Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0003

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AEs-DC	AEs leading to discontinuation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMS	Bristol-Myers Squibb
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
EU	European Union
GI	gastrointestinal
HCP	healthcare providers
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator Brochure
ICU	Intensive care unit
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

Abbreviation	Definition
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
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 7 July 2015 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment in combination with ipilimumab of advanced (unresectable or metastatic) melanoma in adults based on interim data from study CA209067 and the final CSR of study CA209069. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II and Package Leaflet. An updated RMP version 3.0 was provided as part of the application as well as a paediatric non-clinical biomarker study provided to fulfil paediatric requirements.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II 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(s) P/0064/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0064/2014was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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 applicant 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 and the evaluation teams were:

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

Timetable	Actual dates
Submission date	7 July 2015
Start of procedure	25 July 2015
CHMP Co-Rapporteur Assessment Report	21 September 2015
CHMP Rapporteur Assessment Report	2 October 2015
PRAC Rapporteur Assessment Report	25 September 2015
PRAC members comments	30 September 2015
Updated PRAC Rapporteur Assessment Report	1 October 2015
PRAC Outcome	8 October 2015
CHMP members comments	12 October 2015
Updated CHMP Rapporteurs' Joint Assessment Report	15 October 2015
Request for supplementary information (RSI)	22 October 2015
CHMP Rapporteurs' Joint Assessment Report	4 January 2016
PRAC Rapporteur Assessment Report	4 January 2016
PRAC Outcome	14 January 2016
CHMP members comments	20 January 2016
Updated CHMP Rapporteurs' Joint Assessment Report	22 January 2016
Oral Explanation	26 January 2016
2nd Request for supplementary information (RSI)	28 January 2016
CHMP Rapporteurs' Joint Assessment Report	17 March 2016
CHMP members comments	21 March 2016
Updated CHMP Rapporteurs' Joint Assessment Report	23 March 2016
CHMP Opinion	1 April 2016

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 1.0mm 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 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]

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 includethe 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.

At the time of the submission of the application, OPDIVO was indicated for the following indications:

- Opdivo as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

- Opdivo is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

Yervory (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

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

- Opdivo as monotherapy or in combination with ipilimumab (OPDIVO+ipilimumab immuno regimen) is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

The recommended dose and schedule is nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks (Q3W) administered as an intravenous (IV) infusion for 4 doses followed by nivolumab 3 mg/kg every 2 weeks (Q2W). Treatment will continue until disease progression or unacceptable toxicity.

The final agreed indication is as follows:

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[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).

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 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).

2.2. Non-clinical aspects

In the initial marketing authorisation application for nivolumab, some pharmacology and toxicity studies with the combination of ipilimumab and nivolumab were submitted and are described below. No new relevant non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

The combination of nivolumab and ipilimumab was evaluated *in vitro* in mixed lymphocyte response assay (MDX-1106-010-001R 930036348) and in activation of PBMCs by SEB (MDX-1106-323R 930074314) and *in vivo* in syngeneic tumour models (study Study MDX-1106-010-002R 930036349, Study MDX-1106-010-003R 930036351, Study MDX-1106-010-004R 930036352).

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies on the combination nivolumab and ipilimumab

The mixed lymphocyte response (MLR) (Study MDX-1106-010-001R 930036348): Allogeneic dentrictic cells (DC) and CD4+ T cells were used to assess the ability of nivolumab and ipilimumab alone and in combination to promote T cell reactivity. In combination, ipilimumab enhanced IFN-γ production mediated by nivolumab in 2 of the 3 donor DC-CD+ T-cell pairs tested.

Activation of PBMCs by SEB (Study MDX-1106-323R 930074314): The effects of nivolumab and ipilimumab individually and in combination were evaluated in an assay where SEB (staphylococcal enterotoxin B) promotes polyclonal activation of T cells, resulting in cytokine release. In 3 of 6 donors, the combination caused a greater increase in IL-2 release than each antibody alone.

Activity of anti-PD-1 and CTLA-4 antibodies in syngeneic tumour models

Murine syngeneic subcutaneous tumour models have been analysed for antitumor responses using the combined treatment of anti-mouse PD-1 (4H2) and anti-mouse CTLA-4 (9D9) antibodies. 9D9 is a murine antibody of the IgG2 isotype with the ability to deplete some intratumoral T reg cells. Five subcutaneous mouse tumour models were used to test the antitumor effect of anti-mouse PD-1 and anti-mouse CTLA-4 mAbs using established tumours:

- Three studies using an MC38 tumor model were conducted in syngeneic C57BL/6 mice.

    o In the first study, MC38 tumor model (Study MDX-1106-010-002R 930036349): anti-mouse PD-1 and anti-mouse CTLA-4 mAbs were evaluated in staged MC38 tumours. Both mAbs were dosed IP at 10 mg/kg on days 7, 10, 13 and 16. Results are shown in Table 1.

Table 1: **Antitumor activity of combined PD-1 and CTLA-4 antibodies in MC38 colon adenocarcinoma tumours**

Group	N	Mean Tumor Volume (mm^3) (Day 13)	% Mean TGI (Day 13)	% Tumor-Free Mice (Day 83)
G20 (4 single doses)	10	566	0	0
P10 + G10 (4 concurrent doses)	10	331	42	10
C10 + G10 (4 concurrent doses)	10	288	49	0
C10 + P10 (4 concurrent doses)	10	148	74	80
C10, C10, P10, P10 (4 single doses)	10	350	38	10
P10, P10, C10, C10 (4 single doses)	10	356	37	20

G = mouse IgG; P = anti-mouse PD-1 mAb; and C = anti-mouse CTLA-4 mAb. The numerical designation following each letter indicates the mAb dose (mg/kg).

- A second study in the MC38 model was conducted to determine the antitumor effect of different dose levels of anti-mouse PD-1 and anti-mouse CTLA-4 mAbs given concurrently on days 7, 10, 13 and 16. A dose-response relationship was observed, with maximal antitumor activity at the 10 mg/kg dose level (80% tumour-free mice at the end of the study). At the 3 mg/kg dose level, similar antitumor activity was observed at day 13 (76% tumour growth inhibition [TGI]), but there were fewer tumour-free mice (20%) at study termination. Concurrent treatment with each mAb at the 1 mg/kg dose level showed the lowest antitumor activity.

- In a third study in the MC38 model, the antitumor activity of combined anti-PD-1 and anti-CTLA-4 antibodies was evaluated using fixed doses of either mAb at 10 mg/kg with varying doses of the reciprocal antibody on days 7, 10, 13 and 16. Results are shown in Table 2. At the highest dose of anti-mouse PD-1 mAb used in this study (10 mg/kg), anti-mouse CTLA-4 at 10 mg/kg required anti-mouse PD-1 at ≥1 mg/kg for maximal antitumor effect. Intermediate antitumor effects were observed at the other combined dose levels.

Table 2: **Effect of varying relative doses of anti-PD-1 and anti-CTLA-4 antibodies**

Group	N	Day 14 Mean Tumor Volume (mm^3)	Day 14 % Mean TGI	Day 106 % Tumor-Free Mice
G20 (3 single doses)	10	630	0	10
P10 + C10 (3 concurrent doses)	10	102	84	70[a]
P10 + C3 (3 concurrent doses)	10	154	76	50
P10 + C1 (3 concurrent doses)	10	327	48	10
P3 + C10 (3 concurrent doses)	10	284	55	60
P1 + C10 (3 concurrent doses)	10	105	83	70[a]

[a] One mouse in each group was tumor-free up to Day 35, but was found dead on Day 40; each has been tumor-free for 4 and 7 days, respectively

G = mouse IgG; P = anti-mouse PD-1 mAb; and C = anti-mouse CTLA-4 mAb. The numerical designation following each letter indicates the amount of mouse IgG. The numerical ratios indicate the relative amounts of mAbs used (mg/kg).

- CT26 colon carcinoma model (Study MDX-1106-010-003R 930036351): repeated dose of anti-PD-1 antibody had little or no antitumor activity in the CT26 colon adenocarcinoma. However, the combined dosing of anti-mouse PD-1 and anti-mouse CTLA-4 mAbs was superior to anti-CTLA-4 mAb alone. Mean TGI was 38% at day 21 in mice treated with anti-mouse CTLA-4 mAb at 10 mg/kg while 66% TGI in mice treated with the combination was obtained. No mice were tumour-free at the end of the study.

- SA1/N fibrosarcoma model (Study MDX-1106-010-004R 930036352): in the SA1/N fibrosarcoma model in A/J mice, treatment with anti-mouse CTLA-4 mAb alone at 10 mg/kg on days 1, 4, 7 and 11 resulted in the eradication of the implanted tumours. Results are included in Table 3. Treatment with a suboptimal dose of anti-mouse CTLA-4 (0.2 mg/kg) resulted in modest antitumor activity.

Table 3: **Antitumor activity of anti-mouse PD-1 and CTLA-4 in the SA1/N fibrosarcoma model in A/J mice**

Group	N	Tumor Volume (mm^3) (Day 14)	% Mean TGI (Day 14)	% Tumor-free Mice (Day 40)
Vehicle (4 single doses)	9	984	0	0
G10 (4 single doses)	10	634	0	0
P10 (4 single doses)	10	463	27	40
C10 (4 single doses)	10	234	63	40
C0.2 (4 single doses)	10	597	6	0
P10 + C0.2 (4 concurrent doses)	10	330	48	80

G = mouse IgG; P = anti-mouse PD-1 mAb; C = anti-mouse CTLA-4 mAb. The numerical designation following each letter indicates the mAb dose (mg/kg).

- B16 melanoma model and J558 myeloma model (Study MDX-1106/010-005R 930036353): Combined PD-1 and CTLA-4 antibodies using 4 doses at 10 mg/kg in the B16 melanoma model had no effect on tumour growth. There was also no antitumor activity following combined anti-mouse PD-1 and anti-mouse CTLA-4 mAb treatment using the J558 myeloma tumour model.

Safety pharmacology programme

Safety pharmacology findings in repeat-dose toxicity studies

Repeat-dose toxicity studies of up to 3 months were conducted in cynomolgus monkeys to characterise the toxicity of IV administration of nivolumab (studies SUV0025, WIL552003). In these studies, weekly or twice weekly IV doses of nivolumab were administered for 1 or 3 months, respectively, at dose levels up to 50 mg/kg (Cmax ≤ 3610 µg/mL; AUC(0-168h) ≤ 531000 µg·h/mL). No nivolumab-related clinical signs of toxicity or effects on body weight, food consumption, blood pressure, heart rate, respiration rate, ophthalmic or electrocardiographic parameters were observed.

In addition, nivolumab was also evaluated in repeat-dose toxicity studies in combination with ipilimumab (studies SUV00106). Weekly administration of nivolumab at up to 50 mg/kg in combination with ipilimumab at up to 10 mg/kg for 1 month had no effect on blood pressure, heart rate, respiration rate, or electrocardiographic parameters. Nivolumab exposures in this combination was comparable to exposures observed in the 1 month toxicity study of nivolumab alone, administered once weekly.

Pharmacodynamic drug interactions

Combination study of nivolumab and ipilimumab (SUV00106 930036346)

The pharmacodynamic activity of nivolumab when administered in combination with ipilimumab was studied in a 1-month combination study in cynomolgus monkeys which included an assessment of the antibody response to keyhole limpet haemocyanin (KLH) (study SUV00106). This study included 5 animals/sex/group treated at 3 mg/kg ipilimumab and 10 mg/kg nivolumab or 10 mg/kg ipilimumab and 50 mg/kg nivolumab

infused IV once weekly for 4 consecutive weeks. The high dose combination showed variable but significant increases in the number and frequency of peripheral blood CD3+CD4+ T cells and CD3+CD8+ T cells on day 7, whereas no changes were observed in the number or frequency of monocytes or natural killer cells. Similar changes were observed in the 3-month toxicity study with nivolumab alone (study WIL-552003). In addition, an increased incidence of immune-mediated adverse effects (GI toxicity/colitis) was also observed in this combination study. These effects have been observed in single agent and combination therapy trials in humans with nivolumab and/or ipilimumab.

2.2.3. Pharmacokinetics

In the combination toxicity study submitted in the initial MAA, no accumulation or TK drug-drug interactions based on pivotal toxicity studies with each antibody alone were observed. No PK interactions between nivolumab and ipilimumab were submitted (see non-clinical discussion).

2.2.4. Toxicology

The pharmacodynamic activity of nivolumab when administered in combination with ipilimumab was studied in a 1-month combination study in cynomolgus monkeys. The immune function was evaluated by measurement of antibody response to keyhole limpet haemocyanin (KLH) (study SUV00106). This study included 5 animals/sex/group treated at 3 mg/kg ipilimumab and 10 mg/kg nivolumab or 10 mg/kg ipilimumab and 50 mg/kg nivolumab infused IV once weekly for 4 consecutive weeks. The high dose combination showed variable but significant increases in the number and frequency of peripheral blood CD3+CD4+ T cells and CD3+CD8+ T cells on day 7, whereas no changes were observed in the number or frequency of monocytes or natural killer cells. Similar changes were observed in the 3-month toxicity study with nivolumab alone (study WIL-552003). In addition, an increased incidence of immune-mediated adverse effects (GI toxicity/colitis) was also observed in this combination study, which was consistent with the observed potentially enhanced T cell numbers and activity. These effects have been observed in single agent and combination therapy trials in humans with nivolumab and/or ipilimumab.

2.2.5. 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), nivolumab 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.

2.2.6. Discussion on non-clinical aspects

Pharmacology and toxicity studies conducted with the combination of anti-mouse PD-1 and anti-mouse CTLA-4 were submitted in the initial marketing authorisation application, showing enhanced antitumor activity with the combination in murine tumour models and enhanced toxicity compared to nivolumab alone. Although the anti- mouse PD-1 alone or in combination with the anti-mouse –CTLA-4 did not show any effect in the growth of tumours in B16F10 or B16 melanoma models, it is accepted that anti-tumour activity of anti-PD-1 and anti-CTLA-4 in tumour models is related to the inherent immunogenicity of the tumours and is not necessarily related to the specific tumour types. No additional data concerning the effects on the combination of nivolumab with ipilimumab was submitted. The absence of PK interactions studies between nivolumab and ipilimumab is acceptable as no PK interactions between nivolumab and ipilimumab are expected. The combination of nivolumab with ipilimumab (Study SUV00106 930036346) in cynomolgus monkey study showed enhanced toxicity compared to nivolumab alone. Combined administration of nivolumab and ipilimumab resulted in GI toxicity/colitis. The exposures are higher than the exposures in

humans, and the safety margins for nivolumab were considered adequate. The enhanced effects were anticipated as both nivolumab and ipilimumab induce immune-mediated adverse reactions using a similar mechanism. The exposures were higher than the exposures in humans, and the safety margins for nivolumab were considered adequate. Therefore, no new non-clinical safety data has been provided, which is considered acceptable.

2.2.7. Conclusion on the non-clinical aspects

Nivolumab is not expected to pose a significant risk to the environment, thus the lack of an ERA is acceptable. The MAH did not submit additional data than what had been submitted in the initial MA application. This is considered acceptable. The non-clinical data that had been submitted was considered adequate and sufficient to support the proposed indication. No further amendments were proposed to section 5.3 of the SmPC.

2.3. Clinical aspects

2.3.1. Introduction

The clinical program of nivolumab in combination with ipilimumab was based on data from three studies: two primary studies, a Phase 3, randomised, double-blind study of nivolumab monotherapy (3 mg/kg) or nivolumab (1 mg/kg) combined with ipilimumab (3 mg/kg) versus ipilimumab monotherapy (3 mg/kg) in subjects with previously untreated unresectable or metastatic melanoma (CA209067) and a Phase 2, randomised, 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).

GCP

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

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

• Tabular overview of clinical studies

Study #/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.	<u>Dose Escalation Cohorts 1-3:</u> 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 <u>Sequential Dosing Cohorts 6-7</u>: nivo Q2W for 48 doses after prior ipi Cohort 6: 1 mg/kg Cohort 7: 3 mg/kg <u>Expansion Cohort 8</u>: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses; then nivolumab 3 mg/kg Q2W	127 Treated <u>Cohorts 1-3</u>: 53 <u>Cohort 8</u>: 41 (27 BRAF WT, 12 BRAF mutation +, 2 UNK BRAF) <u>Cohorts 6-7</u>: 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: <u>Nivo+Ipi group</u>: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses; then nivo 3 mg/kg Q2W <u>Ipi group</u>: ipi 3 mg/kg Q3W for 4 doses	N= 140 Treated <u>Nivo+ipi group</u>: 94 (71 BRAF WT and 23 BRAF mutation+) <u>Ipi group</u>: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: <u>Nivo group</u>: nivo 3 mg/kg IV Q2W. <u>Nivo+Ipi group</u>: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses followed by nivo 3 mg/kg Q2W <u>Ipi group</u>: 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

Absorption, distribution and elimination

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

Pharmacokinetic characteristics of nivolumab and ipilimumab as previously described for their respective melanoma monotherapy indications is summarised in Table 4.

Table 4: **Summary of pharmacokinetic parameters for nivolumab and ipilimumab 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 nivolumab and ipilimumab was evaluated by peak and trough concentrations of each nivolumab and ipilimumab when given in combination using distinct regimens.

Nivolumab and ipilimumab 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 5:   Dosing and duration of treatment for each cohort

Study Drug	Cohort						
	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.

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

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

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

BMS-734016 StudyDay=1
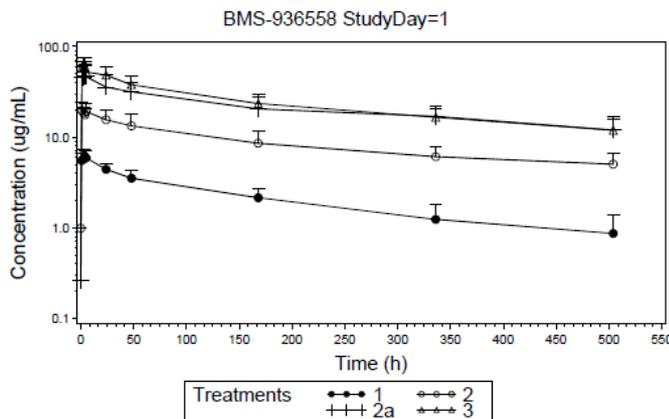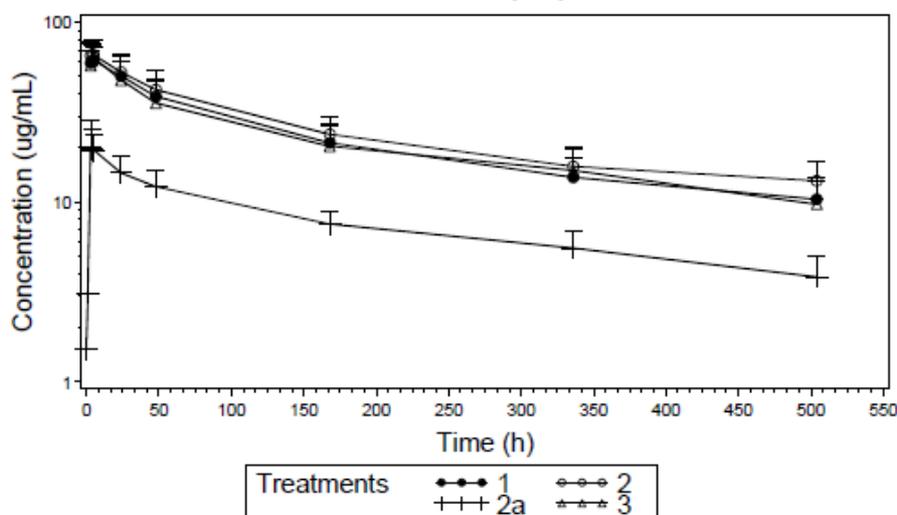
TREATMENT CODES:
1 = 0.3 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 3 mg/kg of I
2 = 1 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 3 mg/kg of ipi
2a = 3 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 1 mg/kg of ipi
3 = 3 mg/kg of nivolumab Q3 wks for induction period and Q12 wks for maintenance period + 3 mg/kg of ipi

Summary statistics for nivolumab peak and troughs after Dose 1 and Dose 4 are provided in Table 6. 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.

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.

Table 6:   **Summary statistics of nivolumab peak and trough concentrations after first and fourth dose - cohorts 1-3 and 8 - Study CA209004**

	Dose 1		Dose 4 [a]	
	Cmax (µg/mL)	Cmin (µg/mL)	Cmax (µg/mL)	Cmin (µg/mL)
	Geo Mean[N] (%CV)	Geo Mean[N] (%CV)	Geo Mean[N] (%CV)	Geo Mean[N] (%CV)
Cohort 1 0.3 Nivo: 3 Ipi	6.5 [13] (17.2)	0.7 [10] (55.7)	5.3 [10] (52.4)	1.5 [5] (44.9)
Cohort 2 1 Nivo: 3 Ipi	21.5 [17] (17.9)	4.8 [12] (30.3)	23.2 [11] (26.2)	2.6 [11] (94.4)
Cohort 2a 3 Nivo: 1 Ipi	49.8 [15] (24.7)	11.4 [15] (29.4)	54.3 [14] (38.9)	27.7 [9] (23.9)
Cohort 3 3 Nivo: 3 Ipi	63.4 [6] (18.0)	10.8 [4] (43.5)	45.3 [4] (53.5)	23.9 [3] (37.5)
Cohort 8 1 Nivo: 3 Ipi/3 Nivo	18.1 [40] (38.1)	3.2 [31] (60.7)	17.2 [23] (36.6)	5.9 [13] (49.3)

[a] The Cmin corresponds to the trough concentration after the fourth dose of nivolumab (measured at Week 12).

Interaction between nivolumab and ipilimumab PK was further evaluated in the popPK analysis including sparse PK data from phase 2 study CA209069 and phase 3 study CA209067. 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 (Figure 3) 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.

The effect of nivolumab coadministration on ipilimumab clearance in the popPK analysis ranged from -7.5% to 11%.

Figure 3:   Distribution of popPK model predicted nivolumab by ipilimumab co-administration

| GM of CL [mL/h] | 9.13 | 12.3 |
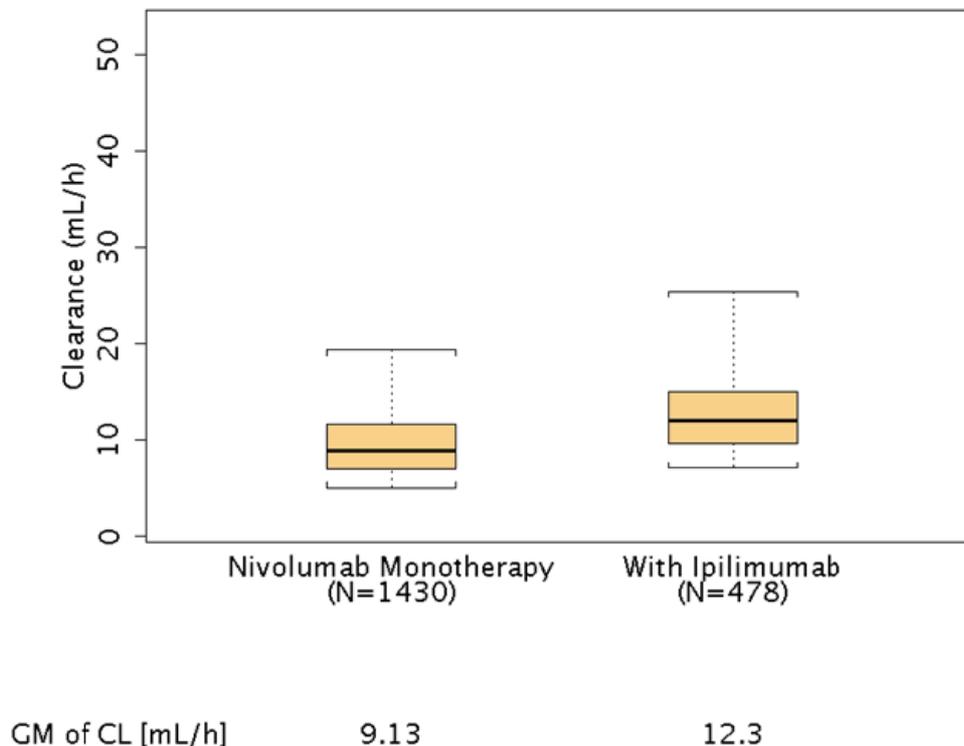
Dose proportionalities and time dependencies

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

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 7.

Table 7: **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)

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 8.

Table 8: **Summary statistics of ipilimumab PK parameters using post-hoc Bayesian estimates of individual PK parameters**

PK Parameter	Mean (SD)	Geometric Mean (CV%)	Median (Min, Max)
CL [L/h]	0.0149 (0.00579)	0.0139 (38.9)	0.0139 (0.00459, 0.0529)
VC [L]	4.09 (0.829)	4.01 (20.2)	4.06 (1.51, 7.24)
VSS [L]	7.56 (0.829)	7.52 (11)	7.53 (4.98, 10.7)
T-HALFα [d]	1.67 (0.169)	1.66 (10.1)	1.67 (0.814, 2.16)
T-HALFβ [d]	18.2 (5)	17.5 (27.5)	17.6 (6.86, 43.1)

