and the median age was 65.0 years, with 52.1% and 12.0% of subjects aged 65 or ≥ 75 years.
- Subjects had advanced disease and a high proportion of subjects had poor prognostic factors, which were balanced between the nivolumab+ipilimumab and ipilimumab groups:
- Most subjects had ≥ 2 sites of disease; the most common were lung (59.2%), lymph node (47.9%), and liver (29.6%) metastases. Eighty-eight (62.0%) subjects had ≥ 2 sites of metastatic disease.
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 in81.7% of subjects and 1 in 16.9% of subjects.
- At trial entry, the majority of subjects were AJCC Stage IV, with 16.2%, 27.5%, and 45.8% M1a, M1b, or M1c, respectively.
- 24.6% of subjects had elevated LDH (>ULN).
- A slight difference was observed in the proportion of subjects with the following melanoma subtypes: cutaneous melanoma: 84.2% vs. 61.7% of subjects, and acral/mucosal melanoma: 8.5% vs. 21.3% of subjects.

Outcomes

- ORR (Table 30)

Table 30: Best overall response per investigator and IRRC in BRAF WT subjects and all randomized subjects – Study CA209069

	BRAF WT		All Randomized	
Efficacy Parameter	**Nivolumab + Ipilimumab N = 72**	**Ipilimumab N = 37**	**Nivolumab + Ipilimumab N = 95**	**Ipilimumab N = 47**
Investigator-assessed ORR[a] (primary analysis)				
Number (%) of responders	43 (59.7)	4 (10.8)	53 (55.8)	4 (8.5)
Exact 95% CI	47.5, 71.1	3.0, 25.4	45.2, 66.0	2.4, 20.4
Estimate of odds ratio (95% CI)[b]	12.23 (3.69, 51.40)		15.08 (4.85, 46.93)	
P-value[c]	< 0.0001		< 0.0001	
BOR per Investigator, n (%)[d]				
Complete response (CR)	12 (16.7)	0	16 (16.8)	0
Partial response (PR)	31 (43.1)	4 (10.8)	37 (38.9)	4 (8.5)
Stable disease (SD)	10 (13.9)	12 (32.4)	15 (15.8)	14 (29.8)
Progressive disease (PD)	10 (13.9)	16 (43.2)	15 (15.8)	23 (48.9)
Unable to determine	9 (12.5)	5 (13.5)	12 (12.6)	6 (12.8)
IRRC-assessed ORR[a] (sensitivity analysis)				
Number (%) of responders	42 (58.3)	5 (13.5)	50 (52.6)	5 (10.6)
Exact 95% CI	46.1, 69.8	4.5, 28.8	42.1, 63.0	3.5, 23.1
Estimate of odds ratio (95% CI)[b]	8.96 (2.93, 32.26)		10.72 (3.75, 30.61)	
P-value[c]	< 0.0001		< 0.0001	
BOR per IRRC, n (%)[d]				
Complete response (CR)	13 (18.1)	0	17 (17.9)	0
Partial response (PR)	29 (40.3)	5 (13.5)	33 (34.7)	5 (10.6)
Stable disease (SD)	11 (15.3)	12 (32.4)	15 (15.8)	15 (31.9)
Progressive disease (PD)	8 (11.1)	13 (35.1)	15 (15.8)	18 (38.3)
Unable to determine	11 (15.3)	7 (18.9)	15 (15.8)	9 (19.1)

[a] CR+PR, confidence interval based on the Clopper and Pearson method.

[b] Ratio of nivo+ipi over ipilimumab.

[c] P-value for BRAF WT is 2-sided p-value from Fisher's exact test. P-Value for all randomized subjects is two-sided p-value from CMH Test for the comparison of the odds ratio of nivo+ipi over ipilimumab.

- PFS (Table 31)

Table 31: Progression Free Survival in BRAF WT patients – Study CA209069

	BRAF Wildtype Subjects		All Randomized Subjects	
	Nivolumab+ipilimumab N = 72	Ipilimumab N = 37	Nivolumab+ipilimumab N = 95	Ipilimumab N = 47
# EVENTS / # SUBJECTS (%)	27/72 (37.5)	23/37 (62.2)	38/95 (40.0)	30/47 (63.8)
MEDIAN PFS (MONTHS) (95% CI) (3)	8.87 (7.03, N.A.)	4.73 (2.76, 5.32)	8.57 (7.03, N.A.)	3.73 (2.76, 5.13)
PFS RATE AT 6 MONTHS (95% CI) (3)	0.67 (0.54, 0.77)	0.29 (0.14, 0.46)	0.65 (0.54, 0.74)	0.26 (0.13, 0.40)
Hazard ratio (95% CI) (1)	0.40 (0.22, 0.71)		0.38 (0.23, 0.63)	
P-Value (2)	0.0012		<0.0001	

(1) Cox proportional hazard model. Hazard Ratio is Nivolumab+ipilimumab over Ipilimumab.
(2) Log-rank Test.
(3) Based on Kaplan-Meier Estimates.

Results of the sensitivity analysis of IRRC-assessed PFS (HR: 0.31; 95% CI: 0.17, 0.55;P < 0.0001) were consistent with the analysis of investigator-assessed PFS. For the BRAF WT population, the median PFS as assessed by the IRRC was not reached in the nivolumab+ipilimumab group and was 4.4 months in the ipilimumab group.

In all additional sensitivity analyses of PFS, nivolumab+ipilimumab treatment resulted in a statistically significant improvement in PFS compared with the ipilimumab group, similar to the primary PFS analysis. Notably, in a investigator- assessed sensitivity analysis incorporating both clinical and radiographic progression events, the hazard ratio was 0.34 (95% CI: 0.19, 0.60; P < 0.0001) and the estimated median PFS was 8.9 months for the nivolumab+ipilimumab group and 3.0 months for the ipilimumab group.

For the BRAF Mutation-Positive population, the median PFS as assessed by the investigator was also longer in the nivolumab+ipilimumab group (7.4 months) than the ipilimumab group (2.7 months; HR: 0.33; 95% CI: 0.12, 0.90).

- Time to Response and Duration of Response (Table 32)

Table 32: Time to response and Duration of response in BRAF WT patients – Study CA209069

	BRAF Wildtype Subjects		All Randomized Subjects	
	Nivolumab + Ipilimumab N = 72	Ipilimumab N = 37	Nivolumab + Ipilimumab N = 95	Ipilimumab N = 47
TIME TO OBJECTIVE RESPONSE (MONTHS)				
NUMBER OF RESPONDERS	43	4	53	4
MEAN	2.84	2.64	2.96	2.64
MEDIAN	2.76	2.66	2.76	2.66
MIN, MAX	2.3, 5.3	2.5, 2.7	2.3, 7.2	2.5, 2.7
STANDARD DEVIATION	0.512	0.078	0.847	0.078
DURATION OF OBJECTIVE RESPONSE (MONTHS)				
MIN, MAX (A)	0.0+, 7.2+	2.7+, 5.6+	0.0+, 7.2+	2.7+, 5.6+
MEDIAN (95% CI) (B)	N.A. (6.11, N.A.)	N.A.	N.A. (6.11, N.A.)	N.A.
N EVENT/N RESP (%)	5/43 (11.6)	0/4	7/53 (13.2)	0/4

Note: RECIST 1.1 Response Criteria where confirmation of response is required.
(A) Symbol + indicates a censored value (ongoing response).

- OS

OS was an exploratory endpoint and the data were immature at the time of the analysis. While the median OS was not reached in either treatment group no detrimental effect on OS in subjects treated with combination therapy compared with ipilimumab monotherapy was observed at 6 months of follow-up. The OS rate for BRAF WT subjects at 6 months was 83% in the nivolumab+ipilimumab group and 73% in the ipilimumab group. Notably, 43.2% of BRAF WT subjects in the ipilimumab group crossed over to nivolumab. Median follow-up time for survival was 7.6 months (range, 0.0 to 10.3 months) in the nivolumab+ipilimumab group and 7.0 months (range, 1.3 to 10.2 months) in the ipilimumab group.

- PDL-1 results

In CA209069, the potential association between tumour PD-L1 expression and efficacy (ORR and PFS) of nivolumab+ipilimumab combination therapy and ipilimumab monotherapy was evaluated. Among the 118 subjects for whom PD-L1 status was quantifiable, 68/118 (57.6%) had tumours with at least 1% PD-L1 expression, 35/118 (29.7%) had tumours with at least 5% PD-L1 expression, and24/118 (20.3%) had tumours with at least 10% PD-L1 expression. Regardless of PD-L1 expression level (1%, 5%, or 10% tumour cell membrane expression), no meaningful difference in ORR was observed in either of the treatment groups (Table 33).

Table 33: Overall response rate by PD-L1 expression cut-off – Study CA209069

	PD-L1 Expression Cut-off						
	< 1%	≥ 1%	< 5%	≥ 5%	< 10%	≥ 10%	Unknown
Nivo+Ipi (N = 94)[a,b]							
ORR n/N (%)	15/35 (42.9)	27/45 (60.0)	29/56 (51.8)	13/24 (54.2)	33/64 (51.6)	9/16 (56.3)	10/14 (71.4)
Exact 95% CI	26.3, 60.6	44.3, 74.3	38.0, 65.3	32.8, 74.4	38.7, 64.2	29.9, 80.2	41.9, 91.6
Ipilimumab (N = 47)[c]							
ORR n/N (%)	0/15 (0)	2/23 (8.7)	1/27 (3.7)	1/11 (9.1)	1/30 (3.3)	1/8 (12.5)	2/9 (22.2)
Exact 95% CI	0.0, 21.8	1.1, 28.0	0.1, 19.0	0.2, 41.3	0.1, 17.2	0.3, 52.7	2.8, 60.0

[a] Subject CA209069[redacted] was excluded from PD-L1 analyses because the sample collection date was incorrectly annotated as post-treatment.

[b] Tumor samples from subjects CA209069[redacted] and CA209069[redacted] were tested with the verified Dako PD-L1 IHC assay; all other samples tested with the validated Dako PD-L1 IHC assay.

[c] Tumor samples from subjects CA209069-[redacted] and CA209069-[redacted] were tested with the verified Dako PD-L1 IHC assay; all other samples tested with the validated Dako PD-L1 IHC assay.

Abbreviations: CI = confidence interval; ORR = objective response rate; PD-L1 = programmed death-ligand 1.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The combination dose and schedule of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg Q3W for 4 doses followed by continuous nivolumab 3 mg/kg Q2W as single agent was selected for Phase 2/3 studies CA209069 and CA209067 based on an integrated assessment of nivolumab data from in vitro and preclinical studies, as well as clinical PK, safety, and efficacy results from Phase 1 studies, including CA209004. In study CA209004, treatment with 3 mg/kg nivolumab and 3 mg/kg ipilimumab, the doses approved for monotherapy, resulted in dose-limiting toxicities that exceeded the MTD. Treatment with 1 mg/kg nivolumab + 3 mg/kg ipilimumab (Cohort 2) or 3 mg/kg nivolumab + 1 mg/kg ipilimumab (Cohort 2a) were tolerable, establishing both dose combinations as the maximum tolerated dose (MTD).

Evaluation of Exposure-Response (E-R) data suggested that increasing doses of nivolumab above 1 mg/kg did not change the likelihood of response. The dose schedule of 1 mg/kg nivolumab + 3 mg/kg ipilimumab was therefore selected. Data from Cohorts 1-3 indicated maximum tumour reduction occurred by Week 24 before ipilimumab/nivolumab maintenance treatment began suggesting combination maintenance treatment may not add substantially to initial anti-tumour activity. Maintenance treatment was replaced with continuous nivolumab (3 mg/kg) treatment Q2W matching the recommended single agent nivolumab dose/schedule. Continuous nivolumab treatment may ensure that potential counter-regulatory mechanisms of tumour evasion (eg, upregulation of PD-L1 by tumour or TILs) will still be blocked. Results from Cohort 8 supported the clinical activity and safety observed in Cohorts 1-3, despite the modification in dosing schedule.

Study CA209067, was a randomised, double-blind, Phase 3 study of nivolumab monotherapy or nivolumab+ipilimumab vs ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. CA209067 included both BRAF V600 mutation-positive and BRAF WT subjects. The co-primary endpoints were PFS and OS, which are considered acceptable. The type I error of 0.05 was split between OS with 0.04 and PFS with 0.01 and statistical significance can be

claimed for either PFS or OS (or both). From a methodological and statistical perspective, this was considered acceptable.

The study recruited an untreated population, excluding patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases and allowing only patients with stable cerebral metastases. Patients were stratified by PD-L1 status (positive or negative as determined by the verified assay), M Stage at screening (M0/M1a/M1b vs M1c), and BRAF V600 mutation status (wildtype [WT] vs mutation positive). Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18 to 90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy. Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1 ≥ 5% tumour cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry (see section 5.1 of the SmPC). Significant protocol deviations appear to be evenly balanced among the groups of the study. The majority of protocol deviations were related to report SAEs, protocol assessment and incorrect dose and/or schedule. No issues were raised during the assessment concerning the conduct of the studies submitted.

Efficacy data and additional analyses

The MAH submitted efficacy results from the phase 3 study CA209067 primarily based on the final CSR (DBL 13-Sep-2016) and an update based on database lock (24 May 2017). As of the database lock (13-Sep-2016), 249 (79.6%) subjects treated in the nivolumab group, 269 (85.9%) subjects treated in the combination group, and 295 (94.9%) subjects treated in the Ipilimumab group had discontinued study treatment. Although the co-primary analysis of OS is completed, the study is ongoing and additional survival follow-up may continue for up to 5 years from this final analysis.

In All Randomized subjects nivolumab monotherapy 3 mg/kg IV Q2W has shown a statistically significant improvement in OS vs Ipilimumab monotherapy 3 mg/kg every 3 weeks (Q3W) x 4 doses (HR = 0.63 [98% CI: 0.48, 0.81]; stratified log-rank test p-value = < 0.0001) and the combination (Nivo+Ipi) has shown a statistically significant improvement in OS vs IPI monotherapy (HR = 0.55 [98% CI: 0.42, 0.72]; stratified log-rank test p-value = < 0.0001). Based on descriptive analyses, Nivo+Ipi vs Nivo has shown a numeric difference in OS favouring the combination (HR 0.88, 95% CI: [0.69, 1.12]). Median OS for all randomized subjects was not reached in the Nivo+Ipi and Nivo monotherapy groups as compared to 19.98 months in the Ipi group. These results are considered clinically relevant as compared to Ipilimumab monotherapy, revealing a clinical meaningful survival for the combination and supporting the previous data already obtained from other studies with nivolumab in monotherapy. Updated efficacy results at the data cut-off of May 2017, with +9 months additional follow up (OS data at 3-years available) are consistent with those observed at earlier time points. Slightly more mature results in all randomized subjects show a statistically significant improvement in OS for nivolumab monotherapy vs Ipilimumab monotherapy (HR = 0.65 [98% CI: 0.53, 0.80]; stratified log-rank test p-value = < 0.0001) and the combination (Nivo+Ipi) vs Ipi monotherapy (HR = 0.55 [98% CI: 0.45, 0.69]; stratified log-rank test p-value = < 0.0001). Based on descriptive analyses, the combination of Nivo+Ipi showed a numeric difference in OS vs Nivo (HR 0.85, 95% CI: [0.68, 1.07]) not reaching statistical significance which had been previously described. Median OS for all randomized subjects was not reached in the Nivo+Ipi groups whereas it was 37.59 months (95%CI: 29.08, NA) for Nivo monotherapy group as compared to 19.94 months (95%CI: 16.85, 24.61) in the IPI group. 3-year OS rates were 58% for Nivo+Ipi, 52% for Nivo and 34% for Ipi.

Different sensitivity analyses carried out (unstratified analysis and analysis using stratification factors as determined at baseline) were consistent with the main result.

The proportion of events (deaths) were 45%, 41% and 62.5% for Nivo monotherapy, Nivo+Ipi and Ipi monotherapy respectively. Among those censored, a higher proportion of subjects in the Nivo and Nivo+Ipi groups vs the Ipi group were still on treatment (20.3% and 14.0% vs 5.1%, respectively), and a greater proportion in the Nivo and Nivo+Ipi groups were in follow-up (32.6% and 43.6% vs 28.6%, respectively). These figures could be reflecting the worse tolerability of the combination as clearly shown by the discontinuation rates due to drug toxicity (41.9%, 12.8% and 16.1% Nivo+Ipi, Nivo and Ipi respectively).

Results were supported by the co-primary endpoint PFS. For the all randomised population, the median PFS was 11.7 months in the combination group versus 2.9 months in the IPI mono group and 6.9 months in the nivo mono group. The combination of ipi+nivo showed an improved PFS compared to ipi (HR = 0.42, 95% CI: 0.34, 0.51) as well as to nivo monotherapy (HR=0.76, 95% CI: 0.62, 0.94). Nivo monotherapy showed improved PFS compared to ipi monotherapy (HR=0.54; 95% CI: 0.45, 0.66). The investigator-assessed ORR using RECIST v1.1 in All Randomized subjects were significantly higher in the NIVO+IPI group compared with the IPI group and numerically higher compared to the nivo monotherapy. Corresponding ORRs were 58.9% in the combination group, 19.0% with ipi and 44.6% with nivo monotherapy. The median duration of response (DOR) was 31.1 months in the NIVO arm, not reached in the NIVO+IPI group and 18.2 months in the IPI arm.

The proportion of patients that received subsequent anti-cancer therapies was 44.3%, 31.8%, and 62.2% of subjects in the Nivo, Nivo+Ipi, and Ipi treatment groups, respectively. Ipilimumab was the most frequent therapy received in the Nivo group (26.3%) whereas dabrafenib (9.2%) and pembrolizumab (39.4%) were in Nivo+Ipi and Ipi groups respectively.

Results of the sensitivity analysis that accounts for subsequent therapies received by patients (patients initiating next-line therapies are censored) though affected by informative censoring, maintain a trend for both nivolumab and the combination of Nivo+Ipi superiority over Ipi monotherapy, supporting the improved OS observed with Nivo+Ipi. For the comparison of Nivo+Ipi vs. Nivo montherapy, the HR crosses the 1 boundary. Although no clear conclusions can be reached, it appears that there may be a lack of benefit of the combination over the nivolumab monotherapy in some patients. The analysis of subgroups reveals important aspects to be considered, being PD-L1 expression and BRAF status the most relevant. Regarding the latter, the mechanism of action and data from retrospective analyses suggest that the anti-tumour effects of immunotherapies, including both ipilimumab and nivolumab, are independent of the BRAFV600 mutation status. However, there seems to be a difference in terms of OS between the combination of Nivo+Ipi and Nivo monotherapy, with a greater benefit with the combination in those patients BRAF mutated (HR 0.71 95% CI 0.45-1.11 vs HR 0.97 95% CI 0.74-1.28), though CIs overlap and are not statistically significant. Analysis of subgroups according to the most recent database lock have also been submitted and a similar trend for greater benefit is observed with the combination vs. nivolumab monotherapy) in those patients BRAF mutated (vs. BRAF wild-type) (HR 0.69 95% CI 0.44-1.07 vs HR 0.94 95% CI 0.72-1.22). These OS results may have been biased as a result of subsequent anticancer therapies (i.e. BRAF MUT patients may receive BRAF(/MEK) targeted therapies while BRAF WT patients may not) and it could be accepted also that the combination of baseline characteristics, better prognostic factors and maybe access to further drugs, might have influenced the results. In terms of ORR, results are also favouring those patients with BRAF[V600] mutation-positive; 66.7% vs 36.7% Nivo+Ipi vs Nivo in BRAF mutated respectively. Corresponding data in BRAF WT patients were 53.3% (Nivo+ Ipi) vs 46.8% (Nivo). There is not a straightforward explanation of this apparently higher activity of the combination in patients with mutated BRAF.

OS in the combination treatment appeared to be improved compared to nivo monotherapy in patients with a designated PD-L1 low tumour expression (<1%) vs those that had a designated higher expression of PD-L1 (≥1) (HR 0.74 95%CI 0.52-1.06 vs HR 1.03 95%CI 0.72-1.48). Despite the fact that the results were not statistical significant in patients with low PD-L1 tumour expression, the Kaplan-Meier plots of OS clearly separate which suggests that perhaps the study was underpowered to test this hypothesis. ORR was found to be also higher in the combination in patients with low PD-L1 tumour expression (54.5% vs. 35%). In patients with PD-L1 expression ≥1%, no differences were observed in the Kaplan Meier curves or the HR between the combination treatment and the nivo monotherapy where the K-M curve for OS for the combination treatment overlaps with that of nivo monotherapy. However, a 10% higher antitumour activity is still exhibited in patients with PD-L1 tumour expression ≥ 1% in the combination arm compared to patients with PD-L1 tumour expression <1%. The landmark analysis of OS from month 6 by response status suggests a survival benefit for those patients who achieve a response (CR or PR). Updated OS data (cut-off of May 2017) in patients with PD-L1 status below 1% vs. PD-L1 above 1% (HR 0.70 95% CI 0.49-0.99 vs HR 1.02 95% CI 0.73-1.43; Nivo+Ipi vs Nivo) seem to show that patients with PD-L1 status above 1% would obtain a similar benefit than those treated with the monotherapy with nivolumab. This information is reflected in section 4.1. Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see section 4.4 and 5.1).

While the available IHC assay (Dako/Agilent assay) can detect levels of PD-L1 tumor cell expression, the test is not able to provide a clear demarcation of a bimodal population that could be defined by a dichotomous cut-off. In addition, there are doubts related to the utility of using PD-L1 as a marker in clinical practice, given the temporal variability of PD-L1 expression in tissues. There are many uncertainties also regarding the heterogeneity of expression of PD-L1 within the patient's tumours as the expression can be discordant between primary tumors and metastases and between intrapatient metastases, as well as the reproducibility and consistency of the testing methods used between the different labs (tissue processing and storage). Therefore, considering the efficacy data and the issues related to the PD-L1 test itself, it would not at this time be feasible to restrict the indication as there is no clear way to define a population with a PD-L1 cut-off that would maximize the benefit while outweighing the risk of toxicity.

The results of the combination vs ipilimumab were supported by the Study CA209069, a randomized, double-blind Phase 2 study of nivolumab+ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma. In the all randomized population (N = 142), the majority of subjects (76.8%) were BRAF WT and 23.2% of subjects were BRAF mutation positive. Results for ORR were 55.8% vs. 8.5% (nivolumab+ipilimumab vs ipilimumab) with 17% vs 0% of CR (nivolumab+ipilimumab vs ipilimumab alone respectively). ORR compared with ipilimumab alone in BRAF WT subjects was 59.7% vs. 10.8%. The HR for PFS was 0.38 with a mPFS 8.57 months in the whole population.

2.4.1. Conclusions on the clinical efficacy

In the all randomised patient population, the combination of nivolumab and ipilimumab has shown a clinically meaningful superiority over ipilimumab in terms of OS and PFS. This benefit is more modest but still relevant when compared to nivolumab monotherapy.

Treatment with the combination of ipilimumab+nivolumab in patients that have tumours with low PD-L1 tumour expression appear to have an increase in OS and PFS compared to those with a higher tumour expression of PD-L1. This reflected in the indication in section 4.1. The SmPC has also been updated in 5.1 to reflect the results of the study. Analysis of subgroups according to the most recent database lock have shown potential differences to relevant subgroups of patients with BRAF mutated vs. wildtype and PD-L1 $\geq$ 1% vs. PD-L1 < 1% in tumours. No restriction or other measures are currently needed within the SmPC. However, the CHMP has requested further analyses on the value of biomarkers, including PD-L1 and PD-L2, in studies using the combination therapy of ipilimumab+ nivolumab as part of the Annex II conditions for Opdivo and it is recommended that any relevant information that arises from these studies should be included in parallel in the product information of ipilimumab:

- To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab and/or nivolumab + ipilimumab combination therapy efficacy. This will be provided for all the approved indications:

  - Melanoma combination (with ipilimumab): studies CA209038, CA209067 and CA209069

  In addition, levels of myeloid-derived suppressor cells in circulation will be explored in study CA209038.