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Effect of nivolumab and ipilimumab 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 nivolumab and ipilimumab 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 nivolumab and ipilimumab mAbs alone or in combination did not stimulate cytokine secretion at concentrations up to 100 µg/mL. Addition of the nivolumab and ipilimumab 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. 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 4: **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**
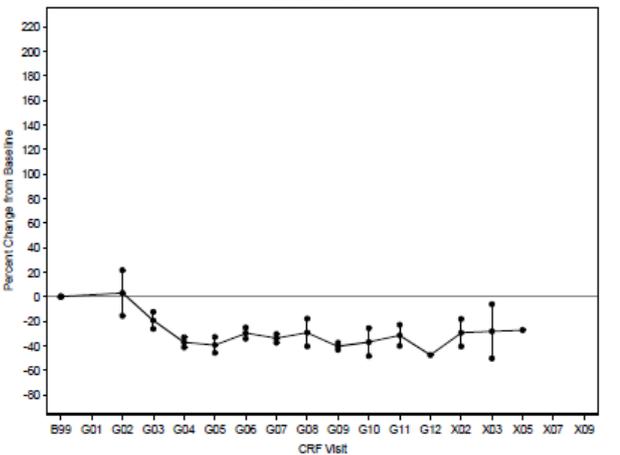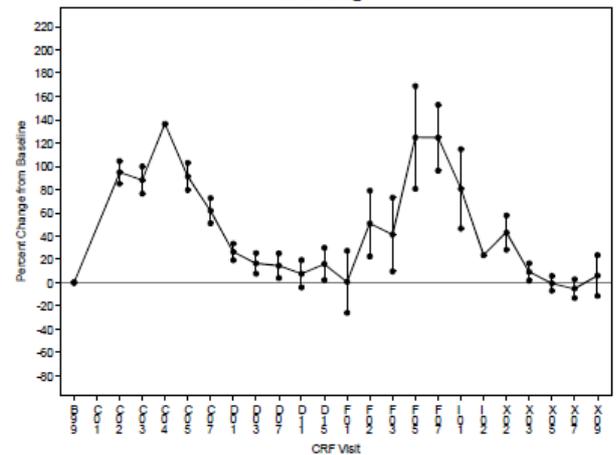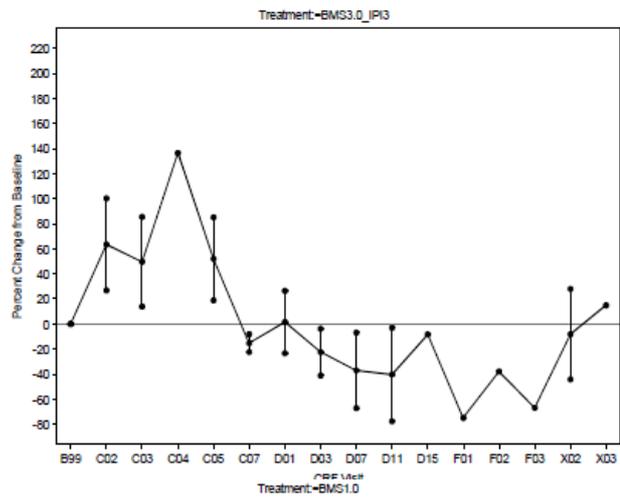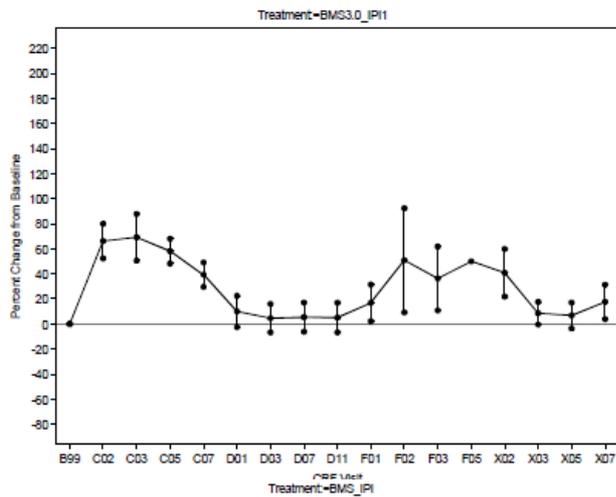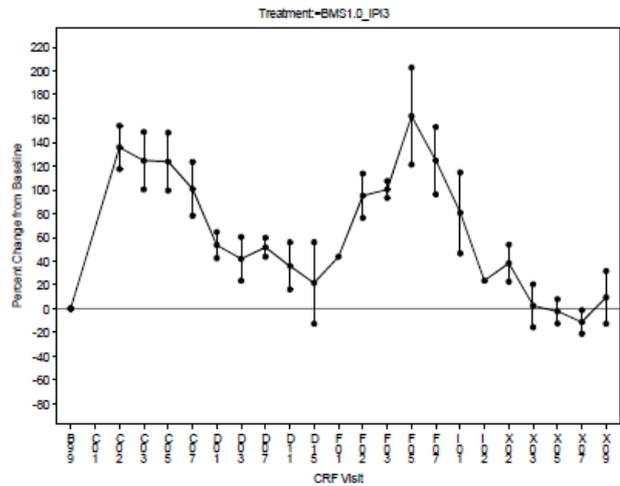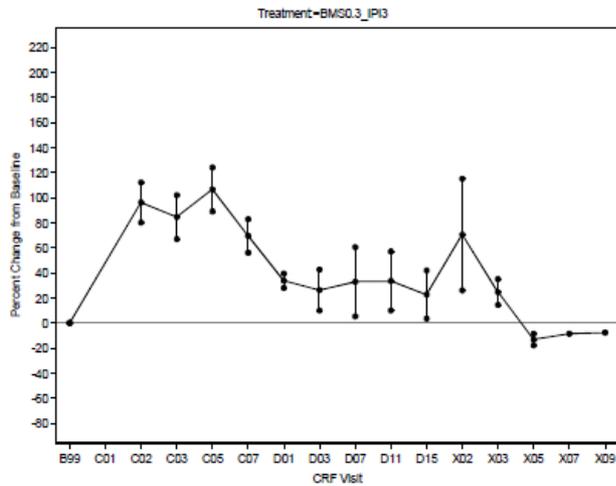
Absolute lymphocyte counts (ALC) were measured from whole blood samples at pre-treatment and during treatment. No meaningful rise over baseline was observed in mean ALC. The maximum mean increase in absolute levels was 0.25 (x10*9 cells/liter) during the first 12 weeks of the induction period in Cohorts 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 nivolumab and ipilimumab 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 5. 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 5: **Estimated covariate effects of exposure-PFS by Cox Proportional-Hazards Analysis**
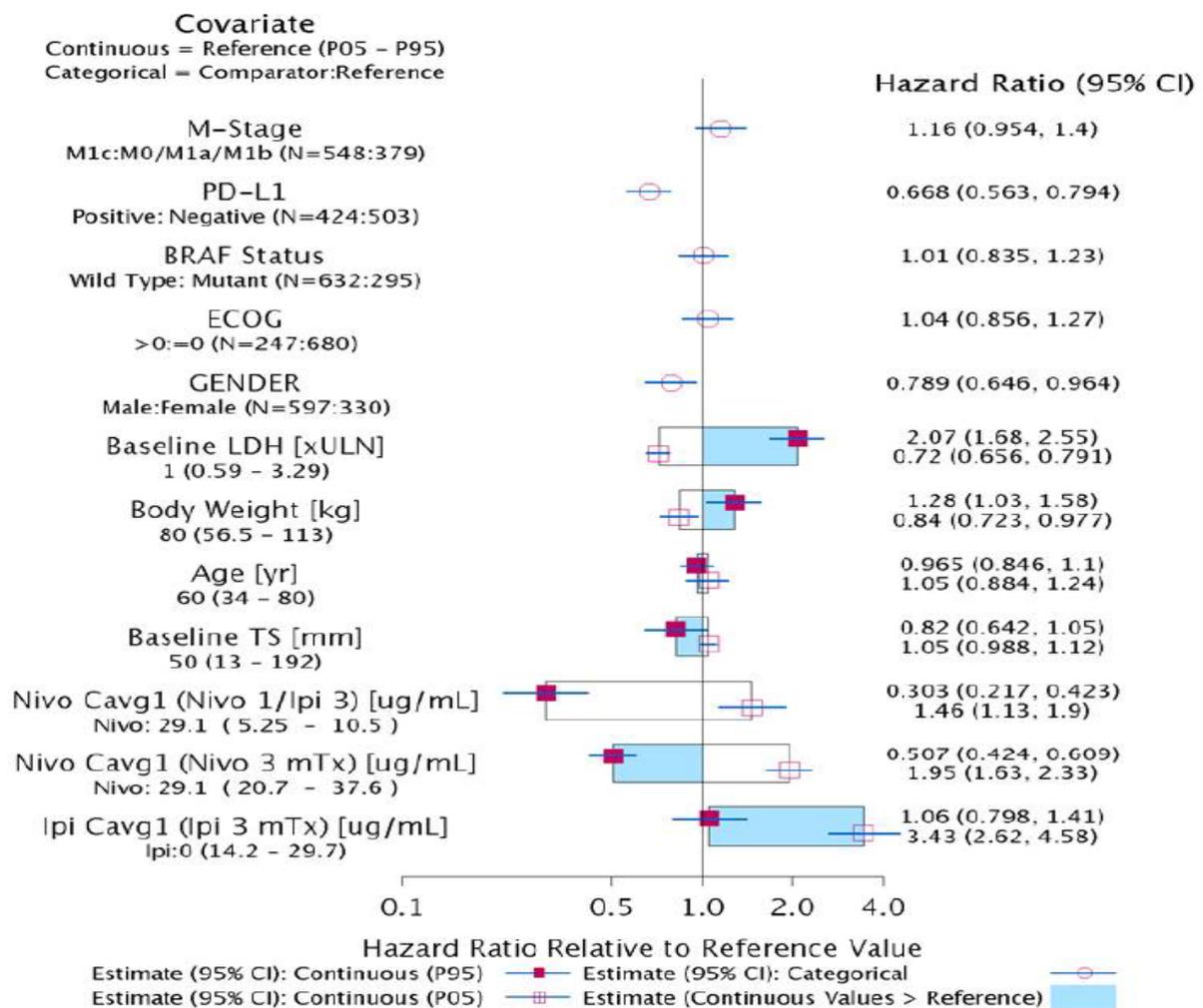
The hazard ratio (HR) of PFS was predicted from the full model at various values of Cavg1, in order to understand the impact of nivolumab and ipilimumab regimens on the risk of disease progression. The median Cavg1 at nivolumab 3 mg/kg monotherapy was used as the reference. The estimated hazard ratios 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 nivolumab and ipilimumab in CA209004, CA209037, CA209069, CA209066 and CA209067 in 1543 subjects. The popPK model predicted Cavg1 was used as the measure of exposure of both nivolumab and ipilimumab and the relationship between nivolumab and ipilimumab 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 nivolumab and ipilimumab 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 6. 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.

Figure 6: **Estimated covariate effects of exposure-safety (adverse events leading to dose discontinuation or death) by Cox Proportional-Hazards analysis**
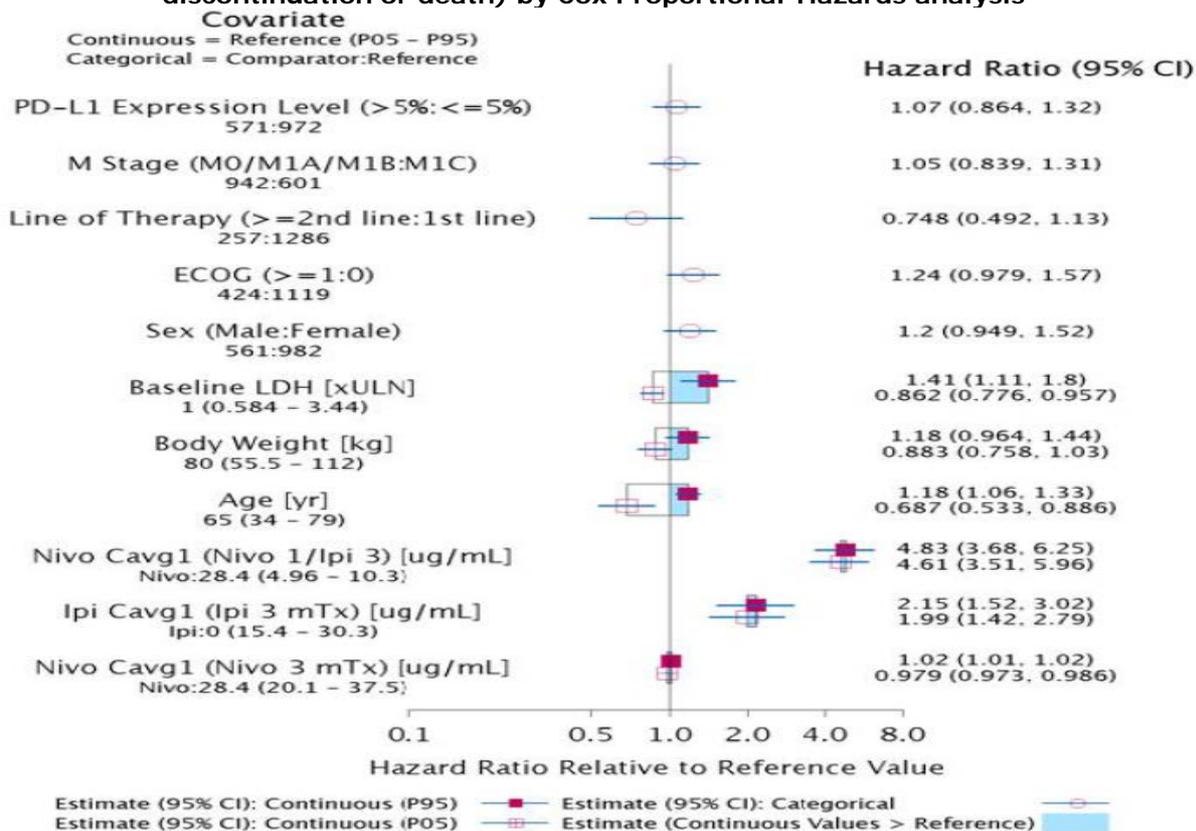
Note: hazard ratio at nivolumab 1 + ipilimumab 3 mg/kg was calculated by using median ipilimumab Cavg1 and varying nivolumab Cavg1

Immunogenicity

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.

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.

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.

2.3.5. Discussion on clinical pharmacology

The geometric mean CL, Vss, and terminal half-life of nivolumab were 9.83 mL/h, 7.62 L, and 24.1 days, respectively. When administered in combination, the CL of nivolumab was increased by 35%, whereas there was no effect on the CL of ipilimumab. When administered in combination, the CL of nivolumab increased by 25% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the CL of ipilimumab. Ipilimumab clearance increased with increasing baseline LDH (approximately 28% higher for LDH at 95th percentile). Nivolumab trough concentrations in the presence of ipilimumab 3 mg/kg (gMean 7.43 µg/ml) is still higher than the nivolumab concentrations of <0.5µg/ml which showed activity in in vitro studies. Furthermore, receptor occupancy (studies MDX1106-03 and CA209009) reached maximal occupancy at 0.1 mg/kg nivolumab and, based on the initial evaluation, it is known that there is no dose response of nivolumab in melanoma (range 0.1 – 10 mg/kg).Therefore, the modest effect of ipilimumab on nivolumab clearance is unlikely to be clinically relevant.

The risk of disease progression was evaluated in sensitivities analyses to evaluate further covariates. The risk of disease progression appeared to increase with lower nivolumab and ipilimumab 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.

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.

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

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).

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 9: **Treatment regimen for cohorts 1 − 8 for combination of nivolumab and ipilimumab − Study CA209004**

Study Drug	Cohort						
	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

Table 10: **Subjects in cohorts 1-3 (Dose Escalation Combination Therapy) − Study CA209004**

	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 11: 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 12: 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

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 7:   Study design schematic - CA209067
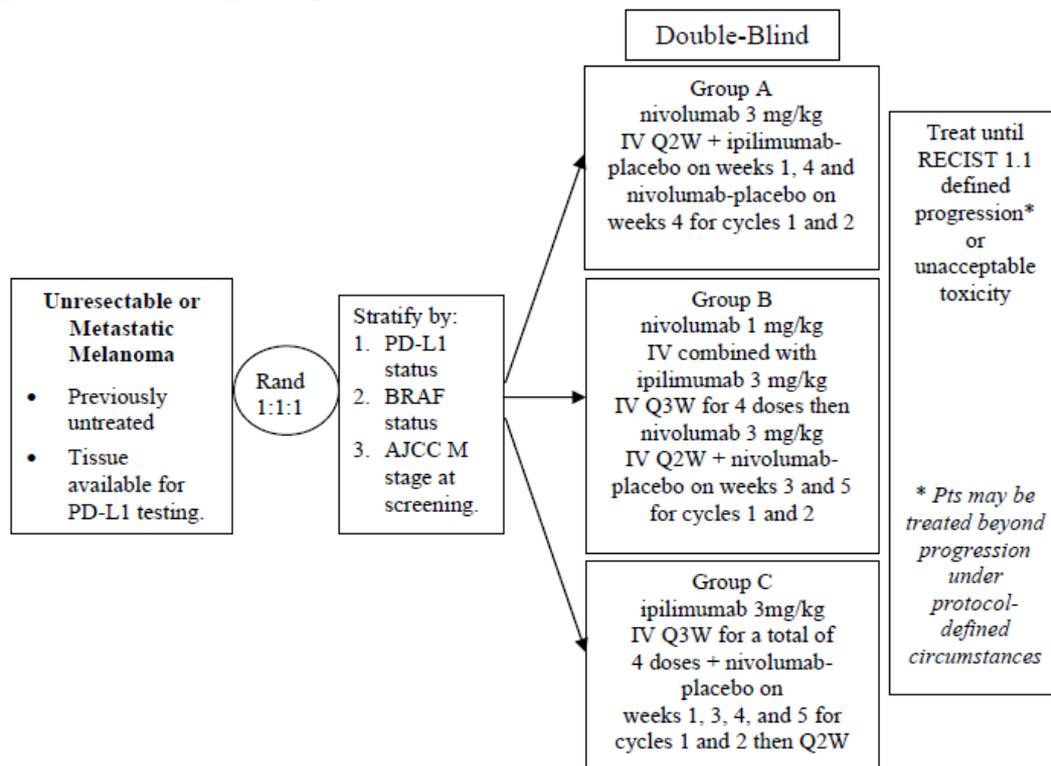
Study participants

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-L1positive, 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 least 8 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.

Table 13: 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 14: 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 PFS and 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 PFS and 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% cutoff.

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 enrol 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 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).

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 pairwise difference in ORRs between each of the 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.

<u>Primary Endpoint</u>

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 tumour 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 tumour PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in all randomised subjects using Hochberg's procedure to address multiplicity

Results

Participant flow

Patients enrolled (n=1296)

Patients randomized (n=945)

Reason for not being randomized

    Adverse event (n=7)

    Withdrew consent (n=45)

    Death (n=5)

    Lost to Follow up (n=1)

    Poor/non-compliance (n=7)

    No longer meeting study criteria (n=273)

    Other (n=13)

Allocation

Allocated to **nivolumab monotherapy 3 mg/kg Q2W** (n=316)	Allocated to **nivolumab 1 mg/kg + ipilimumab 3 mg/kg** (n=314)	Allocated to **Ipilimumab monotherapy 3 mg/kg Q3W** (n=315)
Received study treatment (n=313)	Received study treatment (n=313)	Received study treatment (n=311)

Follow-up

Patient status:
 Treatment Ongoing: n= 117
 Reason not continuing in the treatment
   Disease progression (n=154)
   Study drug toxicity (n=27)
   Death (n=1)
   Adverse event unrelated to study drug (n=5)
   Request to discontinue study treatment (n=5)
   With drew consent (n=0)
   Lost to follow-up (n=1)
   Maximum clinical benefit (n=2)
   Poor/non-compliance (n=1)
   No longer meeting s study criteria (n=0)
	Patient status:
	 Treatment Ongoing: n= 93
	 Reason not continuing in the treatment
	   Disease progression (n=69)
	   Study drug toxicity (n=120)
	   Death (n=4)
	   Adverse event unrelated to study drug (n=12)
	   Request to discontinue study treatment (n=5)
	   With drew consent (n=3)
	   Lost to follow-up (n=0)
	   Maximum clinical benefit (n=2)
	   Poor/non-compliance (n=1)
	   No longer meeting s study criteria (n=1)
		Patient status:
		 Treatment Ongoing: n= 50
		 Reason not continuing in the treatment
		   Disease progression (n=202)
		   Study drug toxicity (n=47)
		   Death (n=1)
		   Adverse event unrelated to study drug (n=4)
		   Request to discontinue study treatment (n=4)
		   With drew consent (n=0)
		   Lost to follow-up (n=0)
		   Maximum clinical benefit (n=0)
		   Poor/non-compliance (n=1)
		   No longer meeting s study criteria (n=0)

Analysis

All reandomized population (n=316) All treated population (n=313) Response-evaluable subjects (n=281) ADA evaluable subjects (n=288) Subjects treated beyond progession (n=81) PD-L1 ≥ 5% (n=143) PD-L1 < 5%(n=173)	All reandomized population (n=314) All treated population (n=313) Response-evaluable subjects (n=287) ADA evaluable subjects (n=289) Subjects treated beyond progession (n=46) PD-L1 ≥5% (n=144) PD-L1 <5% (n=170)	All reandomized population (n=315) All treated population (n=311) Response-evaluable subjects (n=270) ADA evaluable subjects (n=294) Subjects treated beyond progession (n=92) PD-L1 ≥5% (n=144) PD-L1 <5% (n=171)

The proportions of subjects continuing in the treatment period at the time of database lock (Feb 2015) in the nivolumab, nivolumab+ipilimumab, and ipilimumab groups were 37.4% (117/313) vs 29.7% (93/313) vs 16.1% (50/311), respectively.

Protocol Deviations

Significant protocol deviations were defined as study conduct that differed significantly from the protocol, including GCP noncompliance.

The one relevant protocol deviation reported at study entry was baseline ECOG performance status >1 (1 subject [0.3%] in the nivolumab group); this subject's ECOG PS was 0 at screening, but at the time of randomisation/first dose of study medication it was 2. Receiving concurrent anticancer therapy while on treatment was a deviation observed in 2 subjects (0.6%) in the nivolumab group and 3 subjects (1.0%) in the ipilimumab group. Two of the ipilimumab subjects had incomplete start dates for subsequent cancer therapy, which has resulted in the subsequent therapy to be considered as concurrent anti-cancer therapy.

Table 15: 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	3 (0.9)	0	3 (1.0)	6 (0.6)
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	0	0	0
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	2 (0.6)	0	3 (1.0)	5 (0.5)
SUBJECTS TREATED DIFFERENTLY AS RANDOMIZED	0	0	0	0

The majority of the deviations were due to failure to report serious adverse events (SAEs) within the time period required by the protocol (n = 89), protocol required assessment not done (n = 76) or performed outside of required schedule (n = 42), incorrect dosing (n = 66), incorrect informed consent form or process (n = 43), and inclusion exclusion criteria deviations (n = 41).The significant protocol deviations were equally distributed across the three treatment groups (nivolumab monotherapy 32%, nivolumab + ipilimumab combination therapy 35%, and ipilimumab monotherapy 32%).

Recruitment

This study was conducted 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). The enrolment period was from Jun-2013 until Mar-2014. The initial clinical database lock occurred on 17-Feb-2015 to allow for all subjects to have a minimum of approximately 9 months follow-up after their first dose of study therapy (31-Mar-2014, date the last subject was randomised, to 31-Dec-2014, date of last patient last visit for the database lock). A subsequent database lock occurred on 13-Nov-2015 (LPLV 02 Oct 2015) which allowed for all subjects to have a minimum of 18 months follow-up after first dose of study therapy.

Conduct of the study

The most relevant amendment was the amendment number 6. The study was originally designed with a single primary endpoint of overall survival. The study was modified to have the co-primary endpoints of PFS

and OS. This amendment only changes the statistical analysis plan and did not change the conduct of the study. The rationale to add PFS as co-primary endpoint was the increased number of anti-melanoma therapies, which can be used after progression, impacting on OS. This amendment was introduced after 945 patients were treated. The Amendment number 7 allowed to collect radiographic images in order to carry out a retrospective re-assessment of responses by an independent review of radiologic data. Amendment 8 allowed patients who discontinued study drug to be followed for a collection of outcomes and survival follow up data.

Baseline data

Baseline demographic and disease characteristics are presented in Table 16 - Table 19.

Table 16: **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 17: Baseline PD-L1 (at 5% expression level)*, 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 18: 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 +
                                     Nivolumab     Ipilimumab       Ipilimumab       Total
                                     N = 316       N = 314          N = 315          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 19:   Prior cancer therapy summary (all randomised subjects) – Study CA209067

```
-------------------------------------------------------------------------------------------------
                                                          Number of Subjects (%)
                                          -------------------------------------------------------
                                                         Nivolumab +
                                          Nivolumab      Ipilimumab      Ipilimumab        Total
                                          N = 316        N = 314         N = 315           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)
```

Numbers analysed

The primary datasets used are the All Randomized Population for the primary efficacy analysis and the All Treated Population for the safety analyses.

Table 20:   Analysis populations – Study CA209067

	Nivo	Nivo + Ipi	Ipi	Total
All Enrolled Subjects	NA	NA	NA	1296
All Randomized Population	316	314	315	945
All Treated Population	313	313	311	937
Response-Evaluable Subjects[a]	281	287	270	838
ADA Evaluable Subjects	288	289	294	871
Subjects Treated Beyond Progression[b]	81	46	92	219
M-stage at Study Entry (IVRS)				
M1c	184 (58.2)	181 (57.6)	183 (58.1)	548 (58)
M0/M1a/M1b	132 (41.8)	133 (42.4)	132 (41.9)	397 (42.0)
AJCC stage at Study Entry				
Stage IV	291 (92.1)	297 (94.6)	293 (93.0)	881 (93.2)
Stage III	25 (7.9)	17 (5.4)	22 (7.0)	64 (6.8)
PD-L1 status (verified assay; ≥ 5%)				
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)
BRAF status				
Wild-type	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)
Mutant	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)

[a] All randomized subjects who have **CR, PR, SD or PD as best response**, have baseline and at least one valid post-baseline target lesion assessments

[b] Subjects with last available dose after initial progression date (per investigator)

Table 21:   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 tumour PD-L1 expression levels (Figure 8). The difference in patient numbers between the ≥ 1% vs the ≥ 5% subgroup was 267subjects (490 vs 223, respectively), and between the ≥ 5% vs the ≥ 10% subgroup was 64 subjects (223 vs 159, respectively).

Figure 8: Frequency of pre-study (Baseline) tumour PD-L1 expression at the 1%, 5%, and 10% expression levels - All PD-L1 quantifiable subjects
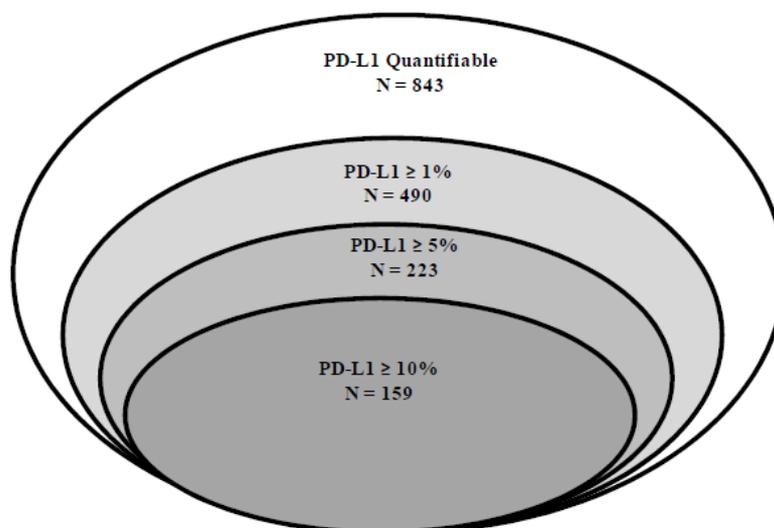

Outcomes and estimation

Co-primary efficacy endpoints

Progression-Free Survival (PFS)

The results of the primary PFS analysis for the all randomised population are presented in Figure 9. The median PFS was 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR=0.57, 99.5% CI: 0.43, 0.76; p<0.0001). The median PFS was 11.5 months in the nivolumab+ipilimumab group, as compared with 2.9 months in the ipilimumab group (HR=0.42, 99.5% CI: 0.31, 0.57; p<0.0001). There were 142 (44.9%) subjects in the nivolumab group, 163 (51.9%) subjects in the nivolumab+ipilimumab group, and 81 (25.7%) subjects in the ipilimumab group censored, with the most common reasons for censoring listed as 'still on treatment' across all 3 groups. An updated analysis based on Nov 2015 DBL showed similar results, i.e. a difference of 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR=0.55, 99.5% CI: 0.42, 0.73; p<0.0001). The median PFS was 11.5 months in the nivolumab+ipilimumab group, as compared with 2.9 months in the ipilimumab group (HR=0.42, 99.5% CI: 0.32, 0.56; p<0.0001).

Figure 9: Kaplan-Meier Plot of Progression Free Survival per Investigator (all randomised subjects) - Study CA209067 (Nov 2015 DBL)
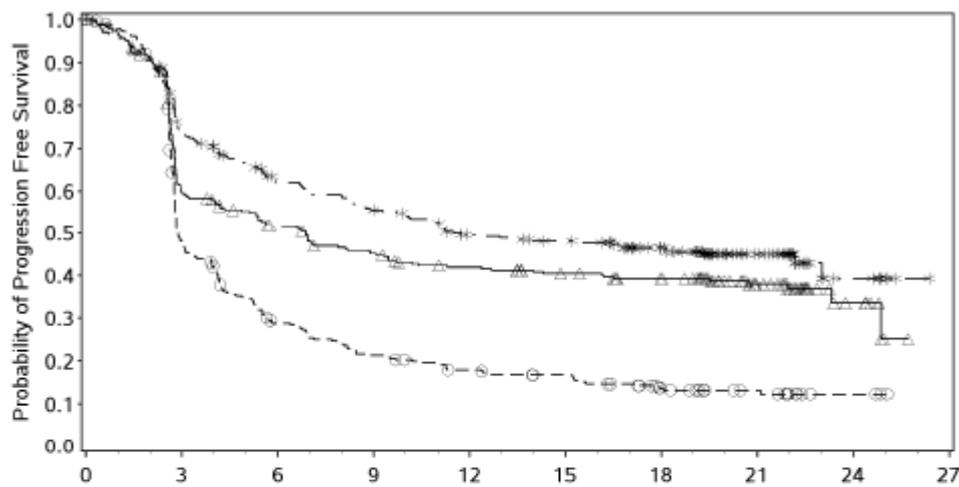
Number of Subjects at Risk
Nivolumab

| 316 | 177 | 148 | 127 | 114 | 104 | 94 | 46 | 8 | 0 |

Nivolumab + Ipilimumab

| 314 | 219 | 174 | 156 | 133 | 126 | 103 | 48 | 8 | 0 |

Ipilimumab

| 315 | 137 | 78 | 58 | 46 | 40 | 25 | 15 | 3 | 0 |

— △ — Nivolumab (events: 183/316), median and 95% CI: 6.87 (4.34, 9.46)
· — ✳ — Nivolumab + Ipilimumab (events: 161/314), median and 95% CI: 11.50 (8.90, 22.18)
— ⊝ — Ipilimumab (events: 245/315), median and 95% CI: 2.89 (2.79, 3.42)

Nivolumab vs Ipilimumab - hazard ratio and 99.5% CI: 0.55 (0.42, 0.73); p-value: <0.0001
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 99.5% CI: 0.42 (0.32, 0.56); p-value: <0.0001
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.76 (0.62, 0.95)

Symbols represent censored observations.

Secondary Efficacy Endpoints

Objective Response Rate (ORR)

The results for ORR (based on the Nov 2015 DBL) are presented in Table 22.

Table 22:   Best overall response per Investigator (all randomised subjects) — Study CA209067

```
----------------------------------------------------------------------------------------------------
                                                         Number of Subjects (%)
                                      --------------------------------------------------------------
                                         Nivolumab        Nivolumab + Ipilimumab       Ipilimumab
                                          N = 316              N = 314                   N = 315
----------------------------------------------------------------------------------------------------

BEST OVERALL RESPONSE (A):

COMPLETE RESPONSE (CR)                  28 (  8.9)          36 ( 11.5)               7 (  2.2)
PARTIAL RESPONSE (PR)                  110 ( 34.8)         145 ( 46.2)              53 ( 16.8)
STABLE DISEASE (SD)                     34 ( 10.8)          41 ( 13.1)              69 ( 21.9)
PROGRESSIVE DISEASE (PD)               119 ( 37.7)          71 ( 22.6)             154 ( 48.9)
UNABLE TO DETERMINE (UTD)               25 (  7.9)          21 (  6.7)              32 ( 10.2)

OBJECTIVE RESPONSE RATE (1)         138/316 ( 43.7%)     181/314 ( 57.6%)        60/315 ( 19.0%)
  (95% CI)                            (38.1, 49.3)         (52.0, 63.2)            (14.9, 23.8)

DIFFERENCE OF OBJECTIVE RESPONSE RATES (2)  24.7% (B)          38.4% (C)
  (95% CI)                            (17.9, 31.5)         (31.5, 45.2)

ESTIMATE OF ODDS RATIO (3)               3.40 (D)            6.11 (E)
  (99.5% CI)                          (2.02, 5.72)         (3.59, 10.38)

P-VALUE (4)                             <0.0001             <0.0001

DIFFERENCE OF OBJECTIVE RESPONSE RATES (2)                     13.8% (F)
  (95% CI)                                                  (6.3, 21.3)

ESTIMATE OF ODDS RATIO (3)                                     1.80 (G)
  (95% CI)                                                  (1.30, 2.49)
----------------------------------------------------------------------------------------------------
(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.
(4) Two-sided p-value from CMH Test.
(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.
```

At 9 months of follow-up (Feb 2015 DBL), the median percent reduction in tumour volume was 34.5% and 51.9% in the nivolumab and nivolumab+ipilimumab groups, respectively. There was a 5.9% increase in tumour volume in the ipilimumab group. The waterfall plots depicting reduction in tumour volume by subject are presented in Figure 10.