- To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies (CA209009, CA209038 and CA209064).

Additional OS data (up to 5 years) from Study CA209069 is expected to be provided by the MAH when available.

2.5. Clinical safety

Introduction

Updated safety data associated with the final analysis of the co-primary endpoint overall survival in Study CA209067 (database lock (DBL) of 13-Sep-2016) and reference is made to the corresponding EPAR for this variation (EMEA/H/C/003985/II/0032). Safety data generated at the time of the primary progression-free survival (PFS) analysis (database lock [DBL] 17-Feb-2015) with a minimum follow-up of 9 months after first dose of study therapy was reported in an interim clinical study report (CSR) and served as the basis of approval for an EU Type II variation (post-authorization measure).

For the interim study report (DBL 17-Feb-2015) reference is made to the corresponding EPAR for the variation EMEA/H/C/003985/II/0003. The EPAR contains pooled safety data for nivolumab monotherapy from the nivolumab treatment groups in CA209067 (N = 313), CA209066 (N = 200), and CA209037 (N = 268) and pooled safety data for nivolumab+ipilimumab combination therapy is presented from the nivolumab+ipilimumab treatment groups in CA209067 (N = 313) and CA209069 (N = 94). The safety data derived from the CA209067 study were generated at the time of the primary PFS analysis (DBL 17-Feb-2015) with a minimum follow-up of 9 months after first dose of study therapy. In addition, safety data from Cohort 8 of the Phase 1b study, CA209004 (N = 41 subjects), were provided. Cohort 8 included subjects with unresectable or metastatic Stage III or IV melanoma treated with a similar dosing regimen as CA209067 and CA209069 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W), but up to 48 doses of nivolumab during the monotherapy period.

Methods – analysis of data submitted

The characterization of the safety profile of nivolumab monotherapy and nivolumab+ipilimumab combination therapy is derived from 313 subjects treated with NIVO and 313 subjects treated with NIVO+IPI in the primary Phase 3 study, CA209067, respectively. Updated safety data is based on the final analysis of the co-primary endpoint overall survival in Study CA209067 (database lock (DBL) of 13-Sep-2016) which provides a minimum follow-up of 28 months for all patients. It was submitted in support of a post-authorisation measure (ANX 016) which originated from procedure EMEA/H/C/003985/II/003, Type II variation to extend the approved OPDIVO indications to include OPDIVO in combination with ipilimumab for treatment of advanced (unresectable or metastatic) melanoma in adults (EC Decision granted on 11 May 2016).

Safety presentations of AEs, SAEs, AEs leading to discontinuation, select AEs, and laboratory abnormalities 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 clean characterization of the safety experience of nivolumab monotherapy and the combination of nivolumab and ipilimumab without influence of AEs associated with subsequent therapies.

Table 34: Tabular Listing of MAH-sponsored Studies of Nivolumab Monotherapy and Combination with ipilimumab

Study Type	Study Identifier/ Report Location in CTD (Study Status)	Study Objective	Study Design	Treatment Cohorts	No. of Treated Subjects	Study Population
Anti-tumor therapy in melanoma						
Efficacy, Safety,	CA209067 / 5.3.5.1 (study completed, final report available)	To compare the PFS and OS of nivo monotherapy to ipi monotherapy, nivo+ipi to ipi monotherapy	Phase 3, randomized (1:1:1), double-blind study of nivo or nivo+ipi vs ipi	Active dosing regimens: Nivo group: nivo 3 mg/kg IV Q2W Nivo+ipi group: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses followed by nivo 3 mg/kg Q2W Ipi group: ipi 3 mg/kg Q3W for 4 doses	N= 945 Treated Nivo group: 326 (218 BRAF WT and 98 BRAF mutation+) Nivo+ipi group: 314 (212 BRAF WT and 102 BRAF mutation +) Ipi group:315 (215 BRAF WT and 100 BRAF positive)	Previously untreated, unresectable or metastatic melanoma

Abbreviations: BMS = Bristol-Myers Squibb, CTD = common technical document, Ipi = Ipilimumab; IV = intravenous, Nivo = nivolumab; No = number, OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks, Q3W = every 3 weeks, WT = wild-type

The overall safety evaluation is based on data from 937 patients who received at least one dose of study drug (NIVO Group: (n = 313) nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W), NIVO+IPI Group: (n = 313) nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W and IPI Group: (n = 311) ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses from the study CA209067.

Patient exposure

Of the 945 subjects randomized (316 to NIVO, 314 to NIVO+IPI, and 315 to IPI), 937 (99.2%) were treated (NIVO: 313, NIVO+IPI: 313, and IPI: 311). As of the database lock for the CA209067 Final OS CSR, the proportion of subjects continuing in the treatment period in the NIVO, NIVO+IPI, and IPI groups were 20.4% (64/313), 14.1% (44/313), and 5.1% (16/311), respectively (see Table 35).

Table 35: Subject Status Summary - End of Treatment Period, Treated Subjects in CA209067

	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	Total
SUBJECTS	313	313	311	937
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	64 (20.4)	44 (14.1)	16 (5.1)	124 (13.2)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	249 (79.6)	269 (85.9)	295 (94.9)	813 (86.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)				
DISEASE PROGRESSION	170 (54.3)	88 (28.1)	224 (72.0)	482 (51.4)
STUDY DRUG TOXICITY	40 (12.8)	131 (41.9)	50 (16.1)	221 (23.6)
DEATH	1 (0.3)	3 (1.0)	1 (0.3)	5 (0.5)
ADVERSE EVENT UNRELATED TO STUDY DRUG	7 (2.2)	15 (4.8)	6 (1.9)	28 (3.0)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	17 (5.4)	14 (4.5)	8 (2.6)	39 (4.2)
SUBJECT WITHDREW CONSENT	0	3 (1.0)	0	3 (0.3)
LOST TO FOLLOW-UP	1 (0.3)	0	0	1 (0.1)
MAXIMUM CLINICAL BENEFIT	8 (2.6)	11 (3.5)	2 (0.6)	21 (2.2)
POOR/NON-COMPLIANCE	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)
PREGNANCY	0	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.3)	0	1 (0.1)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	0
OTHER	4 (1.3)	2 (0.6)	2 (0.6)	8 (0.9)
NOT REPORTED	0	0	1 (0.3)	1 (0.1)
SUBJECTS CONTINUING IN THE STUDY (%)	167 (53.4)	181 (57.8)	106 (34.1)	454 (48.5)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	146 (46.6)	132 (42.2)	205 (65.9)	483 (51.5)

Percentages based on subjects entering period.
Source: Table 5.1-1 of the CA209067 Final OS CSR[2]

The enrolment period lasted approximately 10 months (Jun-2013 to Mar-2014). The last patient was randomized on 31-Mar-2014 and the last patient first treatment was on 01-Apr-2014. The median duration of therapy was 6.60 months in the NIVO group, 2.83 months in the NIVO+IPI group, and 3.02 months in the IPI group.

87.8% of treated subjects in the NIVO group received ≥ 90% of the planned dose intensity, which was similar to ipilimumab in the IPI group (88.4%) and greater than nivolumab and ipilimumab in the NIVO+IPI group (69.0% and 70.6%, respectively); see Table 36.

Table 36: Relative Dose Intensity and Number of Doses Received - All Treated Subjects - CA209067

	Nivolumab N = 313	Nivolumab + Ipilimumab N = 313		Ipilimumab N = 311
	Nivolumab	Nivolumab	Ipilimumab	Ipilimumab
RELATIVE DOSE INTENSITY				
>= 110%	1 (0.3)	0	2 (0.6)	0
90% TO < 110%	274 (87.5)	216 (69.0)	219 (70.0)	275 (88.4)
70% TO < 90%	33 (10.5)	62 (19.8)	60 (19.2)	25 (8.0)
50% TO < 70%	4 (1.3)	24 (7.7)	28 (8.9)	10 (3.2)
< 50%	1 (0.3)	11 (3.5)	4 (1.3)	1 (0.3)
NUMBER OF DOSES RECEIVED				
MEAN (SD)	27.6 (25.35)	18.9 (23.67)	3.2 (1.05)	3.5 (0.87)
MEDIAN (MIN - MAX)	15.0 (1 - 77)	4.0 (1 - 76)	4.0 (1 - 4)	4.0 (1 - 4)
NUMBER OF DOSES RECEIVED				
0	0	0	0	0
1	9 (2.9)	29 (9.3)	30 (9.6)	16 (5.1)
2	8 (2.6)	59 (18.8)	60 (19.2)	31 (10.0)
3	18 (5.8)	42 (13.4)	45 (14.4)	48 (15.4)
4	11 (3.5)	36 (11.5)	178 (56.9)	216 (69.5)
>4	267 (85.3)	147 (47.0)	0	0

Source: Table 6.1-1 of the CA209067 Final OS CSR

Reasons for infusion interruption, infusion rate reduction, or dose delay are provided in Table 37. Dose reductions/escalations were not permitted in any treatment group.

Table 37: Infusion Interruption, Infusion Rate Reduction, and Dose Delays of Study Therapy - All Treated Subjects - CA209067

	Nivolumab N = 313	Nivolumab + Ipilimumab N = 313		Ipilimumab N = 311
	Nivolumab	Nivolumab	Ipilimumab	Ipilimumab
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	20 (6.4)	12 (3.8)	8 (2.6)	10 (3.2)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT				
0	293 (93.6)	301 (96.2)	305 (97.4)	301 (96.8)
1	16 (5.1)	10 (3.2)	8 (2.6)	10 (3.2)
2	2 (0.6)	2 (0.6)	0	0
>= 3	2 (0.6)	0	0	0
TOTAL NUMBER INFUSIONS INTERRUPTED/ TOTAL NUMBER INFUSIONS RECEIVED	26/ 8627 (0.3)	14/ 5925 (0.2)	8/ 997 (0.8)	10/ 1086 (0.9)
REASON FOR INFUSION INTERRUPTION (a)				
HYPERSENSITIVITY REACTION	12 (46.2)	0	2 (25.0)	3 (30.0)
INFUSION ADMIN ISSUES	5 (19.2)	8 (57.1)	3 (37.5)	2 (20.0)
OTHER	9 (34.6)	6 (42.9)	3 (37.5)	5 (50.0)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	15 (4.8)	4 (1.3)	3 (1.0)	4 (1.3)
NUMBER OF INFUSIONS WITH IV RATE REDUCED PER SUBJECT				
0	298 (95.2)	309 (98.7)	310 (99.0)	307 (98.7)
1	11 (3.5)	4 (1.3)	3 (1.0)	4 (1.3)
2	1 (0.3)	0	0	0
>= 3	3 (1.0)	0	0	0
TOTAL NUMBER INFUSIONS WITH IV RATE REDUCED/ TOTAL NUMBER INFUSIONS RECEIVED	128/ 8627 (1.5)	4/ 5925 (<0.1)	3/ 997 (0.3)	4/ 1086 (0.4)
REASON FOR INFUSION IV RATE REDUCTION (b)				
HYPERSENSITIVITY REACTION	6 (4.7)	0	0	1 (25.0)
INFUSION ADMIN ISSUES	3 (2.3)	2 (50.0)	2 (66.7)	2 (50.0)
OTHER	119 (93.0)	2 (50.0)	1 (33.3)	1 (25.0)
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	152 (48.6)	143 (45.7)	74 (23.6)	46 (14.8)
NUMBER OF DOSE DELAYS PER SUBJECT				
0	161 (51.4)	170 (54.3)	239 (76.4)	265 (85.2)
1	73 (23.3)	59 (18.8)	67 (21.4)	44 (14.1)
2	27 (8.6)	34 (10.9)	7 (2.2)	2 (0.6)
>= 3	52 (16.6)	50 (16.0)	0	0
TOTAL NUMBER DOSES DELAYED/ TOTAL NUMBER DOSES RECEIVED (c)	358/ 8314 (4.3)	393/ 5612 (7.0)	81/ 684 (11.8)	48/ 775 (6.2)
LENGTH OF DELAY (d)				
ON TIME	7956 (95.7)	5219 (93.0)	603 (88.2)	727 (93.8)
4 - 7 DAYS	151 (1.8)	137 (2.4)	23 (3.4)	23 (3.0)
8 - 14 DAYS	128 (1.5)	137 (2.4)	21 (3.1)	11 (1.4)
15 - 42 DAYS	70 (0.8)	97 (1.7)	29 (4.2)	12 (1.5)
> 42 DAYS	9 (0.1)	22 (0.4)	8 (1.2)	2 (0.3)
REASON FOR DOSE DELAY (e)				
ADVERSE EVENT	129 (36.0)	206 (52.4)	63 (77.8)	33 (68.8)
OTHER	209 (58.4)	171 (43.5)	14 (17.3)	12 (25.0)
NOT REPORTED	20 (5.6)	16 (4.1)	4 (4.9)	3 (6.3)

(a) Counts include all infusions interrupted. Percentages are computed out of the total number of infusions interrupted.
(b) Counts include all infusions with IV rate reduction. Percentages are computed out of the total number of infusions with IV rate reduced.
(c) TOTAL NUMBER DOSES RECEIVED is excluding first dose.
(d) Percentages are computed out of the total number of doses received excluding first dose.
(e) Counts include all dose delays. Percentages are computed out of the total number of doses delayed.
Source: Table 6.3-1 of the CA209067 OS Final CSR[2]

Adverse events

The characterization of the safety profile of NIVO or NIVO+IPI for the interim and the final analysis is shown in Table 38. Slightly higher AE frequencies were reported at the updated database lock relative to the CA209067 Interim CSR database lock (17-Feb-2015) consistent with the longer duration of treatment and follow-up.

Table 38: Summary of Safety Results in CA209067 After 9 Months and 28 Months Follow Up – All Treated Subjects

	Number (%) Subjects							
	CA209067 Interim CSR DBL: 17-Feb-2015				CA209067 Final OS CSR DBL 13-Sep-2016			
	Nivolumab (N=313)		Nivolumab + Ipilimumab (N=313)		Nivolumab (N=313)		Nivolumab + Ipilimumab (N=313)	
Deaths								
Within 30 days	14 (4.5)		20 (6.4)		14 (4.5)		21 (6.7)	
Within 100 days	50 (16.0)		44 (14.1)		52 (16.6)		46 (14.7)	
Study Drug Toxicity	1 (0.3)		0		1 (0.3)		2 (0.6)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All SAEs	113 (36.1)	88 (28.1)	217 (69.3)	159 (50.8)	133 (42.5)	104 (33.2)	223 (71.2)	167 (53.4)
Drug-related SAEs	25 (8.0)	18 (5.8)	150 (47.9)	112 (35.8)	31 (9.9)	25 (8.0)	152 (48.6)	115 (36.7)
All AEs Leading to DC	43 (13.7)	27 (8.6)	135 (43.1)	105 (33.5)	57 (18.2)	38 (12.1)	147 (47.0)	111 (35.5)
Drug-related AEs Leading to DC	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	36 (11.5)	24 (7.7)	124 (39.6))	97 (31.0)
All AEs (Regardless of Causality)	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	312 (99.7)	159 (50.8)	312 (99.7)	226 (72.2)
Drug-related AEs	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	270 (86.3)	65 (20.8)	300 (95.8)	183 (58.5)
SELECT AE CATEGORY (All Causality)								
Endocrine	54 (17.3)	2 (0.6)	105 (33.5)	19 (6.1)	63 (20.1)	5 (1.6)	119 (38.0)	23 (7.3)
Gastrointestinal	99 (31.6)	12 (3.8)	171 (54.6)	50 (16.0)	114 (36.4)	18 (5.8)	177 (56.5)	53 (16.9)
Hepatic	40 (12.8)	16 (5.1)	105 (33.5)	62 (19.8)	43 (13.7)	16 (5.1)	115 (36.7)	66 (21.1)
Pulmonary	7 (2.2)	2 (0.6)	23 (7.3)	4 (1.3)	7 (2.2)	2 (0.6)	24 (7.7)	4 (1.3)
Renal	10 (3.2)	2 (0.6)	32 (10.2)	11 (3.5)	10 (3.2)	2 (0.6)	35 (11.2)	11 (3.5)
Skin	167 (53.4)	6 (1.9)	201 (64.2)	19 (6.1)	178 (56.9)	9 (2.9)	205 (65.5)	20 (6.4)
Hypersensitivity/Infusion reaction	16 (5.1)	1 (0.3)	14 (4.5)	0	17 (5.4)	1 (0.3)	15 (4.8)	0
SELECT AE CATEGORY (Drug-Related)								
Endocrine	45 (14.4)	2 (0.6)	94 (30.0)	15 (4.8)	54 (17.3)	5 (1.6)	104 (33.2)	20 (6.4)
Gastrointestinal	61 (19.5)	7 (2.2)	145 (46.3)	46 (14.7)	70 (22.4)	11 (3.5)	150 (47.9)	48 (15.3)
Hepatic	22 (7.0)	8 (2.6)	95 (30.4)	60 (19.2)	24 (7.7)	8 (2.6)	102 (32.6)	62 (19.8)
Pulmonary	5 (1.6)	1 (0.3)	22 (7.0)	3 (1.0)	5 (1.6)	1 (0.3)	23 (7.3)	3 (1.0)
Renal	3 (1.0)	1 (0.3)	17 (5.4)	6 (1.9)	3 (1.0)	1 (0.3)	21 (6.7)	6 (1.9)
Skin	131 (41.9)	5 (1.6)	185 (59.1)	18 (5.8)	143 (45.7)	7 (2.2)	192 (61.3)	19 (6.1)
Hypersensitivty/Infusion reactions	13 (4.2)	1 (0.3)	13 (4.2)	0	14 (4.5)	1 (0.3)	13 (4.2)	0

Source: Table 2-1 of the CA209067 SCS

- **Common Adverse Events**

Any grade AEs (regardless of causality) were reported in 99.7% of subjects in the NIVO group, 99.7% in the NIVO+IPI group, and 99.0% of subjects in the IPI group.

In the NIVO group, the most frequently reported AEs (≥ 20% of subjects) were fatigue (47.9%), diarrhoea (35.8%), nausea (30.4%), rash (29.7%), cough (27.5%), pruritus (26.5%), decreased appetite (22.4%), headache (22.0%), constipation (21.4%), arthralgia (21.1%), and vomiting (20.1%).

In the NIVO+IPI group, the most frequently reported AEs (≥ 20% of subjects) were diarrhoea (54.0%), fatigue (51.8%), nausea (43.8%), pyrexia (39.9%), pruritus (39.0%), rash (32.9%), vomiting (31.3%), decreased appetite (29.4%), headache (25.6%), cough (24.3%), dyspnoea (23.0%), arthralgia (21.4%), and increased alanine aminotransferase (ALT) (20.8%).

In the IPI group, the most frequently reported AEs (≥ 20% of subjects) were diarrhoea (46.9%), fatigue (42.8%), pruritus (39.9%), nausea (30.5%), rash (26.0%), headache (24.1%), decreased appetite (23.5%), constipation (22.5%), cough (20.9%), and abdominal pain (20.3%).

- **AEs Grade 3-4**

Grade 3-4 AEs (regardless of causality) were reported in 50.8% of subjects in the NIVO group, 72.2% in the NIVO+IPI group, and 57.9% of subjects in the IPI group (Table 39).

In the NIVO group, the most frequently reported Grade 3-4 AEs (≥ 5% of subjects) were malignant neoplasm progression (6.4%) and hypertension and diarrhoea (each 5.1%) in the NIVO+IPI group were lipase increased (12.5%), diarrhoea (11.2%), increased ALT (9.3%), colitis (8.3%), increased aspartate aminotransferase (AST) (6.7%), and fatigue (6.4%) and in the IPI group were colitis (7.7%), diarrhoea (7.4%), anaemia (6.4%), and malignant neoplasm progression (6.1%).