Figure 10: **Waterfall plot of best reduction from baseline in sum of diameters of target lesions per investigator for all treatment arms (all response evaluable subjects) – Study CA209067**
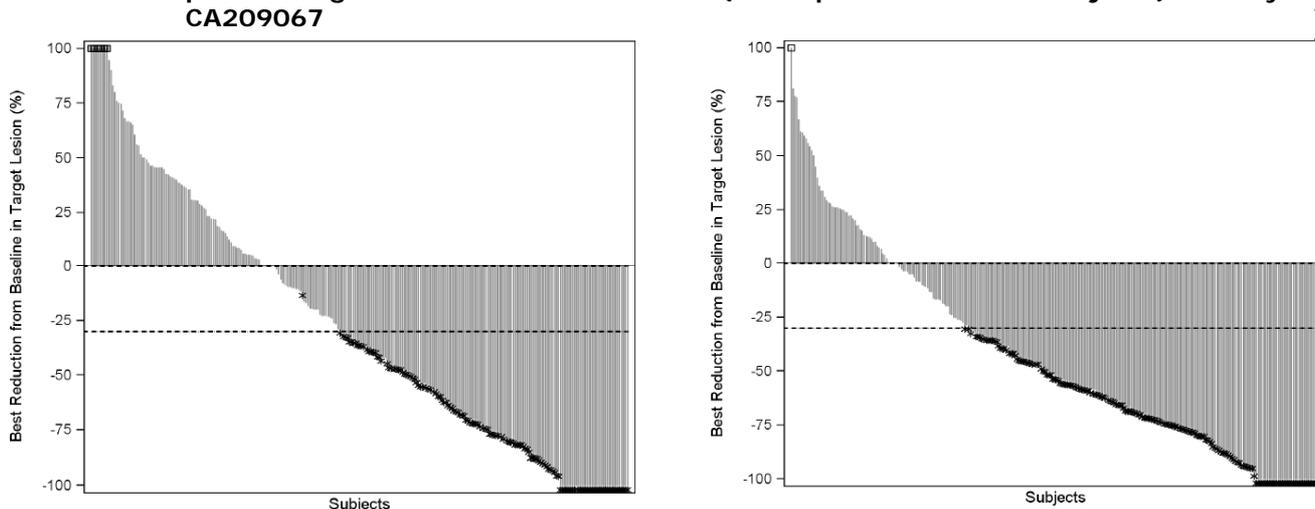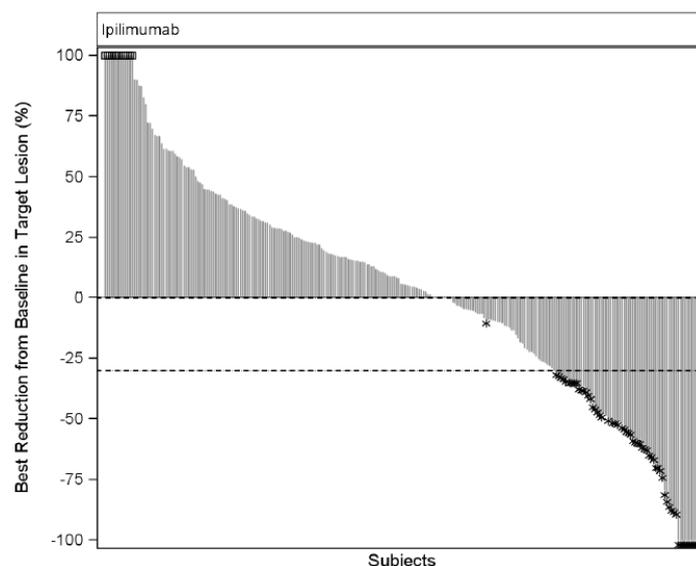
PD-L1 expression as a predictive biomarker for PFS, OS and ORR

Progression-free Survival

Nivolumab and the combination of nivolumab with ipilimumab demonstrated improved PFS compared to ipilimumab across all tumour PD-L1 expression subgroups.

Among tumour PD-L1-low and absent expression subgroups (<1%, <5% and <10%), PFS was improved for subjects in the combination treatment group relative to the nivolumab and ipilimumab treatment groups. At the time of the primary analysis, for the <1% and <5% tumour PD-L1 expression subgroups, the hazard ratios (95% confidence interval [CI]) for the combination versus nivolumab were 0.56 (0.40, 0.79) and 0.70 (0.54, 0.91), respectively. In the PD-L1-expression subgroups (≥1%, ≥5%, and ≥10%), PFS was comparable in the nivolumab and combination nivolumab + ipilimumab groups. The hazard ratios (95% CI) for nivolumab + ipilimumab versus nivolumab were 0.95 (0.69, 1.31) and 0.96 (0.58, 1.58) for the ≥1% and ≥5% subgroups, respectively.

Table 23: Summary of Progression-free Survival by PD-L1 level and treatment group (all randomised subjects) — Study CA209067

Cut-off PD-L1 Status	Nivolumab Median PFS (95% CI)	Ipilimumab Median PFS (95% CI)	Hazard Ratio (95% CI)[a]
≥1%	12.39 (8.11, NR)	3.91 (2.83, 4.17)	0,46 (0.35, 0.62)
<1%	2.83 (2.76, 5.13)	2.79 (2.66, 2.96)	0.65 (0.48, 0.89)
≥5%	14.00 (9.07, NR)	3.94 (2.79, 4.21)	0.43 (0.28, 0.66)
<5%	5.32 (2.83, 7.06)	2.83 (2.76, 3.09)	0.59 (0.46, 0.75)
≥10%	14.00 (9.07, NR)	4.11 (2.79, 5.72)	0.46 (0.28, 0.77)
<10%	5.49 (3.09, 8.11)	2.83 (2.79, 3.06)	0.56 (0.45, 0.71)
	Nivolumab + Ipilimumab Median PFS (95% CI)	Ipilimumab Median PFS (95% CI)	Hazard Ratio (95% CI)[a]
≥1%	12.35 (8.51, NR)	3.91 (2.83, 4.17)	0.44 (0.33, 0.60)
<1%	11.17 (6.93, NR)	2.79 (2.66, 2.96)	0.36 (0.26, 0.51)
≥5%	13.96 (9.72, NR)	3.94 (2.79, 4.21)	0.41 (026, 0.65)
<5%	11.24 (7.98, NR)	2.83 (2.76, 3.09)	0.41 (0.32, 0.53)
≥10%	13.96 (11.07, NR)	4.11 (2.79, 5.72)	0.30 (0.17, 0.56)
<10%	11.17 (6.97, 13.21)	2.83 (2.79, 3.06)	0.43 (0.34, 0.55)

Note: PD-L1 expression results from validated assay.

Source: Figure S.10.3 (K-M PFS plot) and Table S.10.11 (interaction test)

[a] Hazard ratio for treatment effect based on Cox proportional hazard model with treatment, PD-L1 status, and treatment by PD-L1 status interaction

Abbreviations: CI = confidence interval, NR = not reached, PFS = progression-free survival

At the Nov 2015 DBL, an updated analysis was provided for PFS by PD-L1 tumour expression levels (following table and figures). In a Cox proportional hazard model using PD-L1 status, treatment, and the interaction term as covariates, a significant interaction was only observed using a 1% expression cut-off: p-values of 0.0659, 0.3964, and 0.5363 observed for the 1%, 5% and 10% cut-offs, respectively (based on the Feb 2015 DBL). The full results at the Nov 2015 DBL are presented in the table and figures below.

Table 24: Summary of Progression-free Survival by PD-L1 level and treatment group (all randomised subjects) (Nov 2015 DBL) – Study CA209067

Cut-off PD-L1 Status	Nivolumab Median PFS (95% CI)	Ipilimumab Median PFS (95% CI)	Hazard Ratio (95% CI)[a]
≥1%	12.39 (8.11, NR)	3.91 (2.83, 4.17)	0,46 (0.35, 0.62)
<1%	2.83 (2.76, 5.13)	2.79 (2.66, 2.96)	0.65 (0.48, 0.89)
≥5%	14.00 (9.07, NR)	3.94 (2.79, 4.21)	0.43 (0.28, 0.66)
<5%	5.32 (2.83, 7.06)	2.83 (2.76, 3.09)	0.59 (0.46, 0.75)
≥10%	14.00 (9.07, NR)	4.11 (2.79, 5.72)	0.46 (0.28, 0.77)
<10%	5.49 (3.09, 8.11)	2.83 (2.79, 3.06)	0.56 (0.45, 0.71)

	Nivolumab + Ipilimumab Median PFS (95% CI)	Ipilimumab Median PFS (95% CI)	Hazard Ratio (95% CI)[a]
≥1%	12.35 (8.51, NR)	3.91 (2.83, 4.17)	0.44 (0.33, 0.60)
<1%	11.17 (6.93, NR)	2.79 (2.66, 2.96)	0.36 (0.26, 0.51)
≥5%	13.96 (9.72, NR)	3.94 (2.79, 4.21)	0.41 (026, 0.65)
<5%	11.24 (7.98, NR)	2.83 (2.76, 3.09)	0.41 (0.32, 0.53)
≥10%	13.96 (11.07, NR)	4.11 (2.79, 5.72)	0.30 (0.17, 0.56)
<10%	11.17 (6.97, 13.21)	2.83 (2.79, 3.06)	0.43 (0.34, 0.55)

Note: PD-L1 expression results from validated assay.

Source: Figure S.10.3 (K-M PFS plot) and Table S.10.11 (interaction test)

[a] Hazard ratio for treatment effect based on Cox proportional hazard model with treatment, PD-L1 status, and treatment by PD-L1 status interaction

Abbreviations: CI = confidence interval, NR = not reached, PFS = progression-free survival

Figure 11: PFS by treatment in tumour PD-L1 < 5%, PD-L1 ≥5%, PD-L1<1, PD-L1 ≥1% subgroups (Nov 2015 DBL) – Study CA209067

**Progression-free survival by PD-L1 expression: 5% cutoff (CA209067)**

PD-L1 Expression < 5%
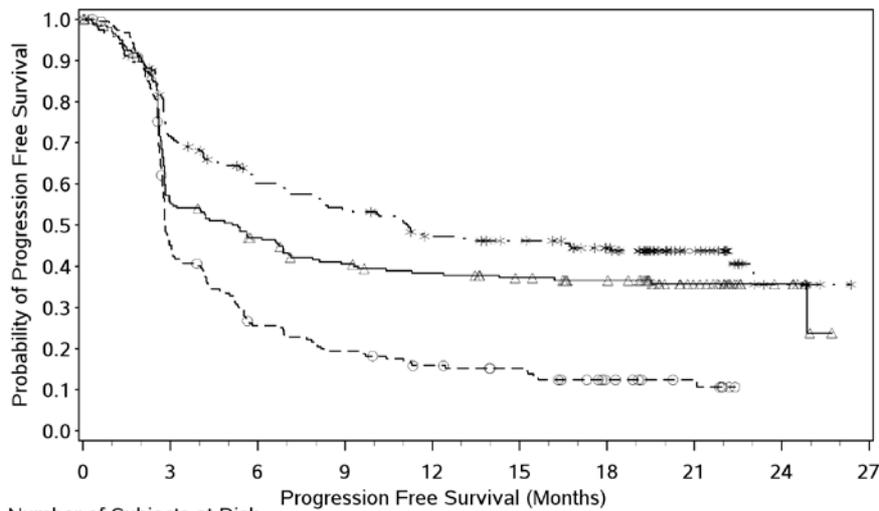
Number of Subjects at Risk

Nivolumab

| 208 | 108 | 89 | 75 | 69 | 62 | 55 | 29 | 7 | 0 |

Nivolumab+Ipilimumab

| 210 | 142 | 113 | 101 | 86 | 81 | 69 | 31 | 5 | 0 |

Ipilimumab

| 202 | 82 | 45 | 34 | 26 | 22 | 12 | 7 | 0 | 0 |

—△— Nivolumab (events : 125/208), median and 95% CI : 5.32 (2.83, 7.06)
· —*— Nivolumab+Ipilimumab (events : 111/210), median and 95% CI : 11.10 (7.98, 22.18)
— ⊖ — Ipilimumab (events : 159/202), median and 95% CI : 2.83 (2.76, 3.09)

Nivolumab vs. Ipilimumab - hazard ratio: 0.57 (0.45, 0.72)
Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.33, 0.54)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.74 (0.58, 0.96)

PD-L1 Expression >= 5%
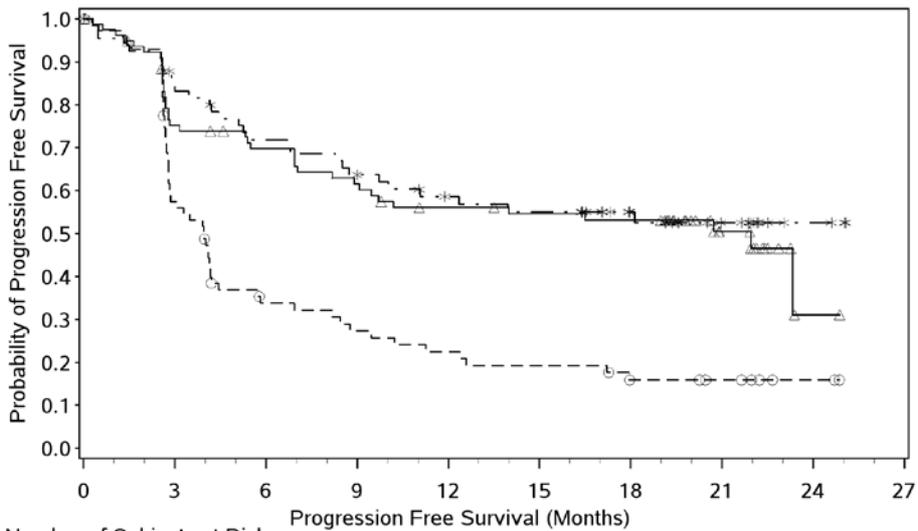
Number of Subjects at Risk

Nivolumab

| 80 | 57 | 51 | 45 | 39 | 37 | 36 | 16 | 1 | 0 |

Nivolumab+Ipilimumab

| 68 | 53 | 44 | 39 | 33 | 31 | 22 | 13 | 3 | 0 |

Ipilimumab

| 75 | 40 | 21 | 17 | 14 | 12 | 8 | 6 | 2 | 0 |

—△— Nivolumab (events : 38/80), median and 95% CI : 21.95 (8.90, N.A.)
· —*— Nivolumab+Ipilimumab (events : 29/68), median and 95% CI : N.A. (9.72, N.A.)
— ⊖ — Ipilimumab (events : 57/75), median and 95% CI : 3.94 (2.79, 4.21)

Nivolumab vs. Ipilimumab - hazard ratio: 0.41 (0.27, 0.62)
Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.35 (0.22, 0.55)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.87 (0.54, 1.41)

**Progression-free survival by PD-L1 expression: 1% cutoff (CA209067)**

PD-L1 expression < 1%
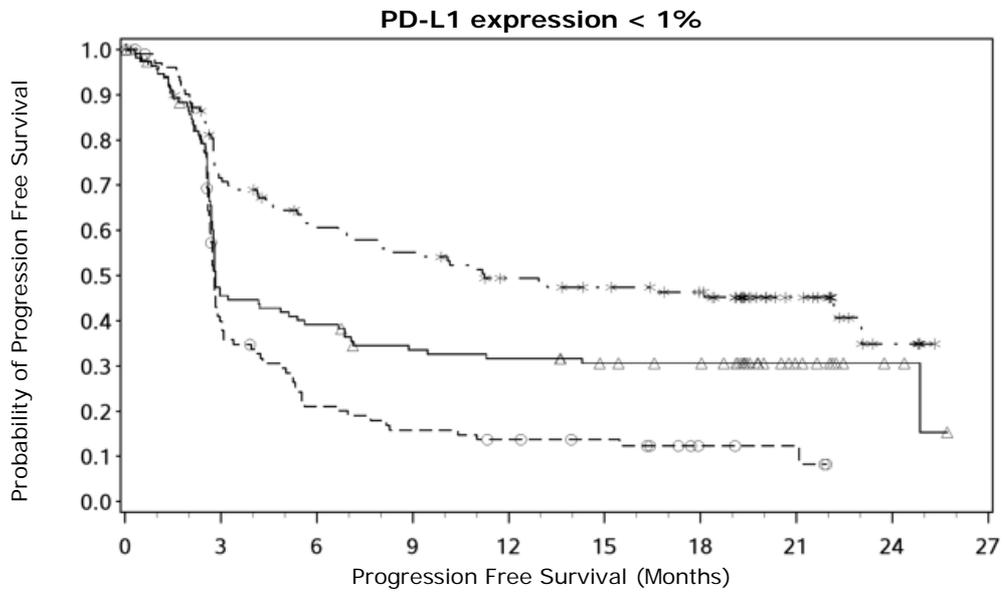
Number of Subjects at Risk

Nivolumab + Ipilimumab

123	82	65	59	50	46	41	18	4	0

Nivolumab

117	50	43	35	33	29	27	11	3	0

Ipilimumab

113	39	20	15	12	10	4	3	0	0

- - -*- - - -   Nivolumab+Ipilimumab (events: 63/123), median and 95% CI: 11.24 (6.93, 23.03)
——Δ——   Nivolumab (events: 77/117), median and 95% CI: 2.83 (2.76, 5.13)
- - -O- - -   Ipilimumab (events: 87/113), median and 95% CI: 2.79 (2.66, 2.96)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.39 (0.28, 0.54)
Nivolumab vs. Ipilimumab - hazard ratio: 0.65 (0.48, 0.88)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.60 (0.43, 0.84)

PD-L1 expression ≥ 1%
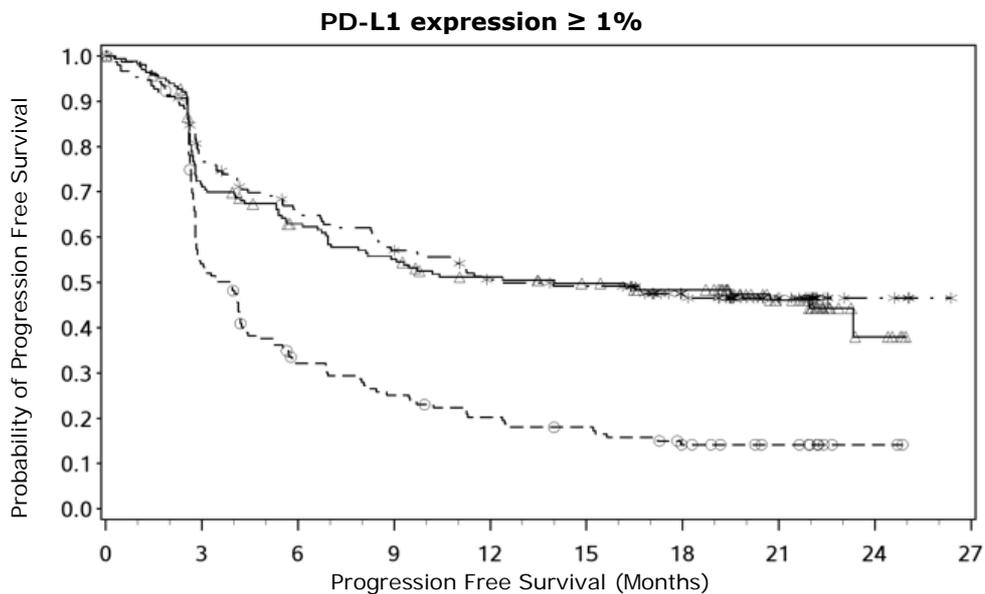
Number of Subjects at Risk
Nivolumab + Ipilimumab

155	113	92	81	69	66	50	26	4	0

Nivolumab

171	115	97	85	75	70	64	34	5	0

Ipilimumab

| 164	83	46	36	28	24	16	10	2	0

- - -*- - - -   Nivolumab+Ipilimumab (events: 77/155), median and 95% CI: 12.35 (8.74, N.A.)
——Δ——   Nivolumab (events: 86/171), median and 95% CI: 14.00 (7.03, N.A.)
- - -O- - -   Ipilimumab (events: 129/164), median and 95% CI: 3.91 (2.83, 4.17)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.31, 0.55)
Nivolumab vs. Ipilimumab - hazard ratio: 0.44 (0.34, 0.58)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.94 (0.69, 1.28)

PFS was analysed in PD-L1 subgroups subdivided into tumour expression levels <1%, <5% and <10% (Figure 12).

Figure 12:   Forest Plot of PFS Hazard Ratios by PD-L1 expression results subgroup – Study CA209067
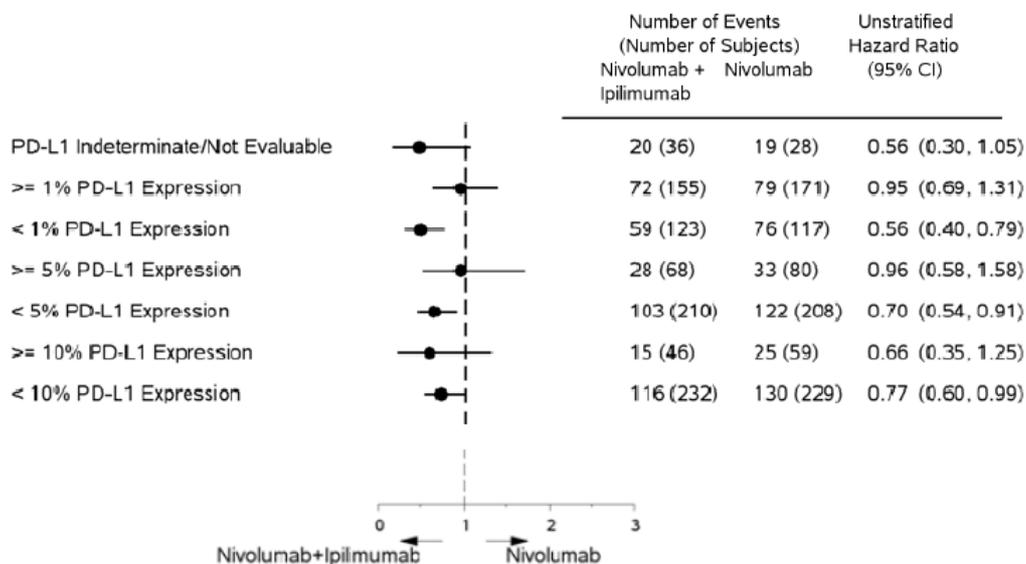
PD-L1 expression result from validated assay.

Objective Response Rate

Higher ORRs were observed in the nivolumab and nivolumab + ipilimumab treatment groups irrespective of PD-L1 expression status at all definitions of PD-L1 expression (1%, 5%, or 10% tumour cell membrane expression) relative to the ipilimumab treatment group. Higher rates of tumour response were reported in patients treated with the combination nivolumab + ipilimumab compared to nivolumab monotherapy in all definitions of PD-L1 expression. Subjects treated with nivolumab and nivolumab + ipilimumab who had ≥ 1%, ≥5% or ≥10% PD- L1 expression levels had a numerically higher ORR compared to those who had low

to absent PD-L1 expression. In the ipilimumab group, ORRs were comparable across all PD-L1 expression subgroups (Table 25).

Table 25: **Investigator-assessed ORR by PD-L1 expression level (Validated Assay) - PD-L1 tested subjects - CA209067 (Nov 2015 DBL)**

	\<1%	≥1%	\<5%	≥5%	\<10%	≥10%	Indeterminate or Not Evaluable[a]
Nivolumab Group N=316							
PD-L1 Expression Level							
PD-L1 expression	\<1%	≥1%	\<5%	≥5%	\<10%	≥10%	Indeterminate or Not Evaluable[a]
ORR (%)	39/117 (33.3%)	93/171 (54.4%)	86/208 (41.3%)	46/80 (57.5%)	98/229 (42.8%)	34/59 (57.6%)	6/28 (21.4%)
Exact 95% CI	24.9, 42.6	46.6, 62.0	34.6, 48.4	45.9, 68.5	36.3, 49.5	44.1, 70.4	8.3, 41.0
CR rate (%)	5/117 (4.3%)	23/171 (13.5%)	16/208 (7.7%)	12/80 (15.0%)	19/229 (8.3%)	9/59 (15.3%)	0
Nivolumab + Ipilimumab Group N=314							
PD-L1 Expression Level							
PD-L1 expression	\<1%	≥1%	\<5%	≥5%	\<10%	≥10%	Indeterminate or Not Evaluable[a]
ORR (%)	64/123 (52.0%)	100/155 (64.5%)	115/210 (54.8%)	49/68 (72.1%)	125/232 (53.9%)	39/46 (84.8%)	17/36 (47.2%)
Exact 95% CI	42.8, 61.1	56.4, 72.0	47.8, 61.6	59.9, 82.3	47.2, 60.4	71.1, 93.7	30.4, 64.5
CR rate (%)	16/123 (13.0%)	16/155 (10.3%)	25/210 (11.9%)	7/68 (10.3%)	25/232 (10.8%)	7/46 (15.2%)	4/36 (11.1%)
Ipilimumab Group N=315							
PD-L1 Expression LEvel							
PD-L1 expression	\<1%	≥1%	\<5%	≥5%	\<10%	≥10%	Indeterminate or Not Evaluable[a]
ORR (%)	21/113 (18.6%)	31/164 (18.9%)	36/202 (17.8%)	16/75 (21.3%)	41/223 (18.4%)	11/54 (20.4%)	8/38 (21.1%)
Exact 95% CI	11.9, 27.0	13.2, 25.7	12.8, 23.8	12.7, 32.3	13.5, 24,1	10.6, 33.5	9.6, 37.3
CR rate (%)	3/113 (2.7%)	3/164 (1.8%)	3/202 (1.5%)	3/75 (4.0%)	5/223 (2.2%)	1/54 (17.1%)	1/38 (2.6%)

[a] Indeterminate or not evaluable PD-L1 results
Abbreviations: CI = confidence interval; CR = complete response; PD-L1 = programmed cell death ligand 1; ORR = objective response rate

Outcomes Research Analysis (EORTC QLQ-C30)

Questionnaire completion rate at baseline for all randomized subjects was 92.4% (290/314) for the nivolumab/ipilimumab group, 89.9% (284/316) for the nivolumab group, and 88.6% (279/315) for the ipilimumab group and remained at least 53% for each visit with a sample size greater than 10 for subjects that were still participating in the study from baseline to visit week 67.

The global health status/QoL, physical functioning, role functioning, cognitive function and social functioning scores showed deterioration over time and across all treatment groups but the deteriorations were generally less pronounced for the nivolumab group than those observed in the nivolumab+ipilimumab and ipilimumab groups. Role functioning change scores reached a clinically meaningful threshold of deterioration (a change greater than or equal to 10 points is considered a clinically relevant minimally important difference) at week 7 and week 17 in the nivolumab+ipilimumab group. The deteriorations, when observed in the three groups, appeared to be less pronounced after week 25 and even modest improvements could be observed in some subscales after those time points (social functioning for the nivolumab+ipilimumab and ipilimumab groups; Global health status/QoL, social functioning, physical functioning for the nivolumab group). Emotional functioning improved for all treatment groups with change scores reaching the clinically meaningful threshold of improvement at week 55 and week 61 in the ipilimumab group, and almost reaching the clinically meaningful threshold of improvement at week 61 and week 67 in the nivolumab+ipilimumab group, and week 37 in the nivolumab group

Exploratory endpoints

Time to and Duration of Response

The median time to response was approximately 3 months in all treatment groups.

The median duration of response (DOR) (Nov 2015 DBL) was not reached in in the nivolumab+ipilimumab group and was 22.34 months and 14.39 months in the nivolumab and ipilimumab treatment groups, respectively. The minimum follow-up was 18 months.

Ancillary analyses

As of the Feb 2015 DBL, subsequent systemic cancer therapy was received by 43.7%, 30.9%, and 61.3% of subjects in the nivolumab, nivolumab+ipilimumab and ipilimumab treatment groups, respectively. Of the subjects in the nivolumab group who went on to subsequent therapy, 19.3% received ipilimumab. Of the subjects in the nivolumab+ipilimumab group who went on to subsequent therapy, 3.5% received pembrolizumab. Of the subjects in the ipilimumab group who went on to subsequent therapy, 29.2% went onto pembrolizumab. A sensitivity analysis for PFS is presented in Table 26.

Table 26:   **Progression Free Survival per Investigator, sensitivity analysis (all randomised subjects) — Study CA209067 (Feb 2015 DBL)**

	Median PFS (Months) (95% CI) (1)		
Sensitivity Analysis	Nivolumab N = 316	Nivolumab + Ipilimumab N = 314	Ipilimumab N = 315
ANALYSIS ACCOUNTING FOR ASSESSMENT AFTER SUBSEQUENT THERAPY	6.87 (5.13, 9.46)	11.17 (8.51, 13.96)	2.89 (2.79, 3.48)
HR (99.5% CI)	0.55 (0.42, 0.73) (A)	0.43 (0.32, 0.57) (B)	
P-VALUE (2)	<0.0001	<0.0001	
ANALYSIS ACCOUNTING FOR MISSING TUMOR ASSESSMENT PRIOR TO PFS EVENT	5.49 (3.15, 8.11)	11.27 (8.51, N.A.)	2.83 (2.76, 3.02)
HR (99.5% CI)	0.58 (0.44, 0.77) (A)	0.41 (0.31, 0.55) (B)	
P-VALUE (2)	<0.0001	<0.0001	

(1) Based on Kaplan-Meier Estimates.
(2) Log-rank Test stratified by PD-L1 status, BRAF status and M stage at screening as entered into the IVRS.
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Ipilimumab.
(B) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Ipilimumab.

Progression-free Survival in Subpopulations

Progression-free survival benefit was observed with nivolumab vs ipilimumab across pre-defined subsets, with each unstratified hazard ratio < 1, including BRAF mutant and WT groups. The results from the subgroup analyses were consistent with the overall population.

Objective Response Rate in Subpopulations

Objective response rate benefit was observed with nivolumab vs ipilimumab across pre-defined subsets. The results from the subgroup analyses were consistent with the overall population.

Treatment post-progression

In the pivotal study CA209067, patients were permitted to continue nivolumab treatment beyond disease progression in case there was still an investigator's assessed clinical benefit and the study drug was tolerated well. Of 344 subjects with best overall response of progressive disease as of the Nov 2015 DBL (120 [nivolumab], 71 [nivolumab+ipilimumab], and 153 [ipilimumab] subjects), 254 subjects were treated beyond progression, including 93 subjects in the nivolumab group, 56 subjects in the nivolumab+ipilimumab group, and 105 subjects in the ipilimumab group. Of the 235 subjects who were treated beyond progression (as of the Feb 2015 DBL), 219 were evaluable for response, including 81 subjects in the nivolumab group, 46 subjects in the nivolumab+ipilimumab group, and 92 subjects in the ipilimumab group. Following progression, the subject and the investigator were unblinded but BMS personnel remained blinded. Data for these subjects were censored at the initial progressive event.