Table 39: AEs (All Causality) by Worst CTC Grade Reported in ≥ 10% of Treated Subjects in CA209067

System Organ Class (%) Preferred Term (%)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	312 (99.7)	159 (50.8)	5 (1.6)	312 (99.7)	226 (72.2)	15 (4.8)	308 (99.0)	180 (57.9)	12 (3.9)
GASTROINTESTINAL DISORDERS	234 (74.8)	39 (12.5)	2 (0.6)	252 (80.5)	76 (24.3)	0	249 (80.1)	67 (21.5)	0
DIARRHEA	112 (35.8)	16 (5.1)	0	169 (54.0)	35 (11.2)	0	146 (46.9)	23 (7.4)	0
NAUSEA	95 (30.4)	2 (0.6)	0	137 (43.8)	12 (3.8)	0	95 (30.5)	6 (1.9)	0
CONSTIPATION	67 (21.4)	1 (0.3)	0	60 (19.2)	1 (0.3)	0	70 (22.5)	0	0
VOMITING	63 (20.1)	3 (1.0)	0	98 (31.3)	12 (3.8)	0	52 (16.7)	5 (1.6)	0
ABDOMINAL PAIN	53 (16.9)	3 (1.0)	0	58 (18.5)	5 (1.6)	0	63 (20.3)	6 (1.9)	0
DRY MOUTH	24 (7.7)	0	0	32 (10.2)	0	0	17 (5.5)	0	0
COLITIS	8 (2.6)	3 (1.0)	0	41 (13.1)	26 (8.3)	0	35 (11.3)	24 (7.7)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	233 (74.4)	13 (4.2)	1 (0.3)	255 (81.5)	34 (10.9)	3 (1.0)	221 (71.1)	20 (6.4)	0
FATIGUE	150 (47.9)	4 (1.3)	0	162 (51.8)	20 (6.4)	0	133 (42.8)	6 (1.9)	0
PYREXIA	50 (16.0)	0	0	125 (39.9)	5 (1.6)	0	56 (18.0)	2 (0.6)	0
ASTHENIA	46 (14.7)	1 (0.3)	0	48 (15.3)	3 (1.0)	0	32 (10.3)	7 (2.3)	0
OEDEMA PERIPHERAL	33 (10.5)	1 (0.3)	0	35 (11.2)	0	0	34 (10.9)	2 (0.6)	0
CHILLS	20 (6.4)	0	0	32 (10.2)	0	0	18 (5.8)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	207 (66.1)	10 (3.2)	0	231 (73.8)	23 (7.3)	0	211 (67.8)	13 (4.2)	0
RASH	93 (29.7)	1 (0.3)	0	103 (32.9)	10 (3.2)	0	81 (26.0)	8 (2.6)	0
PRURITUS	83 (26.5)	1 (0.3)	0	122 (39.0)	6 (1.9)	0	124 (39.9)	1 (0.3)	0
VITILIGO	32 (10.2)	1 (0.3)	0	28 (8.9)	0	0	16 (5.1)	0	0
RASH MACULO-PAPULAR	18 (5.8)	2 (0.6)	0	43 (13.7)	6 (1.9)	0	42 (13.5)	1 (0.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	175 (55.9)	22 (7.0)	0	148 (47.3)	18 (5.8)	0	149 (47.9)	10 (3.2)	0
ARTHRALGIA	66 (21.1)	3 (1.0)	0	67 (21.4)	1 (0.3)	0	51 (16.4)	1 (0.3)	0
BACK PAIN	53 (16.9)	6 (1.9)	0	38 (12.1)	2 (0.6)	0	48 (15.4)	4 (1.3)	0
PAIN IN EXTREMITY	43 (13.7)	3 (1.0)	0	31 (9.9)	1 (0.3)	0	36 (11.6)	0	0
MYALGIA	30 (9.6)	1 (0.3)	0	34 (10.9)	1 (0.3)	0	22 (7.1)	0	0
MUSCULOSKELETAL PAIN	28 (8.9)	3 (1.0)	0	21 (6.7)	1 (0.3)	0	31 (10.0)	2 (0.6)	0
INFECTIONS AND INFESTATIONS	155 (49.5)	12 (3.8)	0	154 (49.2)	31 (9.9)	1 (0.3)	125 (40.2)	23 (7.4)	0
NASOPHARYNGITIS	38 (12.1)	0	0	30 (9.6)	0	0	28 (9.0)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	152 (48.6)	16 (5.1)	1 (0.3)	164 (52.4)	28 (8.9)	4 (1.3)	130 (41.8)	10 (3.2)	1 (0.3)
COUGH	86 (27.5)	2 (0.6)	0	76 (24.3)	1 (0.3)	0	65 (20.9)	0	0
DYSPNOEA	45 (14.4)	4 (1.3)	0	72 (23.0)	9 (2.9)	0	42 (13.5)	2 (0.6)	0
NERVOUS SYSTEM DISORDERS	147 (47.0)	11 (3.5)	0	147 (47.0)	22 (7.0)	0	143 (46.0)	15 (4.8)	0
HEADACHE	69 (22.0)	1 (0.3)	0	80 (25.6)	2 (0.6)	0	75 (24.1)	3 (1.0)	0
DIZZINESS	28 (8.9)	0	0	38 (12.1)	0	0	28 (9.0)	0	0
METABOLISM AND NUTRITION DISORDERS	108 (34.5)	13 (4.2)	0	150 (47.9)	33 (10.5)	0	116 (37.3)	24 (7.7)	0
DECREASED APPETITE	70 (22.4)	0	0	92 (29.4)	6 (1.9)	0	73 (23.5)	4 (1.3)	0
HYPOKALAEMIA	9 (2.9)	1 (0.3)	0	33 (10.5)	6 (1.9)	0	11 (3.5)	3 (1.0)	0
INVESTIGATIONS	99 (31.6)	28 (8.9)	0	173 (55.3)	94 (30.0)	0	97 (31.2)	33 (10.6)	0
LIPASE INCREASED	27 (8.6)	15 (4.8)	0	49 (15.7)	39 (12.5)	0	21 (6.8)	13 (4.2)	0
ALANINE AMINOTRANSFERASE INCREASED	24 (7.7)	4 (1.3)	0	65 (20.8)	29 (9.3)	0	16 (5.1)	7 (2.3)	0
ASPARTATE AMINOTRANSFERASE INCREASED	23 (7.3)	5 (1.6)	0	57 (18.2)	21 (6.7)	0	17 (5.5)	4 (1.3)	0
WEIGHT DECREASED	23 (7.3)	0	0	38 (12.1)	0	0	21 (6.8)	1 (0.3)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	75 (24.0)	36 (11.5)	2 (0.6)	42 (13.4)	12 (3.8)	8 (2.6)	59 (19.0)	28 (9.0)	10 (3.2)
MALIGNANT NEOPLASM PROGRESSION	28 (8.9)	20 (6.4)	2 (0.6)	18 (5.8)	5 (1.6)	8 (2.6)	36 (11.6)	19 (6.1)	10 (3.2)
PSYCHIATRIC DISORDERS	69 (22.0)	2 (0.6)	0	84 (26.8)	8 (2.6)	0	74 (23.8)	4 (1.3)	0
INSOMNIA	41 (13.1)	1 (0.3)	0	45 (14.4)	2 (0.6)	0	39 (12.5)	0	0
VASCULAR DISORDERS	67 (21.4)	19 (6.1)	0	66 (21.1)	12 (3.8)	0	62 (19.9)	9 (2.9)	0
HYPERTENSION	32 (10.2)	16 (5.1)	0	23 (7.3)	7 (2.2)	0	27 (8.7)	7 (2.3)	0
ENDOCRINE DISORDERS	63 (20.1)	4 (1.3)	0	109 (34.8)	21 (6.7)	0	39 (12.5)	9 (2.9)	0
HYPOTHYROIDISM	34 (10.9)	0	0	60 (19.2)	2 (0.6)	0	16 (5.1)	0	0
HYPERTHYROIDISM	19 (6.1)	0	0	35 (11.2)	4 (1.3)	0	3 (1.0)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	56 (17.9)	12 (3.8)	0	66 (21.1)	10 (3.2)	0	54 (17.4)	23 (7.4)	0
ANAEMIA	32 (10.2)	7 (2.2)	0	35 (11.2)	4 (1.3)	0	40 (12.9)	20 (6.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table 8.4-1 of the CA209067 Final OS CSR[2]

- **Drug-related AEs**

Any grade drug-related AEs were reported in 86.3% of subjects in the NIVO group, 95.8% in the NIVO+IPI group, and 86.2% of subjects in the IPI group (Table 40).

In the NIVO group, the most frequently reported drug-related AEs (≥ 15% of subjects) were fatigue (35.5%), rash (23.0%), and diarrhoea and pruritus (each 21.4%), in the NIVO+IPI group were diarrhoea (45.4%), fatigue (37.7%), pruritus (35.8%), rash (29.1%), nausea (28.1%), pyrexia and decreased appetite (each 19.2%), ALT increased (18.8%), hypothyroidism and AST increased (each 16.3%), and vomiting (16.0%) and in the IPI group were pruritus (36.3%), diarrhoea (33.8%), fatigue (28.6%), rash (21.9%), and nausea (16.4%).

Exposure-adjusted incidence rates of AEs (all causality; incidence rate per 100 person-years) were 1300.8 in the NIVO group, 2150.2 in the NIVO+IPI group, and 2039.4 in the IPI group.

The overall frequency of AEs (regardless of causality) leading to a dose delay was 35.8% in the NIVO group, 58.1% in the NIVO+IPI group, and 40.8% in the IPI group.

Table 40: Drug-related AEs by Worst CTC Grade Reported in ≥ 5% of Treated Subjects in CA209067

System Organ Class (a) Preferred Term (a)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	270 (86.3)	65 (20.8)	0	300 (95.8)	183 (58.5)	0	268 (86.2)	86 (27.7)	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	158 (50.5)	8 (2.6)	0	207 (66.1)	21 (6.7)	0	177 (56.9)	9 (2.9)	0
RASH	72 (23.0)	1 (0.3)	0	91 (29.1)	10 (3.2)	0	68 (21.9)	5 (1.6)	0
PRURITUS	67 (21.4)	1 (0.3)	0	112 (35.8)	6 (1.9)	0	113 (36.3)	1 (0.3)	0
VITILIGO	28 (8.9)	1 (0.3)	0	27 (8.6)	0	0	16 (5.1)	0	0
DRY SKIN	17 (5.4)	0	0	15 (4.8)	0	0	11 (3.5)	0	0
RASH MACULO-PAPULAR	14 (4.5)	2 (0.6)	0	38 (12.1)	6 (1.9)	0	38 (12.2)	1 (0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	145 (46.3)	5 (1.6)	0	181 (57.8)	15 (4.8)	0	127 (40.8)	8 (2.6)	0
FATIGUE	111 (35.5)	3 (1.0)	0	118 (37.7)	13 (4.2)	0	89 (28.6)	3 (1.0)	0
ASTHENIA	25 (8.0)	1 (0.3)	0	31 (9.9)	1 (0.3)	0	17 (5.5)	2 (0.6)	0
PYREXIA	21 (6.7)	0	0	60 (19.2)	2 (0.6)	0	21 (6.8)	1 (0.3)	0
CHILLS	12 (3.8)	0	0	22 (7.0)	0	0	10 (3.2)	0	0
GASTROINTESTINAL DISORDERS	123 (39.3)	14 (4.5)	0	198 (63.3)	57 (18.2)	0	170 (54.7)	39 (12.5)	0
DIARRHEA	67 (21.4)	9 (2.9)	0	142 (45.4)	30 (9.6)	0	105 (33.8)	18 (5.8)	0
NAUSEA	41 (13.1)	0	0	88 (28.1)	7 (2.2)	0	51 (16.4)	2 (0.6)	0
VOMITING	22 (7.0)	1 (0.3)	0	50 (16.0)	8 (2.6)	0	24 (7.7)	1 (0.3)	0
CONSTIPATION	19 (6.1)	0	0	12 (3.8)	0	0	17 (5.5)	0	0
ABDOMINAL PAIN	18 (5.8)	0	0	28 (8.9)	1 (0.3)	0	28 (9.0)	2 (0.6)	0
DRY MOUTH	13 (4.2)	0	0	19 (6.1)	0	0	7 (2.3)	0	0
COLITIS	7 (2.2)	3 (1.0)	0	40 (12.8)	26 (8.3)	0	35 (11.3)	24 (7.7)	0
NERVOUS SYSTEM DISORDERS	66 (21.1)	3 (1.0)	0	86 (27.5)	12 (3.8)	0	57 (18.3)	1 (0.3)	0
HEADACHE	24 (7.7)	0	0	34 (10.9)	2 (0.6)	0	25 (8.0)	1 (0.3)	0
DYSGEUSIA	18 (5.8)	0	0	14 (4.5)	0	0	9 (2.9)	0	0
DIZZINESS	15 (4.8)	0	0	17 (5.4)	0	0	11 (3.5)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	64 (20.4)	5 (1.6)	0	71 (22.7)	7 (2.2)	0	47 (15.1)	1 (0.3)	0
ARTHRALGIA	29 (9.3)	1 (0.3)	0	42 (13.4)	1 (0.3)	0	21 (6.8)	0	0
MYALGIA	15 (4.8)	1 (0.3)	0	17 (5.4)	1 (0.3)	0	9 (2.9)	0	0
INVESTIGATIONS	58 (18.5)	17 (5.4)	0	141 (45.0)	82 (26.2)	0	55 (17.7)	22 (7.1)	0
LIPASE INCREASED	24 (7.7)	12 (3.8)	0	43 (13.7)	34 (10.9)	0	18 (5.8)	12 (3.9)	0
AMYLASE INCREASED	17 (5.4)	5 (1.6)	0	23 (7.3)	9 (2.9)	0	15 (4.8)	4 (1.3)	0
ASPARTATE AMINOTRANSFERASE INCREASED	13 (4.2)	3 (1.0)	0	51 (16.3)	19 (6.1)	0	12 (3.9)	2 (0.6)	0
ALANINE AMINOTRANSFERASE INCREASED	12 (3.8)	3 (1.0)	0	59 (18.8)	27 (8.6)	0	12 (3.9)	5 (1.6)	0
WEIGHT DECREASED	10 (3.2)	0	0	19 (6.1)	0	0	4 (1.3)	1 (0.3)	0
ENDOCRINE DISORDERS	53 (16.9)	4 (1.3)	0	96 (30.7)	18 (5.8)	0	33 (10.6)	8 (2.6)	0
HYPOTHYROIDISM	32 (10.2)	0	0	51 (16.3)	1 (0.3)	0	14 (4.5)	0	0
HYPERTHYROIDISM	15 (4.8)	0	0	34 (10.9)	3 (1.0)	0	3 (1.0)	0	0
HYPOPHYSITIS	2 (0.6)	2 (0.6)	0	23 (7.3)	5 (1.6)	0	12 (3.9)	5 (1.6)	0
METABOLISM AND NUTRITION DISORDERS	47 (15.0)	5 (1.6)	0	87 (27.8)	17 (5.4)	0	52 (16.7)	5 (1.6)	0
DECREASED APPETITE	36 (11.5)	0	0	60 (19.2)	4 (1.3)	0	41 (13.2)	1 (0.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	44 (14.1)	4 (1.3)	0	69 (22.0)	8 (2.6)	0	39 (12.5)	2 (0.6)	0
COUGH	20 (6.4)	2 (0.6)	0	24 (7.7)	0	0	15 (4.8)	0	0
DYSPNOEA	20 (6.4)	1 (0.3)	0	36 (11.5)	3 (1.0)	0	12 (3.9)	0	0
PNEUMONITIS	4 (1.3)	1 (0.3)	0	21 (6.7)	3 (1.0)	0	5 (1.6)	1 (0.3)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table 8.4-2 of CA209067 Final OS CSR[2]

The number of subjects in CA209067 with at least 1 AE per individual standardized MedDRA query (SMQ) occurring up to 30 days after last dose was analyzed by treatment group using both broad scope and narrow scope SMQs. Results of these analyses did not lead to the identification of new types of clinically important events.

Late-emergent drug-related AEs were defined as drug-related AEs with an onset date > 100 days after the last dose of study therapy. The overall frequency of late-emergent drug-related AEs (any grade) was greater in the NIVO+IPI group (17/313, 5.4%) compared to the NIVO and IPI groups (6/313, 1.9% and 7/311, 2.3%, respectively). Of subjects with late-emergent drug-related AEs, the majority of the events in each treatment group were of Grade 1/2 intensity, except in the IPI group where 4/7 subjects reported Grade 3 events of diarrhoea, acute polyneuropathy, pruritus, and hypertension.

Grade 3-4 drug-related AEs were reported in 20.8% of subjects in the NIVO group, 58.5% in the NIVO+IPI group, and 27.7% of subjects in the IPI group (Table 40).

In the NIVO group, no drug-related Grade 3/4 AEs in ≥ 5% of subjects were reported. In the NIVO+IPI group, the most frequently reported Grade 3-4 drug-related AEs (≥ 5% of subjects) were increased lipase (10.9%), diarrhoea (9.6%), increased ALT (8.6%), colitis (8.3%), and increased AST (6.1%) and in the IPI group were colitis (7.7%) and diarrhoea (5.8%).

Deaths, AEs, SAEs, and AEs leading to discontinuation in the pooled analysis for the monotherapy and combination therapy groups are summarized in Table 38.

Table 41: Summary of Safety Results - All Treated Subjects in CA209067

	Number (%) Subjects		
	Nivolumab N = 313	Nivolumab + Ipilimumab N = 313	Ipilimumab N = 311
DEATHS	141 (45.0)	127 (40.6)	195 (62.7)
WITHIN 30 DAYS OF LAST DOSE	14 (4.5)	21 (6.7)	20 (6.4)
WITHIN 100 DAYS OF LAST DOSE	52 (16.6)	46 (14.7)	59 (19.0)
DUE TO STUDY DRUG TOXICITY	1 (0.3)	2 (0.6)	1 (0.3)

	Number (%) Subjects					
	Nivolumab N = 313		Nivolumab + Ipilimumab N = 313		Ipilimumab N = 311	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	133 (42.5)	104 (33.2)	223 (71.2)	167 (53.4)	171 (55.0)	126 (40.5)
DRUG-RELATED SAEs	31 (9.9)	25 (8.0)	152 (48.6)	115 (36.7)	70 (22.5)	52 (16.7)
ALL CAUSALITY AEs LEADING TO DC	57 (18.2)	38 (12.1)	147 (47.0)	111 (35.5)	78 (25.1)	68 (21.9)
DRUG-RELATED AEs LEADING TO DC	36 (11.5)	24 (7.7)	124 (39.6)	97 (31.0)	50 (16.1)	44 (14.1)
ALL CAUSALITY AEs	312 (99.7)	159 (50.8)	312 (99.7)	226 (72.2)	308 (99.0)	180 (57.9)
Most Frequent AEs (≥ 20% of Any Grade in any treatment group)						
FATIGUE	150 (47.9)	4 (1.3)	162 (51.8)	20 (6.4)	133 (42.8)	6 (1.9)
DIARRHEA	112 (35.8)	16 (5.1)	169 (54.0)	35 (11.2)	146 (46.9)	23 (7.4)
NAUSEA	95 (30.4)	2 (0.6)	137 (43.8)	12 (3.8)	95 (30.5)	6 (1.9)
RASH	93 (29.7)	1 (0.3)	103 (32.9)	10 (3.2)	81 (26.0)	8 (2.6)
COUGH	86 (27.5)	2 (0.6)	76 (24.3)	1 (0.3)	65 (20.9)	0
PRURITUS	83 (26.5)	1 (0.3)	122 (39.0)	6 (1.9)	124 (39.9)	1 (0.3)
DECREASED APPETITE	70 (22.4)	0	92 (29.4)	6 (1.9)	73 (23.5)	4 (1.3)
HEADACHE	69 (22.0)	1 (0.3)	80 (25.6)	2 (0.6)	75 (24.1)	3 (1.0)
CONSTIPATION	67 (21.4)	1 (0.3)	60 (19.2)	1 (0.3)	70 (22.5)	0
ARTHRALGIA	66 (21.1)	3 (1.0)	67 (21.4)	1 (0.3)	51 (16.4)	1 (0.3)
VOMITING	63 (20.1)	3 (1.0)	98 (31.3)	12 (3.8)	52 (16.7)	5 (1.6)
ABDOMINAL PAIN	53 (16.9)	3 (1.0)	58 (18.5)	5 (1.6)	63 (20.3)	6 (1.9)
PYREXIA	50 (16.0)	0	125 (39.9)	5 (1.6)	56 (18.0)	2 (0.6)
DYSPNOEA	45 (14.4)	4 (1.3)	72 (23.0)	9 (2.9)	42 (13.5)	2 (0.6)
ALT INCREASED	24 (7.7)	4 (1.3)	65 (20.8)	29 (9.3)	16 (5.1)	7 (2.3)
DRUG-RELATED AEs	270 (86.3)	65 (20.8)	300 (95.8)	183 (58.5)	268 (86.2)	86 (27.7)
Most Frequent AEs (≥ 15% of Any Grade in any treatment group)						
FATIGUE	111 (35.5)	3 (1.0)	118 (37.7)	13 (4.2)	89 (28.6)	3 (1.0)
RASH	72 (23.0)	1 (0.3)	91 (29.1)	10 (3.2)	68 (21.9)	5 (1.6)
PRURITUS	67 (21.4)	1 (0.3)	112 (35.8)	6 (1.9)	113 (36.3)	1 (0.3)
DIARRHEA	67 (21.4)	9 (2.9)	142 (45.4)	30 (9.6)	105 (33.8)	18 (5.8)
NAUSEA	41 (13.1)	0	88 (28.1)	7 (2.2)	51 (16.4)	2 (0.6)
DECREASED APPETITE	36 (11.5)	0	60 (19.2)	4 (1.3)	41 (13.2)	1 (0.3)
HYPOTHYROIDISM	32 (10.2)	0	51 (16.3)	1 (0.3)	14 (4.5)	0
VOMITING	22 (7.0)	1 (0.3)	50 (16.0)	8 (2.6)	24 (7.7)	1 (0.3)
PYREXIA	21 (6.7)	0	60 (19.2)	2 (0.6)	21 (6.8)	1 (0.3)
AST INCREASED	13 (4.2)	3 (1.0)	51 (16.3)	19 (6.1)	12 (3.9)	2 (0.6)
ALT INCREASED	12 (3.8)	3 (1.0)	59 (18.8)	27 (8.6)	12 (3.9)	5 (1.6)
ALL CAUSALITY SELECT AEs, BY CATEGORY						
SKIN	178 (56.9)	9 (2.9)	205 (65.5)	20 (6.4)	198 (63.7)	12 (3.9)
GASTROINTESTINAL	114 (36.4)	18 (5.8)	177 (56.5)	53 (16.9)	155 (49.8)	40 (12.9)
ENDOCRINE	63 (20.1)	5 (1.6)	119 (38.0)	23 (7.3)	40 (12.9)	8 (2.6)
HEPATIC	43 (13.7)	16 (5.1)	115 (36.7)	66 (21.1)	35 (11.3)	14 (4.5)
RENAL	10 (3.2)	2 (0.6)	35 (11.2)	11 (3.5)	15 (4.8)	4 (1.3)
PULMONARY	7 (2.2)	2 (0.6)	24 (7.7)	4 (1.3)	10 (3.2)	2 (0.6)
HYPERSENSITIVITY/INFUSION REACTION	17 (5.4)	1 (0.3)	15 (4.8)	0	9 (2.9)	1 (0.3)
DRUG-RELATED SELECT AEs, BY CATEGORY						
SKIN	143 (45.7)	7 (2.2)	192 (61.3)	19 (6.1)	172 (55.3)	9 (2.9)
GASTROINTESTINAL	70 (22.4)	11 (3.5)	150 (47.9)	48 (15.3)	117 (37.6)	36 (11.6)
ENDOCRINE	54 (17.3)	5 (1.6)	104 (33.2)	20 (6.4)	36 (11.6)	8 (2.6)
HEPATIC	24 (7.7)	8 (2.6)	102 (32.6)	62 (19.8)	23 (7.4)	5 (1.6)
PULMONARY	5 (1.6)	1 (0.3)	23 (7.3)	3 (1.0)	6 (1.9)	1 (0.3)
RENAL	3 (1.0)	1 (0.3)	21 (6.7)	6 (1.9)	8 (2.6)	1 (0.3)
HYPERSENSITIVITY/INFUSION REACTION	14 (4.5)	1 (0.3)	13 (4.2)	0	8 (2.6)	1 (0.3)

MedDRA Version: 19.0; CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy unless otherwise stated.

Source: Table 8-1 of the CA209067 Final OS CSR[2]

In the updated adverse reactions in Section 4.8 of the SmPC (Table 3) and shown below (Table 42), adverse reactions are presented by system organ class and by frequency grouping (eg, common, uncommon, rare, or very rare). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Section 4 of the nivolumab Package Leaflet has been updated accordingly.

Table 42: Adverse Reactions in Clinical Trials (Provided in Updated SmPC Table 2 of Section 4.8)

	Nivolumab monotherapy	Nivolumab in combination with ipilimumab
Infections and infestations		
Common	upper respiratory tract infection	pneumonia, upper respiratory tract infection
Uncommon	pneumonia[a], bronchitis	bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	
Blood and lymphatic system disorders		
Very common	neutropaenia[a,b]	
Common		eosinophilia
Uncommon	eosinophilia	
Immune system disorders		
Common	infusion related reaction[c], hypersensitivity[c]	infusion related reaction, hypersensitivity
Uncommon		sarcoidosis
Rare	anaphylactic reaction[c]	
Endocrine disorders		
Very common		hypothyroidism
Common	hypothyroidism, hyperthyroidism	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus	diabetic ketoacidosis[c], diabetes mellitus[c]
Rare	diabetic ketoacidosis	
Metabolism and nutrition disorders		
Very common		decreased appetite
Common	decreased appetite	dehydration
Uncommon	dehydration, metabolic acidosis	
Hepatobiliary disorders		
Common		hepatitis[c]
Uncommon	hepatitis[c]	
Rare	cholestasis	
Nervous system disorders		
Very common		headache
Common	peripheral neuropathy, headache, dizziness	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]

	Nivolumab monotherapy	Nivolumab in combination with ipilimumab
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c]	
Eye disorders		
Common		uveitis, blurred vision
Uncommon	uveitis, blurred vision, dry eye	
Cardiac disorders		
Common		tachycardia
Uncommon	tachycardia	arrhythmia (including ventricular arrhythmia)[a,d], atrial fibrillation, myocarditis[a,f]
Rare	arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[a,f]	
Vascular disorders		
Common	hypertension	hypertension
Rare	vasculitis	
Respiratory, thoracic and mediastinal disorders		
Very common		dyspnoea
Common	pneumonitis[a,c], dyspnoea[a], cough	pneumonitis[a,c], pulmonary embolism[a], cough
Uncommon	pleural effusion	pleural effusion
Rare	lung infiltration	
Gastrointestinal disorders		
Very common	diarrhoea, nausea	colitis[a], diarrhoea, vomiting, nausea, abdominal pain
Common	colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth	stomatitis, pancreatitis, constipation, dry mouth
Uncommon	pancreatitis, gastritis	intestinal perforation[a], gastritis, duodenitis
Rare	duodenal ulcer	
Skin and subcutaneous tissue disorders		
Very common	rash[e], pruritus	rash[e], pruritus
Common	vitiligo, dry skin, erythema, alopecia	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	erythema multiforme, psoriasis, rosacea, urticaria	psoriasis
Rare	toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[a,f]	toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[f]
Musculoskeletal and connective tissue disorders		
Very common		arthralgia

	Nivolumab monotherapy	Nivolumab in combination with ipilimumab
Common	musculoskeletal pain[g], arthralgia,	musculoskeletal pain[g]
Uncommon	polymyalgia rheumatica, arthritis	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]	
Renal and urinary disorders		
Common		renal failure (including acute kidney injury)[a,c]
Uncommon	tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,c]	tubulointerstitial nephritis
General disorders and administration site conditions		
Very common	fatigue	fatigue, pyrexia
Common	pyrexia, oedema (including peripheral oedema)	oedema (including peripheral oedema), pain
Uncommon	pain, chest pain	chest pain
Investigations[b]		
Very common	increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatinine, hyperglycaemia[c], lymphopaenia, leucopoenia, thrombocytopaenia, anaemia, hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	increased total bilirubin, hypoglycaemia, hypermagnesaemia, hypernatraemia, weight decreased	hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased

[a] Fatal cases have been reported in completed or ongoing clinical studies

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

[c] Life-threatening cases have been reported in completed or ongoing clinical studies.

[d] The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0; serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator's choice group. The frequency of cardiac adverse events was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia).

[e] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, and drug eruption.

[f] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[g] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

- **Select Adverse Events**

Endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively.

The majority of select AEs reported were Grade 1-2, and most were considered drug-related by the investigator. The most frequently reported any-grade drug-related select AE categories (in order of descending frequency) across all treatment groups were skin, GI, endocrine, and hepatic. Within these categories, the most common drug-related select AEs across all 3 treatment groups were rash and pruritus, diarrhoea, hypothyroidism, and ALT increased, respectively. Higher frequencies of drug-related select AEs in these categories were observed in the NIVO+IPI combination group than in the NIVO and IPI monotherapy 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 were not considered resolved due to the continuing need for hormone replacement therapy. In Table 43 the frequency of selected immune-related AEs which required high-dose corticosteroids across the pooled melanoma safety database of patients treated with Ipilimumab in combination with nivolumab have been summarized.

Table 43: Immune-related adverse reactions leading requiring high-dose corticosteroids by dosing regimen

	Ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg %
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]	
Pneumonitis	63
Colitis	46
Hepatitis	46
Nephritis and Renal Dysfunction	17
Endocrinopathies	27
Skin	7
Hypersensitivity/Infusion Reaction	6

[a] at least 40 mg daily prednisone equivalents

[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Endocrine Events

The endocrine select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders.

The overall frequency of endocrine select AEs (all-causality, by worst CTC grade) were greater in the NIVO+IPI group (38.0%) compared to the NIVO group (20.1%) and the IPI group (12.9%).

Drug-related endocrine select AEs were reported in 17.3% subjects in the NIVO group, 33.2% in the NIVO+IPI group, and 11.6% in the IPI group (Table 44). The most commonly reported drug-related endocrine select AE in all 3 treatment groups was hypothyroidism. The majority of the drug-related endocrine events were Grade 1-2, with Grade 3-4 events reported in 1.6% subjects in the NIVO group, 6.4% in the NIVO+IPI group, and 2.6% in the IPI group. No subjects in the NIVO group experienced drug-related endocrine select events that led to permanent discontinuation. Endocrine drug-related select AEs (any grade) led to permanent discontinuation of 2.6% and 0.3% of subjects in the NIVO+IPI and IPI group, respectively.

The median time to onset of drug-related endocrine AEs was 13.71 weeks in the NIVO group, 8.07 weeks in the NIVO+IPI group, and 8.57 weeks in the IPI group. 4 (7.4%) subjects in the NIVO group, 28 (26.9%) subjects in the NIVO+IPI group, and 10 (27.8%) subjects in the IPI group were treated with high-dose corticosteroids for a median duration of 2-3 weeks.

Overall, 48.1% in the NIVO group, 53.8% in the NIVO+IPI group, and 44.4% of drug-related endocrine select AEs in the IPI group resolved. Median time to resolution was not available in the NIVO group, was approximately 28 weeks in the NIVO+IPI group, and was 77 weeks in the IPI group.

Table 44: Summary of Drug-related Endocrine Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects - CA209067

Sub Category (%) Preferred Term (%)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	54 (17.3)	5 (1.6)	0	104 (33.2)	20 (6.4)	0	36 (11.6)	8 (2.6)	0
THYROID DISORDER	47 (15.0)	0	0	87 (27.8)	5 (1.6)	0	19 (6.1)	0	0
HYPOTHYROIDISM	32 (10.2)	0	0	51 (16.3)	1 (0.3)	0	14 (4.5)	0	0
HYPERTHYROIDISM	15 (4.8)	0	0	34 (10.9)	3 (1.0)	0	3 (1.0)	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	4 (1.3)	0	0	6 (1.9)	0	0	2 (0.6)	0	0
THYROIDITIS	3 (1.0)	0	0	13 (4.2)	1 (0.3)	0	1 (0.3)	0	0
AUTOIMMUNE THYROIDITIS	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0	0	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	1 (0.3)	0	0	3 (1.0)	0	0	0	0	0
PRIMARY HYPOTHYROIDISM	1 (0.3)	0	0	0	0	0	0	0	0
THYROXINE FREE DECREASED	1 (0.3)	0	0	1 (0.3)	0	0	1 (0.3)	0	0
THYROXINE DECREASED	0	0	0	1 (0.3)	0	0	0	0	0
THYROXINE FREE INCREASED	0	0	0	1 (0.3)	0	0	0	0	0
THYROXINE INCREASED	0	0	0	1 (0.3)	0	0	0	0	0
ADRENAL DISORDER	3 (1.0)	1 (0.3)	0	14 (4.5)	6 (1.9)	0	5 (1.6)	1 (0.3)	0
ADRENAL INSUFFICIENCY	3 (1.0)	1 (0.3)	0	11 (3.5)	6 (1.9)	0	4 (1.3)	1 (0.3)	0
BLOOD CORTICOTROPHIN DECREASED	0	0	0	2 (0.6)	0	0	1 (0.3)	0	0
SECONDARY ADRENOCORTICAL INSUFFICIENCY	0	0	0	1 (0.3)	0	0	0	0	0
PITUITARY DISORDER	3 (1.0)	3 (1.0)	0	27 (8.6)	8 (2.6)	0	16 (5.1)	7 (2.3)	0
HYPOPHYSITIS	2 (0.6)	2 (0.6)	0	23 (7.3)	5 (1.6)	0	12 (3.9)	5 (1.6)	0
HYPOPITUITARISM	1 (0.3)	1 (0.3)	0	5 (1.6)	3 (1.0)	0	4 (1.3)	2 (0.6)	0
LYMPHOCYTIC HYPOPHYSITIS	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0
DIABETES	2 (0.6)	1 (0.3)	0	3 (1.0)	2 (0.6)	0	0	0	0
DIABETES MELLITUS	2 (0.6)	1 (0.3)	0	3 (1.0)	2 (0.6)	0	0	0	0

MedDRA Version: 19.0; CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.1-1 of the CA209067 Final OS CSR[2]

Gastrointestinal Events

The overall frequency of GI select AEs (all-causality, any grade) was greater in the NIVO+IPI group (56.5%) compared to the NIVO and IPI groups (36.4% and 49.8%, respectively).

In the NIVO+IPI group, 47.9% had GI select AEs that were considered to be drug related by the investigator compared to 22.4% in the NIVO group and 37.6% in the IPI group (Table 45). The most frequent drug-related event was diarrhoea and 2.9%, 9.6%, and 5.8% of the events were Grade 3-4 in the NIVO, NIVO+IPI, and IPI groups, respectively. Drug-related gastrointestinal select AEs (any grade) led to permanent discontinuation of study drug in 2.9%, 16.6%, and 11.6% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO+IPI group, the median time to onset of drug-related GI select AEs was 4.86 weeks compared to 9.43 and 4.57 weeks in the NIVO and IPI monotherapy groups, respectively. 68 subjects (45.3%) in the NIVO+IPI group, 11 subjects (15.7%) in the NIVO group, and 52 subjects (44.4%) in the IPI group were treated with high-dose corticosteroids for a median duration of 4.21, 3.43, and 4.07 weeks, respectively. Infliximab was used for AE (any grade/any causality) management in 1.3%, 4.8%, and 5.1% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

Overall, 140/149 (94.0%), 61/68 (89.7%), and 109/116 (94.0%) subjects in the NIVO+IPI, NIVO, and IPI groups, respectively, with drug-related GI select AEs had resolution of their events, with a median time to resolution of 2.86, 1.64, and 2.86 weeks, respectively.

Table 45: Summary of Drug-related Gastrointestinal Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	70 (22.4)	11 (3.5)	0	150 (47.9)	48 (15.3)	0	117 (37.6)	36 (11.6)	0
DIARRHEA	67 (21.4)	9 (2.9)	0	142 (45.4)	30 (9.6)	0	105 (33.8)	18 (5.8)	0
COLITIS	7 (2.2)	3 (1.0)	0	40 (12.8)	26 (8.3)	0	35 (11.3)	24 (7.7)	0
AUTOIMMUNE COLITIS	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
FREQUENT BOWEL MOVEMENTS	2 (0.6)	0	0	0	0	0	3 (1.0)	0	0
ENTERITIS	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.3)	0	0
ENTEROCOLITIS	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.2-1 of the CA209067 Final OS CSR[2]

Hepatic Events

The overall frequency of hepatic select AEs (all-causality, any grade) was greater in the NIVO+IPI group (36.7%) compared to the NIVO and IPI monotherapy groups (13.7% and 11.3%, respectively).

In the NIVO+IPI group, 32.6% of subjects had hepatic select AEs that were considered to be drug related by the investigator compared to 7.7% in the NIVO group and 7.4% in the IPI group (Table 46). The most frequent drug-related event across all 3 treatment groups was increased ALT and increased AST. The majority of events were Grade 1-2. Drug-related hepatic select AEs (any grade) led to permanent discontinuation of study drug in 1.9%, 11.2%,and 1.0% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO+IPI group, the median time to onset of drug-related hepatic select AEs was 6.00 weeks compared to 15.07 weeks in the NIVO group and 9.00 weeks in the IPI group. 45 subjects (44.1%) in the NIVO+IPI group, 8 subjects (33.3%) in the NIVO group, and 3 subjects (13.0%) in the IPI group were treated with high-dose corticosteroids for a median duration of 3.57, 3.29, and 3.57 weeks, respectively. Mycophenolic acid was used for AE (any grade/any causality) management only in the NIVO+IPI group (4 subjects [1.3%]).

Overall, 96/102 (94.1%), 22/24 (91.7%), and 23/23 (100%) subjects in the NIVO+IPI, NIVO, and IPI groups, respectively, with drug-related hepatic select AEs had resolution of their events, with a median time to resolution of 5.14, 8.43, and 4.14 weeks, respectively.

Table 46: Summary of Drug-related Hepatic Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	24 (7.7)	8 (2.6)	0	102 (32.6)	62 (19.8)	0	23 (7.4)	5 (1.6)	0
ASPARTATE AMINOTRANSFERASE INCREASED	13 (4.2)	3 (1.0)	0	51 (16.3)	19 (6.1)	0	12 (3.9)	2 (0.6)	0
ALANINE AMINOTRANSFERASE INCREASED	12 (3.8)	3 (1.0)	0	59 (18.8)	27 (8.6)	0	12 (3.9)	5 (1.6)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	4 (1.3)	0	0	12 (3.8)	2 (0.6)	0	2 (0.6)	1 (0.3)	0
AUTOIMMUNE HEPATITIS	2 (0.6)	2 (0.6)	0	6 (1.9)	6 (1.9)	0	2 (0.6)	1 (0.3)	0
HEPATOTOXICITY	2 (0.6)	2 (0.6)	0	10 (3.2)	8 (2.6)	0	1 (0.3)	0	0
TRANSAMINASES INCREASED	2 (0.6)	1 (0.3)	0	12 (3.8)	10 (3.2)	0	3 (1.0)	0	0
BLOOD BILIRUBIN INCREASED	1 (0.3)	0	0	4 (1.3)	0	0	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (0.3)	0	0	10 (3.2)	4 (1.3)	0	6 (1.9)	1 (0.3)	0
HEPATIC ENZYME INCREASED	1 (0.3)	0	0	5 (1.6)	3 (1.0)	0	0	0	0
HYPERBILIRUBINAEMIA	1 (0.3)	0	0	7 (2.2)	0	0	3 (1.0)	0	0
HEPATITIS	0	0	0	7 (2.2)	5 (1.6)	0	0	0	0
HEPATITIS ACUTE	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
LIVER DISORDER	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
LIVER FUNCTION TEST INCREASED	0	0	0	5 (1.6)	4 (1.3)	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.3-1 of the CA209067 Final OS CSR[2]

Pulmonary Events

The overall frequency of pulmonary select AEs (all-causality, any grade) was greater in the NIVO+IPI group (7.7%) compared to the NIVO and IPI monotherapy groups (2.2% and 3.2%, respectively).

In the NIVO+IPI group, 7.3% of subjects experienced pulmonary select AEs that were considered to be drug-related by the investigator compared to 1.6% in the NIVO group and 1.9% in the IPI group (Table 47). Most events were Grade 1-2 and were pneumonitis or interstitial lung disease. Drug-related pulmonary select AEs (any grade) led to permanent discontinuation of study drug in 0.3%, 1.9%, and 0.3% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO+IPI group, the median time to onset of drug-related pulmonary select AEs was 9.43 weeks compared to 9.00 weeks in the NIVO group and 10.07 weeks in the IPI group. 16 subjects (69.6%) in the NIVO+IPI group, 4 subjects (80.0%) in the NIVO group, and 3 subjects (50.0%) in the IPI group were treated with high-dose corticosteroids for a median duration of 4.43, 4.07, and 5.00 weeks, respectively.

Overall, 23/23 (100%), 3/5 (60.0%), and 5/6 (83.3%) subjects in the NIVO+IPI, NIVO, and IPI groups, respectively, with drug-related pulmonary select AEs had resolution of their events, with a median time to resolution of 6.43, 9.14, and 6.29 weeks, respectively.

Table 47: Summary of Drug-related Pulmonary Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	5 (1.6)	1 (0.3)	0	23 (7.3)	3 (1.0)	0	6 (1.9)	1 (0.3)	0
PNEUMONITIS	4 (1.3)	1 (0.3)	0	21 (6.7)	3 (1.0)	0	5 (1.6)	1 (0.3)	0
INTERSTITIAL LUNG DISEASE	1 (0.3)	0	0	2 (0.6)	0	0	1 (0.3)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.4-1 of the CA209067 Final OS CSR[2]

Renal Events

The overall frequency of renal select AEs (all-causality, any grade) was greater in the NIVO+IPI group (11.2%) compared to the NIVO and IPI monotherapy groups (3.2% and 4.8%, respectively).

In the NIVO+IPI group, 6.7% of subjects experienced renal select AEs that were considered to be drug-related by the investigator compared to 3 subjects (1.0%) in the NIVO group and 8 subjects (2.6%) in the IPI group (Table 48). Most events were Grade 1-2. The most frequently reported drug-related event across all groups was increased blood creatinine. Drug-related renal select AEs (any grade) led to permanent discontinuation of study drug in 0.3%, 1.3%, and 0.3% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO+IPI group, the median time to onset of drug-related renal select AEs was 11.43 weeks compared to 4.14 weeks in the NIVO group and 10.00 weeks in the IPI group. 4 subjects (19.0%) in the NIVO+IPI group, 2 subjects (66.7%) in the NIVO group, and 3 subjects (37.5%) in the IPI group were treated with high-dose corticosteroids for a median duration of 2.50, 0.29, and 4.00 weeks, respectively.

Overall, 19/21 (90.5%), 1/3 (33.3%), and 7/8 (87.5%) subjects in the NIVO+IPI, NIVO, and IPI groups, respectively, with drug-related renal select AEs had resolution of their events, with a median time to resolution of 2.14, not achieved, and 2.50 weeks, respectively.

Table 48: Summary of Drug-related Renal Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (1.0)	1 (0.3)	0	21 (6.7)	6 (1.9)	0	8 (2.6)	1 (0.3)	0
BLOOD CREATININE INCREASED	2 (0.6)	1 (0.3)	0	14 (4.5)	1 (0.3)	0	5 (1.6)	0	0
RENAL FAILURE	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	0	0	0
ACUTE KIDNEY INJURY	0	0	0	4 (1.3)	3 (1.0)	0	2 (0.6)	0	0
AUTOIMMUNE NEPHRITIS	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0
BLOOD UREA INCREASED	0	0	0	2 (0.6)	0	0	0	0	0
TUBULOINTERSTITIAL NEPHRITIS	0	0	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.5-1 of the CA209067 Final OS CSR[2]

Skin Events

The overall frequency of skin select AEs (all-causality, any grade) was similar between the NIVO+IPI group and IPI group (65.5% and 63.7%, respectively), while slightly lower in the NIVO group (56.9%).

In the NIVO+IPI group, 61.3% of subjects experienced skin select AEs that were considered to be drug-related by the investigator compared to 45.7% in the NIVO group and 55.3% in the IPI group (Table 49). Most were Grade 1-2. Across all treatment groups, the most frequently reported drug-related skin select AEs were rash and pruritus across all treatment groups. Drug-related skin select AEs (any grade) led to permanent discontinuation of study drug in 0.6%, 1.3%, and 0.6% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO+IPI group, the median time to onset of drug-related skin select AEs was 2.14 weeks compared to 5.43 weeks in the NIVO group and 3.57 weeks in the IPI group. 12 subjects (6.3%) in the NIVO+IPI group, 5 subjects (3.5%) in the NIVO group, and 9 subjects (5.2%) in the IPI group were treated with high-dose corticosteroids for a median duration of 1.36, 3.00, and 1.43 weeks, respectively.

Overall, 134/191 (70.2%), 84/142 (59.2%), and 134/172 (77.9%) subjects in the NIVO+IPI, NIVO, and IPI groups, respectively, with drug-related skin select AEs had resolution of their events, with a median time to resolution of 10.86, 32.43, and 11.00 weeks, respectively.

Table 49: Summary of Drug-related Skin Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	143 (45.7)	7 (2.2)	0	192 (61.3)	19 (6.1)	0	172 (55.3)	9 (2.9)	0
RASH	72 (23.0)	1 (0.3)	0	91 (29.1)	10 (3.2)	0	68 (21.9)	5 (1.6)	0
PRURITUS	67 (21.4)	1 (0.3)	0	112 (35.8)	6 (1.9)	0	113 (36.3)	1 (0.3)	0
VITILIGO	28 (8.9)	1 (0.3)	0	27 (8.6)	0	0	16 (5.1)	0	0
RASH MACULO-PAPULAR	14 (4.5)	2 (0.6)	0	38 (12.1)	6 (1.9)	0	38 (12.2)	1 (0.3)	0
ERYTHEMA	9 (2.9)	0	0	6 (1.9)	1 (0.3)	0	5 (1.6)	1 (0.3)	0
DERMATITIS	8 (2.6)	0	0	4 (1.3)	0	0	2 (0.6)	0	0
SKIN HYPOPIGMENTATION	7 (2.2)	0	0	5 (1.6)	0	0	2 (0.6)	0	0
ECZEMA	6 (1.9)	0	0	9 (2.9)	0	0	2 (0.6)	0	0
PSORIASIS	5 (1.6)	0	0	1 (0.3)	0	0	1 (0.3)	0	0
RASH PAPULAR	4 (1.3)	1 (0.3)	0	7 (2.2)	0	0	4 (1.3)	0	0
PRURITUS GENERALISED	3 (1.0)	0	0	2 (0.6)	0	0	4 (1.3)	0	0
RASH ERYTHEMATOUS	3 (1.0)	0	0	5 (1.6)	0	0	2 (0.6)	0	0
RASH GENERALISED	2 (0.6)	0	0	8 (2.6)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
RASH MACULAR	2 (0.6)	0	0	7 (2.2)	0	0	1 (0.3)	1 (0.3)	0
BLISTER	1 (0.3)	0	0	0	0	0	0	0	0
DERMATITIS EXFOLIATIVE	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (0.3)	0	0	0	0	0	1 (0.3)	0	0
PHOTOSENSITIVITY REACTION	1 (0.3)	0	0	3 (1.0)	0	0	1 (0.3)	0	0
RASH MORBILLIFORM	1 (0.3)	0	0	0	0	0	0	0	0
RASH PRURITIC	1 (0.3)	0	0	5 (1.6)	0	0	7 (2.3)	0	0
DRUG ERUPTION	0	0	0	1 (0.3)	0	0	0	0	0
EXFOLIATIVE RASH	0	0	0	0	0	0	1 (0.3)	0	0
SKIN IRRITATION	0	0	0	1 (0.3)	0	0	0	0	0
TOXIC SKIN ERUPTION	0	0	0	1 (0.3)	0	0	0	0	0
URTICARIA	0	0	0	3 (1.0)	0	0	3 (1.0)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.6-1 of the CA209067 Final OS CSR[2]

Hypersensitivity / Infusion Reactions

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.

The overall frequency of hypersensitivity/infusion reactions (all-causality, any grade) was similar between the NIVO and NIVO+IPI groups (5.4% and 4.8%, respectively) while slightly lower in the IPI group (2.9%).

In the NIVO group, 4.5% of subjects experienced hypersensitivity/infusion reactions that were considered to be drug related by the investigator compared to 4.2% in the NIVO+IPI group and 2.6% in the IPI group (Table 50). The most frequently reported drug-related event across all 3 treatment groups was infusion related reaction and most events were Grade 1-2. No drug-related hypersensitivity/infusion reactions (any grade) led to permanent discontinuation of respective study therapy in the NIVO and NIVO+IPI groups. One subject (0.3%; 1 Grade 3-4) in the IPI group had a drug-related hypersensitivity/infusion reaction that led to permanent discontinuation of study therapy.

In the NIVO group, the median time to onset of drug-related hypersensitivity/infusion reactions was 2.21 weeks compared to 3.14 weeks in the NIVO+IPI group and 4.29 weeks in the IPI group. 3 subjects (21.4%), 1 subject (7.7%), and 1 subject (12.5%) received immune modulating medication for any grade drug-related hypersensitivity/infusion reactions in the NIVO, NIVO+IPI, and IPI groups, respectively. No subjects in the NIVO+IPI and IPI groups and 2 subjects (14.3%) in the NIVO group were treated with high-dose corticosteroids for a median duration of 0.64 weeks in the NIVO group.

Overall, 13/14 (92.9%), 11/13 (84.6%), and 8/8 (100%) subjects in the NIVO, NIVO+IPI, and IPI groups, respectively, with drug-related hypersensitivity/infusion reactions had resolution of their events, with a median time to resolution of 0.14, 0.29, and 0.14 weeks, respectively.