PFS in subjects who discontinued treatment due to drug toxicity

As of the Nov 2015 DBL, among the treated subjects who discontinued treatment due to adverse reactions, the median PFS in the nivolumab group was 23.33 months (95% CI: 9.07, NA), 16.72 months (95% CI: 10.15, NA) in the nivolumab+ipilimumab group and 4.70 months (95% CI: 4.01, 8.18) in the ipilimumab group, respectively (Figure 13).

Figure 13:   Kaplan-Meier Plot of Progression Free Survival per Investigator all treated subjects who discontinued treatment due to adverse reactions – Study CA209067 (Feb 2015 DBL)
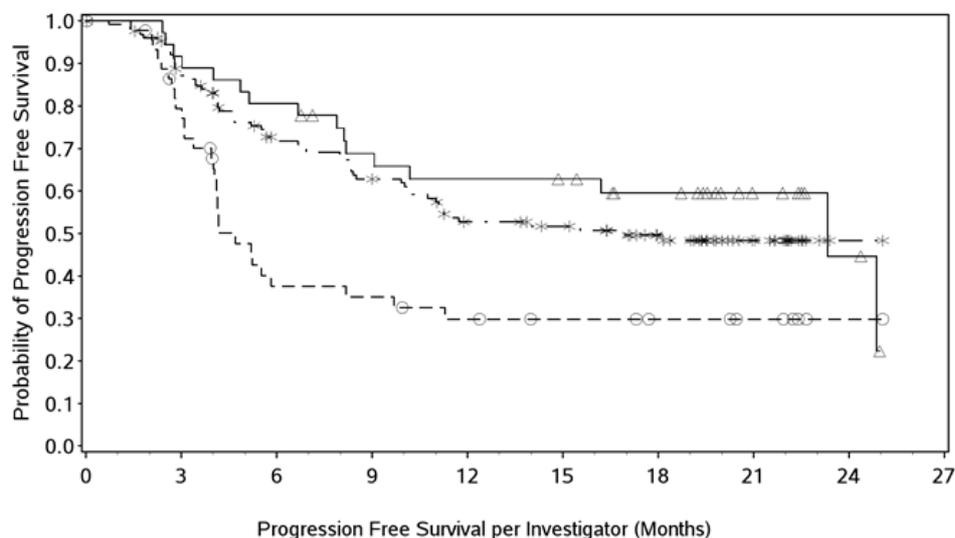
Number of Subjects at Risk
Nivolumab

| 36 | 33 | 29 | 23 | 21 | 20 | 16 | 8 | 3 | 0 |

Nivolumab + Ipilimumab

| 128 | 107 | 80 | 70 | 55 | 51 | 40 | 20 | 1 | 0 |

Ipilimumab

| 48 | 34 | 15 | 14 | 11 | 9 | 7 | 5 | 1 | 0 |

—△— Nivolumab (events: 16/36), median and 95% CI: 23.33 (9.07, N.A.)
· —✳— · Nivolumab + Ipilimumab (events: 59/128), median and 95% CI: 16.72 (10.15, N.A.)
— ⊖ — Ipilimumab (events: 29/48), median and 95% CI: 4.70 (4.01, 8.18)

Analyses of PD-L1 positivity threshold

Additional post-hoc exploratory analyses were conducted to determine ORR using alternative PD L1 expression thresholds and PD-L1 expression intervals. Objective responses were observed across all PD-L1 expression subsets, including in the ranges of 1% - 3% and3% - 5%.

In these intervals of 1% to 3% and 3% to 5% tumour PD-L1 expression, the ORR was numerically higher for nivolumab+ipilimumab compared to nivolumab (48.0% vs 47.5% and 73.0% vs 59.4%, respectively).

		No. of Subjects (%)			
PD-L1 Expression	Nivolumab+ ipilimumab	Odds Ratio (95% CI)[a,b]	Nivolumab	Odds Ratio (95% CI)[c]	Ipilimumab
Post-hoc Analyses					
≥1% to <3%	24/50 (48.0)	4.72 (1.77, 13.18) / 1.02 (0.45, 2.32)	28/59 (47.5)	4.62 (1.79, 12.55)	9/55 (16.4)
≥3% to <5%	27/37 (73.0)	12.60 (3.58, 47.18) / 1.85 (0.60, 5.77)	19/32 (59.4)	6.82 (1.96, 25.34)	6/34 (17.6)
≥5% to <10%	10/22 (45.5)	2.67 (0.61, 12.50) / 0.63 (0.16, 2.44)	12/21 (57.1)	4.27 (0.96, 20.24)	5/21 (23.8)
Pre-specified Analyses					
<1%	64/123 (52.0)	4.75 (2.54, 9.04) / 2.17 (1.25, 3.79)	39/117 (33.3)	2.19 (1.14, 4.26)	21/113 (18.6)
≥1%	100/155 (64.5)	7.80 (4.55, 13.47) / 1.52 (0.95, 2.44)	93/171 (54.4)	5.12 (3.04, 8.67)	31/164 (18.9)

|		No. of Subjects (%)			
PD-L1 Expression	Nivolumab+ ipilimumab	Odds Ratio (95% CI)[a,b]	Nivolumab	Odds Ratio (95% CI)[c]	Ipilimumab
<5%	115/210 (54.8)	5.58 (3.48, 9.03) / 1.72 (1.14, 2.58)	86/208 (41.3)	3.25 (2.02, 5.28)	36/202 (17.8)
≥5%	49/68 (72.1)	9.51 (4.16, 22.03) / 1.91 (0.91, 4.05)	46/80 (57.5)	4.99 (2.33, 10.86)	16/75 (21.3)
≥10%	39/ 46 (84.8)	21.78 (6.97, 71.61) / 4.10 (1.47, 12.51)	34/ 59 (57.6)	5.32 (2.14, 13.61)	11/ 54 (20.4)

[a] First row: Ratio of nivolumab+ipilimumab over ipilimumab.

[b] 2nd row: Ratio of nivolumab+ipilimumab over nivolumab

[c] Ratio of nivolumab over ipilimumab.

In addition, a receiver operating characteristic (ROC) curve for tumour PD-L1 expression by objective response was constructed (Figure 14). As indicated by the shape of the curve and area under the curve (AUC) of 0.61, ROC analysis does not clearly define an optimal PD-L1 cutoff that maximizes sensitivity and specificity. Supporting this conclusion, the test performance characteristics for response by tumour PD-L1 expression level in the nivolumab group and the nivolumab+ipilimumab group demonstrate a gradation of effect.

Figure 14: Receiver Operator Characteristics (ROC) curve based on objective response (all randomized nivolumab and nivolumab+ipilimumab subjects with quantifiable PD-L1 - Nov 2015 DBL) — Study CA209067

Area under the curve: 0.624

Area under the curve: 0.608

Annotation shows the level of PDL1 expression (%)
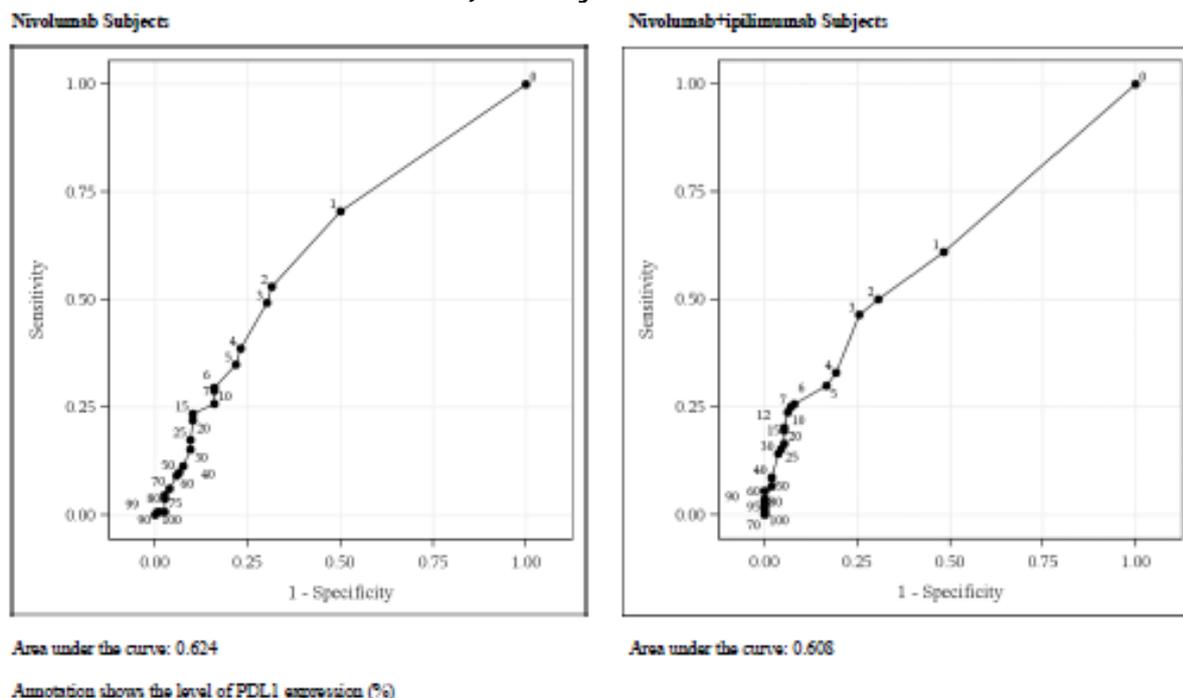
Multivariate Analyses of PD-L1 Expression and Efficacy (based on Nov 2015 DBL)

Multivariate analyses were used to explore the relationship between PD-L1 expression and activity, as well as the association between PD-L1 expression and other clinical prognostic factors. Several multivariate regression models were fitted to explore the treatment effect of nivolumab+ipilimumab combination therapy versus nivolumab monotherapy on PFS and ORR when adjusted for potential prognostic factors. PFS was analyzed using a multivariate Cox proportional hazards model while ORR was analyzed using a multivariate logistic regression model. The model for each endpoint was fitted in 3 sequential steps. In the first step, the following prognostic factors were included as predictor variables in the model in addition to treatment (nivolumab+ipilimumab versus nivolumab). These prognostic factors were pre-specified as subsets of interest in the Statistical Analysis Plan.

- PD-L1 expression level (≥1%, <1%, not quantifiable)

- BRAF mutation status (BRAF mutant and wildtype)

- M Stage at Study Entry (M0/M1a/M1b and M1c)

- Age category (< 65 and ≥65)

- Gender (male and female)

- Race (white, asian, and other)

- Region (US, EU, Australia, and Rest of World)

- Baseline ECOG Performance Status (0 and 1)

- History of Brain Metastases (Yes and No)

- Smoking Status (Yes and No)

- Baseline LDH (≥ ULN and < ULN)

- AJCC Stage (III and IV)

These models showed that treatment, PD-L1 expression, M Stage, Gender, Region, and baseline LDH were significant predictors of clinical outcome for both PFS and ORR.

In addition, ECOG performance status was a significant predictor of PFS and AJCC stage was a significant predictor of ORR. There was no statistically significant interaction with treatment for any of the factors in the ORR model. In the PFS model, treatment-by-region was the only significant interaction term (P=0.1825).

Summary of main study

The following table 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 28: Summary of the main study CA209067

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			
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; LPLV for the Nov 2015 database lock: 02-Oct-2015	
	Duration of Run-in phase:	Not Applicable	
	Duration of Extension phase:	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.	
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 randomised subjects for each treatment group.	
	Secondary Endpoint	OS, PFS, and ORR	See ORR and PFS definitions above. OS: Time between the date of randomisation 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 randomisation to the date of the first documented response (CR or PR). TTR was evaluated in all randomised subjects and for responders (i.e. subjects with a BOR of CR or PR).	

|				
Database Lock	13 November 2015			
Analysis Description	**PFS**			
Analysis Population	**All Randomised subjects (co-primary analysis)**			
	Treatment group	**Nivolumab + Ipilimumab**	**Nivolumab**	**Ipilimumab**
	Number of subjects	**314**	**316**	**315**
Descriptive statistics & estimate variability	Events, n (%)	161 (51)	183 (58)	245 (78)
	Median (95% CI) (Months)	11.5 (8.9, 22.2)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
	Rate at 6 months (95% CI)	0.62 (0.56, 0.67)	0.52 (0.46, 0.57)	0.29 (0.24, 0.34)
	Rate at 12 months (95% CI)	0.49 (0.44, 0.55)	0.42 (0.36, 0.47)	0.18 (0.14, 0.23)
	Rate at 18 months (95% CI)	0.46 (0.41, 0.52)	0.39 (0.34, 0.45)	0.14 (0.10, 0.18)
Effect estimate per comparison	Hazard ratio (99.5% CI)	0.42 (0.32, 0.56)	0.55 (0.42, 0.73)	
	P-value	<0.0001	<0.0001	
Analysis Population	**BRAF WT and BRAF Mutant subjects (ancilliary subgroup analysis)**			
BRAF WT Subjects	Events, n (%)	110/112 (51.9)	120/218 (55.0)	174/215 (80.9)
	Median (95% CI) (Months)	11.27 (8.34, 22.18)	7.13 (4.86, 14.29)	2.83 (2.76, 3.09)
	Hazard ratio (95% CI) (versus ipilimumab)	0.41 (0.33, 0.53)	0.48 (0.38, 0.60)	
	Hazard ratio (95% CI) (versus nivolumab)	0.87 (0.67, 1.13)		
BRAF Mutant Subjects	Events, n (%)	51/102 (50.0)	63/98 (64.3)	71/100 (71.0)
	Median (95% CI) (Months)	15.54 (8.02, NA)	5.62 (2.79, 9.30)	4.04 (2.79, 5.52)
	Hazard ratio (95% CI) (versus ipilimumab)	0.44 (0.31, 0.63)	0.76 (0.54, 1.07)	
	Hazard ratio (95% CI) (versus nivolumab)	0.58 (0.40, 0.84)		
Analysis Population	**Tumour PD-L1 status expression (pre-specified subgroup analysis)**			
<1%	Events, n/N	63/123	77/177	87/113
	Median (95% CI) (Months)	11.2 (6.9, 23.0)	2.8 (2.8, 5.1)	2.8 (2.7, 3.0)
	Hazard ratio (95% CI) (versus ipilimumab)	0.39 (0.28, 0.54)	0.65 (0.48, 0.88)	
	Hazard ratio (95% CI) (versus nivolumab)	0.60 (0.43, 0.84)		
≥1%	Events, n/N	77/155	86/171	129/164
	Median (95% CI) (Months)	12.4 (8.7, NA)	14.0 (7.0, NA)	3.9 (2.8, 4.2)
	Hazard ratio (95% CI)	0.42 (0.31, 0.55)	0.44 (0.34, 0.58)	

	(versus ipilimumab)			
	Hazard ratio (95% CI) (versus nivolumab)	0.94 (0.69, 1.28)		
<5%	Events, n/N	111/210	125/208	159/202
	Median (95% CI) (Months)	11.1 (8.0, 22.2)	5.3 (2.8, 7.1)	2.8 (2.8, 3.1)
	Hazard ratio (95% CI) (versus ipilimumab)	0.42 (0.33, 0.54)	0.57 (0.45, 0.72)	
	Hazard ratio (95% CI) (versus nivolumab)	0.74 (0.58, 0.96)		
≥5%	Events, n/N	29/68	38/80	57/75
	Median (95% CI) (Months)	NA (9.7, NA)	22.0 (8.9, NA)	3.9 (2.8, 4.2)
	Hazard ratio (95% CI) (versus ipilimumab)	0.35 (0.22, 0.55)	0.41 (0.27, 0.62)	
	Hazard ratio (95% CI) (versus nivolumab)	0.87 (0.54, 1.41)		
Analysis Description	**ORR**			
Analysis Population	**All Randomised subjects (secondary analysis)**			
	CR	38 (12)	31 (10)	7 (2)
	PR	143 (46)	107 (34)	53 (17)
	SD	41 (13)	33 (10)	69 (22)
	PD	71 (22.6)	120 (38.0)	153 (48.6)
	Unable to determine	21 (6.7)	25 (7.9)	33 (10.5)
Descriptive statistics & estimate variability	Number (%) of responders	181 (58)	138 (44)	60 (19)
	95% CI	(52.0, 63.2)	(38.1, 49.3)	(14.9, 23.8)
Effect estimate per comparison	Odds ratio (95% CI)	6.09 (3.59, 10.33)	3.40 (2.02, 5.72)	
	p-value	<0.0001	<0.0001	
Analysis Description	**Investigator-Assessed Cumulative Response Rate**			
Analysis Population	**All Randomised subjects (exploratory analysis)**			
	Treatment group	Nivolumab + Ipilimumab	Nivolumab	Ipilimumab
	Number of subjects	**314**	**316**	**315**
Descriptive statistics& estimate variability	Number of responders, n (%)	181 (58)	138 (44)	60 (19)
	Median (Months)	2.76	2.78	2.79
	Min-Max	1.1, 15.2	2.3, 12.5	2.5, 12.4
Analysis Description	**DOR**			
Analysis Population	**All Randomised subjects (exploratory analysis)**			
Descriptive statistics& estimate variability	Ongoing responders, n/N (%)	131/181 (72)	100/138 (72)	31/60 (52)
	Median (95% CI) (Months)	NA (20.50, NA)	20.34 (20.76, NA)	14.39 (8.34, NA)
	Min - Max	0.0, 24.0	0.0, 23.0	1.4, 22.3
Analysis Description	**ORR**			
Analysis Population	**BRAF WT and BRAF Mutant subjects (ancilliary subgroup analysis)**			
BRAF WT Subjects	n/N (%)	113/212 (53.3)	102/218 (46.8)	38/215 (17.7)
	(95% CI)	(46.3, 60.2)	(40.0, 53.6)	(12.8, 23.4)
BRAF Mutant Subjects	n/N (%)	68/102 (66.7)	36/98 (36.7)	22/100 (22.0)
	(95% CI)	(56.6, 75.7)	(27.2, 47.1)	(14.3, 31.4)
Analysis Population	**Tumour PD-L1 status (pre-specified subgroup analysis)**			
<1%	ORR (%)	52	33	19
	(95% CI)	(42.8, 61.1)	(24.9, 42.6)	(11.9, 27.0)
	Median DOR (Months)	Not reached	22.3	11.6
	Range	0^+-22.8^+	0^+-23^+	1.4-19.4^+
≥1%	ORR (%)	65	54	19
	(95% CI)	(56.4, 72.0)	(46.6, 62.0)	(13.2, 25.7)
	Median DOR (Months)	Not reached	Not reached	Not reached
	Range	0^+-24^+	1.3^+-22.2^+	1.4-19.9^+
<5%	ORR (%)	55	41	18
	(95% CI)	(47.8, 61.6)	(34.6, 48.4)	(12.8, 23.8)
	Median DOR	Not reached	22.3	18.2

	(Months)			
	Range	0^+-24^+	0^+-23^+	1.4-19.8^+
≥5%	ORR (%)	72	58	21
	(95% CI)	(59.9, 82.3)	(45.9, 68.5)	(12.7, 32.3)
	Median DOR (Months)	Not reached	20.8	Not reached
	Range	0^+-22.3^+	2.8-20.8	1.4-19.9^+

Supportive study

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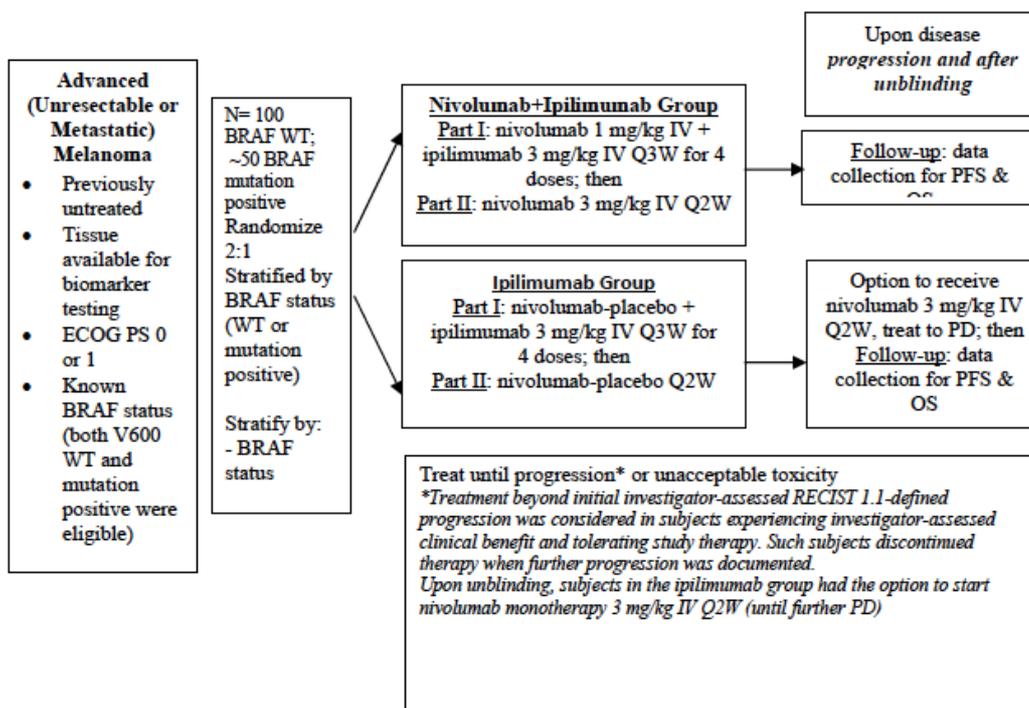
Abbreviations: IV = intravenous; OS = overall survival; PD = progressive disease; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; WT = wild type.

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 BRAF WT 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 initial analysis, the minimum follow-up was approximately 24 weeks (~6 months) (from 06-Feb-2014 [date last subject was randomized] to 24-Jul-2014). A subsequent database lock took place on 30-Jan-2015 with a minimum follow-up of ~11 months and analyses from this DBL were submitted as part of this application.

Subject disposition for all treated subjects (N = 140) is summarized below (Jan 2015 DBL):

– At the time of analysis, 23.4% of subjects in the nivolumab+ipilimumab group and 30.4% 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 44.7% in the nivolumab+ipilimumab group and 21.7% 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 29: Best overall response per investigator and IRRC in BRAF WT subjects and all randomized subjects – Study CA209069 (July 2014 DBL)

Efficacy Parameter	BRAF WT		All Randomized	
	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 30: Progression Free Survival in BRAF WT patients – Study CA209069 (July 2014 DBL)

	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 (July 2014 DBL) 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 an 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 31: Time to response and Duration of response in BRAF WT patients – Study CA209069 (July 2014 DBL)

	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 (July 2014 DBL). 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.

- PD-L1 results (January 2015 DBL)

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 tumour 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, and 24/118 (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 32:   Overall response rate by tumour PD-L1 expression — Study CA209069 (Jan 2015 DBL)

	PD-L1 Expression						
	<1%	≥1%	< 5%	≥5%	<10%	≥10%	Unknown
Nivolumab/Ipilimumab, N = 94							
ORR, n/N (%)[a]	16/35 (45.7)	29/45 (64.4)	31/56 (55.4)	14/24 (58.3)	35/64 (54.7)	10/16 (62.5)	10/14 (71.4)
Exact 95% CI	28.8, 63.4	48.8, 78.1	41.5, 68.7	36.6, 77.9	41.7, 67.2	35.4, 84.8	41.9, 91.6
Ipilimumab, N = 47							
ORR, n/N (%)[a]	0/15 (0)	2/23 (8.7)	1/27 (3.7)	2/11 (18.2)	2/30 (6.7)	1/8 (12.5)	2/9 (22.2)
Exact 95% CI	0.0, 21.8	2.8, 33.6	0.1, 19.0	2.3, 51.8	0.8, 22.1	0.3, 52.7	2.8, 60.0

Note: RECIST 1.1 response criteria where response confirmation was required. PD-L1 Expression results from verified or validated assay.
[a] CR+PR, confidence interval based on the Clopper and Pearson method.

Analysis performed across trials (pooled analyses and meta-analysis): Updated OS analyses from studies CA209066, CA209069 and CA209004

Updated survival data for subjects treated with the combination of nivolumab and ipilimumab (CA209069 and CA209004 cohort 8) and nivolumab monotherapy (CA209066) are presented in Table 33.

Table 33:   Overall survival rates and PFS rates-all randomised subjects treated with nivolumab or nivolumab+ipilimumab — Studies CA209069, CA209066 and CA209004 cohort 8

	CA209069 Nivo+Ipi N = 95	CA209066 Nivo N = 210	CA209004 Cohort 8 Nivo+Ipi N = 41
Overall Survival			
No. of events/No. subjects (%)	30/95 (31.6)	80/210 (38.1)	14/41 (34.1)
Median OS (months) (95% CI)[a]	NA	N.A. (23.13, N.A.)	N.A. (19.88, N.A.)
OS Rate (95% CI)			
6-month	81.9 (72.5, 88.3)	84.0 (78.2, 88.3)	NR
12-month	73.4 (63.2, 81.2)	70.7 (63.9, 76.4)	75 (59, 86)
18-month	69.1 (58.7, 77.4)	64.1 (57.1, 70.3)	68 (51, 80)
24-month	NA[b]	57.7 (49.7, 64.9)	NA[b]
PFS per Investigator (95% CI)			
No. events/No. subjects (%)	43/95 (45.3)	114/210 (54.3)	30/41 (73.2)
Median PFS (months) (95% CI)	NA	5.42 (3.71, 12.22)	7.36 (2.96, 11.07)
6-month	66.6 (55.9, 75.4)	49.2 (42.0, 56.0)	NR
12-month	52.5 (41.6, 62.3)	44.3 (37.2, 51.2)	33 (19, 48)
18-month	51.2 (40.3, 61.1)	42.3 (35.2, 49.2)	27 (14, 41)
24-month	NA[b]	39.2 (31.8, 46.5)	NA[b]

[a] Based on Kaplan-Meier Estimates.

[b] N.A.: Not Available: minimum follow up not reached, while rates presented at 6, 12, 18, and 24 months regardless of the minimum follow-up.

Data cut-off dates: CA209069 (18-Aug-2015), CA209066 (15-Jul-2015) and CA209004 (30-Jul-2015)

Abbreviations: CI: confidence interval, Ipi:ipilimumab, Nivo: nivolumab, NR: not reported

In response to the request for supplementary information, the MAH has submitted the following information to support the OS data:

• OS data from CA209066 (first-line nivolumab monotherapy in BRAF wild-type [WT] subjects).

- OS data from CA209069 (first-line combination of nivolumab and ipilimumab regardless of BRAF status).

The survival data from the All Randomized primary BRAF WT populations are summarized in Table 34 and the Kaplan-Meier curve in Figure 15.

Table 34:   **Summary of Overall OS Rates and OS Rates treated BRAF WT Subjects with a Minimum of 18-months Follow-up – Studies CA209069 and CA209066**

	Nivolumab (066) N = 210	Nivolumab+Ipilimumab (069) N = 72
OS Rates in All Randomized Primary BRAF WT Population		
6-month	84.0 (78.2, 88.3)	83.1 (72.2, 90.0)
12-month	70.7 (63.9, 76.4)	78.9 (67.4, 86.7)
18-month	64.1 (57.1, 70.3)	73.2 (61.3, 82.0)
24-month	57.7 (49.7, 64.9)	NA

Figure 15:   **Kaplan-Meier Plot of OS - All randomised BRAF WT subjects - subjects in the nivolumab arm of study CA209066 and in the nivolumab+ipilimumab arm of Study CA209069**
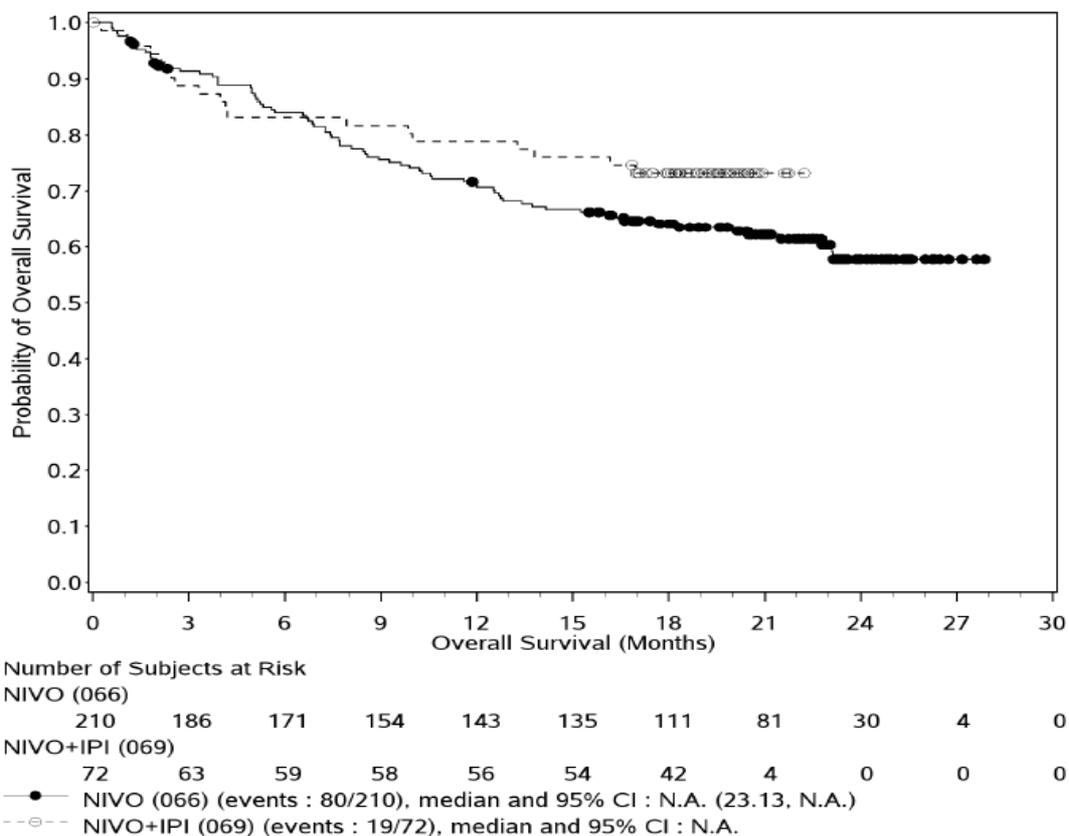
The survival data by PD-L1 expression are summarised in Table 35 and in the Kaplan-Meier curves in Figure 16 and Figure 17.

Table 35:   **Summary of OS rates by tumour PD-L1 expression in nivolumab+ipilimumab and nivolumab-treated BRAF WT subjects in CA209069 and CA209066 respectively with a minimum of 18-months Follow-up**

		Nivolumab (066) N = 210	Nivolumab+Ipilimumab (069) N = 72
		OS Rates by PD-L1 Expression	
≥1% Expression	N (%)	110 (52.4)	34 (47.2)
6-month		86.9 (78.9, 92.0)	82.4 (64.9, 91.7)
12-month		77.5 (68.3, 84.3)	79.4 (61.6, 89.6)
18-month		70.7 (61.0, 78.4)	73.5 (55.3, 85.3)
24-month		62.2 (50.8, 71.8)	NA
<1% Expression	N (%)	76 (36.2)	26 (36.1)
6-month		80.0 (69.0, 87.4)	84.0 (62.8, 93.7)
12-month		62.4 (50.3, 72.3)	80.0 (58.4, 91.1)
18-month		56.9 (44.8, 67.2)	72.0 (50.1, 85.5)
24-month		53.5 (40.5, 64.9)	NA
≥5% Expression	N (%)	59 (28.1)	19 (26.4)
6-month		91.4 (80.6, 96.3)	84.2 (58.7, 94.6)
12-month		80.9 (68.1, 88.9)	78.9 (53.2, 91.5)
18-month		77.3 (64.2, 86.2)	73.7 (47.9, 88.1)
24-month		68.3 (52.1, 80.0)	NA
<5% Expression	N (%)	127 (60.5)	41 (56.9)
6-month		80.7 (72.5, 86.6)	82.5 (66.8, 91.2)
12-month		66.8 (57.8, 74.4)	80.0 (64.0, 89.5)
18-month		59.2 (49.9, 67.3)	72.4 (55.7, 83.7)
24-month		54.2 (44.0, 63.4)	NA

Based on Kaplan-Meier Estimates

NA: not available, minimum follow-up not reached, while rates presented at 6, 12, 18, and 24 months regardless of the minimum follow-up

Figure 16: **Kaplan-Meier Plot of OS on Tumour PD-L1 Expression (≥1% and ≥5% Expression) in nivolumab and nivolumab+ipilimumab - treated BRAF WT subjects in CA209069 and CA209066 with ~ 18 month follow-up**
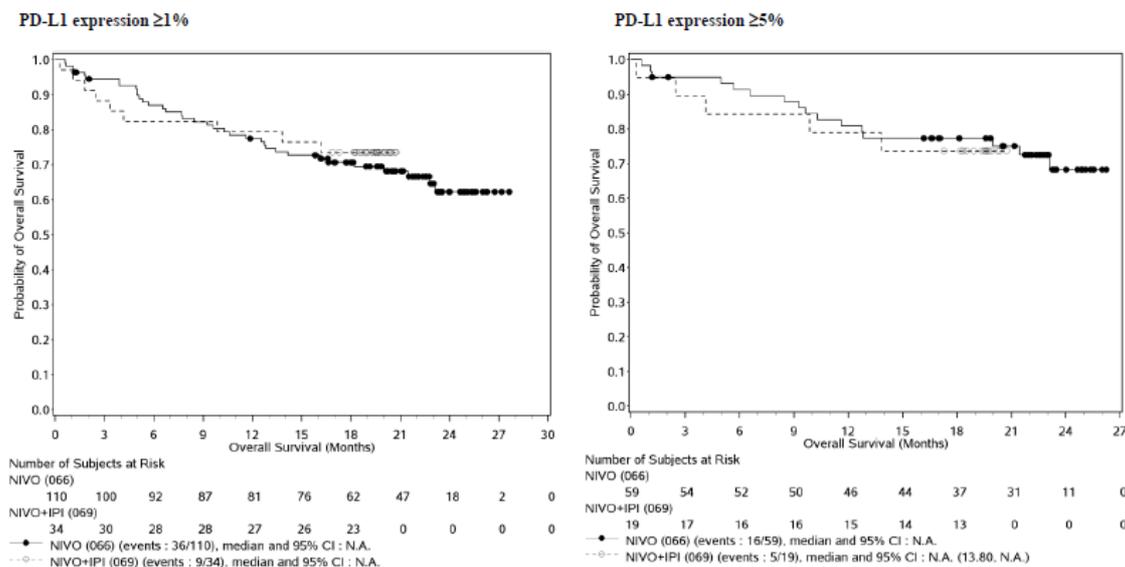

Figure 17: **Kaplan-Meier Plot of OS on Tumour PD-L1 Expression (<1% and <5% Expression) in nivolumab and nivolumab+ipilimumab - treated BRAF WT subjects in CA209069 and CA209066 with ~ 18-month Follow-up**

PD-L1 expression <1%

Probability of Overall Survival

Overall Survival (Months)

Number of Subjects at Risk
NIVO (066)
76   65   59   48   46   44   37   27   9   1   0
NIVO+IPI (069)
26   23   21   21   20   19   13   2   0   0

— NIVO (066) (events : 33/76), median and 95% CI : N.A. (12.55, N.A.)
---○--- NIVO+IPI (069) (events : 7/26), median and 95% CI : N.A.

PD-L1 expression <5%

Probability of Overall Survival

Overall Survival (Months)

Number of Subjects at Risk
NIVO (066)
127   111   99   85   81   76   62   43   16   3   0
NIVO+IPI (069)
41   36   33   33   32   31   23   2   0   0   0

— NIVO (066) (events : 53/127), median and 95% CI : N.A. (16.62, N.A.)
---○--- NIVO+IPI (069) (events : 11/41), median and 95% CI : N.A.
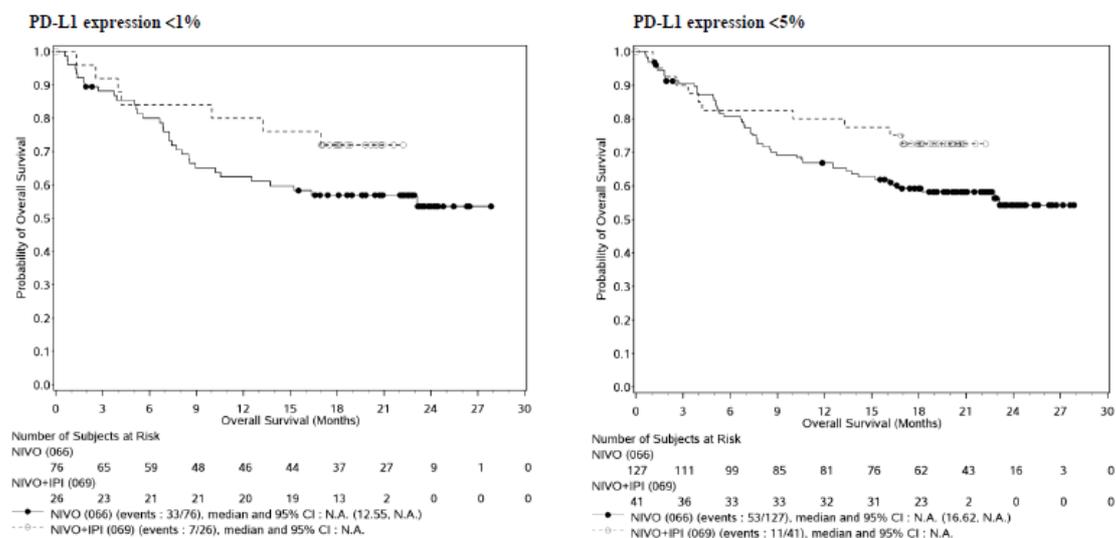
2.4.3. Discussion on clinical efficacy

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.

Design and conduct of clinical studies
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 tumour PD-L1 expression level 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 $\geq$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).Despite the high number of significant protocol deviations, these 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.

A higher percentage of patients in the combination treatment arms of nivolumab and ipilimumab were censored, the majority were considered non-informative (still in treatment). Patients were permitted to continue nivolumab treatment beyond disease progression if the study drug was tolerated and a clinical benefit was still derived as assessed by the investigator. Treatment following progression was administered to 43.7%, 30.9%, and 61.3% of patients in the nivolumab, nivolumab+ipilimumab, and ipilimumab treatment groups. It is well-known that patients have experienced documented pseudo-progressions when treated with immunomodulating agents. Therefore, a benefit-risk balance assessment in patients that are considered as having progressed in their disease in the first 12 weeks after start of treatment was required by the investigator.

Efficacy data and additional analyses
The MAH submitted efficacy results from ORR and PFS for studies CA209004 and CA209067. OS results for study CA209067 were not yet available as results from the analysis for the co-primary endpoint will only be available in 4Q2016 with a minimum follow-up of 28 months. However, during the procedure, the MAH submitted the updated OS data from CA209066 (first-line nivolumab monotherapy in BRAF wild-type [WT] subjects), updated OS data from CA209069 (first-line combination of nivolumab and ipilimumab regardless of BRAF status) and a descriptive analysis of OS from CA209067, with minimum follow-up of 18 months as supportive data for OS.

For the overall population (Nov 2015 DBL), in terms of ORR, BOR (CR+PR) was 43.7%(95%CI: 38.1, 49.3), 57.6% (95%CI: 52.0, 63.2) and 19% (95%CI: 14.9, 23.8) of patients and median PFS was 6.87 months (95%CI: 4.34, 9.46), 11.50 months (95%CI: 8.90, 16.72) and 2.89 months (95%CI: 2.79, 3.42) months in the nivolumab, nivo+ipi and ipilimumab treated group, respectively. The PFS HR (99.5%CI) was 0.55 (0.42, 0.73; p-value <0.001) and 0.42 (0.32, 0.56) in favour of nivolumab and nivolumab+ipilimumab compared to ipilimumab treatment, respectively. The results in terms of PFS and ORR, were both considered clinically relevant and meaningful. The combination of nivolumab and ipilimumab appears to delay tumour progression compared to that observed for the monotherapy with ipilimumab. In addition, patients treated with nivo+ipi have a decreased risk of progression or death compared to those treated with ipilimumab alone. The different sensitivity analyses carried out (on or after subsequent therapy and accounting for missing tumour assessment prior to PFS event) support the robustness of the main result. Subgroup analyses were also consistent with the ITT analysis including the BRAF mutated patients (HR 0.44; mPFS 15.54 months; ORR 66.7%) and BRAF WT subjects (HR 0.41; mPFS 11.27 months; ORR 53.3%). The lower antitumor activity in BRAF positive subjects was not expected. These results in BRAF mutated subjects look similar to those obtained with the combination of dabrafenib+trametinib (mPFS 11.4 and ORR 64%). Comparing nivolumab+ipilimumab combination therapy to nivolumab monotherapy, the PFS HR was 0.58 and 0.87, respectively, for BRAF mutated and wild type patients. Therefore, the data suggest a better efficacy with nivolumab+ipilimumab combination therapy compared to nivolumab or ipilimumab monotherapy for patients with BRAF mutated tumours. There is no indication of a detrimental effect on PFS in this population compared with the whole study population.

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 (Jan 2015 DBL) for ORR were 58.9% vs. 10.6% (nivolumab+ipilimumab vs ipilimumab) with 22.1% vs 0% of CR (nivolumab+ipilimumab vs ipilimumab alone respectively). ORR compared with ipilimumab alone in BRAF WT subjects was 61.1% vs. 10.8%. The HR for PFS was 0.39 with the mPFS N.A in the whole population.

Following a request from the CHMP, nivolumab monotherapy was compared to the combination of nivolumab-ipilimumab in the phase III trial (CA209067). Although the results in terms of PFS and ORR continue to favour the combination therapy, the gain in PFS and ORR is more modest (HR 0.74; 95%CI 0.60-0.92; ORR 57.6% vs 43.7%) with 4.6 months of difference between medians of PFS (11.50-6.87) (Nov 2015 DBL). However the estimator used, median of PFS, show a plateau of the curves and hence the magnitude of the effect cannot be appropriately evaluated. The rate of patients free of progression and alive at 6 months (0.52 [0.46, 0.57] and 0.62 [0.56, 0.67] for nivolumab and nivolumab + ipilimumab, respectively) and 12 months (0.42 [0.36, 0.47] and 0.49 [0.44, 0.55], for nivolumab and nivolumab + ipilimumab, respectively) show a difference of 10 points between arms, with a trend to decrease over time, though the limited number of patients at risk at the end of the curves hampers a thorough analysis.

The MAH presented data on PFS in subgroup of patients that had tumours that were designated as PD-L1 positive (≥1%, ≥5%, ≥10%) and PD-L1 negative (<1%). The hazard ratios (95% CI) for nivolumab+ipilimumab versus nivolumab were 0.94 (0.69, 1.28) and 0.87 (0.54, 1.41) for the ≥1% and ≥5% subgroups, respectively. For the <1% and <5% PD-L1 expression subgroups, the hazard ratios (95% [CI]) for the combination versus nivolumab were 0.60 (0.43, 0.84) and 0.74 (0.58, 0.96), respectively. The analysis according to the PD-L1 expression revealed that the efficacy for PFS observed in the ITT population appeared to be driven mainly by patients designated as having tumour expression of PD-L1 <1%. A similar trend was observed in the data according the PD-L1 tumour expression from studies CA209069 and CA209066 with 18 month follow up. Since the OS for study CA209067 is not yet mature, no definitive conclusion can be drawn on the predictive or prognostic value of PD-L1 or whether the combination of nivolumab+ipilimumab is mostly effective in a select PD-L1 tumour expressing subset of the population. Hence, the CHMP has imposed a post-authorisation efficacy study (PAES)for the submission of the final OS data for study CA209067.The CHMP will review the data to guide the decision on whether or not there is a need to review the proposed indication.

In total 85 patients were treated beyond progression (TBP) with nivolumab monotherapy. The group of patients who continued treatment in spite of progressive disease had a slightly better prognosis at baseline than the group of patients who stopped treatment at the moment of progression (n=221), because the TBP group had a better performance status and fewer patients had elevated LDH and M1c disease stage. It is currently unknown which patient groups have any chance for tumour response by treatment continuation after progression. The decision to treat patients after progression and the duration of treatment post-progression is left to the physician to carefully evaluate for each individual patient.

The data related to QoL were inconclusive. Hence, no conclusion can be drawn from the QoL study.

Additional expert consultation
Following a CHMP request, a Scientific Advisory Group meeting was convened on 14 January 2016 to provide advice on the list of questions adopted by the CHMP at its December 2015 meeting.

1. Validity of PD-L1 testing

   a. **Whether an optimal cut-off value for the PD-L1 expression (PD-L1 < x%) can be established, such that patients most likely to benefit from treatment can be reliably defined.**

A positive association between PD-L1 expression and activity of nivolumab appears to be consistent across trials in the non-SQ NSCLC and melanoma indications, although a number of uncertainties remain in view of the inadequate statistical methodology used to identify optimal cut-offs. Notwithstanding the methodological weaknesses, in the non-SQ NSCLC indication, PD-L1 expression ≥10% appeared to be associated with higher increase survival for nivolumab v. docetaxel, compared to lower PD-L1 expression. In the melanoma indication, with PD-L1 expression >1% (or perhaps >5%), the addition of ipilimumab did not appear to be associated with longer progression-free survival compared to nivolumab alone.

However, the analyses presented are mainly based on visual exploration of grouped data plots and subgroup analyses using arbitrary cut-off values and intervals. Adequate statistical analyses of the available data are lacking to clarify the relationship between level of PD-L1 expression and activity, as well as the association between PD-L1 expression and clinical co-variates including prognostic factors. In particular, no comprehensive estimation of cut-off values using conventional statistical approaches (e.g., plots of Martingale residuals; AUC and ROC curves, as appropriate; sensitivity and specificity thresholds; exploration of treatment-covariate interactions such as using the STEPP method; Forrest plots; interaction test) within the framework of multiple regression models for response rate and time-related endpoints has been presented across available nivolumab trials. Such analyses should be conducted to determine the prognostic importance of PD-L1 expression, and the relationship between PD-L1 expression (and other covariates) and nivolumab (and ipilimumab) activity, and to estimate optimal cut-off values (if such threshold values truly exist). If no optimal cut-off values can be estimated, consideration should be given to a score system based on multivariate analysis of PD-L1 expression and other factors associated with clinical benefit to guide patient selection.

Such statistical analyses can be conducted on the available data. In the absence of better evidence, the currently available information based on suboptimal methodology is still considered useful to some extent to guide treatment decisions and should be described in the product information.

b. The reliability and usability of the PD-L1 as biomarker in clinical practice and the possible implications of any restriction/recommendations in the SmPC based on this biomarker

Immunohistochemistry is *per se* a well-established technique and a CE-marked assay is available. However, there are concerns about the reliability and clinical utility of the method in view of the dynamic nature of this marker and tumour environment, and the difficulties with PD-L1 determination in clinical practice are also due to the lack of comparability data between the different assays. Further data on the reliability of this assay in a real-life setting (especially in melanoma if very low cut-offs of 1% are used, which is problematic in relation to the low number of cells which were counted), as well as data to compare the different available assays, should be provided in order to be able to conclude on the reliability and clinical utility of this biomarker.

Still, even acknowledging the current limitations and the fact that optimal cut-off values are lacking, information(e.g., SmPC section 5.1) about PD-L1 expression and activity are considered useful to guide treatment decisions (see answers to questions No. 2-3) but no clear restrictions based on precise cut-offs can be proposed based on the current data due to limitations described above.

Aside from a more comprehensive analysis of the available data, it is recommended to continue to further elucidate other biomarkers in the future, including mutational load as a marker for passenger mutations/neo-antigens, gene expression etc., and to conduct further studies on tumour heterogeneity (intra-tumour and between different lesions, including primary tumours vs. metastatic lesions).

The benefit of the treatment combination in terms of PFS was only demonstrated for patients with low PD-L1 expression (PD-L1 <5%) compared to nivolumab alone whilst no added benefit has been shown in PDL-1 positive patients (apart from higher rates of antitumor activity). In the absence of survival data and bearing in mind the increased toxicity of the treatment combination, the experts are invited to discuss:

- To what extent the observed PFS results can be predictive of a benefit in life expectancy in this setting and if so, whether any restrictions should be applied for the treatment

combination of ipilimumab and nivolumab to limit use only in those patients where the expected benefit of the combination is able to outweigh the increased toxicity.

- To what extent the PD-L1 status should be used to indicate the benefit of the combination nivolumab + ipilimumab (also considering the discussion under 1).

The overall survival results for the combination of nivolumab+ipilimumab are not mature enough to draw conclusions about the long-term effects of the combination, although previous immunotherapy data for check-point inhibitors for malignant melanoma has indicated consistency between progression-free and overall survival. The overall effect in terms of progression-free survival is convincing and of clinical relevance but only at levels of PD-L1 expression <1% (or perhaps <5%). At higher level of expression, the addition of ipilimumab was associated with significant toxicity and no added benefit in terms of progression-free survival.

However, there are a number of limitations about the proposed cut-off (see also answer to question No. 1a about limitations in the statistical methodology used to identify optimal cut-offs), and there is a need for reassurance about the reproducibility of a <1% cut-off in a real-life setting, and in particular (but not limited to) a more detailed exploration of the >1% to >5% subgroup (see also answer to question No. 1b). Thus, clear restrictions cannot be proposed based on the current data. Still, while awaiting the results of further and more comprehensive analyses, as well as more mature overall survival data, the available information is considered useful to guide treatment decisions and should be described in the product information.

Some SAG members expressed concerns about the severe toxicity of the combination of nivolumab+ipilimumab (regardless of PD-L1 expression) given that a positive effect in terms of overall survival has not been clearly established. According to this view, the benefit-risk of the combination is considered negative, regardless of PD-L1 status and the observed effect in terms of progression-free survival. Given the high toxicity, the benefit-risk assessment of the combination should be reconsidered when sufficiently mature overall survival data become available (these data are expected to become available before the end of 2016).

2.4.4. Conclusions on the clinical efficacy

The combination of nivolumab and ipilimumab has shown a clinically meaningful superiority over ipilimumab in terms of PFS. This benefit is more modest but still relevant when compared to nivolumab monotherapy. The CHMP noted that the benefit observed appears to be driven mainly by the subgroup of patients with tumours which has been designated as PD-L1 negative (<1%) and no difference is observed between the combination and the monotherapy with nivolumab in subjects with tumour PD-L1 positive (⩾1%). However, 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 treating population, and there is a lack of appropriate evidence-based rationale for a cut-off value, the CHMP is of the opinion that the indication should not be restricted by according to the expression of tumour PD-L1 and hence the combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. It is however noted that relative to nivolumab monotherapy, an increase in progression-free survival 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 CHMP considers the following measures necessary to address issues related to efficacy:

- Post-authorisation efficacy study (PAES): The MAH should submit the final Study report for study CA209067: a Randomized, Double-Blind Study in Subjects Treated With nivolumab Monotherapy, ipilimumab Monotherapy, And nivolumab combined With Ipilimumab. The final clinical study report should be submitted by 31st March 2017.

- The value of biomarkers to predict the efficacy of nivolumab *and/or nivolumab + ipilimumab combination therapy* should be further explored, specifically: To further investigate the value of

biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., _other 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 monotherapy: studies CA209038 and CA209066,

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

- NSCLC: studies CA209017, CA209057 and CA209026

- RCC: studies CA209025 and CA209009

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

Results should be submitted by 31stMarch 2019.

2.5. Clinical safety

Introduction

Pooled safety data for nivolumab monotherapy is presented from the nivolumab treatment groups in CA209067 (N = 313), CA209066 (N = 200), and CA209037 (N = 268). Pooled safety data for nivolumab+ipilimumab combination therapy will be presented from the nivolumab+ipilimumab treatment groups in CA209067 (N = 313) and CA209069 (N = 94). Safety data will be pooled across studies that utilized the same dose and schedule. For study CA209067, the safety data are based on the February 2015 DBL.

In addition, safety data from Cohort 8 of the Phase 1b study, CA209004 (N = 41 subjects), are 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.

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

Patient exposure
The minimum duration of follow-up after last patient first treatment (LPFT) were comparable across all the studies.

The majority of subjects (86.5%) in the pooled monotherapy group and 67.1% of subjects in the pooled combination therapy group received ≥90% of the initial intended dose of nivolumab.

The median number of doses of nivolumab received was 12.0 in the pooled monotherapy group vs 4.0 in the pooled combination therapy group. Per each study protocol (CA209067 and CA209069), subjects in the pooled combination therapy group who discontinued because of study drug toxicity were to discontinue both nivolumab and ipilimumab therapy at the same time and subjects who experienced a dose-limiting toxicity during the combination therapy portion were prohibited to progress to the monotherapy portion of the study.

Using Kaplan-Meier estimation, the median duration of study therapy was 5.82 months (95% CI: 5.09, 6.67) for nivolumab treatment and 2.76 months (95% CI: 2.33, 3.48) for nivolumab+ipilimumab treatment.

The median cumulative nivolumab dose was 36.0 mg/kg in the pooled monotherapy group and 4.0 mg/kg in the pooled combination therapy group.

In CA209004 Cohort 8, 75.6% and 90.2% of subjects achieved a relative dose intensity of ≥90%for nivolumab and ipilimumab, respectively. The duration of nivolumab therapy was longer than ipilimumab, as expected based on the study design. Subjects were scheduled to receive nivolumab/ipilimumab combination for 4 doses, followed by nivolumab for up to 48 doses. The median duration of therapy was 7.1 months. The median number of nivolumab and ipilimumab doses received was 8.0 and 4.0, respectively. In Cohort 8 of CA209004, 2 (4.9%) of the 41 treated subjects experienced at least 1 nivolumabinfusion interruption, 15 (36.6%) subjects experienced a delay, and 23 (56.1%) subjects experienced a nivolumab dose omission. Ipilimumab dose interruptions, delays, and omissions were experienced by 7 (17.1%), 12 (29.3) and 1 (2.4%) subjects, respectively.

The median duration of study therapy was shorter in the pooled combination therapy group than in the pooled monotherapy group (2.76 vs 5.82 months, respectively), also the median number of doses received, the median cumulative dose and the frequency of patients that received more 90% was lower for patients treated with combination therapy than with nivolumab monotherapy.

Table 36:   Cumulative dose - Study CA209067

	Nivolumab N = 1322	Nivolumab + Ipilimumab N = 448	
	Nivolumab	Nivolumab	Ipilimumab
RELATIVE DOSE INTENSITY			
>= 110%	3 (0.2)	0	3 (0.7)
90% TO < 110%	1128 (85.3)	295 (65.8)	327 (73.0)
70% TO < 90%	163 (12.3)	94 (21.0)	76 (17.0)
50% TO < 70%	24 (1.8)	38 (8.5)	35 (7.8)
< 50%	4 (0.3)	21 (4.7)	7 (1.6)
NUMBER OF DOSES RECEIVED			
MEAN (SD)	14.0 (11.73)	9.9 (9.76)	3.2 (1.06)
MEDIAN (MIN - MAX)	9.0 (1 - 52)	4.0 (1 - 39)	4.0 (1 - 4)
NUMBER OF DOSES RECEIVED			
1	72 (5.4)	42 (9.4)	45 (10.0)
2	81 (6.1)	78 (17.4)	83 (18.5)
3	76 (5.7)	58 (12.9)	66 (14.7)
4	102 (7.7)	58 (12.9)	254 (56.7)
>4	991 (75.0)	212 (47.3)	0
CUMULATIVE DOSE (MG/KG)			
MEAN (SD)	42.09 (35.264)	23.40 (28.118)	9.56 (3.217)
MEDIAN (MIN - MAX)	27.00 (1.4 - 156.0)	4.00 (1.0 - 109.0)	12.00 (2.9 - 17.8)

Nivolumab treatment group consists of Nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066 and CA209067.
Nivolumab+Ipilimumab treatment group consists of Nivolumab+Ipilimumab treatment group from studies CA209067, CA209069 and CA209004 (Cohort 8 only).

Adverse events

 - **Common Adverse Events**

The most common AEs (>5%) are reported in the table below. In the pooled dataset of nivolumab in combination with ipilimumab in melanoma (CA209067 (combination group), CA209069, and CA209004-cohort 8), the most frequent adverse reactions (≥ 10%) were rash (51%), fatigue (43%), diarrhoea (42%), pruritus (35%), nausea (25%), pyrexia (19%), decreased appetite (15%), hypothyroidism (15%), vomiting (14%), colitis (14%), abdominal pain (13%), arthralgia (11%), and headache (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). In patients treated with nivolumab in combination with ipilimumab, the incidence of thyroid disorders was 23.7%

(106/448). Grade 2 and Grade 3 thyroid disorders were reported in 13.4% (60/448) and 1.6% (7/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis occurred in 6.0% (27/448) and 1.8% (8/448) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency each occurred in 1.1% (5/448), and Grade 4 adrenal insufficiency occurred in 0.2% (1/448) of patients. Grade 1 and Grade 2 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.5 months (range: 0.0-10.1). Resolution occurred in 59 patients (45.0%). Time to resolution ranged from 0.4 to 74.4+ weeks (SmPC section 4.8).

Among the patients treated with nivolumab in combination with ipilimumab in CA209067, 151/313 (48%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 37 (25%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

With 18 months follow-up in CA209067, the overall incidence of adverse reactions, Grade 3 or 4 adverse reactions, and discontinuations due to adverse reactions was 96%, 57%, and 39%, respectively, in patients treated with nivolumab in combination with ipilimumab.