Table 50: Summary of Drug-related Hypersensitivity / Infusion Reactions Reported Up to 30 days After Last Dose - All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	14 (4.5)	1 (0.3)	0	13 (4.2)	0	0	8 (2.6)	1 (0.3)	0
INFUSION RELATED REACTION	8 (2.6)	1 (0.3)	0	9 (2.9)	0	0	8 (2.6)	1 (0.3)	0
HYPERSENSITIVITY	6 (1.9)	0	0	4 (1.3)	0	0	0	0	0
BRONCHOSPASM	1 (0.3)	0	0	0	0	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.7-1 of the CA209067 Final OS CSR[2]

- **Other Events of Special Interest in CA209067**

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

All OESIs (regardless of causality or immune-modulating medication treatment reported within 100 days of last dose of study drug) are presented in Table 51.

In the NIVO group, OESIs within 100 days of last dose of nivolumab were reported as follows: 5 subjects with a pancreatitis event (3 with pancreatitis, 2 with autoimmune pancreatitis), 4 subjects with a uveitis event (3 with uveitis, 1 iridocyclitis) and 2 subjects with a myositis events (1 dermatomyositis, 1 polymyositis). In the NIVO+IPI group were reported: 1 subject with Guillain-Barré, 4 subjects with pancreatitis, 5 subjects with uveitis, 1 subject with encephalitis and 3 subjects with myositis, and in the IPI group were reported: 1 subject with myasthenia gravis, 3 subjects with a pancreatitis event (2 with pancreatitis, 1 with acute pancreatitis) and 3 subjects with uveitis.

Among all treatment groups, the following OESI were not reported: demyelination, myocarditis, and rhabdomyolysis.

Table 51: Summary of All Other Events of Special Interest (Regardless of Causality or Immune Modulating Medication Treatment) by Worst CTC Grade - All Treated Subjects - CA209067

	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
MYASTHENIC SYNDROME									
TOTAL SUBJECTS WITH AN EVENT	0	0	0	0	0	0	1 (0.3)	0	0
MYASTHENIA GRAVIS	0	0	0	0	0	0	1 (0.3)	0	0
GUILLAIN-BARRE SYNDROME									
TOTAL SUBJECTS WITH AN EVENT	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
GUILLAIN-BARRE SYNDROME	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
PANCREATITIS EVENT									
TOTAL SUBJECTS WITH AN EVENT	5 (1.6)	5 (1.6)	0	4 (1.3)	2 (0.6)	0	3 (1.0)	1 (0.3)	0
PANCREATITIS	3 (1.0)	3 (1.0)	0	4 (1.3)	2 (0.6)	0	2 (0.6)	0	0
AUTOIMMUNE PANCREATITIS	2 (0.6)	2 (0.6)	0	0	0	0	0	0	0
PANCREATITIS ACUTE	0	0	0	0	0	0	1 (0.3)	1 (0.3)	0
UVEITIS EVENT									
TOTAL SUBJECTS WITH AN EVENT	4 (1.3)	0	0	5 (1.6)	0	0	3 (1.0)	1 (0.3)	0
UVEITIS	3 (1.0)	0	0	5 (1.6)	0	0	3 (1.0)	1 (0.3)	0
IRIDOCYCLITIS	1 (0.3)	0	0	0	0	0	0	0	0
ENCEPHALITIS EVENT									
TOTAL SUBJECTS WITH AN EVENT	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
ENCEPHALITIS	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
MYOSITIS EVENT									
TOTAL SUBJECTS WITH AN EVENT	2 (0.6)	1 (0.3)	0	3 (1.0)	0	0	0	0	0
DERMATOMYOSITIS	1 (0.3)	0	0	0	0	0	0	0	0
POLYMYOSITIS	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
MYOSITIS	0	0	0	3 (1.0)	0	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 100 days after last dose of study therapy.
Source: Table 8.8-1 of the CA209037 Final CSR

Safety by Baseline Tumour PD-L1 Expression

Consistent with that reported in the CA209067 Interim CSR, the overall safety profile of NIVO monotherapy and NIVO+IPI combination therapy is not impacted by tumour PD-L1 expression level. Although interpretation is limited by small numbers of events, no consistent differences in the frequencies of select AEs by tumour PD-L1 expression subgroup (using either a 1% or 5% tumour PD-L1 expression level) were observed in any select AE across the treatment groups in CA209067.

Integration of Nivolumab Monotherapy and Nivolumab+Ipilimumab Combination Safety Data

Safety data to support Section 4.8 of the SmPC were integrated across completed studies in multiple indications using the intended dose and regimen for nivolumab monotherapy (3 mg/kg Q2W) and unresectable or metastatic melanoma using the intended dose and regimen for nivolumab in combination with ipilimumab (nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W).

The integrated dataset for nivolumab monotherapy included safety with longer follow-up from studies CA209037, CA209067 and CA209205. Depending on indication, minimum follow-up for patients in the integrated nivolumab monotherapy safety database ranged from 2.3 months to 28 months.

The integrated dataset for nivolumab in combination with ipilimumab included safety with longer follow-up from study CA209067 with a minimum follow-up of 28 months in all patients.

The studies included in the analyses of nivolumab monotherapy or nivolumab+ipilimumab combination therapy and the database lock (DBL) for each study are provided in Table 52.

Table 52: Summary of Studies Included in Integration of Safety Data for Nivolumab Monotherapy and Nivolumab+Ipilimumab Combination Therapy

Indication	Study number/Report	Database Lock Date
Nivolumab Monotherapy		
SCCHN	CA209141/CSR	18-Dec-2015
Classic Hodgkin lymphoma (cHL)	CA209205 Cohort A CSR (Cohort A+B+C safety analyses)	28-Jun-2016
	CA209039 CSR (all cHL)	11-Aug-2015
Renal cell carcinoma (RCC)	CA209205 CSR	18-Jun-2015
Melanoma	CA209067 Final OS CSR (monotherapy arm)	13-Sep-2016
	CA209037 Final OS CSR	29-Mar-2016
	CA209066 CSR	05-Aug-2014
Non-small cell lung cancer (NSCLC)	CA209057 Final CSR	18-Mar-2015
	CA209017 Final CSR	15-Dec-2014
	CA209063 Addendum CSR	23-Jul-2014
Urothelial Carcinoma	CA209275 CSR	30-May-2016
	CA209032 Interim CSR (bladder cohort only)	22-Mar-2016
Nivolumab+Ipilimumab Combination Therapy		
Melanoma	CA209067 Final OS CSR (nivo+ipi arm)	13-Sep-2016
	CA209069 CSR	04-Sep-2014
	CA209004 (Cohort 8)	13-Jun-2014

Adverse Events in CA209067 and Across Pooled Monotherapy Studies

A summary of AEs (all causality and drug-related) for nivolumab-treated subjects in CA209067 is shown side-by-side with the integrated safety data from all nivolumab monotherapy studies (including CA209067) in Table 53, and from all nivolumab + ipilimumab combination studies (including CA209067) in Table 54.

Table 53: Adverse Events and Reactions with Nivolumab Monotherapy in Clinical Trials using Re-mapped Terms

	CA209067 Nivo Mono N = 313		All Nivo Mono N = 2578	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT (REGARDLESS OF CAUSALITY)	312 (99.7)	159 (50.8)	2527 (98.0)	1192 (46.2)
Most frequent (>20% in any grade in CA209067 or in the pool of other studies)				
FATIGUE	183 (58.5)	5 (1.6)	1279 (49.6)	111 (4.3)
MUSCULOSKELETAL PAIN	131 (41.9)	12 (3.8)	892 (34.6)	84 (3.3)
COUGH	88 (28.1)	2 (0.6)	693 (26.9)	8 (0.3)
NAUSEA	95 (30.4)	2 (0.6)	644 (25.0)	21 (0.8)
DIARRHOEA	112 (35.8)	16 (5.1)	611 (23.7)	50 (1.9)
RASH	124 (39.6)	6 (1.9)	609 (23.6)	33 (1.3)
DYSPNOEA	57 (18.2)	4 (1.3)	543 (21.1)	82 (3.2)
DECREASED APPETITE	70 (22.4)	0	533 (20.7)	25 (1.0)
CONSTIPATION	67 (21.4)	1 (0.3)	496 (19.2)	12 (0.5)
PRURITUS	83 (26.5)	1 (0.3)	459 (17.8)	4 (0.2)
UPPER RESPIRATORY TRACT INFECTION	70 (22.4)	1 (0.3)	428 (16.6)	5 (0.2)
ARTHRALGIA	66 (21.1)	3 (1.0)	397 (15.4)	15 (0.6)
VOMITING	63 (20.1)	3 (1.0)	397 (15.4)	24 (0.9)
ABDOMINAL PAIN	78 (24.9)	5 (1.6)	390 (15.1)	36 (1.4)
HEADACHE	69 (22.0)	1 (0.3)	347 (13.5)	11 (0.4)
TOTAL SUBJECTS WITH AN EVENT (DRUG-REALTED)	270 (86.3)	65 (20.8)	1895 (73.5)	414 (16.1)
Most frequent (>10% in any grade in CA209067 or in the pool of other studies)				
FATIGUE	128 (40.9)	4 (1.3)	782 (30.3)	47 (1.8)
RASH	95 (30.4)	5 (1.6)	442 (17.1)	28 (1.1)
PRURITUS	67 (21.4)	1 (0.3)	344 (13.3)	3 (0.1)
DIARRHOEA	67 (21.4)	9 (2.9)	329 (12.8)	29 (1.1)
NAUSEA	41 (13.1)	0	306 (11.9)	5 (0.2)
DECREASED APPETITE	36 (11.5)	0	232 (9.0)	3 (0.1)
MUSCULOSKELETAL PAIN	34 (10.9)	1 (0.3)	192 (7.4)	10 (0.4)
HYPOTHYROIDISM	32 (10.2)	0	171 (6.6)	2 (<0.1)

MedDRA Version: 19.0, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
All Nivo Mono group consists of Nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067 , CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209032 (bladder subjects), and CA209275.
Grade 3-4 by worst CTC grade.
Some preferred terms are re-mapped or deleted based on BMS medical review.
Source: Appendix M.438-EUSCS (all causality) and Appendix M.439-EUSCS (drug-related) of Appendix 1

Table 54: Adverse Events and Reactions with Nivolumab + Ipilimumab Combination Therapy in Clinical Trials using Re-mapped Terms

	CA209067 Nivo+Ipi Combo N = 313		All Nivo+Ipi Combo N = 448	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT (REGARDLESS OF CAUSALITY)	312 (99.7)	226 (72.2)	447 (99.8)	320 (71.4)
Most frequent (>20% in any grade in CA209067 or in the pool of other studies)				
FATIGUE	193 (61.7)	22 (7.0)	280 (62.5)	30 (6.7)
MUSCULOSKELETAL PAIN	100 (31.9)	8 (2.6)	136 (30.4)	9 (2.0)
COUGH	85 (27.2)	1 (0.3)	123 (27.5)	1 (0.2)
NAUSEA	137 (43.8)	12 (3.8)	189 (42.2)	16 (3.6)
DIARRHOEA	169 (54.0)	35 (11.2)	233 (52.0)	49 (10.9)
RASH	167 (53.4)	18 (5.8)	256 (57.1)	33 (7.4)
DYSPNOEA	74 (23.6)	9 (2.9)	103 (23.0)	13 (2.9)
DECREASED APPETITE	92 (29.4)	6 (1.9)	115 (25.7)	6 (1.3)
CONSTIPATION	60 (19.2)	1 (0.3)	92 (20.5)	2 (0.4)
PRURITUS	122 (39.0)	6 (1.9)	177 (39.5)	7 (1.6)
PYREXIA	125 (39.9)	5 (1.6)	162 (36.2)	9 (2.0)
UPPER RESPIRATORY TRACT INFECTION	72 (23.0)	0	81 (18.1)	0
ARTHRALGIA	67 (21.4)	1 (0.3)	92 (20.5)	1 (0.2)
VOMITING	98 (31.3)	12 (3.8)	131 (29.2)	14 (3.1)
ABDOMINAL PAIN	78 (24.9)	6 (1.9)	110 (24.6)	8 (1.8)
HEADACHE	80 (25.6)	2 (0.6)	116 (25.9)	5 (1.1)
TRANSAMINASES INCREASED	77 (24.6)	42 (13.4)	113 (25.2)	59 (13.2)
TOTAL SUBJECTS WITH AN EVENT (DRUG-RELATED)	300 (95.8)	183 (58.5)	426 (95.1)	257 (57.4)
Most frequent (>10% in any grade in CA209067 or in the pool of other studies)				
FATIGUE	143 (45.7)	13 (4.2)	204 (45.5)	18 (4.0)
RASH	146 (46.6)	17 (5.4)	231 (51.6)	32 (7.1)
PRURITUS	112 (35.8)	6 (1.9)	163 (36.4)	7 (1.6)
DIARRHOEA	142 (45.4)	30 (9.6)	193 (43.1)	42 (9.4)
NAUSEA	88 (28.1)	7 (2.2)	118 (26.3)	9 (2.0)
DECREASED APPETITE	60 (19.2)	4 (1.3)	71 (15.8)	4 (0.9)
HYPOTHYROIDISM	51 (16.3)	1 (0.3)	70 (15.6)	1 (0.2)
ARTHRALGIA	42 (13.4)	1 (0.3)	60 (13.4)	1 (0.2)
PYREXIA	60 (19.2)	2 (0.6)	87 (19.4)	5 (1.1)
VOMITING	50 (16.0)	8 (2.6)	63 (14.1)	9 (2.0)
DYSPNOEA	37 (11.8)	3 (1.0)	45 (10.0)	5 (1.1)
TRANSAMINASES INCREASED	71 (22.7)	40 (12.8)	99 (22.1)	53 (11.8)
HEADACHE	34 (10.9)	2 (0.6)	50 (11.2)	5 (1.1)
ABDOMINAL PAIN	40 (12.8)	1 (0.3)	59 (13.2)	2 (0.4)
LIPASE INCREASED	43 (13.7)	34 (10.9)	60 (13.4)	45 (10.0)
HYPERTHYROIDISM	34 (10.9)	3 (1.0)	38 (8.5)	3 (0.7)
COLITIS	41 (13.1)	27 (8.6)	66 (14.7)	46 (10.3)

MedDRA Version: 19.0, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
All Nivo + Ipi combo group consists of Nivolumab+Ipilimumab treatment group from studies CA209067, CA209069 and CA209004 (Cohort 8 only).
Grade 3-4 by worst CTC grade.
Some preferred terms are re-mapped or deleted based on BMS medical review.
Source: Appendix M.438-EUSCS (all causality) and Appendix M.439-EUSCS (drug-related) of Appendix 1

Serious adverse event / deaths / other significant events

Consistent with the CA209067 Interim CSR (Table 38), the overall frequencies of SAEs and drug-related SAEs were lowest in the NIVO group and highest in the NIVO+IPI group (Table 55 and Table 56).

SAEs were reported in 42.5% of subjects in the NIVO group, 71.2% of subjects in the NIVO+IPI group, and 55.0% of subjects in the IPI group (Table 55). Grade 3-4 SAEs were reported in 33.2%, 53.4%, and 40.5% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO group, the most frequently reported SAE was malignant neoplasm progression (8.0%), in the NIVO+IPI group were diarrhoea (10.5%), colitis (9.9%), and pyrexia (8.3%) and in the IPI group, the most frequently reported SAEs were malignant neoplasm progression (10.6%), colitis (8.4%) and diarrhoea (8.0%).

Drug-related SAEs were reported in 9.9% of subjects in the NIVO group, 48.6% of subjects in the NIVO+IPI group, and 22.5% of subjects in the IPI group (Table 56). Grade 3-4 drug-related SAEs were reported in 8.0%, 36.7%, and 16.7% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO group, drug-related SAEs reported in at least 2 subjects included colitis (1%), and diarrhoea, adrenal insufficiency, hypophysitis, fatigue, autoimmune hepatitis, dyspnoea, and renal failure (each 0.6%), in the NIVO+IPI group were colitis (9.6%), diarrhoea (8.9%), and pyrexia (4.2%) and in the IPI group were colitis (8.4%), and diarrhoea (7.4%).

Table 55: SAEs (All Causality) by Worst CTC Grade Reported in ≥ 1% of Treated Subjects - CA209067

System Organ Class (%) Preferred Term (%)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	133 (42.5)	104 (33.2)	5 (1.6)	223 (71.2)	167 (53.4)	15 (4.8)	171 (55.0)	126 (40.5)	12 (3.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	48 (15.3)	34 (10.9)	2 (0.6)	24 (7.7)	10 (3.2)	8 (2.6)	45 (14.5)	28 (9.0)	10 (3.2)
MALIGNANT NEOPLASM PROGRESSION	25 (8.0)	19 (6.1)	2 (0.6)	16 (5.1)	5 (1.6)	8 (2.6)	33 (10.6)	19 (6.1)	10 (3.2)
SQUAMOUS CELL CARCINOMA	8 (2.6)	3 (1.0)	0	1 (0.3)	0	0	0	0	0
BASAL CELL CARCINOMA	7 (2.2)	2 (0.6)	0	2 (0.6)	1 (0.3)	0	3 (1.0)	0	0
MALIGNANT MELANOMA	4 (1.3)	4 (1.3)	0	0	0	0	1 (0.3)	1 (0.3)	0
METASTASES TO CENTRAL NERVOUS SYSTEM	2 (0.6)	2 (0.6)	0	0	0	0	4 (1.3)	4 (1.3)	0
GASTROINTESTINAL DISORDERS	33 (10.5)	23 (7.3)	2 (0.6)	85 (27.2)	63 (20.1)	0	66 (21.2)	49 (15.8)	0
DIARRHOEA	6 (1.9)	5 (1.6)	0	33 (10.5)	19 (6.1)	0	25 (8.0)	16 (5.1)	0
ABDOMINAL PAIN	4 (1.3)	2 (0.6)	0	5 (1.6)	3 (1.0)	0	5 (1.6)	3 (1.0)	0
COLITIS	3 (1.0)	2 (0.6)	0	31 (9.9)	23 (7.3)	0	26 (8.4)	21 (6.8)	0
VOMITING	3 (1.0)	2 (0.6)	0	10 (3.2)	7 (2.2)	0	3 (1.0)	2 (0.6)	0
NAUSEA	2 (0.6)	2 (0.6)	0	9 (2.9)	7 (2.2)	0	1 (0.3)	1 (0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14 (4.5)	8 (2.6)	1 (0.3)	47 (15.0)	16 (5.1)	3 (1.0)	21 (6.8)	8 (2.6)	0
GENERAL PHYSICAL HEALTH DETERIORATION	3 (1.0)	2 (0.6)	0	8 (2.6)	5 (1.6)	0	2 (0.6)	2 (0.6)	0
FATIGUE	2 (0.6)	2 (0.6)	0	5 (1.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
PYREXIA	2 (0.6)	0	0	26 (8.3)	4 (1.3)	0	10 (3.2)	2 (0.6)	0
PAIN	1 (0.3)	1 (0.3)	0	4 (1.3)	4 (1.3)	0	2 (0.6)	1 (0.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14 (4.5)	11 (3.5)	1 (0.3)	27 (8.6)	17 (5.4)	4 (1.3)	14 (4.5)	8 (2.6)	1 (0.3)
DYSPNOEA	3 (1.0)	2 (0.6)	0	6 (1.9)	5 (1.6)	0	3 (1.0)	2 (0.6)	0
PNEUMONITIS	2 (0.6)	2 (0.6)	0	6 (1.9)	3 (1.0)	0	2 (0.6)	1 (0.3)	0
PULMONARY EMBOLISM	2 (0.6)	2 (0.6)	0	8 (2.6)	6 (1.9)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
INFECTIONS AND INFESTATIONS	11 (3.5)	9 (2.9)	0	29 (9.3)	23 (7.3)	1 (0.3)	23 (7.4)	20 (6.4)	0
PNEUMONIA	0	0	0	6 (1.9)	2 (0.6)	1 (0.3)	2 (0.6)	2 (0.6)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6 (1.9)	5 (1.6)	0	9 (2.9)	5 (1.6)	0	5 (1.6)	5 (1.6)	0
ANAEMIA	4 (1.3)	3 (1.0)	0	3 (1.0)	3 (1.0)	0	4 (1.3)	4 (1.3)	0
ENDOCRINE DISORDERS	6 (1.9)	4 (1.3)	0	29 (9.3)	19 (6.1)	0	12 (3.9)	9 (2.9)	0
ADRENAL INSUFFICIENCY	2 (0.6)	1 (0.3)	0	7 (2.2)	6 (1.9)	0	1 (0.3)	1 (0.3)	0
HYPOPHYSITIS	2 (0.6)	2 (0.6)	0	8 (2.6)	5 (1.6)	0	8 (2.6)	5 (1.6)	0
HYPERTHYROIDISM	0	0	0	6 (1.9)	2 (0.6)	0	0	0	0
HEPATOBILIARY DISORDERS	5 (1.6)	5 (1.6)	0	20 (6.4)	20 (6.4)	0	4 (1.3)	1 (0.3)	0
AUTOIMMUNE HEPATITIS	2 (0.6)	2 (0.6)	0	6 (1.9)	6 (1.9)	0	1 (0.3)	0	0
HEPATOTOXICITY	1 (0.3)	1 (0.3)	0	5 (1.6)	5 (1.6)	0	0	0	0
HEPATITIS	0	0	0	4 (1.3)	4 (1.3)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	4 (1.3)	4 (1.3)	0	19 (6.1)	16 (5.1)	0	6 (1.9)	6 (1.9)	0
HYPERGLYCAEMIA	1 (0.3)	1 (0.3)	0	5 (1.6)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
DEHYDRATION	0	0	0	8 (2.6)	7 (2.2)	0	3 (1.0)	3 (1.0)	0
RENAL AND URINARY DISORDERS	4 (1.3)	3 (1.0)	0	17 (5.4)	10 (3.2)	0	6 (1.9)	4 (1.3)	0
ACUTE KIDNEY INJURY	1 (0.3)	1 (0.3)	0	7 (2.2)	6 (1.9)	0	3 (1.0)	2 (0.6)	0
INVESTIGATIONS	3 (1.0)	2 (0.6)	0	17 (5.4)	15 (4.8)	0	4 (1.3)	3 (1.0)	0
TRANSAMINASES INCREASED	1 (0.3)	1 (0.3)	0	8 (2.6)	8 (2.6)	0	0	0	0
CARDIAC DISORDERS	2 (0.6)	1 (0.3)	0	10 (3.2)	6 (1.9)	0	8 (2.6)	7 (2.3)	1 (0.3)
ATRIAL FIBRILLATION	0	0	0	4 (1.3)	2 (0.6)	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.2-1 of the CA209067 Final 08 CSR[2]

Table 56: Drug-related SAEs by Worst CTC Grade Reported in at Least 2 Subjects - Treated Subjects-CA209067