Table 37: **Adverse events (regardless of causality) by worst CTC grade reported in ≥ 5% of treated subjects within 30 Days of last dose - treated subjects**

System Organ Class (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	768 (97.6)	319 (40.5)	42 (5.3)	406 (99.8)	280 (68.8)	18 (4.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	545 (69.3)	50 (6.4)	1 (0.1)	324 (79.6)	49 (12.0)	3 (0.7)
FATIGUE	328 (41.7)	13 (1.7)	0	203 (49.9)	24 (5.9)	0
PYREXIA	114 (14.5)	2 (0.3)	0	140 (34.4)	9 (2.2)	0
ASTHENIA	105 (13.3)	5 (0.6)	0	56 (13.8)	4 (1.0)	0
OEDEMA PERIPHERAL	74 (9.4)	3 (0.4)	0	43 (10.6)	0	0
PAIN	54 (6.9)	10 (1.3)	0	33 (8.1)	6 (1.5)	0
CHILLS	39 (5.0)	0	0	41 (10.1)	0	0
INFLUENZA LIKE ILLNESS	37 (4.7)	0	0	23 (5.7)	1 (0.2)	0
GASTROINTESTINAL DISORDERS	516 (65.6)	66 (8.4)	1 (0.1)	318 (78.1)	101 (24.8)	0
DIARRHOEA	223 (28.3)	19 (2.4)	0	209 (51.4)	41 (10.1)	0
NAUSEA	213 (27.1)	5 (0.6)	0	157 (38.6)	14 (3.4)	0
CONSTIPATION	155 (19.7)	3 (0.4)	0	76 (18.7)	2 (0.5)	0
VOMITING	123 (15.6)	10 (1.3)	0	110 (27.0)	13 (3.2)	0
ABDOMINAL PAIN	103 (13.1)	13 (1.7)	0	60 (14.7)	5 (1.2)	0
ABDOMINAL PAIN UPPER	42 (5.3)	3 (0.4)	0	25 (6.1)	1 (0.2)	0
DRY MOUTH	37 (4.7)	0	0	36 (8.8)	0	0
COLITIS	11 (1.4)	5 (0.6)	0	59 (14.5)	39 (9.6)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	438 (55.7)	14 (1.8)	0	300 (73.7)	30 (7.4)	0
PRURITUS	182 (23.1)	1 (0.1)	0	149 (36.6)	7 (1.7)	0
RASH	176 (22.4)	3 (0.4)	0	140 (34.4)	13 (3.2)	0
VITILIGO	72 (9.1)	1 (0.1)	0	33 (8.1)	0	0
DRY SKIN	52 (6.6)	0	0	26 (6.4)	1 (0.2)	0
ERYTHEMA	47 (6.0)	0	0	19 (4.7)	1 (0.2)	0
RASH MACULO-PAPULAR	39 (5.0)	3 (0.4)	0	56 (13.8)	9 (2.2)	0
HYPERHIDROSIS	19 (2.4)	0	0	24 (5.9)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	368 (46.8)	38 (4.8)	0	181 (44.5)	16 (3.9)	0
ARTHRALGIA	121 (15.4)	4 (0.5)	0	67 (16.5)	1 (0.2)	0
BACK PAIN	104 (13.2)	13 (1.7)	0	39 (9.6)	1 (0.2)	0
PAIN IN EXTREMITY	85 (10.8)	6 (0.8)	0	29 (7.1)	1 (0.2)	0
MUSCULOSKELETAL PAIN	61 (7.8)	3 (0.4)	0	27 (6.6)	1 (0.2)	0
MYALGIA	56 (7.1)	0	0	34 (8.4)	1 (0.2)	0
MUSCULAR WEAKNESS	21 (2.7)	2 (0.3)	0	23 (5.7)	2 (0.5)	0

System Organ Class (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
INFECTIONS AND INFESTATIONS	309 (39.3)	42 (5.3)	1 (0.1)	175 (43.0)	35 (8.6)	2 (0.5)
NASOPHARYNGITIS	69 (8.8)	0	0	26 (6.4)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	303 (38.5)	31 (3.9)	1 (0.1)	194 (47.7)	33 (8.1)	5 (1.2)
COUGH	148 (18.8)	1 (0.1)	0	88 (21.6)	0	0
DYSPNOEA	102 (13.0)	9 (1.1)	0	83 (20.4)	10 (2.5)	0
PNEUMONITIS	17 (2.2)	2 (0.3)	0	28 (6.9)	5 (1.2)	0
NERVOUS SYSTEM DISORDERS	301 (38.2)	23 (2.9)	1 (0.1)	178 (43.7)	28 (6.9)	0
HEADACHE	126 (16.0)	2 (0.3)	0	94 (23.1)	3 (0.7)	0
DIZZINESS	57 (7.2)	1 (0.1)	0	41 (10.1)	1 (0.2)	0
DYSGEUSIA	45 (5.7)	0	0	27 (6.6)	0	0
METABOLISM AND NUTRITION DISORDERS	233 (29.6)	42 (5.3)	0	186 (45.7)	45 (11.1)	0
DECREASED APPETITE	132 (16.8)	1 (0.1)	0	103 (25.3)	6 (1.5)	0
HYPONATRAEMIA	31 (3.9)	13 (1.7)	0	32 (7.9)	13 (3.2)	0
HYPOALBUMINAEMIA	27 (3.4)	3 (0.4)	0	21 (5.2)	2 (0.5)	0
HYPERGLYCAEMIA	26 (3.3)	6 (0.8)	0	23 (5.7)	10 (2.5)	0
HYPOKALAEMIA	22 (2.8)	2 (0.3)	0	36 (8.8)	7 (1.7)	0
DEHYDRATION	12 (1.5)	5 (0.6)	0	37 (9.1)	11 (2.7)	0
INVESTIGATIONS	220 (28.0)	64 (8.1)	0	214 (52.6)	105 (25.8)	0
ASPARTATE AMINOTRANSFERASE INCREASED	60 (7.6)	16 (2.0)	0	79 (19.4)	27 (6.6)	0
ALANINE AMINOTRANSFERASE INCREASED	56 (7.1)	16 (2.0)	0	85 (20.9)	36 (8.8)	0
WEIGHT DECREASED	44 (5.6)	0	0	46 (11.3)	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	39 (5.0)	9 (1.1)	0	23 (5.7)	2 (0.5)	0
LIPASE INCREASED	38 (4.8)	20 (2.5)	0	51 (12.5)	40 (9.8)	0
BLOOD CREATININE INCREASED	28 (3.6)	2 (0.3)	0	26 (6.4)	4 (1.0)	0
AMYLASE INCREASED	25 (3.2)	8 (1.0)	0	30 (7.4)	12 (2.9)	0

System Organ Class (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	161 (20.5)	60 (7.6)	35 (4.4)	37 (9.1)	10 (2.5)	8 (2.0)
MALIGNANT NEOPLASM PROGRESSION	74 (9.4)	31 (3.9)	34 (4.3)	15 (3.7)	3 (0.7)	8 (2.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	147 (18.7)	35 (4.4)	1 (0.1)	74 (18.2)	14 (3.4)	0
ANAEMIA	106 (13.5)	25 (3.2)	0	44 (10.8)	5 (1.2)	0
PSYCHIATRIC DISORDERS	144 (18.3)	6 (0.8)	0	96 (23.6)	9 (2.2)	0
INSOMNIA	78 (9.9)	2 (0.3)	0	54 (13.3)	2 (0.5)	0
VASCULAR DISORDERS	143 (18.2)	27 (3.4)	0	73 (17.9)	12 (2.9)	0
HYPERTENSION	57 (7.2)	19 (2.4)	0	20 (4.9)	5 (1.2)	0
EYE DISORDERS	114 (14.5)	5 (0.6)	0	81 (19.9)	1 (0.2)	0
VISION BLURRED	22 (2.8)	0	0	23 (5.7)	0	0
ENDOCRINE DISORDERS	109 (13.9)	6 (0.8)	0	126 (31.0)	25 (6.1)	0
HYPOTHYROIDISM	65 (8.3)	0	0	67 (16.5)	2 (0.5)	0
HYPERTHYROIDISM	33 (4.2)	1 (0.1)	0	34 (8.4)	4 (1.0)	0
HYPOPHYSITIS	4 (0.5)	2 (0.3)	0	36 (8.8)	8 (2.0)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab treatment group consists of Nivolumab monotherapy treatment group from studies CA209037, CA209066 and CA209067.
Nivolumab+Ipilimumab treatment group consists of Nivolumab+Ipilimumab treatment group from studies CA209069 and CA209067.

- **AEs grade 3-4**

In CA209067 and CA209069, Grade 3-4 AEs, SAEs, and AEs leading to discontinuation were more frequently reported in the nivolumab+ipilimumab group compared with the ipilimumab group.

In CA209069, Grade 3-4 AEs, SAEs, and AEs leading to discontinuation were more frequently reported in the nivolumab+ipilimumab group compared with the ipilimumab group. The increased AEs associated with the combination of nivolumab+ipilimumab were primarily colitis (22%, Grade 3-4: 16%) compared to ipilimumab monotherapy at 3 mg/kg (11%, Grade 3-4: 7%) and liver function test elevations (AST 28% and ALT 26% compared to AST 7% and ALT 7%, respectively) which were most often lab abnormalities without associated symptoms. Deaths due to study drug toxicity were reported for ≤ 2% of subjects treated with nivolumab+ipilimumab in CA209069/CA209004. The safety profile in Cohort 8 of CA209004 was consistent with that of the nivolumab+ipilimumab group in CA209069. In CA209069, a higher proportion of subjects discontinued treatment due to study drug toxicity in the nivolumab+ipilimumab group compared with the ipilimumab group.

In patients treated with nivolumab in combination with ipilimumab, the incidence of diarrhoea or colitis was 45.5% (204/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.2% (59/448), 15.4% (69/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.1 months (range: 0.0-10.4). Resolution occurred in 184 patients (90.6%) with a median time to resolution of 3.0 weeks (range: 0.1-78.7+) (SmPC section 4.8).The increased AEs associated with the combination of nivolumab+ipilimumab were primarily diarrhoea (52%, Grade 3-4: 11%) compared with ipilimumab monotherapy at 3 mg/kg (46%, Grade 3-4: 8%) and liver function test elevations (ALT 20% and AST 17% compared with ALT and AST 5% each, respectively) which were most often lab abnormalities without associated symptoms. One death in the pooled monotherapy and 2 deaths in the pooled combination therapy group were due to study drug toxicity within 100 days of the last dose. High grade (Grade 3 - 4) drug-related AEs and AEs leading to discontinuation were higher in the pooled combination therapy group than in the pooled monotherapy group, but overall were infrequent.

In patients treated with nivolumab in combination with ipilimumab, the incidence of rash was 63.4% (284/448). Grade 2 and Grade 3 cases were reported in 19.2% (86/448) and 7.4% (33/448) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.5 months (range: 0.0-9.7). Resolution occurred in 192 patients (67.6%) with a median time to resolution of 10.4 weeks (range: 0.1-74.0+) (SmPC section 4.8).

In patients treated with nivolumab in combination with ipilimumab, the incidence of pneumonitis including interstitial lung disease, was 7.4% (33/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.5% (20/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis worsened over 11 days with a fatal outcome. Median time to onset was 2.3 months (range: 0.7-6.7). Resolution occurred in 29 patients (87.9%) with a median time to resolution of 6.1 weeks (range: 0.3-46.9+) (SmPC section 4.8).

In patients treated with nivolumab in combination with ipilimumab, the incidence of liver function test abnormalities was 27.9% (125/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.3% (28/448), 15.0% (67/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.4 months (range: 0.0-11.0). Resolution occurred in 116 patients (92.8%) with a median time to resolution of 5.0 weeks (range: 0.1-53.1) (SmPC section 4.8). In patients treated with nivolumab in combination with ipilimumab, the incidence of nephritis and renal dysfunction was 4.2% (19/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.1% (5/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-14.7). Resolution occurred in 17 patients (89.5%) with a median time to resolution of 1.9 weeks (range: 0.4-42.6+) (SmPC section 4.8).

In patients treated with nivolumab in combination with ipilimumab, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 1.2% for thrombocytopenia, 0.5% for leukopenia, 6.4% for lymphopenia, 0.7% for neutropenia, 4.1% for increased alkaline phosphatase, 11.9% for increased AST, 14.6% for increased ALT, 0.9% for increased total bilirubin, 2.4% for increased creatinine, 8.5% for increased amylase, 18.2% for increased lipase, 1.3% for hypocalcemia, 0.3% each for hypercalcemia, hyperkalemia, hypermagnesemia, and hypernatremia, 4.5% for hypokalemia, and 9.2% for hyponatremia (SmPC section 4.8).

- **Drug-related AEs**

The overall frequency of drug related AEs occurring up to 30 days after last dose were reported less frequently in the pooled monotherapy group (77.4%) than in the pooled combination therapy group (94.6%).

Grade 3-4 drug-related AEs were reported less frequently in the pooled monotherapy group (13.7%) than pooled combination therapy group (54.1%). Grade 3-4 drug-related AEs of lipase increased (2.0%),

diarrhoea (1.3%), and ALT increased (1.1%) occurred in more than 8 subjects (> 1%) in the pooled monotherapy group.

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

Table 38: Summary of safety results in all subjects treated with nivolumab monotherapy vs nivolumab+ipilimumab combination therapy – pooled studies CA209067, CA209066 and CA209037

	Number (%) Subjects			
	067+066+037 Pooled Monotherapy Group (N = 787)		067+069 Pooled Combination Therapy Group (N = 407)	
DEATHS				
Within 30 days	57 (7.2)		25 (6.1)	
Within 100 days	151 (19.2)		62 (15.2)	
Due to Study Drug Toxicity	1 (0.1)		2 (0.5)	
AEs REPORTED WITHIN 30 DAYS OF LAST DOSE	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All AEs (Regardless of Causality)	768 (97.6)	319 (40.5)	406 (99.8)	280 (68.8)
Most Frequent AEs (> 20%)				
Fatigue	328 (41.7)	13 (1.7)	203 (49.9)	24 (5.9)
Diarrhea	223 (28.3)	19 (2.4)	209 (51.4)	41 (10.1)
Nausea	213 (27.1)	5 (0.6)	157 (38.6)	14 (3.4)
Pruritus	182 (23.1)	1 (0.1)	149 (36.6)	7 (1.7)
Rash	176 (22.4)	3 (0.4)	140 (34.4)	13 (3.2)
Pyrexia	114 (14.5)	2 (0.3)	140 (34.4)	9 (2.2)
Cough	148 (18.8)	1 (0.1)	88 (21.6)	0
Decreased appetite	132 (16.8)	1 (0.1)	103 (25.3)	6 (1.5)
Vomiting	123 (15.6)	10 (1.3)	110 (27.0)	13 (3.2)
Headache	126 (16.0)	2 (0.3)	94 (23.1)	3 (0.7)
Dyspnea	102 (13.0)	9 (1.1)	83 (20.4)	10 (2.5)
Alanine aminotransferase increased	56 (7.1)	16 (2.0)	85 (20.9)	36 (8.8)
Drug-related AEs				
Most Frequent AEs (> 10%)				
Fatigue	230 (29.2)	7 (0.9)	144 (35.4)	18 (4.4)
Diarrhea	135 (17.2)	10 (1.3)	175 (43.0)	36 (8.8)
Pruritus	145 (18.4)	1 (0.1)	136 (33.4)	7 (1.7)
Rash	133 (16.9)	3 (0.4)	126 (31.0)	13 (3.2)
Nausea	108 (13.7)	0	101 (24.8)	8 (2.0)
Decreased appetite	63 (8.0)	0	66 (16.2)	4 (1.0)
Pyrexia	45 (5.7)	0	76 (18.7)	5 (1.2)
Alanine aminotransferase increased	29 (3.7)	9 (1.1)	74 (18.2)	34 (8.4)
Aspartate aminotransferase increased	29 (3.7)	6 (0.8)	68 (16.7)	24 (5.9)
Vomiting	45 (5.7)	3 (0.4)	58 (14.3)	9 (2.2)
Rash maculo-papular	35 (4.4)	2 (0.3)	52 (12.8)	9 (2.2)
Arthralgia	51 (6.5)	0	43 (10.6)	1 (0.2)
Colitis	9 (1.1)	5 (0.6)	57 (14.0)	39 (9.6)
Hypothyroidism	54 (6.9)	0	60 (14.7)	1 (0.2)
Lipase increased	28 (3.6)	16 (2.0)	45 (11.1)	34 (8.4)
Headache	42 (5.3)	0	43 (10.6)	3 (0.7)
All SAEs (Regardless of Causality)	319 (40.5)	220 (28.0)	275 (67.6)	208 (51.1)
Drug-related SAEs	64 (8.1)	45 (5.7)	195 (47.9)	146 (35.9)

Table 39: Listing of all ADRs and AEs reported in the clinical trials of nivolumab in combination with ipilimumab or nivolumab monotherapy by frequency

Combination		
	Frequency	
	Drug-related[a]	All AEs

Combination			
		Frequency	
		Drug-related[a]	**All AEs**
Infections and infestations			
Common	Pneumonia	5 (1.1)	15 (3.3)
Common	Upper respiratory tract infection	6 (1.3)	66 (14.7)
Uncommon	Bronchitis	2 (0.4)	8 (1.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Blood and lymphatic system disorders			
Common	Eosinophilia	8 (1.8)	10 (2.2)
Immune system disorders			
Common	Infusion related reaction	10 (2.2)	10 (2.2)
Common	Hypersensitivity	7 (1.6)	8 (1.8)
Uncommon	Sarcoidosis	1 (0.2)	1 (0.2)
Endocrine disorders			
Very common	Hypothyroidism	66 (14.7)	73 (16.3)
Common	Adrenal insufficiency	12 (2.7)	15 (3.3)
Common	Hypopituitarism	6 (1.3)	6 (1.3)
Common	Hypophysitis	40 (8.9)	40 (8.9)
Common	Hyperthyroidism	35 (7.8)	36 (8.0)
Common	Thyroiditis	21 (4.7)	21 (4.7)
Common	Hyperglycaemia	10 (2.2)	25 (5.6)
Uncommon	Diabetic ketoacidosis	1 (0.2)	3 (0.7)
Uncommon	Diabetes mellitus	2 (0.4)	4 (0.9)
Metabolism and nutrition disorders			
Very common	Decreased appetite	67 (15.0)	108 (24.1)
Common	Dehydration	19 (4.2)	40 (8.9)

Combination			
		Frequency	
		Drug-related[a]	**All AEs**
Hepatobiliary disorders			
Common	Hepatitis	16 (3.6)	17 (3.8)
(Increased total bilirubin is reported under the investigations SOC)			
Nervous system disorders			
Very common	Headache	48 (10.7)	107 (23.9)
Common	Peripheral neuropathy	17 (3.8)	32 (7.1)
Common	Dizziness	22 (4.9)	52 (11.6)
Uncommon	Guillain-Barré syndrome	2 (0.4)	2 (0.4)
Uncommon	Polyneuropathy	2 (0.4)	2 (0.4)
Uncommon	Neuritis	1 (0.2)	1 (0.2)
Uncommon	Peroneal nerve palsy	1 (0.2)	2 (0.4)
Uncommon	Autoimmune neuropthy (including facial and abducens nerve paresis)[c]	1 (0.2)	2 (0.4)
Eye disorders			
Common	Uveitis	6 (1.3)	8 (1.8)
Common	Vision blurred	13 (2.9)	27 (6.0)
Cardiac disorders			
Common	Tachycardia	6 (1.3)	26 (5.8)
Uncommon	Arrhythmia (including ventricular arrhythmia)	2 (0.4)	3 (0.7)
Uncommon	Atrial fibrillation	1 (0.2)	11 (2.5)
Vascular disorders			
Common	Hypertension	5 (1.1)	23 (5.1)
Respiratory, thoracic and mediastinal disorders			
Common	Pneumonitis	33 (7.4)	33 (7.4)

Combination			
		Frequency	
		Drug-related[a]	**All AEs**
Common	Pulmonary embolism[d]	0	15 (3.3)
Common	Dyspnoea	40 (8.9)	94 (21.0)
Common	Cough	30 (6.7)	112 (25.0)
Uncommon	Pleural effusion	1 (0.2)	11 (2.5)
Gastrointestinal disorders			
Very common	Colitis	62 (13.8)	64 (14.3)
Very common	Diarrhoea	189 (42.2)	228 (50.9)
Very common	Vomiting	61 (13.6)	121 (27.0)
Very common	Nausea	111 (24.8)	177 (39.5)
Very common	Abdominal pain	56 (12.5)	101 (22.5)
Common	Stomatitis	16 (3.6)	26 (5.8)
Common	Gastritis	5 (1.1)	12 (2.7)
Common	Constipation	21 (4.7)	86 (19.2)
Common	Dry mouth	26 (5.8)	42 (9.4)
Uncommon	Pancreatitis	4 (0.9)	5 (1.1)
Uncommon	Intestinal perforation	1 (0.2)	1 (0.2)
Uncommon	Duodenitis[e]	0	1 (0.2)
Skin and subcutaneous tissue disorders			
Very common	Rash	228 (50.9)	251 (56.0)
Very common	Pruritus	155 (34.6)	170 (37.9)
Common	Vitiligo	34 (7.6)	37 (8.3)
Common	Dry skin	16 (3.6)	31 (6.9)
Common	Erythema	13 (2.9)	20 (4.5)
Common	Alopecia	9 (2.0)	16 (3.6)
Common	Urticaria	5 (1.1)	5 (1.1)
Uncommon	Psoriasis	2 (0.4)	2 (0.4)

Combination			
		Frequency	
		Drug-related[a]	**All AEs**
Rare	Toxic epidermal necrolysis	*From SmPC Table 2 footnotes:* *- Fatal cases have been reported in completed or ongoing clinical studies* *Reported in studies outside the pooled dataset.* *- The frequency is based on the program-wide exposure.*	
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia	51 (11.4)	79 (17.6)
Common	Musculoskeletal pain	37 (8.3)	124 (27.7)
Uncommon	Spondyloarthropathy	1 (0.2)	1 (0.2)
Uncommon	Sjogren's syndrome[e]	0	1 (0.2)
Uncommon	Arthritis	2 (0.4)	5 (1.1)
Uncommon	Myopathy	0	4 (0.9)
Renal and urinary disorders			
Common	Renal failure	5 (1.1)	16 (3.6)
Uncommon	Tubulointerstitial nephritis	1 (0.2)	1 (0.2)
General disorders and administration site conditions			
Very common	Fatigue	194 (43.3)	272 (60.7)
Very common	Pyrexia	85 (19.0)	154 (34.4)
Common	Oedema (including peripheral oedema)	16 (3.6)	65 (14.5)
Common	Pain	7 (1.6)	36 (8.0)
Uncommon	Chest pain	1 (0.2)	17 (3.8)

- **AEs of special interest (AESI)**

Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving nivolumab in combination with ipilimumab than in those receiving nivolumab monotherapy for immune-related colitis (16% and 0.7%, respectively), immune-related hepatitis (9% and 0.9%), and immune-related endocrinopathies (2.5% and 0.1%). Among patients who experienced an event, high-dose corticosteroids

(at least 40 mg prednisone equivalents) were required in a greater proportion of patients receiving the combination regimen than in patients receiving nivolumab monotherapy for the management of immune-related colitis (47% and 14%, respectively) and immune-related hepatitis (46% and 16%).The management guidelines for these adverse reactions are described in section 4.4 (SmPC section 4.8).

Grade 3 diarrhoea or colitis observed with nivolumab in combination with ipilimumab also requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents (SmPC section 4.4).

Across clinical trials of nivolumab in combination with ipilimumab, the following additional clinically significant, immune-related adverse reactions were reported in less than 1% of patients: gastritis, sarcoidosis, and duodenitis (SmPC Section 4.4).

The following AEs were considered to be select AEs: endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, and rash. Multiple event terms that may describe each of these are grouped into endocrine, GI, liver, pulmonary, renal, and skin select AE categories, respectively. Hypersensitivity/infusion reactions are analysed along with the select AE categories because multiple event terms may be used to describe such events and pooling of terms is therefore necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs. In addition, time to onset, time to resolution, and time to resolution in subjects who received immune-modulating medications were analysed.

The majority of events reported were Grade 1-2, except for hepatic select AEs. No Grade 5 select AEs were reported in either group. Immune-mediated AEs were manageable using the recommended treatment guidelines for early work-up and intervention. Grade 3-4 select AEs resolved, except for events belonging to the endocrine select AE categories.

The majority of events were manageable with resolution occurring even when immunosuppressive medications (mostly systemic corticosteroids) were needed across the select AE categories. Some endocrine select AEs, though well-controlled with hormone replacement therapy, were not considered resolved due to the continuing need for hormone replacement therapy. Most select AEs resolved within 6 months of onset, with the exception of endocrine and skin events.

Table 40: Summary of all drug-related select AEs in all subjects treated with nivolumab monotherapy and nivolumab+ipilimumab combination therapy – Study CA209067

Subcategory (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Select Adverse Events Category: ENDOCRINE ADVERSE EVENT						
TOTAL SUBJECTS WITH AN ENDOCRINE ADVERSE EVENT	85 (10.8)	5 (0.6)	0	121 (29.7)	20 (4.9)	0
THYROID DISORDER	77 (9.8)	1 (0.1)	0	99 (24.3)	7 (1.7)	0
ADRENAL DISORDER	3 (0.4)	1 (0.1)	0	15 (3.7)	6 (1.5)	0
PITUITARY DISORDER	3 (0.4)	2 (0.3)	0	36 (8.8)	7 (1.7)	0
DIABETES	2 (0.3)	1 (0.1)	0	2 (0.5)	1 (0.2)	0
Select Adverse Events Category: GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	139 (17.7)	13 (1.7)	0	189 (46.4)	64 (15.7)	0
DIARRHOEA	135 (17.2)	10 (1.3)	0	175 (43.0)	36 (8.8)	0
COLITIS	9 (1.1)	5 (0.6)	0	57 (14.0)	39 (9.6)	0
FREQUENT BOWEL MOVEMENTS	4 (0.5)	0	0	0	0	0
ENTEROCOLITIS	0	0	0	2 (0.5)	2 (0.5)	0
Select Adverse Events Category: HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	54 (6.9)	17 (2.2)	0	118 (29.0)	71 (17.4)	0
ALANINE AMINOTRANSFERASE INCREASED	29 (3.7)	9 (1.1)	0	74 (18.2)	34 (8.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	29 (3.7)	6 (0.8)	0	68 (16.7)	24 (5.9)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	10 (1.3)	1 (0.1)	0	15 (3.7)	2 (0.5)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	4 (0.5)	1 (0.1)	0	9 (2.2)	4 (1.0)	0
BLOOD BILIRUBIN INCREASED	3 (0.4)	0	0	6 (1.5)	0	0
TRANSAMINASES INCREASED	3 (0.4)	1 (0.1)	0	14 (3.4)	11 (2.7)	0
AUTOIMMUNE HEPATITIS	2 (0.3)	2 (0.3)	0	6 (1.5)	6 (1.5)	0
HEPATIC ENZYME INCREASED	2 (0.3)	1 (0.1)	0	4 (1.0)	2 (0.5)	0
HEPATOTOXICITY	2 (0.3)	1 (0.1)	0	10 (2.5)	8 (2.0)	0
LIVER FUNCTION TEST ABNORMAL	2 (0.3)	2 (0.3)	0	8 (2.0)	5 (1.2)	0
HYPERBILIRUBINAEMIA	1 (0.1)	0	0	6 (1.5)	0	0
HEPATITIS	0	0	0	9 (2.2)	8 (2.0)	0
HEPATITIS ACUTE	0	0	0	1 (0.)	1 (0.2)	0
LIVER DISORDER	0	0	0	1 (0.2)	1 (0.2)	0
Select Adverse Events Category: PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	16 (2.0)	1 (0.1)	0	31 (7.6)	5 (1.2)	0
PNEUMONITIS	14 (1.8)	1 (0.1)	0	28 (6.9)	5 (1.2)	0
INTERSTITIAL LUNG DISEASE	2 (0.3)	0	0	3 (0.7)	0	0

Subcategory (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Select Adverse Events Category: RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	12 (1.5)	4 (0.5)	0	19 (4.7)	7 (1.7)	0
BLOOD CREATININE INCREASED	4 (0.5)	0	0	12 (2.9)	2 (0.5)	0
RENAL FAILURE	3 (0.4)	0	0	1 (0.2)	1 (0.2)	0
RENAL FAILURE ACUTE	3 (0.4)	3 (0.4)	0	4 (1.0)	3 (0.7)	0
BLOOD UREA INCREASED	1 (0.1)	0	0	1 (0.2)	0	0
TUBULOINTERSTITIAL NEPHRITIS	1 (0.1)	1 (0.1)	0	1 (0.2)	1 (0.2)	0
NEPHRITIS AUTOIMMUNE	0	0	0	2 (0.5)	1 (0.2)	0
Select Adverse Events Category: SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	302 (38.4)	9 (1.1)	0	252 (61.9)	26 (6.4)	0
PRURITUS	145 (18.4)	1 (0.1)	0	136 (33.4)	7 (1.7)	0
RASH	133 (16.9)	3 (0.4)	0	126 (31.0)	13 (3.2)	0
VITILIGO	69 (8.8)	1 (0.1)	0	31 (7.6)	0	0
RASH MACULO-PAPULAR	35 (4.4)	2 (0.3)	0	52 (12.8)	9 (2.2)	0
ERYTHEMA	20 (2.5)	0	0	12 (2.9)	1 (0.2)	0
ECZEMA	12 (1.5)	0	0	7 (1.7)	0	0
DERMATITIS	11 (1.4)	0	0	3 (0.7)	0	0
RASH PAPULAR	10 (1.3)	1 (0.1)	0	9 (2.2)	0	0
SKIN HYPOPIGMENTATION	9 (1.1)	0	0	8 (2.0)	0	0
RASH ERYTHEMATOUS	8 (1.0)	0	0	6 (1.5)	0	0
PHOTOSENSITIVITY REACTION	7 (0.9)	0	0	3 (0.7)	0	0
RASH MACULAR	6 (0.8)	0	0	7 (1.7)	0	0
PRURITUS GENERALISED	4 (0.5)	0	0	2 (0.5)	0	0
RASH PRURITIC	4 (0.5)	0	0	7 (1.7)	0	0
DERMATITIS EXFOLIATIVE	3 (0.4)	1 (0.1)	0	0	0	0
PSORIASIS	3 (0.4)	0	0	2 (0.5)	0	0
BLISTER	2 (0.3)	0	0	0	0	0
RASH GENERALISED	2 (0.3)	0	0	7 (1.7)	2 (0.5)	0
ERYTHEMA MULTIFORME	1 (0.1)	0	0	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (0.1)	0	0	1 (0.2)	0	0
SKIN IRRITATION	1 (0.1)	0	0	1 (0.2)	0	0
DRUG ERUPTION	0	0	0	1 (0.2)	0	0
URTICARIA	0	0	0	4 (1.0)	0	0
Select Adverse Events Category: HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	38 (4.8)	2 (0.3)	0	16 (3.9)	0	0
INFUSION RELATED REACTION	20 (2.5)	2 (0.3)	0	10 (2.5)	0	0
HYPERSENSITIVITY 1	8 (2.3)	0	0	6 (1.5)	0	0
BRONCHOSPASM	1 (0.1)	0	0	0	0	0

MedDRA Version: 17.1; CTC Version 4.0

Includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab treatment group consists of Nivolumab monotherapy treatment group from studies CA209037, CA209066 and CA209067.
Nivolumab+Ipilimumab treatment group consists of Nivolumab+Ipilimumab treatment group from studies CA209067 and CA209069.

Endocrine Select Adverse Events

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

The incidence of drug-related endocrine select AEs considered SAEs was higher in the pooled combination therapy group than in the pooled monotherapy group (7.1% vs 0.9%). Drug related SAEs of autoimmune thyroiditis, hyperthyroidism and thyroiditis were reported only in patients in the pooled combination therapy group. In 2.5% of the subject in the pooled combination therapy group endocrine select AEs (adrenal insufficiency, hypophysitis, hypothyroidism, and thyroiditis) led to treatment discontinuation.