System Organ Class (%) Preferred Term (%)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	31 (9.9)	25 (8.0)	0	152 (48.6)	115 (36.7)	0	70 (22.5)	52 (16.7)	1 (0.3)
GASTROINTESTINAL DISORDERS	9 (2.9)	6 (1.9)	0	67 (21.4)	49 (15.7)	0	44 (14.1)	34 (10.9)	0
COLITIS	3 (1.0)	2 (0.6)	0	30 (9.6)	22 (7.0)	0	26 (8.4)	21 (6.8)	0
DIARRHEA	2 (0.6)	1 (0.3)	0	28 (8.9)	18 (5.8)	0	23 (7.4)	14 (4.5)	0
ABDOMINAL PAIN	1 (0.3)	0	0	2 (0.6)	0	0	0	0	0
AUTOIMMUNE COLITIS	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
NAUSEA	0	0	0	7 (2.2)	5 (1.6)	0	0	0	0
VOMITING	0	0	0	5 (1.6)	4 (1.3)	0	1 (0.3)	0	0
ENDOCRINE DISORDERS	5 (1.6)	4 (1.3)	0	27 (8.6)	17 (5.4)	0	11 (3.5)	8 (2.6)	0
ADRENAL INSUFFICIENCY	2 (0.6)	1 (0.3)	0	7 (2.2)	6 (1.9)	0	1 (0.3)	1 (0.3)	0
HYPOPHYSITIS	2 (0.6)	2 (0.6)	0	7 (2.2)	4 (1.3)	0	8 (2.6)	5 (1.6)	0
HYPOPITUITARISM	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0	2 (0.6)	2 (0.6)	0
HYPERTHYROIDISM	0	0	0	6 (1.9)	2 (0.6)	0	0	0	0
HYPOTHYROIDISM	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0
THYROIDITIS	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (1.3)	3 (1.0)	0	22 (7.0)	4 (1.3)	0	9 (2.9)	3 (1.0)	0
FATIGUE	2 (0.6)	2 (0.6)	0	4 (1.3)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
PYREXIA	1 (0.3)	0	0	13 (4.2)	1 (0.3)	0	6 (1.9)	1 (0.3)	0
GENERAL PHYSICAL HEALTH DETERIORATION	0	0	0	3 (1.0)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
HEPATOBILIARY DISORDERS	3 (1.0)	3 (1.0)	0	18 (5.8)	18 (5.8)	0	1 (0.3)	0	0
AUTOIMMUNE HEPATITIS	2 (0.6)	2 (0.6)	0	6 (1.9)	6 (1.9)	0	1 (0.3)	0	0
HEPATOTOXICITY	1 (0.3)	1 (0.3)	0	5 (1.6)	5 (1.6)	0	0	0	0
HEPATITIS	0	0	0	4 (1.3)	4 (1.3)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (1.0)	2 (0.6)	0	11 (3.5)	5 (1.6)	0	2 (0.6)	1 (0.3)	0
DYSPNOEA	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)	0	0	0	0
PNEUMONITIS	1 (0.3)	1 (0.3)	0	6 (1.9)	3 (1.0)	0	2 (0.6)	1 (0.3)	0
INTERSTITIAL LUNG DISEASE	0	0	0	2 (0.6)	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.6)	2 (0.6)	0	5 (1.6)	4 (1.3)	0	0	0	0
ANAEMIA	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	2 (0.6)	2 (0.6)	0	10 (3.2)	8 (2.6)	0	0	0	0
HYPERGLYCAEMIA	1 (0.3)	1 (0.3)	0	3 (1.0)	1 (0.3)	0	0	0	0
DEHYDRATION	0	0	0	4 (1.3)	4 (1.3)	0	0	0	0
HYPONATRAEMIA	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
NERVOUS SYSTEM DISORDERS	2 (0.6)	1 (0.3)	0	7 (2.2)	7 (2.2)	0	0	0	0
HEADACHE	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
RENAL AND URINARY DISORDERS	2 (0.6)	1 (0.3)	0	10 (3.2)	6 (1.9)	0	2 (0.6)	1 (0.3)	0
RENAL FAILURE	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	0	0	0
ACUTE KIDNEY INJURY	0	0	0	3 (1.0)	3 (1.0)	0	1 (0.3)	0	0
INVESTIGATIONS	1 (0.3)	1 (0.3)	0	16 (5.1)	15 (4.8)	0	3 (1.0)	2 (0.6)	0
TRANSAMINASES INCREASED	1 (0.3)	1 (0.3)	0	8 (2.6)	8 (2.6)	0	0	0	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
HEPATIC ENZYME INCREASED	0	0	0	3 (1.0)	2 (0.6)	0	0	0	0
LIPASE INCREASED	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	2 (0.6)	0	0	0	0	0
CONFUSIONAL STATE	0	0	0	2 (0.6)	0	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.2-2 of the CA209067 Final OS CSR[2]

Deaths

As of the 13-Sep-2016 database lock, a total of 141 (45%), 127 (40.6%), and 195 (62.7%) deaths were reported in the NIVO, NIVO+IPI, and IPI groups, respectively (Table 57). Disease progression was the most common cause of death for all groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose.

Table 57: Summary of Deaths - All Treated Subjects - CA209067

	Nivolumab N = 313	Nivolumab + Ipilimumab N = 313	Ipilimumab N = 311
NUMBER OF SUBJECTS WHO DIED (%)	141 (45.0)	127 (40.6)	195 (62.7)
PRIMARY REASON FOR DEATH (%)			
DISEASE	123 (39.3)	109 (34.8)	181 (58.2)
STUDY DRUG TOXICITY	1 (0.3)	2 (0.6)	1 (0.3)
UNKNOWN	4 (1.3)	2 (0.6)	2 (0.6)
OTHER	13 (4.2)	14 (4.5)	11 (3.5)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	14 (4.5)	21 (6.7)	20 (6.4)
PRIMARY REASON FOR DEATH (%)			
DISEASE	9 (2.9)	11 (3.5)	17 (5.5)
STUDY DRUG TOXICITY	0	0	0
UNKNOWN	1 (0.3)	1 (0.3)	0
OTHER	4 (1.3)	9 (2.9)	3 (1.0)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	52 (16.6)	46 (14.7)	59 (19.0)
PRIMARY REASON FOR DEATH (%)			
DISEASE	41 (13.1)	32 (10.2)	49 (15.8)
STUDY DRUG TOXICITY	1 (0.3)	0	1 (0.3)
UNKNOWN	3 (1.0)	1 (0.3)	1 (0.3)
OTHER	7 (2.2)	13 (4.2)	8 (2.6)

Source: Table 8.1-1 of the CA209067 Final OS CSR[2]

No additional drug-related deaths were reported within 100 days of the last dose of study drug since the database lock for the CA209067 Interim CSR. In total:

- Two drug-related deaths were reported within 100 days after last dose of study drug: 1 subject in the NIVO group died due to drug-related neutropenia and 1 subject in the IPI group died due to drug-related colon perforation.
- No drug-related deaths were reported in the NIVO+IPI group within 100 days after last dose of study drug.
- Two new drug-related deaths were reported >100 days after last dose of study drug, in the NIVO+IPI group, one due to global cardiac insufficiency of autoimmune myocarditis, and one due to liver toxicity/liver necrosis.

The verbatim terms reported for the 'other' reasons for death are provided below. Bolding in the list below indicates newly reported (since the Interim CSR) deaths due to other reasons: NIVO 5, NIVO+IPI 1, and IPI 3. These verbatim terms were consistent with events expected in the population under study and none were considered related to study drug.

Nivolumab (13 subjects)

- CA209067 (disease progression, euthanasia)
- CA209067 (disease progression, euthanasia)
- **CA209067 (metastatic disease)**
- CA209067(intra-abdominal problem)
- CA209067(intracranial haemorrhage and subarachnoid haemorrhage)
- **CA209067(sepsis)**
- CA209067(perforated diverticulitis)
- **CA209067(macrophagic activation syndrome)**
- **CA209067(intraparenchymal haemorrhage due to hemorrhagic metastases and melanoma)**
- CA209067(sepsis)
- CA209067(upper gastrointestinal bleeding)
- **CA209067(gastro-intestinal bleeding)**
- CA209067(sepsis)

Nivolumab+ipilimumab (14 subjects):

- CA209067(pulmonary embolism)
- CA209067(pulmonary embolism)
- CA209067(emphysema & lung fibrosis)
- CA209067(pneumonia)
- **CA209067(heart attack)**
- CA209067(multi organ failure)
- CA209067(euthanasia)
- CA209067(presumed pulmonary embolism)
- CA209067(respiratory failure)
- CA209067(accident)
- CA209067(sudden cardiac death)
- CA209067(pneumonia)
- CA209067(worsening of general condition)
- CA209067(respiratory failure)

Ipilimumab (11 subjects):

- CA209067(euthanasia due to disease progression)
- **CA209067(cardiac complications)**
- CA209067(colitis/perforation due to subsequent ipilimumab)
- **CA209067(pulmonary embolism)**
- CA209067(cardiac arrest)
- **CA209067(intracranial haemorrhage)**
- CA209067(cardiac arrest)
- CA209067(sepsis)
- CA209067(severe acute lithium intoxication)
- CA209067(respiratory distress and cardiac decompensation)
- CA209067(respiratory failure)

Laboratory findings

Among all treated subjects, any grade shifts from baseline value were reported within 30 days of last dose for selected laboratory tests including absolute neutrophils, haemoglobin, leukocytes, lymphocytes, platelet count, alkaline phosphatase (ALP), total bilirubin, AST, ALT, creatinine, and thyroid stimulating hormone (TSH). Laboratory measurements were recorded regardless of causality and some were correlated with reported laboratory-based AEs.

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 across all treatment groups.

In the NIVO group, the only Grade 3-4 hematologic abnormality reported in ≥ 5% of subjects was decreased absolute lymphocytes (5.6% Grade 3 only), in the NIVO+IPI group was decreased absolute lymphocytes (5.5% Grade 3 only) and in the IPI group were decreased haemoglobin (6.0% Grade 3 only) and decreased absolute lymphocytes (5.4% Grade 3; 0.3% Grade 4).

Serum Chemistry

Liver Function Tests

In all 3 treatment groups, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2.

Five subjects in the NIVO group and 7 subjects in the NIVO+IPI group had concurrent ALT or AST elevation > 3 x upper limit of normal (ULN) with total bilirubin > 2 x ULN within 30 days of last dose of study therapy in subjects with available specific liver test results. Four subjects in the NIVO group and 7 subjects in the NIVO+IPI group had concurrent ALT or AST elevation > 3 x upper limit of normal (ULN) with total bilirubin > 2 x ULN within 1 day of last dose of study therapy in subjects with available specific liver test results. A summary of on-treatment laboratory abnormalities in specific liver tests is provided in Table 58.

Table 58: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects - CA209067

	Nivolumab N = 313	Nivolumab + Ipilimumab N = 313	Ipilimumab N = 311	Total N = 937
	N = 305	N = 297	N = 299	N = 901
ALT OR AST > 3XULN	23 (7.5)	76 (25.6)	16 (5.4)	115 (12.8)
ALT OR AST > 5XULN	13 (4.3)	52 (17.5)	9 (3.0)	74 (8.2)
ALT OR AST > 10XULN	5 (1.6)	22 (7.4)	6 (2.0)	33 (3.7)
ALT OR AST > 20XULN	3 (1.0)	8 (2.7)	2 (0.7)	13 (1.4)
	N = 304	N = 295	N = 299	N = 898
TOTAL BILIRUBIN > 2XULN	9 (3.0)	9 (3.1)	3 (1.0)	21 (2.3)
	N = 304	N = 295	N = 299	N = 898
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	4 (1.3)	7 (2.4)	0	11 (1.2)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	5 (1.6)	7 (2.4)	0	12 (1.3)

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.
Source: Table 8.12.2.1-1 of the CA209067 Final CSR[2]

Kidney Function Tests

In all treatment groups, the majority of subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period.

In the NIVO group, on-treatment abnormalities in creatinine (increases) were Grade 1 or 2, except in 2 subjects with Grade 3 abnormalities. In the NIVO+IPI group, there were 7 subjects with Grade 3 and 1 subject with a Grade 4 on-treatment increased creatinine levels. In the IPI group, there were 4 subjects with Grade 3 on-treatment increased creatinine and no subject with Grade 4 abnormalities.

Thyroid Function Tests

The majority of subjects in all treatment groups had normal thyroid-stimulating hormone (TSH) levels at baseline and throughout the treatment period (Table 59). The proportion of subjects with TSH increases (> ULN) from baseline was numerically similar compared to the NIVO and NIVO+IPI groups, and greater than the proportion of subjects with TSH increases in the IPI group. In the NIVO+IPI group, the proportion of subjects with TSH decreases (< lower limit of normal [LLN]) from baseline was greater than that reported in the NIVO and IPI groups.

Table 59: Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests - (SI Units) – Treated Subjects with at Least One On-Treatment TSH - CA209067

	Nivolumab N = 304	Nivolumab + Ipilimumab N = 292	Ipilimumab N = 298	Total N = 894
TSH > ULN	99 (32.6)	92 (31.5)	52 (17.4)	243 (27.2)
TSH > ULN				
WITH TSH <= ULN AT BASELINE	74 (24.3)	73 (25.0)	21 (7.0)	168 (18.8)
TSH > ULN				
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	43 (14.1)	57 (19.5)	16 (5.4)	116 (13.0)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	36 (11.8)	25 (8.6)	24 (8.1)	85 (9.5)
WITH FT3/FT4 TEST MISSING (A) (B)	20 (6.6)	10 (3.4)	12 (4.0)	42 (4.7)
TSH < LLN	72 (23.7)	126 (43.2)	49 (16.4)	247 (27.6)
TSH < LLN				
WITH TSH >= LLN AT BASELINE	66 (21.7)	115 (39.4)	43 (14.4)	224 (25.1)
TSH < LLN				
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	38 (12.5)	76 (26.0)	13 (4.4)	127 (14.2)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	26 (8.6)	33 (11.3)	23 (7.7)	82 (9.2)
WITH FT3/FT4 TEST MISSING (A) (B)	8 (2.6)	17 (5.8)	13 (4.4)	38 (4.3)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date.
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.
Source: Table 8.12.2.3-1 of the CA209067 Final OS CSR

Electrolytes

In all 3 treatment groups, most subjects had normal electrolyte levels during the treatment reporting period. In all groups, abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. In all groups, the only Grade 3-4 abnormalities in electrolytes reported in ≥ 2% of subjects were hyponatremia and hypokalaemia: NIVO group: hyponatremia (2.6% Grade 3, 0.7% Grade 4); NIVO+IPI group: hypokalaemia (3.4% Grade 3, 1.0% Grade 4), hyponatremia (9.9% Grade 3, 0.7% Grade 4); IPI group: hyponatremia (6.7% Grade 3, 0.3% Grade 4)

Vital Signs

Vital signs and oxygen saturation by pulse oximetry were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

Safety in special populations

The frequencies of all-causality AEs for subgroups of gender, race, age, and region were similar in all treatment groups and consistent with that reported in the CA209067 Interim CSR.

Safety by age in CA209067 Study

In CA209067, the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented for nivolumab monotherapy in Table 60, and for nivolumab + ipilimumab combination therapy in Table 61. Interpretation is limited by small number of subjects in the 75 to 84 years of age subgroup (n = 29 in the NIVO group, and n = 31 in the NIVO+IPI group) and in the ≥ 85 years of age subgroup (n = 10 in the NIVO group, and n = 3 in the NIVO+IPI group).

Table 60: Summary of Safety Results by Age Group- All Nivolumab Monotherapy Treated Subjects in CA209067

	Number of Subjects (%)			
MedDRA Terms	Age < 65 years (N = 196)	Age 65-74 years (N = 78)	Age 75-84 years (N = 29)	Age 85+ years (N = 10)
Total AEs	195 (99.5)	78 (100.0)	29 (100.0)	10 (100.0)
Serious AEs -Total	73 (37.2)	37 (47.4)	17 (58.6)	6 (60.0)
Fatal	8 (4.1)	5 (6.4)	5 (17.2)	3 (30.0)
Hospitalization/prolong existing hospitalization	60 (30.6)	28 (35.9)	15 (51.7)	3 (30.0)
Life-threatening	1 (0.5)	0	1 (3.4)	0
Cancer	8 (4.1)	3 (3.8)	4 (13.8)	1 (10.0)
Congenital anomaly	0	0	0	0
Drug dependence/abuse	0	0	0	0
Important medical event	8 (4.1)	5 (6.4)	0	1 (10.0)
Persistent/significant disability	0	0	0	0
Other	0	1 (1.3)	0	0
AEs leading to drop-out	25 (12.8)	22 (28.2)	6 (20.7)	4 (40.0)
Psychiatric disorders	45 (23.0)	15 (19.2)	6 (20.7)	3 (30.0)
Nervous system disorders	91 (46.4)	37 (47.4)	13 (44.8)	6 (60.0)
Accidents and Injuries	29 (14.8)	7 (9.0)	8 (27.6)	1 (10.0)
Cardiac disorders	18 (9.2)	4 (5.1)	3 (10.3)	0
Vascular disorders	38 (19.4)	16 (20.5)	9 (31.0)	4 (40.0)
Central nervous system vascular disorders (SMQ)	3 (1.5)	5 (6.4)	1 (3.4)	0
Central nervous system vascular disorders (HLGT)	0	1 (1.3)	1 (3.4)	0
Infections and infestations	99 (50.5)	41 (52.6)	10 (34.5)	5 (50.0)
Anticholinergic syndrome	76 (38.8)	28 (35.9)	13 (44.8)	4 (40.0)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	30 (15.3)	10 (12.8)	7 (24.1)	3 (30.0)

MedDRA Version: 19.0; CTC version 4.0
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.

Source: Appendix M.431-EUSCS (total AEs), Appendix M.432-EUSCS (SAEs), Appendix M.433-EUSCS (AEs leading to dropout), Appendix M.434-EUSCS (AEs by HLGT/SOC/SMQ), Appendix M.435-EUSCS (summary of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures), Appendix M.436-EUSCS (SAEs by categories), Appendix M.437-EUSCS (QoL) of Appendix 2.

Table 61: Summary of Safety Results by Age Group- All Nivolumab + Ipilimumab Combination Therapy Treated Subjects in CA209067

	Number of Subjects (%)			
MedDRA Terms	Age < 65 years (N = 185)	Age 65-74 years (N = 94)	Age 75-84 years (N = 31)	Age 85+ years (N = 3)
Total AEs	184 (99.5)	94 (100.0)	31 (100.0)	3 (100.0)
Serious AEs -Total	130 (70.3)	68 (72.3)	22 (71.0)	3 (100.0)
Fatal	12 (6.5)	10 (10.6)	3 (9.7)	0
Hospitalization/prolong existing hospitalization	119 (64.3)	63 (67.0)	17 (54.8)	3 (100.0)
Life-threatening	5 (2.7)	3 (3.2)	0	0
Cancer	3 (1.6)	1 (1.1)	1 (3.2)	0
Congenital anomaly	0	0	0	0
Drug dependence/abuse	0	0	0	0
Important medical event	20 (10.8)	11 (11.7)	5 (16.1)	0
Persistent/significant disability	1 (0.5)	0	0	0
Other	3 (1.6)	0	1 (3.2)	0
AEs leading to drop-out	91 (49.2)	42 (44.7)	13 (41.9)	1 (33.3)
Psychiatric disorders	47 (25.4)	30 (31.9)	7 (22.6)	0
Nervous system disorders	96 (51.9)	40 (42.6)	10 (32.3)	1 (33.3)
Accidents and Injuries	17 (9.2)	16 (17.0)	7 (22.6)	0
Cardiac disorders	19 (10.3)	16 (17.0)	7 (22.6)	0
Vascular disorders	35 (18.9)	23 (24.5)	7 (22.6)	1 (33.3)
Central nervous system vascular disorders (SMQ)	4 (2.2)	4 (4.3)	2 (6.5)	0
Central nervous system vascular disorders (HLGT)	2 (1.1)	1 (1.1)	2 (6.5)	0
Infections and infestations	92 (49.7)	48 (51.1)	13 (41.9)	1 (33.3)
Anticholinergic syndrome	114 (61.6)	51 (54.3)	17 (54.8)	1 (33.3)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	31 (16.8)	18 (19.1)	8 (25.8)	1 (33.3)

MedDRA Version: 19.0; CTC version 4.0
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.
Source: Appendix M.431-EUSCS (total AEs), Appendix M.432-EUSCS (SAEs), Appendix M.433-EUSCS (AEs leading to dropout), Appendix M.434-EUSCS (AEs by HLGT/SOC/SMQ), Appendix M.435-EUSCS (summary of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures), Appendix M.436-EUSCS (SAEs by categories), Appendix M.437-EUSCS (QoL) of Appendix 2.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Nivolumab has minor influence on the ability to drive and use machines. Fatigue is a very common side effect which may also impair the ability to drive and use machines. Patients should be advised not to drive or use machines if they feel tired.

Safety related to drug-drug interactions and other interactions

Immunogenicity

The immunogenicity of nivolumab and ipilimumab in study CA209067 was updated with this final OS analysis. The incidence of nivolumab anti-drug antibodies (ADA) was 12.3% (36/292 subjects) and 44% (128/291 subjects) following NIVO monotherapy and NIVO+IPI in combination, respectively, in the updated analysis for CA209067. The presence of ADA did not appear to have an effect on the safety of nivolumab when administered alone or in combination with ipilimumab (refer to Table 62).

There was low to minimal impact on ipilimumab immunogenicity when ipilimumab was administered in combination with nivolumab. Of the ADA evaluable subjects in the NIVO+IPI group, 24/290 (8.3%) were ipilimumab ADA positive after treatment. This incidence of ADA to ipilimumab was similar, 5.7%, in the IPI monotherapy group. Ipilimumab ADA results are consistent with those in the Interim CSR.

In the NIVO+IPI combination group, the nivolumab ADA titers appear to decrease after Week 12 (C3W1), corresponding to the beginning of the maintenance phase when ipilimumab treatment was discontinued as per the schedule.

Table 62: Summary of Anti-drug Antibody Assessments - All Nivolumab or Ipilimumab Treated Subjects with Baseline and at Least One Post-Baseline Assessment

	Number of Subjects (%)			
	Nivolumab	Nivolumab + Ipilimumab		Ipilimumab
	Nivolumab N = 292	Nivolumab N = 291	Ipilimumab N = 290	Ipilimumab N = 296
BASELINE ADA POSITIVE	11 (3.8)	9 (3.1)	18 (6.2)	13 (4.4)
ADA POSITIVE	36 (12.3)	128 (44.0)	24 (8.3)	17 (5.7)
PERSISTENT POSITIVE	1 (0.3)	15 (5.2)	0	0
NOT PP - LAST SAMPLE POSITIVE	10 (3.4)	34 (11.7)	8 (2.8)	4 (1.4)
OTHER POSITIVE	25 (8.6)	79 (27.1)	16 (5.5)	13 (4.4)
NEUTRALIZING ADA POSITIVE	1 (0.3)	17 (5.8)	1 (0.3)	0
ADA NEGATIVE	256 (87.7)	163 (56.0)	266 (91.7)	279 (94.3)

Baseline ADA Positive Subject: A subject with Baseline ADA positive sample.
ADA Positive Subject: 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 with the first and last ADA positive samples at least 16 weeks apart.
Not PP - 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.
Neutralising ADA Positive: At least one ADA positive sample with neutralising antibodies detected post-baseline.
ADA Negative Subject: A subject with no ADA positive sample after the initiation of treatment.
Post-baseline assessments are assessments reported after initiation of treatment.
End of Infusion samples are excluded from determination of ADA status.
Source: Table 8.7.10

Effect of ADA on Safety

For nivolumab: 1/36 (2.8%) nivolumab ADA positive and 16/256 (6.3%) nivolumab ADA negative subjects in the NIVO group and 8/128 (6.3%) nivolumab ADA positive and 7/163 (4.3%) nivolumab ADA negative subjects in the NIVO+IPI combination group experienced AEs in the hypersensitivity/infusion reaction category. (Table 63).