No SAEs were reported only in the pooled monotherapy group.

Drug-related SAEs of autoimmune thyroiditis (1/407; 0.2%), hyperthyroidism (6/407; 1.5%), and thyroiditis (2/407; 0.5%) were reported only in subjects in the pooled combination therapy group. No drug-related endocrine select AEs led to treatment discontinuation in the pooled monotherapy group. In the pooled combination therapy group, 2.5% of subjects experienced drug-related endocrine select AEs that led to treatment discontinuation, including events of adrenal insufficiency (0.5%), hypophysitis (1.0%), hypothyroidism (0.7%), and thyroiditis (0.5%).

In the adrenal disorder subcategory, more events reported in both the pooled monotherapy and pooled combination therapy group were Grade 1-2: The median time to onset was longer in the pooled monotherapy group (4.2 months) than in the pooled combination therapy group (3.6 months).

For diabetes select AEs, the frequency of drug-related select AEs was low in both pooled treatment groups with 2 subjects in each group experiencing either diabetes or diabetic ketoacidosis. The median time to onset for any grade drug-related diabetes select AEs was comparable in the pooled monotherapy (2.5 months) and pooled combination therapy (1.7 months) groups. No subjects in either group were treated with immune-modulating medication for any grade drug-related diabetes select AEs.

For pituitary disorders (hypophysitis), the frequency of any grade, drug-related hypophysitis was higher in the pooled combination therapy group (8.8%) than in the pooled monotherapy group (0.4%). The median time to onset for any grade drug-related hypophysitis was higher in the pooled monotherapy group (5.5 months) than in the pooled combination therapy group (2.7 months).

For thyroid disorders, the frequency of any grade drug-related events was higher in the pooled combination therapy group (29.7%) than in the pooled monotherapy group (10.8%). The median time to onset for any grade drug-related thyroid disorders was higher in the pooled monotherapy group (2.3 months) than in the pooled combination therapy group (1.4 months).

Gastrointestinal Select Adverse Events

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

More subjects in the pooled combination therapy group experienced drug-related GI events considered SAEs than in the pooled monotherapy group. In the pooled monotherapy group, 8 (1.0%) subjects experienced drug-related GI events of colitis (1 subject had Grade 2, 3 subject had Grade 3) and diarrhoea (1 subject had Grade 2, 3 subjects had Grade 3). In the pooled combination therapy group 75 (18.4%) subjects experienced drug-related GI events of colitis, diarrhoea and enterocolitis, 2 subjects experienced Grade 4 events (colitis and diarrhoea in both subjects).

Drug –related GI events that led to either treatment discontinuation or dose delay were more frequently reported in the pooled combination therapy group than in the pooled monotherapy group. In the pooled

monotherapy group 1.1% and in the pooled combination therapy group 16.7% of the patients had drug-related GI events that led to treatment discontinuation.

The median time to onset of drug-related GI events was 1.9 months in the pooled monotherapy group compared to 1.2 months in the pooled combination therapy group.

The majority of subjects with drug-related GI events in both groups experienced resolution (investigator assessed). Median time to resolution of any grade GI events in the pooled combination therapy group (3.0 weeks) was longer than that in the pooled monotherapy group (1.5 weeks).

Hepatic Select Adverse Events

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

Drug-related hepatic events that led to either treatment discontinuation or dose delay were more frequent in the pooled combination therapy group compared with the pooled monotherapy group. Twelve (1.5%) subjects in the pooled monotherapy group had drug-related hepatic events that led to treatment discontinuation and in 11 (1.4%) subjects, drug-related hepatic events led to dose delay, whereas 40 (9.8%) subjects in the pooled combination therapy group had drug-related hepatic events that led to treatment discontinuation and 48 (11.8%) subjects had drug-related hepatic events led to dose delay.

The median time to onset of drug-related hepatic events was 3.0 months in the pooled monotherapy group compared to 1.4 months the pooled combination therapy group.

The majority of subjects with drug-related hepatic events in both groups experienced resolution with a median time to resolution of any grade hepatic events in the pooled combination therapy group of 5.1 weeks and in the pooled monotherapy group of 4.1 weeks.

Pulmonary Adverse Events

The pulmonary select AE category included the following terms: acute respiratory distress syndrome, acute respiratory failure, interstitial lung disease, lung infiltration, and pneumonitis. These terms were selected to encompass those most likely to be reported in a subject with pneumonitis.

The frequency of subjects in the pooled combination therapy group who experienced drug-related pulmonary events that were considered SAEs (3.2%) was higher than in the pooled monotherapy group (0.6%).

Drug-related pulmonary events that led to either discontinuation or dose delay were more frequent in the pooled combination therapy group compared with the pooled monotherapy group. One (0.1%) subject in the pooled monotherapy group had drug-related pulmonary events that led to treatment discontinuation and in 9 (1.1%) subject drug-related pulmonary events led to dose delay whereas 9 (2.2%) subjects in the pooled combination therapy group had drug-related pulmonary events that led to treatment discontinuation and in 18 (4.4%) subjects, drug-related pulmonary events led to dose delay.

The median time to onset of drug-related pulmonary events was comparable between the pooled monotherapy group and the pooled combination therapy group (2.1 and 2.2 months respectively).

In the majority of subjects who experienced a drug-related pulmonary event, the event has resolved. The median time to resolution of any grade pulmonary event in the pooled combination therapy group was 6.1 week and 4.1 weeks in the pooled monotherapy group.

Renal Select Adverse Events

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

In order to monitor for renal select AEs, all studies in the pooled analyses included routine testing of serum creatinine and blood urea nitrogen (BUN) or serum urea level prior to each dose. Three (0.4%) subjects in the pooled monotherapy groups and 7 (1.7%) subjects in the pooled combination therapy group experienced drug-related renal events that were considered SAES. In the monotherapy group 1 subject experienced renal failure (Grade 2) and 1 subjects experienced acute renal failure (Grade 3) and 1 subject experienced tubulointerstitial nephritis (Grade 3). In the combination therapy group 3 subjects experienced acute renal failure (Grade 3) and 1 subject each experienced renal failure (Grade 4), tubulointestitial nephritis (Grade 4), blood creatinine increased (Grade 4) and nephritis autoimmune (Grade 2).

Drug-related renal events that led to either treatment discontinuation or dose delay were more frequent in the pooled combination therapy group compared with the pooled monotherapy group. In the pooled monotherapy group 6 (0.8%) subjects had a drug-related renal event that led to dose delay. In the pooled combination therapy group 4 (1.0%) had a drug-related renal event that led to treatment discontinuation and in 5 (1.2%) subjects a drug-related renal events that led to dose delay was reported.

The median time to onset of drug-related events was longer in the pooled monotherapy group (3.5 months) compared with the pooled combination therapy group (2.6 months). The median time to resolution of any grade renal events in the pooled monotherapy groups was 5.4 weeks and 1.9 weeks in the pooled combination therapy group.

Skin Select Adverse Events

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

Four (0.5%) subjects in the pooled monotherapy group and 2 (0.5%) in the combination therapy group experienced skin events considered SAEs.

The most frequently reported drug-related select AE in both groups was pruritus.

In the pooled monotherapy group, 2 (0.3%) subjects had drug-related skin events that led to treatment discontinuation and 9 (1.1%) subjects had a skin event led to dose delay. In the pooled combination therapy group, 3 (0.7%) subjects had drug related skin events that led to treatment discontinuation and in 25 (6.1%) subjects, drug-related skin events led to dose delay.

The median time to onset of drug-related skin events was longer in the pooled monotherapy group (1.3 months) compared with the pooled combination therapy group (0.5 months). The median time to resolution of any grade skin events in the pooled group was 23.4 weeks and 10.0 weeks in the combination therapy group and in the monotherapy group respectively.

Hypersensitivity/Infusion Reactions

Hypersensitivity/infusion reactions included the following terms: anaphylactic reaction and shock, bronchospasm, hypersensitivity, and infusion-related reaction.

Four (0.5%) subjects in the pooled monotherapy group and no subjects in the combination therapy group experienced hypersensitivity/infusion reactions AEs that were considered drug related SAEs.

The frequencies of drug-related hypersensitivity/infusion reaction that led to treatment discontinuation and dose delay were comparable between the treatment groups.

The median time to onset of drug related hypersensitivity/infusion reactions was similar in the pooled monotherapy and the pooled combination therapy group (0.5 and 0.7 months respectively). The median time to resolution of any grade hypersensitivity/infusion reaction events in the pooled monotherapy group and pooled combination therapy group were 0.1 weeks in both groups.

Other Events of Special Interest

Myasthenic Syndrome

No subjects in the pooled monotherapy group or the pooled combination therapy group experienced drug-related Myasthenic Syndrome events within 30 days of the last dose of study therapy.

Demyelination

In the pooled monotherapy group, 1 (0.1%) subject experienced a drug-related demyelination event (Grade 3 demyelination) that was considered an SAE and led to treatment discontinuation. This subject received high-dose corticosteroids (at least 40-mg prednisone equivalents per day) and the event did not resolve as of the database lock.

Immune-modulating medications administered in the subject with the demyelination event included corticosteroids and gamma globulin.

Guillain-Barré Syndrome

In the pooled monotherapy group, 1 (0.1%) subject experienced Grade 3 Guillain-Barré Syndrome within 30 days of the last dose of study therapy. In the pooled combination therapy group, 1 (0.2%) subject each experienced Grade 3 or Grade 4 Guillain-Barré Syndrome within 30 days of the last dose of study therapy. All Guillain-Barré Syndrome events were considered SAEs and led to treatment discontinuation. Two of the 3 Guillain-Barré Syndrome events did not resolve as of the database lock; the subject who resolved was in the pooled combination therapy group.

Pancreatitis

Four (0.5%) subjects in the pooled monotherapy group and 4 (1.0%) in the pooled combination therapy group experienced drug-related pancreatitis events within 30 days of the last dose of study therapy. No drug-related pancreatitis events were Grade 5 in either group; 2 subjects in the pooled combination therapy group experienced Grade 4 drug-related pancreatitis events.

The majority of drug-related pancreatitis events were considered SAEs in both groups.

Events of drug-related pancreatitis led to treatment discontinuation in 3 subjects in the pooled monotherapy group (1 subject with Grade 2 and 2 subjects with Grade 3 pancreatitis) and1 subject in the pooled combination therapy group (Grade 4 event),and the majority of events led to dose delay in these subjects.

The median time to onset of drug-related pancreatitis events was longer in the pooled monotherapy group (10.5 months, 4 subjects) and the pooled combination therapy group (1.6 months, 4 subjects).

All subjects in the pooled monotherapy group experienced resolution and a majority (3/4) of subjects in the pooled combination therapy group with drug-related pancreatitis events experienced resolution.

Median time to resolution of any grade drug-related pancreatitis events in the pooled monotherapy group was 8.6 months compared to 3.6 weeks in the pooled combination therapy group.

Uveitis

Six (0.8%) subjects in the pooled monotherapy group and 5 (1.2%) subjects in the pooled combination therapy group experienced drug-related uveitis events within 30 days of the last dose of study therapy.

One subject experienced an SAE of uveitis in the pooled combination therapy group and no subjects in either group had drug-related uveitis events that led to treatment discontinuation.

3 subjects in the pooled monotherapy group and 2 subjects in the pooled combination therapy group had drug-related uveitis events that led to dose delay.

The median time to onset of drug-related uveitis events was longer in the pooled monotherapy group (2.4 months) compared with the pooled combination therapy group (1.3 months).

The majority of subjects with drug-related uveitis events in both groups experienced resolution (5/6 subjects in the pooled monotherapy group and 4/5 subjects in the pooled combination therapy group).

Median time to resolution of any grade drug-related uveitis events in the pooled monotherapy group was 4.1 weeks and 3.4 weeks with the pooled combination therapy group.

TEN

During ongoing routine pharmacovigilance, 3 cases of fatal toxic epidermal necrolysis (TEN) were reported in ongoing studies in the nivolumab program. In a separate safety variation (II/004) TEN has been added to the special warning and precaution for use (section 4.4) of the SmPC.

Serious adverse event/deaths/other significant events
- **Serious Adverse Events**

The overall frequency of SAEs occurring up to 30 days after last dose (regardless of causality) was lower in the pooled monotherapy group (40.5%) than in the pooled combination therapy group (67.6%).

Table 41: **Summary of serious adverse events (regardless of causality) by worst CTC grade reported in ≥ 1% of treated subjects within 30 Days of last dose - treated subjects – Study CA209067**

System Organ Class (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	319 (40.5)	220 (28.0)	42 (5.3)	275 (67.6)	208 (51.1)	18 (4.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	114 (14.5)	58 (7.4)	35 (4.4)	18 (4.4)	7 (1.7)	8 (2.0)
MALIGNANT NEOPLASM PROGRESSION	70 (8.9)	30 (3.8)	34 (4.3)	13 (3.2)	3 (0.7)	8 (2.0)
SQUAMOUS CELL CARCINOMA	9 (1.1)	5 (0.6)	0	0	0	0
GASTROINTESTINAL DISORDERS	57 (7.2)	41 (5.2)	1 (0.1)	113 (27.8)	83 (20.4)	0
ABDOMINAL PAIN	10 (1.3)	8 (1.0)	0	5 (1.2)	2 (0.5)	0
DIARRHOEA	10 (1.3)	8 (1.0)	0	42 (10.3)	24 (5.9)	0
VOMITING	7 (0.9)	5 (0.6)	0	11 (2.7)	7 (1.7)	0
COLITIS	4 (0.5)	3 (0.4)	0	45 (11.1)	36 (8.8)	0
CONSTIPATION	4 (0.5)	1 (0.1)	0	4 (1.0)	1 (0.2)	0
NAUSEA	4 (0.5)	3 (0.4)	0	9 (2.2)	7 (1.7)	0
PANCREATITIS	3 (0.4)	3 (0.4)	0	4 (1.0)	4 (1.0)	0
INFECTIONS AND INFESTATIONS	41 (5.2)	34 (4.3)	1 (0.1)	34 (8.4)	25 (6.1)	2 (0.5)
PNEUMONIA	8 (1.0)	6 (0.8)	1 (0.1)	5 (1.2)	4 (1.0)	1 (0.2)
SEPSIS	4 (0.5)	4 (0.5)	0	4 (1.0)	4 (1.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	38 (4.8)	25 (3.2)	1 (0.1)	58 (14.3)	23 (5.7)	3 (0.7)
GENERAL PHYSICAL HEALTH DETERIORATION	9 (1.1)	7 (0.9)	0	9 (2.2)	6 (1.5)	0
PYREXIA	9 (1.1)	2 (0.3)	0	32 (7.9)	7 (1.7)	0
PAIN	5 (0.6)	5 (0.6)	0	4 (1.0)	4 (1.0)	0
FATIGUE	4 (0.5)	3 (0.4)	0	5 (1.2)	2 (0.5)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (4.1)	20 (2.5)	1 (0.1)	36 (8.8)	22 (5.4)	5 (1.2)
DYSPNOEA	8 (1.0)	4 (0.5)	0	7 (1.7)	6 (1.5)	0
PLEURAL EFFUSION	5 (0.6)	5 (0.6)	0	4 (1.0)	4 (1.0)	0
PNEUMONITIS	5 (0.6)	2 (0.3)	0	11 (2.7)	5 (1.2)	0
PULMONARY EMBOLISM	4 (0.5)	4 (0.5)	0	9 (2.2)	6 (1.5)	3 (0.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	21 (2.7)	18 (2.3)	0	10 (2.5)	8 (2.0)	0
BACK PAIN	10 (1.3)	8 (1.0)	0	2 (0.5)	1 (0.2)	0
CARDIAC DISORDERS	18 (2.3)	12 (1.5)	1 (0.1)	10 (2.5)	7 (1.7)	1 (0.2)
ATRIAL FIBRILLATION	5 (0.6)	4 (0.5)	0	5 (1.2)	3 (0.7)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab treatment group consists of Nivolumab monotherapy treatment group from studies CA209037, CA209066 and CA209067.
Nivolumab+Ipilimumab treatment group consists of Nivolumab+Ipilimumab treatment group from studies CA209069 and CA209067.

Drug related serious adverse events

The overall frequency of drug-related SAEs occurring up to 30 days after last dose was lower in the pooled monotherapy group (8.1%) than in the pooled combination therapy group (47.9%).

No individual drug-related SAE was reported with a frequency ≥ 2% in the pooled monotherapy therapy group. In the pooled combination therapy group, colitis (11.1%), diarrhoea (8.8%), pyrexia (3.7%), pneumonitis (2.7%), hypophysitis (2.2%), transaminases increased (2.2%), and adrenal insufficiency (2.0%) were reported with a frequency ≥ 2%.

One (0.2%) subject in each group experienced a Grade 5 drug-related SAE (neutropenia in the pooled monotherapy therapy group and ventricular arrhythmia in the pooled combination therapy group).

- **Deaths**

Across the melanoma nivolumab program (CA209067, CA209069, CA209066, and CA209037), disease progression was the most common cause of death in subjects treated with both nivolumab monotherapy (29.1%) and nivolumab+ipilimumab combination therapy (19.7%). Four deaths due to study drug toxicity have been reported (3 within100 days of the last dose of study therapy and 1 reported after database lock for this SCS):

- Nivolumab monotherapy: Subject died due to drug-related neutropenia on Day 152, 39 days after last dose.

- Nivolumab+ipilimumab combination therapy: Subject died due to pneumonitis on Day 114, 69 days after last dose; subject died due to ventricular arrhythmia on Day 29, 29 days after last dose;

subject died suddenly on Day 262; death occurred 86 days after the last dose (3 days after the resolution of Grade 3 pneumonia and Grade 4 hypercalcemia)

"Other" reasons for death were provided by the investigator for 15 (1.9%) subjects in the pooled monotherapy group:

- CA209067: 8 subjects - euthanasia, disease progression euthanasia, cardiac arrest, intracranial haemorrhage and subarachnoid haemorrhage, perforated diverticulitis, sepsis, upperGI bleed, and sepsis.

- CA209066: 3 subjects - heart failure, sepsis with multi-organ failure, and subarachnoidal bleeding.

- CA209037: 4 subjects - cardiopulmonary arrest, pneumonia, pneumocystis jiroveci pneumonia, and infectious syndrome.

Twenty (4.9%) subjects in the pooled combination therapy group died due to "other" reasons provided by the investigator:

- CA209067: 13 subjects - pulmonary embolus, pulmonary embolism, dyspnoea due to emphysema, pneumonia, intercurrent illness, likely infection leading to multi organ failure, euthanasia, presumed pulmonary embolism, respiratory failure, accident, sudden cardiac death, pneumonia, worsening of general condition, and respiratory failure.

- CA209069: 7 subjects - supraventriclar tachycardia, myocardial infarction, heart failure, pulmonary embolism and respiratory failure secondary to Stage IV melanoma, unrelated -likely due to hepatic metastases and infection, pulmonary embolism, and stroke.

In CA209004 Cohort 8, 8 (19.5%) subjects died: 5 subjects died of progressive disease and one subject each died due to reasons reported as study drug toxicity, "unknown," and "other"; subject died on Day 93 with death reported due to multiple organ failure and systemic infection considered related to study drug by the investigator; subject died due to reasons reported as 'unknown' (death was noted as due to disease progression by the investigator); subject died due to reasons reported as "other".

Of note, no deaths due to study drug toxicity were reported in the dose escalation treatment cohorts in CA209004.

Table 42: **Drug-related deaths reported in all subjects treated with nivolumab + ipilimumab in ongoing studies with combination therapy**

Patient ID[a]	Treatment Group	Day of Death	Days After Last Dose	Cause of Death
CA209012-10-161	3 mg/kg nivolumab + 1 mg/kg ipilimumab	79	79	Toxic epidermal necrolysis[b]
CA209012-4-215	1 mg/kg nivolumab + 3 mg/kg ipilimumab	38	17	Respiratory failure[b]
CA209012-14-228	3 mg/kg nivolumab + 1 mg/kg ipilimumab	101	3	Bronchopulmonary hemorrhage[b]
CA209032-8-255	1 mg/kg nivolumab + 3 mg/kg ipilimumab	46	46	Myasthenia gravis, Sepsis

Abbreviation: CIOMS: Council for International Organizations of Medical Sciences.

[a] See CIOMS forms for individual subjects in SCS Appendix 3.

[b] Confounded by contributing factors (see CIOMS forms for individual subjects in SCS Appendix 3).

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last treatment dose were primarily Grade 1-2 in severity in the nivolumab monotherapy and nivolumab+ipilimumab combination therapy groups in CA209067 and CA209069.

The most frequently reported Grade 3-4 hematologic abnormalities (≥2% of subjects) were decreased hemoglobin and absolute lymphocyte decrease in the nivolumab monotherapy group and the nivolumab+ipilimumab groups in study CA209067 . The number of subjects who experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality were as follows: In the nivolumab monotherapy group, 10 (3.2%) subjects with decreased absolute lymphocytes, 5 (1.6%) subjects with decreased hemoglobin, 1 (0.3%) subject with decreased platelet count, 1 (0.3%) subject with decreased leukocytes, and 1 (0.3%) subject with decreased absolute neutrophil count. In the nivolumab+ipilimumab combination therapy group, 10 (3.2%) subjects with decreased absolute lymphocytes, 6 (1.9%) subjects with decreased hemoglobin, 4 (1.3%) subjects with decreased platelet count, 2 (0.6%) subjects with decreased absolute neutrophil count, and 1 (0.3%) subject with decreased leukocytes.

The most frequently reported Grade 3-4 hematologic abnormality in study CA209069 was absolute lymphocyte count decreased (9/94 subjects, 9.6%) in the nivolumab+ipilimumab In the nivolumab+ipilimumab group, of the 9 subjects with Grade 3-4 decreased lymphocytes, all experienced a ≥2-grade shift from baseline. One subject each experienced ≥2-grade shift from baseline in platelet count (Grade 0 to Grade 3), leukocyte (Grade 0 to Grade 3), and ANC (Grade 0 to Grade 4). There were no other subjects in the nivolumab+ipilimumab group with a Grade 3-4 hematologic abnormality that experienced a ≥2-grade shift from baseline.

Liver Function Tests

The most frequently reported Grade 3-4 hepatic function abnormalities (≥2% of subjects) was ALP in all 3 treatment groups in study CA209067.The number of subjects who experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: In the nivolumab group, 2 (0.6%) subjects for ALP, 9 (2.9%) subjects for AST, 9 (2.9%) subjects for ALT, and 4 (1.3%) subjects for total bilirubin. In the nivolumab+ipilimumab group, 14 (4.5 %) subjects for ALP, 37 (11.8%) subjects for AST, 44 (14.1 %) subjects for ALT, and 3 (1.0%) subjects for total bilirubin. Overall, 4 subjects in the nivolumab monotherapy group and 6 subjects in the nivolumab+ipilimumab group had concurrent ALT or AST elevation >3xULN with total bilirubin >2xULN within 1 day.

In study CA209069 the most frequently observed Grade 3-4 hepatic function abnormalities was ALT (11/94 subjects, 11.7%) and AST (9/94 subjects, 9.6%) in the nivolumab+ipilimumab group. In the nivolumab+ipilimumab group, all 11 subjects with Grade 3-4 ALT and all 9 subjects with Grade 3-4 AST experienced a ≥2-grade shift from baseline. No subjects in the nivolumab+ipilimumab had concurrent ALT or AST elevation >3xULN with total bilirubin >2xULN within 1 day. One subject in the nivolumab+ipilimumab group, met these criteria more than 30 days after last dose.

Kidney Function Tests

In CA209067, 1 (0.3%) and 8 (2.6%) subjects experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality in the nivolumab and nivolumab+ipilimumab groups, respectively.

In the nivolumab+ipilimumab group in CA209069, 1 subject had a Grade 4 abnormality in creatinine, this subject experienced 4-grade shift from baseline. None were reported in the ipilimumab group.

Thyroid Function Tests

The overall frequency of subjects with elevated TSH >ULN who had TSH ≤ULN at baseline was similar between the nivolumab and nivolumab+ipilimumab groups.

Elevated TSH levels (TSH >ULN) with at least one T3/T4 test value <LLN were reported in19.5% of subjects in the nivolumab+ipilimumab. Low TSH levels (TSH <LLN) with at least one T3/T4 test value >ULN were reported in 19.5% of subjects in the nivolumab+ipilimumab group.

 Electrolytes

In CA209067: Electrolytes were not analysed.

In CA209069, most subjects had normal electrolyte levels during the treatment reporting period Appendix MC.26-069). Abnormalities in electrolytes were primarily Grade 1-2 in severity. Grade 3-4 abnormalities in electrolyte levels were reported in 14 subjects in the nivolumab+ipilimumab group; hyponatremia (8 subjects, 9.2%), hypokalemia (3 subjects, 3.4%), hypocalcemia (2 subjects, 2.3%), and hypercalcemia (1 subject, 1.1%).

Safety in special populations

Age

Median age was 65.0 years, with 12.0% of subjects aged 75 years or older.

The frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level ≥75 years is presented in Table 43.

Table 43: **Summary of on-treatment adverse events by age group in all subjects treated with pooled nivolumab monotherapy and pooled nivolumab combination therapy data across indications**

MedDRA Terms	Pooled Monotherapy Data Across Indications[a]				Pooled Combination Data Across Indications[b]			
	Age < 65 years (N = 791) n (%)	Age 65-74 years (N = 379) n (%)	Age 75-84 years (N = 135) n (%)	Age 85+ years (N = 17) n (%)	Age < 65 years (N = 265) n (%)	Age 65-74 years (N = 135) n (%)	Age 75-84 years (N = 42) n (%)	Age 85+ years (N = 6) n (%)
Total AEs	774 (97.9)	369 (97.4)	132 (97.8)	17 (100.0)	264 (99.6)	135 (100.0)	42 (100.0)	6 (100.0)
Serious AEs -Total	340 (43.0)	168 (44.3)	64 (47.4)	10 (58.8)	173 (65.3)	94 (69.6)	30 (71.4)	3 (50.0)
- Fatal	89 (11.3)	38 (10.0)	16 (11.9)	3 (17.6)	14 (5.3)	10 (7.4)	5 (11.9)	0
- Hospitalization/prolong existing hospitalization	294 (37.2)	150 (39.6)	56 (41.5)	6 (35.3)	158 (59.6)	87 (64.4)	24 (57.1)	3 (50.0)
- Life-threatening	15 (1.9)	4 (1.1)	1 (0.7)	0	5 (1.9)	3 (2.2)	0	0
- Cancer	11 (1.4)	7 (1.8)	8 (5.9)	1 (5.9)	0	1 (0.7)	1 (2.4)	0
- Disability/incapacity	1 (0.1)	1 (0.3)	0	0	2 (0.8)	0	0	0
AEs leading to drop-out	105 (13.3)	53 (14.0)	28 (20.7)	4 (23.5)	113 (42.6)	53 (39.3)	19 (45.2)	1 (16.7)
Psychiatric disorders	146 (18.5)	60 (15.8)	21 (15.6)	6 (35.3)	60 (22.6)	35 (25.9)	8 (19.0)	1 (16.7)
Nervous system disorders	290 (36.7)	135 (35.6)	46 (34.1)	9 (52.9)	125 (47.2)	56 (41.5)	11 (26.2)	2 (33.3)
Accidents and Injuries	54 (6.8)	31 (8.2)	12 (8.9)	3 (17.6)	18 (6.8)	19 (14.1)	5 (11.9)	0
Cardiac disorders	72 (9.1)	40 (10.6)	12 (8.9)	3 (17.6)	24 (9.1)	18 (13.3)	8 (19.0)	0
Vascular disorders	121 (15.3)	69 (18.2)	23 (17.0)	7 (41.2)	35 (13.2)	35 (25.9)	9 (21.4)	1 (16.7)
Cerebrovascular disorders	13 (1.6)	14 (3.7)	1 (0.7)	1 (5.9)	5 (1.9)	5 (3.7)	2 (4.8)	0
Infections and infestations	279 (35.3)	158 (41.7)	52 (38.5)	7 (41.2)	119 (44.9)	58 (43.0)	15 (35.7)	1 (16.7)
Anticholinergic syndrome	260 (32.9)	124 (32.7)	46 (34.1)	6 (35.3)	154 (58.1)	64 (47.4)	20 (47.6)	1 (16.7)
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	86 (10.9)	49 (12.9)	18 (13.3)	4 (23.5)	40 (15.1)	17 (12.6)	7 (16.7)	1 (16.7)

Abbreviations: AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities.

[a] Includes data from Studies CA209063, CA209017, CA209057, CA209037, CA209066, and CA209067 (monotherapy arm only).

[b] Includes data from Studies CA209067 (combination arm only), CA209069, and CA209004 (Cohort 8 only).

Source: Appendix LM.5.51-PI (total AEs), Appendix LM.5.52-PI (SAEs), Appendix LM.5.53-PI (AEs leading to discontinuation); Appendix LM.5.54-PI (AEs by High-level Group Term/System Organ Class/Standardized MedDRA Queries), Appendix LM.5.55-PI (summary of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures), Appendix LM.5.56-PI (serious AEs by categories), and Appendix LM.5.57-PI (quality of life) of SCS Appendix 2

Gender, race and region

For gender, race and region subgroup analyses show for each of these factors similar safety profile of nivolumab and nivolumab+ipilimumab, between subgroups. Some numeric differences were observed

among subgroups: however, the small sample size in some subgroups and small number of events limits the interpretability of these data.

<u>Baseline PD-L1 Expression Status</u>

A descriptive safety analysis of PD-L1 expression utilising the validated assay and select AEs was conducted based on PD-L1 evaluable subjects in Study CA209067 (Table 44).