Table 63: Summary of select Adverse Evemnts of Hypersensitivity / Infusion reaction by ADA Status (Positive, Negative). All Treated Subjects with ADA Positive or ADA Negative

Select Adverse Events Category: HYPERSENSITIVITY/INFUSION REACTION

	Nivolumab		Nivolumab + Ipilimumab				Ipilimumab	
	Nivolumab ADA		Nivolumab ADA		Ipilimumab ADA		Ipilimumab ADA	
Preferred Term	Positive N = 36	Negative N = 256	Positive N = 128	Negative N = 163	Positive N = 24	Negative N = 266	Positive N = 17	Negative N = 279
TOTAL SUBJECTS WITH AN EVENT	1 (2.8)	16 (6.3)	8 (6.3)	7 (4.3)	1 (4.2)	14 (5.3)	1 (5.9)	9 (3.2)
INFUSION RELATED REACTION	0	8 (3.1)	4 (3.1)	4 (2.5)	0	8 (3.0)	1 (5.9)	7 (2.5)
HYPERSENSITIVITY	0	9 (3.5)	3 (2.3)	2 (1.2)	1 (4.2)	4 (1.5)	0	1 (0.4)
BRONCHOSPASM	1 (2.8)	0	1 (0.8)	0	0	1 (0.4)	0	0
ANAPHYLACTIC REACTION	0	0	0	1 (0.6)	0	1 (0.4)	0	0
ANAPHYLACTIC SHOCK	0	0	0	0	0	0	0	1 (0.4)

Discontinuation due to adverse events

The overall frequencies of AEs leading to discontinuation (regardless of causality and drug-related) were lowest in the NIVO group and highest in the NIVO+IPI group.

AEs leading to discontinuation were reported in 18.2% of subjects in the NIVO group, 47.0% of subjects in the NIVO+IPI group and 25.1% of subjects in the IPI group (Table 64). Grade 3-4 AEs

leading to discontinuation were reported in 12.1%, 35.5%, and 21.9% of the subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO group, the most frequently reported AEs leading to discontinuation were malignant neoplasm progression (3.2%), and diarrhoea (2.2%), in the NIVO+IPI group were colitis (9.6%), diarrhoea (8.0%), ALT increased (4.8%), and AST increased (4.5%) and in the IPI group were colitis (7.1%), diarrhoea (4.8%), and malignant neoplasm progression (3.9%).

Drug-related AEs leading to discontinuation were reported in 11.5% of subjects in the NIVO group, 39.6% of subjects in the NIVO+IPI group, and 16.1% of subjects in the IPI group (Table 65). Grade 3-4 drug-related AEs leading to discontinuation were reported in 7.7%, 31.0%, and 14.1% of the subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

In the NIVO group, the most frequently reported drug-related AE leading to discontinuation reported were diarrhoea (2.2%) and fatigue and ALT increased (each 1.0%), in the NIVO+IPI group were colitis (9.6%), diarrhoea (8.0%), ALT increased (4.8%), and AST increased (4.5%) and in the IPI group were colitis (7.1%) and diarrhoea (4.8%).

Immune related adverse reactions leading to permanent discontinuation across the pooled melanoma safety database of patients treated with Ipilimumab in combination with nivolumab have been summarized in Table 66. The percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment with ipilimumab in combination with nivolumab.

Table 64: AEs Leading to Discontinuation (All Causality) by Worst CTC Grade Reported in at Least 2 Treated Subjects - CA209067

System Organ Class (%) Preferred Term (%)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	57 (18.2)	38 (12.1)	2 (0.6)	147 (47.0)	111 (35.5)	5 (1.6)	78 (25.1)	68 (21.9)	1 (0.3)
GASTROINTESTINAL DISORDERS	15 (4.8)	10 (3.2)	1 (0.3)	55 (17.6)	45 (14.4)	0	39 (12.5)	35 (11.3)	0
DIARRHEA	7 (2.2)	4 (1.3)	0	25 (8.0)	21 (6.7)	0	15 (4.8)	13 (4.2)	0
COLITIS	2 (0.6)	2 (0.6)	0	30 (9.6)	23 (7.3)	0	22 (7.1)	21 (6.8)	0
PANCREATITIS	2 (0.6)	2 (0.6)	0	0	0	0	0	0	0
AUTOIMMUNE COLITIS	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
NAUSEA	1 (0.3)	0	0	2 (0.6)	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	13 (4.2)	8 (2.6)	1 (0.3)	5 (1.6)	2 (0.6)	1 (0.3)	14 (4.5)	13 (4.2)	0
MALIGNANT NEOPLASM PROGRESSION	10 (3.2)	7 (2.2)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	12 (3.9)	11 (3.5)	0
METASTASES TO CENTRAL NERVOUS SYSTEM	0	0	0	0	0	0	2 (0.6)	2 (0.6)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (1.6)	2 (0.6)	0	8 (2.6)	2 (0.6)	0	2 (0.6)	1 (0.3)	0
ARTHRALGIA	0	0	0	3 (1.0)	0	0	0	0	0
MYOSITIS	0	0	0	2 (0.6)	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (1.6)	3 (1.0)	1 (0.3)	16 (5.1)	8 (2.6)	3 (1.0)	4 (1.3)	3 (1.0)	0
COUGH	2 (0.6)	1 (0.3)	0	0	0	0	0	0	0
DYSPNOEA	1 (0.3)	1 (0.3)	0	4 (1.3)	3 (1.0)	0	0	0	0
PNEUMONITIS	1 (0.3)	1 (0.3)	0	6 (1.9)	2 (0.6)	0	1 (0.3)	0	0
RESPIRATORY FAILURE	1 (0.3)	0	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0
PLEURAL EFFUSION	0	0	0	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
PULMONARY EMBOLISM	0	0	0	2 (0.6)	0	2 (0.6)	1 (0.3)	1 (0.3)	0
INVESTIGATIONS	4 (1.3)	4 (1.3)	0	31 (9.9)	28 (8.9)	0	3 (1.0)	3 (1.0)	0
ALANINE AMINOTRANSFERASE INCREASED	3 (1.0)	3 (1.0)	0	15 (4.8)	14 (4.5)	0	3 (1.0)	3 (1.0)	0
ASPARTATE AMINOTRANSFERASE INCREASED	2 (0.6)	2 (0.6)	0	14 (4.5)	12 (3.8)	0	2 (0.6)	2 (0.6)	0
HEPATIC ENZYME INCREASED	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
LIPASE INCREASED	0	0	0	4 (1.3)	3 (1.0)	0	0	0	0
TRANSAMINASES INCREASED	0	0	0	7 (2.2)	6 (1.9)	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (1.0)	2 (0.6)	0	1 (0.3)	1 (0.3)	0	3 (1.0)	3 (1.0)	0
NEUTROPENIA	2 (0.6)	1 (0.3)	0	0	0	0	1 (0.3)	1 (0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (1.0)	2 (0.6)	0	9 (2.9)	3 (1.0)	1 (0.3)	1 (0.3)	1 (0.3)	0
FATIGUE	3 (1.0)	2 (0.6)	0	3 (1.0)	1 (0.3)	0	0	0	0
GENERAL PHYSICAL HEALTH DETERIORATION	0	0	0	3 (1.0)	2 (0.6)	0	0	0	0
PYREXIA	0	0	0	2 (0.6)	0	0	0	0	0
HEPATOBILIARY DISORDERS	3 (1.0)	2 (0.6)	0	12 (3.8)	8 (2.6)	0	1 (0.3)	1 (0.3)	0
AUTOIMMUNE HEPATITIS	2 (0.6)	1 (0.3)	0	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
HEPATOTOXICITY	1 (0.3)	1 (0.3)	0	6 (1.9)	4 (1.3)	0	0	0	0
HEPATITIS	0	0	0	3 (1.0)	2 (0.6)	0	0	0	0
HYPERBILIRUBINAEMIA	0	0	0	2 (0.6)	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.6)	1 (0.3)	0	5 (1.6)	4 (1.3)	0	2 (0.6)	1 (0.3)	0
PRURITUS	0	0	0	2 (0.6)	2 (0.6)	0	1 (0.3)	0	0
RASH	0	0	0	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
ENDOCRINE DISORDERS	1 (0.3)	1 (0.3)	0	8 (2.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
HYPOPHYSITIS	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0	0	0	0
HYPOTHYROIDISM	0	0	0	2 (0.6)	0	0	0	0	0
THYROIDITIS	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0

MedDRA Version: 19.0, CTC version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.3-1 of the CA209067 Final OS CSR[2].

Table 65: Drug-related AEs Leading to Discontinuation by Worst CTC Grade Reported in at Least 2 Subjects - All Treated Subjects - CA209067

System Organ Class (%) Preferred Term (%)	Nivolumab N = 313			Nivolumab + Ipilimumab N = 313			Ipilimumab N = 311		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	36 (11.5)	24 (7.7)	0	124 (39.6)	97 (31.0)	0	50 (16.1)	44 (14.1)	1 (0.3)
GASTROINTESTINAL DISORDERS	11 (3.5)	8 (2.6)	0	54 (17.3)	43 (13.7)	0	36 (11.6)	34 (10.9)	0
DIARRHEA	7 (2.2)	4 (1.3)	0	25 (8.0)	21 (6.7)	0	15 (4.8)	13 (4.2)	0
COLITIS	2 (0.6)	2 (0.6)	0	30 (9.6)	23 (7.3)	0	22 (7.1)	21 (6.8)	0
PANCREATITIS	2 (0.6)	2 (0.6)	0	0	0	0	0	0	0
AUTOIMMUNE COLITIS	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
NAUSEA	1 (0.3)	0	0	2 (0.6)	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (1.6)	2 (0.6)	0	6 (1.9)	1 (0.3)	0	1 (0.3)	0	0
ARTHRALGIA	0	0	0	2 (0.6)	0	0	0	0	0
MYOSITIS	0	0	0	2 (0.6)	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (1.3)	3 (1.0)	0	10 (3.2)	5 (1.6)	0	1 (0.3)	0	0
COUGH	2 (0.6)	1 (0.3)	0	0	0	0	0	0	0
DYSPNOEA	1 (0.3)	1 (0.3)	0	3 (1.0)	2 (0.6)	0	0	0	0
PNEUMONITIS	1 (0.3)	1 (0.3)	0	6 (1.9)	2 (0.6)	0	1 (0.3)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (1.0)	2 (0.6)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
NEUTROPENIA	2 (0.6)	1 (0.3)	0	0	0	0	1 (0.3)	1 (0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (1.0)	2 (0.6)	0	3 (1.0)	0	0	0	0	0
FATIGUE	3 (1.0)	2 (0.6)	0	2 (0.6)	0	0	0	0	0
HEPATOBILIARY DISORDERS	3 (1.0)	2 (0.6)	0	12 (3.8)	8 (2.6)	0	1 (0.3)	1 (0.3)	0
AUTOIMMUNE HEPATITIS	2 (0.6)	1 (0.3)	0	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
HEPATOTOXICITY	1 (0.3)	1 (0.3)	0	6 (1.9)	4 (1.3)	0	0	0	0
HEPATITIS	0	0	0	3 (1.0)	2 (0.6)	0	0	0	0
HYPERBILIRUBINAEMIA	0	0	0	2 (0.6)	0	0	0	0	0
INVESTIGATIONS	3 (1.0)	3 (1.0)	0	31 (9.9)	28 (8.9)	0	3 (1.0)	3 (1.0)	0
ALANINE AMINOTRANSFERASE INCREASED	3 (1.0)	3 (1.0)	0	15 (4.8)	14 (4.5)	0	3 (1.0)	3 (1.0)	0
ASPARTATE AMINOTRANSFERASE INCREASED	2 (0.6)	2 (0.6)	0	14 (4.5)	12 (3.8)	0	2 (0.6)	2 (0.6)	0
HEPATIC ENZYME INCREASED	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
LIPASE INCREASED	0	0	0	4 (1.3)	3 (1.0)	0	0	0	0
TRANSAMINASES INCREASED	0	0	0	7 (2.2)	6 (1.9)	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.6)	1 (0.3)	0	5 (1.6)	4 (1.3)	0	2 (0.6)	1 (0.3)	0
PRURITUS	0	0	0	2 (0.6)	2 (0.6)	0	1 (0.3)	0	0
RASH	0	0	0	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
ENDOCRINE DISORDERS	1 (0.3)	1 (0.3)	0	7 (2.2)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
HYPOPHYSITIS	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0
HYPOTHYROIDISM	0	0	0	2 (0.6)	0	0	0	0	0
THYROIDITIS	0	0	0	2 (0.6)	1 (0.3)	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.3-2 of the CA209067 Final OS CSR[2].

Table 66: Immune-related adverse reactions leading to permanent discontinuation

	Ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg %
Immune-related adverse reaction leading to permanent discontinuation	
Pneumonitis	2.0
Colitis	16
Hepatitis	9
Nephritis and Renal Dysfunction	1.1
Endocrinopathies	2.7
Skin	0.9
H Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen ypersensitivity/Infusion Reaction	0

Post marketing experience

Nivolumab + Ipilimumab combination therapy was first approved on 30-Sep-2015 in the US and on 11-May-2016 in the EU for the treatment of patients with unresectable or metastatic melanoma under BLA 125554/S-02 and Type II variation EMEA/H/C/003985/II/0003, respectively, and has since been approved in multiple countries.

On 21-Jun-2016, within a type II variation (refer to EMEA/H/C/003985/II/00176) Section 4.2 of the SmPC was updated with information aimed at guidance for atypical responses to treatment i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage, associated with nivolumab monotherapy and combination therapy with ipilimumab.

On 27-Jul-2016, the MAH submitted a type II variation (refer to EMEA/H/C/003985/II/00187) to revise Sections 4.2, 4.4, and 4.8 of the OPDIVO (nivolumab) SmPC in order to update the safety information for toxic epidermal necrolysis, Stevens-Johnson syndrome, myositis, myocarditis, and rhabdomyolysis based on findings from routine pharmacovigilance activities related to both nivolumab monotherapy and combination therapy with ipilimumab.

On 18-Apr-2017, a type IB variation was submitted (refer to EMEA/H/C/003985/IB/00359) to revise Section 4.8 of the OPDIVO and Yervoy SmPC to implement agreed wording for the signal of "pemphigoid," on 06-Mar-2017 following Pharmacovigilance Risk Assessment Committee (PRAC) adoption 09-Feb-2017 (endorsed by CHMP on 23-Feb-2017).

Further to the PRAC assessment of nivolumab PSUSA/10379/20160710, the Committee for Medicinal Products for Human Use (CHMP) on 26-Jan-2017 issued a scientific conclusion following which Sections 4.4 and 4.8 of the OPDIVO (nivolumab) SmPC were updated to include encephalitis as an undesirable effect for the combination therapy.

Further to the PRAC assessment of nivolumab PSUSA/10379/20170111, the CHMP on 20-Jul-2017 issued a scientific conclusion following Sections 4.4 and 4.8 of the OPDIVO (nivolumab) SmPC were updated to add Vogt-Koyanagi-Harada syndrome as an undesirable effect for the combination therapy.

2.5.1. Discussion on clinical safety

Based on updated analyses of safety data from CA209067, with a database lock of 13-Sep- 2016, findings were consistent with the mechanisms of action of nivolumab and ipilimumab and with expectations based on prior data reported in the CA209067 Interim CSR (DBL 17-Feb-2015) in terms of type, frequency and severity of reported events. During the interval between the CA209067 Interim CSR and this final analysis of safety, no new safety concerns were reported which could alter the characterization of the safety profile of NIVO or NIVO+IPI. As expected with the longer duration of treatment and follow-up, the safety profile is slightly worse at the updated database lock relative to the CA209067 Interim CSR database lock (17-Feb-2015).

The median duration of therapy was 2.83 months in the NIVO+IPI group. 87.8% of treated subjects in the NIVO group received ≥ 90% of the planned dose intensity, which was similar to ipilimumab in the IPI group (88.4%) and greater than nivolumab and ipilimumab in the NIVO+IPI group (69.0% and 70.6%, respectively).

In the NIVO+IPI group the most frequently reported AEs (≥ 20% of subjects) were diarrhoea (54.0%), fatigue (51.8%), nausea (43.8%), pyrexia (39.9%), pruritus (39.0%), rash (32.9%), vomiting (31.3%), decreased appetite (29.4%), headache (25.6%), cough (24.3%), dyspnea (23.0%), arthralgia (21.4%), and increased alanine aminotransferase (ALT) (20.8%).

In the NIVO+IPI group the most frequently reported Grade 3-4 AEs (≥ 5% of subjects) were lipase increased (12.5%), diarrhoea (11.2%), increased ALT (9.3%), colitis (8.3%), increased aspartate aminotransferase (AST) (6.7%), and fatigue (6.4%).

In the NIVO+IPI group the most frequently reported drug-related AEs (≥ 15% of subjects) were diarrhoea (45.4%), fatigue (37.7%), pruritus (35.8%), rash (29.1%), nausea (28.1%), pyrexia and decreased appetite (each 19.2%), ALT increased (18.8%), hypothyroidism and AST increased (each 16.3%), and vomiting (16.0%).

The overall frequency of AEs (regardless of causality) leading to a dose delay was 35.8% in the NIVO group, 58.1% in the NIVO+IPI group, and 40.8% in the IPI group.

Grade 3-4 drug-related AEs were reported in 20.8% of subjects in the NIVO group, 58.5% in the NIVO+IPI group, and 27.7% of subjects in the IPI group. In the NIVO+IPI group, the most frequently reported Grade 3-4 drug-related AEs (≥ 5% of subjects) were increased lipase (10.9%), diarrhoea (9.6%), increased ALT (8.6%), colitis (8.3%), and increased AST (6.1%).

Select AEs: The most frequently reported any-grade drug-related select AE categories (in order of descending frequency) across all treatment groups were skin, GI, endocrine, and hepatic. Within these categories, the most common drug-related select AEs across all 3 treatment groups were rash and pruritus, diarrhoea, hypothyroidism, and ALT increased, respectively. Higher frequencies of drug-related select AEs in these categories were observed in the NIVO+IPI combination group than in the NIVO and IPI monotherapy groups. Most select AEs were Grade 1-2. The majority of select AEs resolved and were manageable using the recommended treatment guidelines for early evaluation and intervention.

The overall frequency of endocrine select AEs were greater in the NIVO+IPI group (38.0%) and drug-related endocrine select AEs were reported 33.2%. The most commonly reported drug-related endocrine select AE in all 3 treatment groups was hypothyroidism. Endocrine drug-related select AEs (any grade) led to permanent discontinuation of 2.6% of subjects in the NIVO+IPI.

The overall frequency of GI select AEs was greater in the NIVO+IPI group (56.5%), and 47.9% had GI select AEs that were considered to be drug related by the investigator. The most frequent drug-related event was diarrhoea, 9.6% of the events were Grade 3-4 in the NIVO+IPI group. Drug-related gastrointestinal select AEs (any grade) led to permanent discontinuation of study drug in 16.6% of subjects in the NIVO+IPI group.

The overall frequency of hepatic select AEs was greater in the NIVO+IPI group (36.7%) and 32.6% of subjects were considered to be drug related by the investigator. The most frequent drug-related event across all 3 treatment groups was increased ALT and increased AST. Drug-related hepatic select AEs led to permanent discontinuation of study drug in 11.2% of subjects in the NIVO+IPI group.

The overall frequency of pulmonary select AEs was greater in the NIVO+IPI group (7.7%) compared to the NIVO and IPI monotherapy groups (2.2% and 3.2%, respectively). In the NIVO+IPI group, 7.3% of subjects experienced pulmonary select AEs that were considered to be drug-related. Drug-related pulmonary select AEs led to permanent discontinuation of study drug in 0.3%, 1.9%, and 0.3% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

The overall frequency of renal select AEs was greater in the NIVO+IPI group (11.2%) compared to the NIVO and IPI monotherapy groups (3.2% and 4.8%, respectively). In the NIVO+IPI group, 6.7% of subjects experienced renal select AEs that were considered to be drug-related by the investigator compared to 3 subjects (1.0%) in the NIVO group and 8 subjects (2.6%) in the IPI group. The most frequently reported drug-related event across all groups was increased blood creatinine. Drug-related renal select AEs (any grade) led to permanent discontinuation of study drug in 0.3%, 1.3%, and 0.3% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

The overall frequency of skin select AEs was similar between the NIVO+IPI group and IPI group (65.5% and 63.7%, respectively), while slightly lower in the NIVO group (56.9%). In the NIVO+IPI group, 61.3% of subjects experienced skin select AEs that were considered to be drug-related by the investigator compared to 45.7% in the NIVO group and 55.3% in the IPI group. Across all treatment groups, the most frequently reported drug-related skin select AEs were rash and pruritus across all treatment groups. Drug-related skin select AEs led to permanent discontinuation of study drug in 0.6%, 1.3%, and 0.6% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively.

The overall frequency of hypersensitivity/infusion reactions was similar between the NIVO and NIVO+IPI groups (5.4% and 4.8%, respectively) while slightly lower in the IPI group (2.9%). In the NIVO group, 4.5% of subjects experienced hypersensitivity/infusion reactions that were considered to be drug related by the investigator compared to 4.2% in the NIVO+IPI group and 2.6% in the IPI group. No drug-related hypersensitivity/infusion reactions led to permanent discontinuation.

In the NIVO+IPI group, OESIs within 100 days of last dose of nivolumab were reported as follows: 1 subject with Guillain-Barré, 4 subjects with pancreatitis, 5 subjects with uveitis, 1 subject with encephalitis and 3 subjects with myositis. In the NIVO group were reported: 5 subjects with a pancreatitis event (3 with pancreatitis, 2 with autoimmune pancreatitis), 4 subjects with a uveitis event (3 with uveitis, 1 iridocyclitis) and 2 subjects with a myositis events (1 dermatomyositis, 1 polymyositis). And in the IPI group, were reported as follows: 1 subject with myasthenia gravis, 3 subjects with a pancreatitis event (2 with pancreatitis, 1 with acute pancreatitis) and 3 subjects with uveitis. Among all treatment groups, the following OESI were not reported: demyelination, myocarditis, and rhabdomyolisis. Cases of fatal toxic epidermal necrolysis (TEN) were not reported.

SAEs were reported in 42.5% of subjects in the NIVO group, 71.2% of subjects in the NIVO+IPI group, and 55.0% of subjects in the IPI group. Consistent with the CA209067 Interim CSR, the overall frequencies of SAEs and drug-related SAEs were lowest in the NIVO group and highest in the NIVO+IPI group. Grade 3-4 SAEs were reported in 33.2%, 53.4%, and 40.5% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively. In the NIVO+IPI group, the most frequently reported SAEs were diarrhoea (10.5%), colitis (9.9%), and pyrexia (8.3%).

Drug-related SAEs were reported in 9.9% of subjects in the NIVO group, 48.6% of subjects in the NIVO+IPI group, and 22.5% of subjects in the IPI group. Grade 3-4 drug-related SAEs were reported in 8.0%, 36.7%, and 16.7% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively. In the NIVO+IPI group, the most frequently reported drug-related SAEs were colitis (9.6%), diarrhoea (8.9%), and pyrexia (4.2%).

Deaths: As of the 13-Sep-2016 database lock, a total of 141 (45%), 127 (40.6%), and 195 (62.7%) deaths were reported in the NIVO, NIVO+IPI, and IPI groups, respectively. Disease progression was the most common cause of death for all groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose.

No additional drug-related deaths were reported within 100 days of the last dose of study drug since the database lock for the CA209067 Interim CSR.

Two new drug-related deaths were reported >100 days after last dose of study drug, in the NIVO+IPI group, one due to global cardiac insufficiency of autoimmune myocarditis, and one due to liver toxicity/liver necrosis.

Consistent with the CA209067 Interim CSR, the overall frequencies of AEs leading to discontinuation (regardless of causality and drug-related) were lowest in the NIVO group and highest in the NIVO+IPI group. AEs leading to discontinuation were reported in 18.2% of subjects in the NIVO group, 47.0% of subjects in the NIVO+IPI group and 25.1% of subjects in the IPI group. Grade 3-4 AEs leading to discontinuation were reported in 12.1%, 35.5%, and 21.9% of the subjects in the NIVO, NIVO+IPI, and IPI groups, respectively. In the NIVO+IPI group, the most frequently reported AEs leading to discontinuation were colitis (9.6%), diarrhoea (8.0%), ALT increased (4.8%), and AST increased (4.5%).

Drug-related AEs leading to discontinuation were reported in 11.5% of subjects in the NIVO group, 39.6% of subjects in the NIVO+IPI group, and 16.1% of subjects in the IPI group. Grade 3-4 drug-related AEs leading to discontinuation were reported in 7.7%, 31.0%, and 14.1% of the subjects in the NIVO, NIVO+IPI, and IPI groups, respectively. In the NIVO+IPI group, the most frequently reported drug-related AEs leading to discontinuation were colitis (9.6%), diarrhoea (8.0%), ALT increased (4.8%), and AST increased (4.5%).

In CA209067, the incidence rates 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.

Consistent with that reported in the CA209067 Interim CSR, the overall safety profile of NIVO monotherapy and NIVO+IPI combination therapy is not impacted by tumour PD-L1 expression level. Although interpretation is limited by small numbers of events, no consistent differences in the frequencies of select AEs by tumour PD-L1 expression subgroup (using either a 1% or 5% tumour PD-L1 expression level) were observed in any select AE across the treatment groups in CA209067.

Clinical laboratory evaluations: Abnormalities in haematology laboratory results, liver tests, kidney function tests, and electrolytes in subjects receiving NIVO monotherapy and NIVO+IPI therapy were primarily Grade 1 or 2. In the NIVO+IPI group, the only Grade 3-4 hematologic abnormality reported in ≥ 5% of subjects was decreased absolute lymphocytes (5.5% Grade 3 only). 7 subjects in the NIVO+IPI group had concurrent ALT or AST elevation > 3 x upper limit of normal (ULN) with total bilirubin > 2 x ULN within 30 days of last dose of study therapy in subjects with available specific liver test results. There were 7 subjects with Grade 3 and 1 subject with a Grade 4 on-treatment increased creatinine levels, hypokalaemia (3.4% Grade 3, 1.0% Grade 4) and hyponatremia (9.9% Grade 3, 0.7% Grade 4). In the NIVO+IPI group, the proportion of subjects with TSH decreases (< lower limit of normal [LLN]) from baseline was greater than that reported in the NIVO and IPI groups.

The incidence of nivolumab anti-drug antibodies (ADA) was 12.3% (36/292 subjects) and 44% (128/291 subjects) following NIVO monotherapy and NIVO+IPI in combination, respectively, in the updated analysis for CA209067. The presence of ADA did not appear to have an effect on the safety of nivolumab when administered alone or in combination with ipilimumab. Nivolumab ADA results from the final OS analysis are consistent with those in the Interim CSR. Of the ADA evaluable subjects in the NIVO+IPI group, 24/290 (8.3%) were ipilimumab ADA positive after treatment.

During the interval between CA209067 Interim CSR and the updated safety analysis, no safety events were reported which would alter the characterization of the safety profile of NIVO or the combination of NIVO+IPI. The overall frequency and type of AEs, AEs leading to discontinuation, and serious adverse events (SAEs) (all causality and related) were consistent with that previously reported for each treatment group. In general, the frequency of AEs was lowest across AE categories in the NIVO group and highest in the NIVO+IPI group.

No new safety signals were identified; generally the frequency and degree of severity of safety events in the pooled combination therapy group was higher than that observed in the pooled monotherapy group. The combination therapy of nivolumab +ipilimumab showed an increased toxicity compared with the monotherapies as shown by a higher incidence of known AE's, G 3-4 AEs, SAEs, and AEs leading to study discontinuation. The number of discontinuations is considered high and suggests that the combination therapy is poorly tolerated. Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics.

2.5.2. Conclusions on clinical safety

No new safety signals were identified; generally the frequency and degree of severity of safety events in the pooled combination therapy group was higher than that observed in the pooled monotherapy group. The combination therapy of ipilimumab+ nivolumab showed an increased toxicity compared with the monotherapies as shown by a higher incidence of known AE's, G 3-4 AEs, SAEs, and AEs leading to study discontinuation. The number of discontinuations is considered high and suggests that the combination therapy is poorly tolerated. The main uncertainties related to the unfavourable effects of the combination therapy have been described previously in the initial marketing authorisation of ipilimumab and in the variation II-03. They have been included in the RMP. The combination of ipilimumab with nivolumab has shown additional PFS and OS benefit relative to nivolumab monotherapy only in patients with low tumour PD-L1 expression. Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed efficacy and safety profile of the combination relative to nivolumab monotherapy (see sections 4.8 and 5.1).

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 20.0 with this application.

During the assessment of this extension of indication, it was considered that the safety profile of nivolumab+ipilimumab was consistent with that already characterized for each agent when administered as monotherapy. There were no new risks identified for the combination therapy and therefore neither new additional pharmacovigilance activities nor additional risk minimisation measures were proposed.

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

The PRAC considered that the risk management plan version 20.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 20.1 (incorporating RMP version 18.6 which was finalised with a different procedure in the meantime) with the following content:

Safety concerns

Important identified risks	- GI irARs (eg, diarrhea, colitis, GI perforation) - Hepatic irARs (eg, hepatitis) - Skin irARs (eg, rash, pruritus, TEN, and DRESS) - Neurologic irARs (eg, neuropathy) - Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) - Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis) - Severe infusion reactions
Important potential risks	- Immunogenicity - Severe skin drug reactions from concurrent or sequential (in any order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors
Missing information	- Reproductive and lactation data - Long-term safety in adolescent patients > 12 years of age - Data in ethnic groups - Potential PD interaction with systemic immunosuppressants

	- Patients with severe hepatic impairment - Patients with severe renal impairment - Patients with autoimmune disease - Long-term safety

Pharmacovigilance plan

Ongoing and Planned Additional PV Studies/ Activities in the Pharmacovigilance Plan

CA184143 - Post-marketing epidemiologic prospective cohort study (3)	To estimate incidence of irARs and assess their management	Post-marketing safety	Ongoing	Annual interim reports: 21-May-2012 23-May-2013 21-May-2014 20-May 2015 May 2016 May 2017 Final study report: 4Q 2018
CA184332 - A Multi-site Retrospective Observational Study of US Patients with Unresectable or Metastatic Melanoma Receiving Ipilimumab (YERVOY) as First-line Therapy in a Community Practice Setting (3)	To assess outcomes in subjects prescribed 3 mg/kg in the first-line setting	AE frequency	Concluded; CSR in preparation	1-year interim report: 2Q 2014 Final study report: 4Q 2017

CA184338 - A Multi-site Retrospective Observational Study of US Patients with Unresectable or Metastatic Melanoma Receiving Ipilimumab (YERVOY) as First-line Therapy (3)	To assess outcomes in subjects prescribed 3 mg/kg in the first-line setting	AE frequency	Concluded; CSR in preparation	1-year interim report: 2Q 2014 Final study report: 4Q 2017
MAH to sponsor extension of the DMTR to include paediatric subjects and to their collect safety data (3)	To obtain additional safety information in paediatric patients	Long-term safety in adolescent patients >12 years of age	Planned	Synopsis of the DMTR: 1Q 2018 Registration of paediatric patients in the DMTR register: 4Q 2018 Interim safety reporting: PSUR Final study report: 4Q 2028

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Immune-related Adverse Reactions (GI irARs, hepatic irARs, skin irARs, neurological irARs, endocrine irARs, and other irARs)	SmPC Section 4.4 Specific warning/precautions; Sections 4.2 and 4.4 Guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list	Additional risk minimization plan to ensure HCPs are informed of the key irARs safety and management messages and provide patient education tools to HCPs.
Severe infusion reactions	SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects	N/A
Important Potential Risks		
Immunogenicity	SmPC section 5.1 Immunogenicity	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe skin drug reactions from concurrent or sequential (in any order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors	SmPC Section 4.4	N/A
Missing Information		
Reproductive and lactation data	SmPC Sections 4.6 and 5.3	N/A
Long-term safety in adolescent patients > 12 years of age	SmPC Section 4.2, 4.4, 4.8 and 5.2	N/A
Data in ethnic groups	SmPC Section 5.2	N/A
Potential PD interaction with systemic immunosuppressants	SmPC Section 4.5	N/A
Patients with severe renal impairment	SmPC Sections 4.2 and 5.2	N/A
Patients with severe hepatic impairment	SmPC Sections 4.2 and 5.1	
Patients with autoimmune disease	SmPC section 4.4	N/A
Long term safety	N/A	N/A

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated and the Package Leaflet is being revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II and Package Leaflet.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the product information have been evaluated in a previous procedures and do not impact the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Each year in Europe, 62,000 new cases of melanoma are diagnosed. It is estimated that 20,000 people die of melanoma per year. The outcome of melanoma depends on the stage at presentation. The 5-year survival rates in patients who present with localised disease and primary tumours 1.0mm or less in thickness are very good, with more than 90% of patients surviving. The 5-year survival rates decrease as the tumour spreads: for tumours of more than 1.0mm in thickness, survival rates range from 50% to 90%, with regional node involvement survival rates are around 50%, for within stage III (regional metastatic melanoma) 5-year survival rates range between 20-70%, depending on primary nodal involvement. The 5-year survival is less than 10% for distant metastatic melanoma.

3.1.2. Available therapies and unmet medical need

Prior to 2011, approved therapies for the treatment of metastatic melanoma were limited and included chemotherapy (DTIC) and immunotherapy (interleukin-2 [IL-2]). Since then, new therapeutic classes have been added to the treatment armamentarium administered as monotherapy or in combination. These include the BRAF inhibitors vemurafenib (Zelboraf), dabrafenib (Tafinlar) and MEK inhibitors trametinib (Mekinist) and cobimetinib (Cotellic), which are inhibitors of the serine threonine kinases BRAF and MEK and monoclonal antibodies ipilimumab (Yervoy), an anti-CTLA-4 blocking antibody, and nivolumab (Opdivo) and pembrolizumab (Keytruda) which bind to the programme cell death (PD-1) receptor. There is still a need for more effective therapies as not all patients respond to treatment and part of the patients relapse.

3.1.3. Main clinical studies

The main study in support of the extension of indication of nivolumab in combination with ipilimumab for the treatment of adults with advanced (unresectable or metastatic melanoma), was study CA209067. This was a Phase 3, randomized, double-blind 3-arm study evaluating nivolumab monotherapy versus nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. The primary objective was to compare PFS and OS of nivolumab monotherapy vs ipilumimab monotherapy and of nivolumab combined with ipilumimab to ipilumimab monotherapy.

3.2. Favourable effects

Based on the 28 month follow-up for OS (DBL 13 Sep 2016) the combination of nivolumab and ipilimumab demonstrated a statistically significant improvement in OS vs Ipi monotherapy (HR = 0.55 [98% CI: 0.42, 0.72]; stratified log-rank test p-value = < 0.0001). Median OS was not yet reached with the combination, whereas median OS was 19.98 months in the Ipi monotherapy group.

The result on OS is consistent with the improvement of PFS, median PFS was 11.73 months for the combination compared to 2.86 months for the ipilimumab monotherapy (HR 0.42; 95%CI 0.34, 0.51). A higher antitumor activity was also observed in the combination treatment compared with ipilimumab (ORR, 58.9% vs 19.0%; CR, 17.2% vs 4.4%).

Nivolumab monotherapy has shown a statistically significant improvement in OS vs Ipilimumab monotherapy (HR = 0.63 [98% CI: 0.48, 0.81]) as well as a significant improvement in PFS (HR=0.54, 95% CI: 0.45, 0.66). ORR rates were 44.6% and 19.0%, respectively.

Based on descriptive analyses, Nivo+Ipi vs Nivo has shown a numeric difference in OS favouring the combination (median not reached in both groups; HR 0.88, 95% CI: [0.69, 1.12]). Corresponding results for median PFS were 11.73 in the combination group vs 6.87 in the Nivo mono group (HR: 0.76, 95% CI: 0.62, 0.94). ORR rates were 58.9% and 44.6%, respectively.

Sensitivity analyses as well as subgroup analyses support the main results. An improvement of OS was seen in both BRAF mutated subjects (HR 0.43, 95% CI: 0.28, 0.66) as well as BRAF WT subjects (HR 0.62, 95% CI: 0.48, 0.80) for the Nivo+Ipi vs Ipi monotherapy. There was also a lower risk of death for Nivo+Ipi versus Ipi monotherapy at all predefined levels of tumour PD-L1 expression (e.g. HR 0.604 95%CI 0.42-0.84 vs HR 0.53 95%CI 0.38-0.74 with a cut-off of 1%).

Updated study results at the data cut-off of May 2017, with +9 months additional follow up (OS data at 3-years available) and results from study CA209069 showed consistent results.

3.3. Uncertainties and limitations about favourable effects

There is uncertainty with regards to the subset of the patient population determined as having tumour PD-L1 negative or positive and the selection of these patients. In patients with PD-L1 low expression, the use of the combination appears to offer better results than those with a higher expression on PD-L1 when comparing nivo+ipi to nivo monotherapy (HR 0.74 95%CI 0.52-1.06 vs HR 1.03 95%CI 0.72-1.48 with a cut-off of 1%). This finding means that in those patients designated as having tumour PD-L1 expression (cut-off >1%) no benefit of the treatment combination over nivolumab monotherapy in terms of OS has been established. Based on the current data, a clear definition of the cutoff for PD-L1 tumour expression is lacking and hence, it is not feasible to select patients who could mostly benefit from treatment, despite the available IHC assay (measuring PD-L1 tumour cell expression only). There is uncertainty as to how this test would be used in a clinical setting taking into account the variability and heterogeneity in the expression of PD-L1 in tumour and immune cells as well as the reproducibility of the method used in the different laboratories. Furthermore, it is of note that a 10% higher antitumour activity is exhibited by the combination even in the subgroup of PD-L1>1%. The landmark analysis of OS from month 6 by response status is pointing towards a promising survival for those patients who achieve a response (CR or PR). Therefore, combination treatment may be beneficial for some patients with high PD-L1 tumour expression as well. Therefore, the indication was not restricted based on PD-L1 tumour expression and a statement to specify the treatment effect was included in 4.1. Efficacy results at all predefined levels of tumour PD-L1 expression are adequately reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

The final safety data from study CA2090672 (database lock (DBL) of 13-Sep-2016) are reported below (refer to EMEA/H/C/003985/II/0032). The safety of the nivolumab and ipilimumab used in combination is consistent with the known effects of the two products as used in monotherapy. However, a higher frequency and severe toxicity were observed in the treated combination group.

The median duration of therapy was 2.83 months in the NIVO+IPI group. 87.8% of treated subjects in the NIVO group received ≥ 90% of the planned dose intensity, which was similar to ipilimumab in the IPI group (88.4%) and greater than nivolumab and ipilimumab in the NIVO+IPI group (69.0% and 70.6%, respectively).

Any grade AEs (regardless of causality) were reported in 99.7% of subjects in the NIVO group, 99.7% in the NIVO+IPI group, and 99.0% of subjects in the IPI group. Any grade drug-related AEs were reported in 86.3% of subjects in the NIVO group, 95.8% in the NIVO+IPI group, and 86.2% of subjects in the IPI group. In the NIVO+IPI group the most frequently reported AEs (≥ 20% of subjects) were diarrhoea (54.0%), fatigue (51.8%), nausea (43.8%), pyrexia (39.9%), pruritus (39.0%), rash (32.9%), vomiting (31.3%), decreased appetite (29.4%), headache (25.6%), cough (24.3%), dyspnoea (23.0%), arthralgia (21.4%), and increased alanine aminotransferase (ALT) (20.8%).

Grade 3-4 AEs (regardless of causality) were reported in 50.8% of subjects in the NIVO group, 72.2% in the NIVO+IPI group, and 57.9% of subjects in the IPI group. In the NIVO+IPI group the most frequently reported Grade 3-4 AEs (≥ 5% of subjects) were lipase increased (12.5%), diarrhoea (11.2%), increased ALT (9.3%), colitis (8.3%), increased aspartate aminotransferase (AST) (6.7%), and fatigue (6.4%).

SAEs were reported in 42.5% of subjects in the NIVO group, 71.2% of subjects in the NIVO+IPI group, and 55.0% of subjects in the IPI group. The overall frequencies of SAEs and drug-related SAEs were lowest in the NIVO group and highest in the NIVO+IPI group. Grade 3-4 SAEs were reported in 33.2%, 53.4%, and 40.5% of subjects in the NIVO, NIVO+IPI, and IPI groups, respectively. In the NIVO+IPI group, the most frequently reported SAEs were diarrhoea (10.5%), colitis (9.9%), and pyrexia (8.3%).

As of the 13-Sep-2016 database lock, a total of 141 (45%), 127 (40.6%), and 195 (62.7%) deaths were reported in the NIVO, NIVO+IPI, and IPI groups, respectively. Disease progression was the most common cause of death for all groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose. No additional drug-related deaths were reported within 100 days of the last dose of study drug since the database lock for the CA209067 Interim CSR.

In the final CSR four drug-related deaths were reported >100 days after last dose of study drug, in the NIVO+IPI group.AEs leading to discontinuation were reported in 18.2% of subjects in the NIVO group, 47.0% of subjects in the NIVO+IPI group and 25.1% of subjects in the IPI group.

The overall frequency of pulmonary select drug related AEs was greater in the NIVO+IPI group (7.7%) compared to the NIVO and IPI monotherapy groups (2.2% and 3.2%, respectively). In the interim study report of CA209067, a total of 8 out 13 deaths classified as “other” reason were pulmonary/respiratory events. Most pneumonitis cases resolved with appropriate immunosuppressant therapy. By contrary, 3 cases of pulmonary embolism led to death in the overall safety database. Pulmonary toxicity, including pulmonary embolism, are relevant toxicities associated with this treatment combination. These are already reflected in the SmPC to inform physicians and in the RMP for further follow up.

Cardiac adverse events have also been reported with combination therapy. Tachycardia and atrial fibrillation were the most frequently reported. The incidence of cardiac arrest/failure was low and similar to that of ipilimumab. A precautionary statement is included in the SmPC recommending periodic monitoring (SmPC Section 4.4).

The immunogenic potential of nivolumab monotherapy was low. The immunogenicity of nivolumab increased when nivolumab was used in combination with ipilimumab. However, no impact on the efficacy and/or safety of the presence of antibodies against nivolumab or ipilimumab could be observed.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainties have been described previously in the initial marketing authorisation of ipilimumab and in the variation II-03. They have been included in the RMP. There is limited data on the incidence of immune-related adverse reactions and how they are managed in clinical practice. Hence a post-marketing epidemiologic cohort study is ongoing to address this concern. In addition, the results of two multi-site retrospective observational studies in patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy in a community practice setting will provide further evidence on the outcomes of subjects prescribed 3 mg/kg in the first-line setting.

3.6. Effects Table

Effects Table for Yervoy in combination with nivolumab (data cut-off: 13-Sep-2016).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Patients alive (all randomised patients)	Median (months)	Nivo –not reached Nivo+Ipi - not reached	Ipilimumab - 19.94	HR combination vs nivolimumab 0.85 (95% CI: 0.68, 1.07) HR combination vs ipilimumab 0.55 (95% CI:0.45, 0.69) Robustness in sensitivity analyses and most subgroups (including BRAF mutated)	36 months follow up
OS	Patients alive (PD-L1 positive >1%)	Median (months)	Nivolumab - Not reached Nivo+ipi - Not reached	Ipilimumab - 21.49	HR combination vs nivolumab HR 1.02 (95% CI: 0.73-1.43)	
OS	Patients alive (PD-L1 negative <1%)	Median (months)	Nivolumab - 23.46 Nivo+ipi – Not reached	Ipilimumab - 18.56	HR 0.70 (95% CI: 0.49-0.99)	
PFS	Patients alive and free of progression (all randomised patients)	Median (months)	Nivolumab - 6.87 Nivo+ipi - 11.70	Ipilimumab - 2.86	HR combination vs 0.76 (95% CI: 0.62-0.95) HR combination vs ipilimumab 0.42 (95% CI: 0.32-0.56)	18 months follow up
Unfavourable Effects						
AEs	Percentage of Adverse events regardless causality	%	99.7 % (combination)	99.7% (monotherapy)	Subjects in the monotherapy group had lower event rates than subjects in the combination therapy group for the majority of AEs. The most frequently reported AEs were diarrhoea, fatigue, nausea, pyrexia, pruritus, rash, vomiting, decreased appetite, headache, cough, dyspnea, arthralgia, and increased alanine aminotransferase.	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
AEs grade 3-4	Percentage of Adverse events grade 3-4 regardless causality	%	72.2% (combination)	50.8% (monotherapy)		
SAEs	Percentage of serious Adverse events regardless causality	%	71.2% (combination)	42.5% (monotherapy)		
Deaths	Percentage of deaths regardless of causality	%	40.6% (combination)	45% (monotherapy)	Disease progression was the most common cause of death for all groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose.	

Abbreviations: AE- adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit observed in terms of PFS and OS for the combination of nivolumab and ipilimumab compared to ipilimumab as monotherapy in the overall population is considered clinically relevant in the target population. This also holds true for the various subgroups, including patients with different levels of PD-L1 expression. An exception is the comparison of combination treatment vs nivolumab monotherapy in patients with high levels of PD-L1 expression for which no difference in PFS and OS was observed. However, a 10% difference in ORR was observed which may be of clinical relevance.

The safety of the combination is consistent with what has been observed in the monotherapy treatments. No new ADRs have been identified. Important identified risks associated with the combination regimen include immune-mediated adverse reactions of pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and rash. Nevertheless, the tolerability and severity of the AEs is clearly worse as, overall, there was significantly higher rate of AEs, grade 3-4 AEs and serious AEs observed in the combination arms compared to the monotherapy arms. This increased toxicity is reflected in the higher rate of discontinuations due to AEs.

Given the increased toxicity with the combination and the absence of an OS benefit of the combination versus nivolumab monotherapy in patients with high PD-L1 expression (≥1%) a precautionary statement is included in section 4.4. Before initiating treatment with the combination of nivolumab and ipilimumab, physicians are advised to carefully evaluate the individual patient, taking into consideration the anti-tumour activity and tolerability of the combination relative to nivolumab monotherapy (see section 4.4, 48 and 5.1). This is acceptable.

Additional proposed revisions to section 4.2, 4.4, 4.8, and 5.2 were all assessed within previous procedures for Opdivo and were found to be acceptable.

3.7.2. Balance of benefits and risks

The benefits of ipilimumab in combination with nivolumab in adult patients with metastatic melanoma are considered to outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Since there are concerns on the use of tumour expression of PD-L1 as a marker, especially its use as a reliable tool in clinical practice to select a population to be treated, and there is a lack of appropriate evidence-based rationale for a cut-off value, the indication was not be restricted according to the expression of tumour PD-L1. Hence, the combination of nivolumab with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in OS and PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. This information is reflected in section 4.1, with a reference to sections 4.4 and 5.1.

3.8. Conclusions

The overall B/R of Yervoy in combination with nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in adults is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults in combination with nivolumab for Yervoy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 20.1) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the contact details of the Irish local representative in the Package Leaflet.

5. EPAR changes

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

Scope

Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults in combination with nivolumab for Yervoy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 20.1) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the contact details of the Irish local representative in the Package Leaflet.