Table 44: **Select AE summary by worst CTC grade and PD-L1 status at baseline (< 5% and ≥ 5%) in all treated PD-L1 evaluable subjects - Study CA209067**

SELECT AE CATEGORY	Number (%) Subjects			
	Nivolumab		Nivolumab + Ipilimumab	
	PD-L1 < 5%	PD-L1 ≥ 5%	PD-L1 < 5%	PD-L1 ≥ 5%
Endocrine (all grades)	32 (15.4)	12 (15.0)	66 (31.4)	26 (38.2)
Grade 3-4	2 (1.0)	0	14 (6.7)	3 (4.4)
Gastrointestinal (all grades)	69 (33.2)	25 (31.3)	114 (54.3)	37 (54.4)
Grade 3-4	7 (3.4)	3 (3.8)	34 (16.2)	11 (16.2)
Hepatic (all grades)	25 (12.0)	9 (11.3)	71 (33.8)	25 (36.8)
Grade 3-4	11 (5.3)	4 (5.0)	43 (20.5)	15 (22.1)
Pulmonary (all grades)	3 (1.4)	1 (1.3)	17 (8.1)	3 (4.4)
Grade 3-4	1 (0.5)	0	3 (1.4)	1 (1.5)
Renal (all grades)	4 (1.9)	2 (2.5)	20 (9.5)	10 (14.7)
Grade 3-4	1 (0.5)	0	8 (3.8)	2 (2.9)
Skin (all grades)	105 (50.5)	48 (60.0)	142 (67.6)	40 (58.8)
Grade 3-4	5 (2.4)	0	13 (6.2)	5 (7.4)
Hypersensitivity/ Infusion Reactions (all grades)	7 (3.4)	9 (11.3)	9 (4.3)	5 (7.4)
Grade 3-4	1 (0.5)	0	0	0

Abbreviations: AE: adverse event; PD-L1: programmed death cell ligand 1.
PD-L1 expression results from validated assay.

<u>Pregnancy and Lactation</u>

Given the potential risk suggested by preliminary data from nonclinical data (see initial marketing authorisation EPAR) study, dosing during pregnancy will not be recommended. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product.

These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab. Females should not breastfeed while receiving nivolumab and for 5 half-lives after the last dose of nivolumab.

Immunological Events

An integrated analysis of nivolumab immunogenicity assessments was performed with data across indications from patients treated with nivolumab monotherapy (studies CA209037, CA209063, CA209066,

CA20917, CA20957 and CA20967) and nivolumab in combination with ipilimumab (studies 209004 [cohort 8], CA209069 and CA209067).

The immunogenicity of nivolumab was assessed when administered as monotherapy and in combination with ipilimumab. Ipilimumab immunogenicity was also assessed when administered as monotherapy and in combination with nivolumab.

Of 1,037 subjects who were treated with nivolumab 3 mg/kg Q2W and evaluable for the presence of ADAs, 128 (12.3%) subjects tested positive for ADA after the initiation of treatment. Of those who were ADA positive, only 1 subject (0.1% of the total) was persistent positive, and neutralizing antibodies (NAb) were detected in only 9 subjects (0.9% of the total).

Of the 394 subjects who were treated with nivolumab+ipilimumab and were evaluable for the presence of anti-nivolumab antibodies, 149 (37.8%) subjects tested positive for ADAs by an electrochemiluminescent (ECL) assay. However, titers of nivolumab ADA appeared to decrease after Week 12 (C3W1) in the nivolumab+ipilimumab group, corresponding to the beginning of the maintenance phase when ipilimumab treatment was discontinued as per the schedule. Additionally, only 18 (4.6%) subjects were persistent positive and neutralizing antibodies were detected in only 18 (4.6% of the total) of the positive antiproduct antibody subjects.

The immunogenicity of ipilimumab when given in combination with nivolumab had an ADA incidence (8.4%). Safety appears not to be affected by the presence of ADA. There were no hypersensitivity, acute infusion reactions, and new AEs observed in persistent or NAb-positive subjects compared to ADA-negative subjects.

Safety related to drug-drug interactions and other interactions

The MAH did not submit data on safety related to drug-drug interaction.

Discontinuation due to adverse events

The overall frequency of AEs leading to discontinuation occurring up to 30 days after last dose (regardless of causality) was lower in the pooled monotherapy group (11.6%) compared with the pooled combination therapy group (43.0%).

Table 45: **Summary of adverse events leading to discontinuation (regardless of causality) by worst CTC grade reported in ≥ 1% of treated subjects within 30 days of last dose - treated subjects**

System Organ Class (%) Preferred Term (%)	Nivolumab N = 787			Nivolumab + Ipilimumab N = 407		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	91 (11.6)	65 (8.3)	9 (1.1)	175 (43.0)	138 (33.9)	7 (1.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	27 (3.4)	18 (2.3)	7 (0.9)	5 (1.2)	2 (0.5)	1 (0.2)
MALIGNANT NEOPLASM PROGRESSION	25 (3.2)	17 (2.2)	7 (0.9)	2 (0.5)	1 (0.2)	1 (0.2)
GASTROINTESTINAL DISORDERS	16 (2.0)	12 (1.5)	0	74 (18.2)	63 (15.5)	0
DIARRHOEA	6 (0.8)	4 (0.5)	0	30 (7.4)	25 (6.1)	0
COLITIS	4 (0.5)	4 (0.5)	0	41 (10.1)	34 (8.4)	0
INVESTIGATIONS	12 (1.5)	12 (1.5)	0	35 (8.6)	33 (8.1)	0
ALANINE AMINOTRANSFERASE INCREASED	8 (1.0)	7 (0.9)	0	19 (4.7)	18 (4.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	5 (0.6)	5 (0.6)	0	17 (4.2)	15 (3.7)	0
LIPASE INCREASED	1 (0.1)	1 (0.1)	0	4 (1.0)	3 (0.7)	0
TRANSAMINASES INCREASED	0	0	0	7 (1.7)	6 (1.5)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (0.6)	2 (0.3)	1 (0.1)	17 (4.2)	9 (2.2)	3 (0.7)
PNEUMONITIS	1 (0.1)	1 (0.1)	0	9 (2.2)	4 (1.0)	0
HEPATOBILIARY DISORDERS	2 (0.3)	1 (0.1)	0	13 (3.2)	10 (2.5)	0
HEPATITIS	0	0	0	4 (1.0)	4 (1.0)	0
HEPATOTOXICITY	0	0	0	6 (1.5)	4 (1.0)	0
ENDOCRINE DISORDERS	0	0	0	10 (2.5)	3 (0.7)	0
HYPOPHYSITIS	0	0	0	4 (1.0)	1 (0.2)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab treatment group consists of Nivolumab monotherapy treatment group from studies CA209037, CA209066 and CA209067.
Nivolumab+Ipilimumab treatment group consists of Nivolumab+Ipilimumab treatment group from studies CA209069 and CA209067.

The overall frequency of drug-related AEs leading to discontinuation occurring up to 30 days after last dose was lower in the pooled monotherapy group (5.2%) compared with the pooled combination therapy group (36.4%).PTs reported in more than 2 subjects in either group included ALT increased (7 subjects,0.9%), diarrhea (6 subjects, 0.8%), AST increased (4 subjects, 0.5%), colitis (4 subjects,0.5%), pancreatitis (3 subjects, 0.4%), and fatigue (3 subjects, 0.4%) in the pooled monotherapy group and colitis (41 subjects, 10.1%), diarrhoea (30 subjects, 7.4%), ALT increased (19 subjects, 4.7%), AST increased (17 subjects, 4.2%), pneumonitis (9 subjects,2.2%), hepatotoxicity (6 subjects, 1.5%), hepatitis (4 subjects, 1.0%), hypophysitis(4 subjects, 1.0%), lipase increased (4 subjects, 1.0%), and hypothyroidism (3 subjects,0.7%) in the pooled combination therapy group. Most subjects with drug-related AEs leading to discontinuation had Grade 3-4 events.

A summary of time to onset of AE leading to discontinuation is presented in Table 46.

Table 46: **Summary of time to onset of adverse events leading to discontinuation treated subjects who experiences at least one adverse event leading to discontinuation**

	Nivolumab		Nivolumab+Ipilimumab	
	Any Grade N = 91	Grade 3-5 N = 74	Any Grade N = 175	Grade 3-5 N = 145
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	8.29 (0.6 - 63.0)	8.36 (0.6 - 63.0)	7.71 (0.1 - 66.0)	7.71 (0.4 - 55.0)

Post-marketing experience

At the time of the submission of this variation, nivolumab was approved as monotherapy for treatment of unresectable melanoma on 04-Jul-2014 in Japan, 22-Dec-2014 in the US, 19-Mar-2015 in Israel, 20-Mar-2015 in Korea, and 07-May-2015 in Macau. No new safety concerns were identified based on the postmarketing reports.

2.5.1. Discussion on clinical safety

The applicant pooled the safety data of the studies CA209067 and CA209069, which is acceptable as comparable patient populations were included.

The overall frequency of AEs occurring up to 30 days after last dose (regardless of causality) was 97.6% (pooled monotherapy) and was 99.8% (pooled combination therapy).

The overall frequency of drug-related AEs leading to discontinuation occurring up to 30 days after last dose was higher in the pooled combination therapy group (36.4%) compared to the pooled monotherapy group (5.2%).

The overall frequency of SAEs occurring up to 30 days after last dose (regardless of causality) was higher in the pooled combination therapy group (67.6%) compared to the pooled monotherapy group (40.5%).

As for the general AEs, the incidence of most AEs of special interest (including endocrine, gastrointestinal, hepatic, pulmonary, renal, skin AEs and hypersensitivity reactions) was higher in the pooled nivolumab+ipilimumab combination therapy group than in the pooled nivolumab monotherapy group. In general the median time to onset was shorter in the combination therapy group than in the monotherapy group whereas the median time to resolution was longer for patients treated with combination therapy than with monotherapy. This supports the findings that tolerability of the combination therapy is worse in comparison to nivolumab alone.

When nivolumab is administered in combination with ipilimumab, refer to the Summary of Product Characteristics for ipilimumab prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared

with nivolumab as monotherapy. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (Section 4.4 SmPC).

Across the melanoma nivolumab program disease progression was the most common cause of death in subjects treated with both nivolumab monotherapy (29.1%) and the combination with ipilimumab (19.7%). Four deaths due to study drug toxicity have been reported, causes of death due to study drug toxicity included, drug-related neutropenia (nivolumab monotherapy), pneumonitis, ventricular arrhythmia, and sudden dead (nivolumab+ipilimumab combination therapy). In total 20 patients treated in the two clinical studies with nivolumab+ipilimumab died by reasons classified as "other reasons". Of these deaths, 11 patients died by pulmonary/respiratory events. The incidence of pulmonary adverse events appears to be higher in the nivolumab+ipilimumab combination compared to nivolumab monotherapy (7.6% vs 2.0%).

Subgroup analyses were conducted to assess the impact of age (eg, < 75 years vs ≥ 75 years), gender, race, and region on frequency of AEs regardless of causality. For each of these factors, the safety profiles of nivolumab and nivolumab+ipilimumab in the primary study, CA209067, were similar between the subgroups. Some numeric differences were observed among subgroups; however, the small sample size in some subgroups and small number of events limits the interpretability of some of these comparisons.

The risk of AEs leading to treatment discontinuation or death was higher when nivolumab given in combination with ipilimumab relative to nivolumab or ipilimumab monotherapy (see PK section). However, there was no relation with either nivolumab or ipilimumab exposure. Further, the risk of AEs leading to treatment discontinuation or death appeared to increase with increasing age and baseline LDH. These factors are either directly or indirectly associated with the overall health status of the subject. The increase in risk of AEs leading to treatment discontinuation or death by age (HR 1.18 for 79 year) and LDH (HR 1.4 for 3.4 ULN) were small compared to the effects of treatment monotherapy nivolumab HR=1, ipilimumab monotherapy HR=2.08 vs. combination HR=4.74.

The immunogenicity of nivolumab increased when nivolumab was used in combination with ipilimumab. Although the clearance of nivolumab was increased by 25% when anti-nivolumab-antibodies were present, the presence of antibodies was not associated with loss of efficacy or altered toxicity profile based on the pharmacokinetic and exposure-response analyses. Of 394 patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies by an ECL assay. Neutralizing antibodies were detected in 18 patients (4.6%). There was no evidence of altered toxicity profile associated with anti-product antibody development. Neutralizing antibodies were not associated with loss of efficacy (SmPC section 4.8).

Incidence of hypersensitivity/infusion reactions appeared not to be increased in subjects positive for either nivolumab or ipilimumab antibodies. Overall, the immunogenic potential of ipilimumab when given in combination with nivolumab was low, as characterized by low incidence of antibody, no impact of ipilimumab antibody on ipilimumab PK as assessed by the PPK analyses. In patients treated with nivolumab in combination with ipilimumab, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported (SmPC section 4.8).

Additional expert consultations

See clinical efficacy discussion.

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 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. The combination of nivolumab with ipilimumab has shown additional PFS 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 annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the RMP version 4.3 (dated 21 March 2016) is acceptable.

The CHMP endorsed this advice. However, it raised a potential safety concern about fatal cases due to pulmonary/respiratory events in the combination of nivolumab + ipilimumab. The company has been requested to discuss the impact of a possible relation between the toxicity of nivolumab+ipilimumab combination therapy and the occurrence of death due to pulmonary events. Depending on the outcome of this discussion, an RMP update may be required.

Table 47:   Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• *Immune-related pneumonitis* • *Immune-related colitis* • *Immune-related hepatitis* • *Immune-related nephritis or renal dysfunction* • *Immune-related endocrinopathies* • *Immune-related rash* • *Other immune-related ARs* • *Severe infusion reactions*
Important potential risks	• *Embryofetal toxicity* • *Immunogenicity* • *Cardiac arrhythmias (previously treated melanoma indication, only)*
Missing information	• *Paediatric patients <18 years of age* • *Patients with severe hepatic and/or renal impairment*

Summary of safety concerns	
	• *Patients with autoimmune disease* • *Patients already receiving systemic immunosuppressants before starting nivolumab*

Pharmacovigilance plan

Table 48: Ongoing and planned studies additional pharmacovigilance studies/activities in the pharmacovigilance plan

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

The PRAC, having considered the data submitted, is of the opinion that the currently proposed pharmacovigilance plan is sufficient to identify and characterise the risks of the product.

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

Table 49: Risk minimisation measures

Safety concern	Pharmacovigilance Activities	Risk Minimisation Activities
Important Identified Risks		
• Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis	Routine PV includes monitoring, evaluation, and reporting of individual case safety reports (ICSR), expedited reporting and periodic safety update reporting. Additional PV includes a post- marketing pharmacoepidemiology study (CA209234).	SmPC; PIL To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan.

Safety concern	Pharmacovigilance Activities	Risk Minimisation Activities
• Immune-related nephritis or renal dysfunction • Immune-related endocrinopathies • Immune related rash • Other immune-related ARs		The Plan comprises 2 tools to be distributed to potential prescribers at launch by BMS: • Adverse Reaction Management Guide • Patient Alert Card
Severe infusion reactions	Routine PV	SmPC
Important Potential Risks		
Embryofetal Toxicity	Routine PV	SmPC; PIL
Immunogenicity	Routine PV; monitor immunogenicity in ongoing Phase 3 clinical trials	SmPC
Cardiac arrhythmias (previously treated melanoma indication, only)	Routine PV; monitor multiple ongoing Phase 3 clinical trials	SmPC
Missing Information		
Pediatric patients	Routine PV. A PIP is/was agreed by EMA.	SmPC
Severe hepatic and/or renal impairment	Routine PV	SmPC
Patients with autoimmune disease	Routine PV	SmPC
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine PV	SmPC

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

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. Two new efficacy measures have also been added to Annex II upon request by the CHMP during the procedure.

2.7.1. User consultation

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

- The variation submitted to extend the current approved therapeutic indication for OPDIVO to include "OPDIVO in combination treatment with ipilimumab for treatment of advanced (unresectable or metastatic) melanoma in adults" does not involve a relevant impact on the Package Leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The MAH submitted an extension of the indication of nivolumab in combination with ipilimumab for the treatment of adults with advanced (unresectable or metastatic melanoma). The application was based on the study CA209067, 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.

Nivolumab and ipilimumab combination vs ipilimumab monotherapy

The combination of nivolumab and ipilimumab (Nov 2015 DBL) demonstrated a statistically significant median PFS of 11.50 months compared to 2.89 months for the ipilimumab monotherapy (HR 0.42; 99.5%CI 0.31, 0.57; p<0.0001). A higher antitumor activity was also observed in the combination treatment compared with ipilimumab (ORR, 57.6% vs 19%; CR, 11.5% vs 2.2%). The duration of the response, even though the median has not been reached yet, appears to be longer for the combination when the percentage of ongoing responders is taken into account (72% vs 52%). Of note, time to response is quite similar among all treatment groups of the study (median around 2.8 months).

The different sensitivity analyses carried out (on or after subsequent therapy and accounting for missing tumour assessment prior to PFS event) and the consistency in terms of PFS and ORR in the subgroup analyses, including BRAF mutated patients (HR 0.44; mPFS 15.54 months; ORR 66.7%) and BRAF WT subjects (HR 0.41; mPFS 11.27 months; ORR 53.3%), support the robustness of the main results.

Data from Study CA209069, a randomized, double-blind Phase 2 study of nivolumab+ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma, was submitted as a supportive study. In the all randomised population (N = 142), the majority of subjects (76.8%) were BRAF WT and 23.2% of subjects were BRAF mutation positive. The results (Jan 2015 DBL) for the all randomised population for ORR were 58.9% vs. 10.6% and for CR, 22.1% vs 0% for the combination vs ipilimumab, respectively. In BRAF WT subjects, ORR in the combination treatment with ipilimumab alone was 61.1% vs. 10.8%. The HR for PFS was 0.39 with mPFS N.A. in the whole population.

Nivolumab + ipilimumab combination vs nivolumab monotherapy

The data comparing nivolumab monotherapy and the combination of nivolumab and ipilimumab demonstrated a favourable effect on PFS for the combination therapy with a PFS HR=0.0.76 (95%CI 0.62-0.95) with 4.6 months of difference between medians of PFS (11.50-6.87); ORR 57.6% vs 43.7% (CR 12%) (nivolumab+ipilimumab vs nivolumab respectively).

Uncertainty in the knowledge about the beneficial effects

In terms of OS, the data is not yet mature. More mature data are required and expected by the end 2016 (annex II condition).

There is uncertainty with regards to the subset of the population determined as PD-L1 negative or positive and the effect observed for PFS. The analysis according to the PD-L1 expression revealed that the results in the whole population of the pivotal study seem to be driven by the subgroup of patients that have been designated as PD-L1 negative. The PFS HR for nivolumab + ipilimumab versus nivolumab were 0.94 (95%CI 0.69, 1.28) and 0.87 (95%CI 0.54, 1.41) for the ≥1% and ≥5% subgroups, respectively. On the other hand, for the <1% and <5% PD-L1 expression subgroups, the PFS HR for the combination versus nivolumab were 0.60 (95%CI 0.43, 0.84) and 0.74 (95%CI 0.58, 0.96), respectively. This finding means that in those patients considered PD-L1 positive (cutoff >1%) no benefit of the treatment combination over nivolumab in monotherapy is terms of PFS has been established. The PFS curves in the subset of patients ≥1% appear to be overlapping, whereas in the subgroup of tumour PD-L1 expression <1% (negative), the PFS results are similar to the whole population. These results are in contrast to the results observed for the ORR outcomes, where the response rate for patients with tumour PD-L1 expression positive ≥5% was higher in the combination treatment nivolumab +ipilimumab than in the nivolumab monotherapy arm (72% vs 57.5%). Based on these data, a clear definition of PD-L1 negative patients is lacking as there is no definitive cut-off point to select patients who could mostly benefit from treatment, despite an available IHC assay that is able to detect PD-L1 in tumour biopsies. There is uncertainty as to how this test would be used in a clinical setting with the heterogeneity in the expression of PD-L1 within the same tumour and intra-metastases. PD-L1, a surface protein expressed in a variety of immune cells, comes with some unpredictability as its expression is known to be time-dependent, hence complicating further the reproducibility of the staining method employed in different labs (tissue processing and storage). Therefore, the CHMP concluded that mature OS data would be needed to resolve this uncertainty and a restriction of the indication to patients designated as having tumours with PD-L1 expression <1% is not currently supported with the available data. However, the inconsistent efficacy results in a relevant subset of the studied population are a matter of concern and are adequately reflected in the SmPC in section 5.1. Mature OS data from the ongoing pivotal Study CA209067 are awaited by the end of 2016 and will be submitted as part of an Annex II condition.

Risks

Unfavourable effects

The safety of the nivolumab and ipilimumab used in combination is consistent with the know effects of the two products as used in monotherapy. However, a higher frequency and severe toxicity were observed in the treated combination group.

The overall frequency of drug related AEs occurring up to 30 days after last dose were reported more frequently in the pooled combination therapy group (94.6%) compared to the monotherapy group (77.4%). The most common drug-related AEs (>15% of subjects) were diarrhoea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), ALT increased (18.2%), AST increased (16.7%), and decreased appetite (16.2%) in the pooled combination therapy group.

A higher proportion of Grade 3-4 drug-related AEs were reported in subjects in the pooled combination therapy group (54.1%) compared to the pooled monotherapy group (13.7%).

The overall frequency of SAEs occurring up to 30 days after last dose (regardless of causality) was higher in the pooled combination therapy group (67.6%) compared to the pooled monotherapy group (40.5%). In the pooled combination therapy group, colitis (11.1%), diarrhoea (10.3%), malignant neoplasm progression (3.2%), pyrexia (7.9%), vomiting (2.7%), general physical health deterioration (2.2%), pneumonitis (2.7%), nausea (2.2%), and pulmonary embolism (2.2%) were reported in ≥ 2% of subjects.

The overall frequency of AEs leading to discontinuation occurring up to 30 days after last dose (regardless of causality) was higher in the pooled combination therapy group (43.0%) compared to the pooled monotherapy group (11.6%).

One (0.1%) death in the pooled monotherapy group and 2 (0.5%) deaths in the pooled combination therapy group were due to study drug toxicity within 100 days of the last dose. After database lock, a third death occurred in the pooled combination therapy group.

In study CA209067, a total of 8 out 13 and in study CA209069 a total of 3 out 7 deaths classified as "other" reason were pulmonary/respiratory events. In NSCLC nivolumab treatment seems to be associated with an increased pulmonary/respiratory toxicity. The overall incidence of respiratory, thoracic and mediastinic disorders were 50.2% any grade AEs, 8.9% G3-4, 1.3% G5 in the treatment combination group vs 46% any grade AE, 4.8% G3-4, 0.3% G 5 in nivolumab monotherapy vs 41.8% AEs, 3.2% G3-4, 0.3% G5 in the ipilimumab treated arm. Cough, dysnea, followed by oropharingeal pain, were the most frequently reported, with a similar incidence among treated arms, followed by pneumonitis (6.7%) and pulmonary embolism (AEs, G 3-4 AEs, G5 AEs were 4.5%, 3.2%, 0.6% in the treatment combination arm). Most pneumonitis cases resolved with appropriate immunosuppressant therapy. By contrary, 3 cases of pulmonary embolism led to death. 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. The overall incidence of AEs, G3-4 AE, G5 AEs cardiac disorders were 12.5%, 2.6%, 0%, respectively, in the treatment combination arm, which is in line with that reported in the ipilimumab treated arm and higher than that of nivolumab monotherapy. 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.

Uncertainty in the knowledge about the unfavourable effects

The main uncertainties have been described previously in the initial marketing authorisation and have been included in the RMP.

The incidence of hyperglycaemia, hypokalemia, hyponatraemia and dehydratation was notably higher in combination therapy. There was no data on the time to onset of hypokalemia, hyponatraemia and dehydratation. The need to monitor clinical signs and symptoms of endocrinopathies and for hyperglycaemia has been included inthe SmPC section 4.4.Section 4.2 of the SmPC has been updated for treatment modifications for nivolumab in combination with ipilimumab for immune-related colitis and endocrinopathies as well as for other adverse reactions.

Rare events of demyelination event, Guillain-Barré Syndrome, pancreatitis, uveitis were identified and have been adequately reflected in the SmPC (SmPC Section 4.4). However, data is lacking concerning their probable cause. Across clinical trials of nivolumab in combination with ipilimumab, the following additional clinically significant, immune-related adverse reactions were reported in less than 1% of patients: gastritis, sarcoidosis, and duodenitis.

The overall frequency of hepatic drug-related select AEs was higher in the pooled combination therapy group (29.0%) compared with the pooled monotherapy group (6.9%). The increase liver enzymes, which might result in potential interactions with other concomitantly administered drugs. The combination therapy appears to be associated with an increased risk of developing liver enzyme increased. Immune-related hepatitis is already described as an important identified risk in the RMP (SmPC section 4.4).

Effects Table

Table 50: **Effects Table for Opdivo in combination with ipilimumab**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects (Nov 2015 DBL)						
PFS	Patients alive and free of progression (all randomised patients)	Median (months)	11.50	6.87 (nivo) 2.89 (Ipi)	HR combination vs nivolumab 0.76 HR combination vs ipilimumab 0.42 Medians in the plateau zone for nivo+ipi vs nivo Trend to overlap at the end of the curve (nivo+ipi vs nivo) Lack of OS data Robustness in sensitivity analyses and most subgroups (including BRAF mutated)	
PFS	Patients alive and free of progression (tumour PD-L1 expression >1% considered positive)	Median (months)	12.35	14 (nivo)	Curves overlapping. HR 0.94 (0.69-1.28)	See assessment report
PFS	Patients alive and free of progression (tumour PD-L1 expression <1% considered negative)	Median (months)	11.24	2.83 (nivo)	HR 0.60 (0.43-0.84)	
Unfavourable Effects (Feb 2015 DBL for CA209067)						
AEs	Percentage of Adverse events regardless causality	%	99.8 (pooled combination)	97.6 (pooled monotherapy)	Subjects in the pooled monotherapy group had lower event rates than subjects in the pooled combination therapy group for the majority of AEs.	
AEs grade 3-4	Percentage of Adverse events grade 3-4 regardless causality	%	68,8 (pooled combination)	40.5 (pooled monotherapy)	The most frequently reported drug-related AEs were diarrhea, fatigue, pruritus, rash, nausea, pyrexia, ALT increased, AST increased, and decreased appetite (pooled combination therapy group)	Assessment report
SAEs	Percentage of serious Adverse events regardless causality	%	67.6 (pooled combination)	40.5 (pooled monotherapy)	colitis, diarrhea, malignant neoplasm progression, pyrexia, vomiting, general physical health deterioration, pneumonitis, nausea, and pulmonary embolism (pooled combination group)	
Discontinuation	frequency of AEs leading to discontinuation%		43 (pooled combination)	11.6 (pooled monotherapy)		

Benefit-Risk Balance

Importance of favourable and unfavourable effects
The benefit observed in terms of PFS for the combination of nivolumab and ipilimumab compared to either nivolumab or ipilimumab as monotherapy in the overall population is considered clinically relevant. The benefit observed in terms of PFS with the combination treatment appears durable, as the median DOR was not reached in the pivotal phase 3 CA209067 study as well as in the phase 2 study CA209069. The shape of the PFS K-M curves indicates a potential long term benefit for a proportion of patients of around 30%. Confirmation of the benefit in terms of OS is awaited, however, there is no evidence to suggest that there will be a detrimental effect on the OS in the long term.

The safety of the combination is consistent with what has been observed in the monotherapy treatments. 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. Therefore, 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).

Benefit-risk balance
The CHMP considers that the benefits of nivolumab in combination with ipilimumab in terms of PFS in patients with metastatic melanoma outweigh the risks. Therefore, the CHMP considers that the benefit-risk balance is positive.

Discussion on the Benefit-Risk Balance

An important consideration has been the prognostic and predictive value of PD-L1 on treatment effect of the combination treatment. In general, the PFS results were consistent between subgroups (demographics and baseline characteristics), except for the analysis and correlative expression of PD-L1 in tumours with PFS. Patients whose tumours were designated as PDL-1 negative (<1%) had a significant difference in PFS compared to PDL-1 positive patients as observed between the combination therapy and the nivolumab monotherapy group. This uncertainty has been reflected in the indication and in the SmPC where the indication is for combination with ipilimumab in the treatment of advanced (unresectable or metastatic) melanoma in adults, however, a statement has been added to highlight that relative to nivolumab monotherapy, an increase in progression-free survival 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 CHMP recommended that the benefits of the combination treatment would need to be balanced against the potential increase in toxicity on a case by case basis in clinical practice, with a careful evaluation of the patient's demographics (e.g., age and performance status) and disease characteristics (e.g., M stage, LDH level, and BRAF mutation status).

The CHMP considers the following measures necessary to address issues related to efficacy:

- Post-authorisation efficacy study (PAES): The MAH should submit the final Study report for study CA209067: a Randomized, Double-Blind Study in Subjects Treated With nivolumab Monotherapy, ipilimumab Monotherapy, And nivolumab combined With Ipilimumab. The final clinical study report should be submitted by 31st March 2017.

- The value of biomarkers to predict the efficacy of nivolumab *and/or nivolumab + ipilimumab combination therapy* should be further explored, specifically: To further investigate the value of

biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., _other 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 monotherapy: studies CA209038 and CA209066,

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

- NSCLC: studies CA209017, CA209057 and CA209026

- RCC: studies CA209025 and CA209009

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

  Results should be submitted by 31stMarch 2019.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 29 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include treatment in combination with ipilimumab of advanced (unresectable or metastatic) melanoma in adults based on interim data from study CA209067 and the final CSR of study CA209069. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II and Package Leaflet, and to provide a paediatric non-clinical biomarker study as part of the application to fulfil paediatric requirements. Further, an updated RMP version 4.3 was agreed during the procedure and two efficacy measures were added to Annex II upon request by the CHMP.

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

This recommendation is subject to the following new condition:

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

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

Description	Due date
Post-authorisation efficacy study (PAES): The MAH should submit the final	31 March 2017

| Study report for study CA209067: a Randomized, Double-Blind Study in Subjects Treated With nivolumab Monotherapy, ipilimumab Monotherapy, And nivolumab combined With Ipilimumab. | |

The recommendation is also subject to the following amended condition:

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

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

Description	Due date
The value of biomarkers to predict the efficacy of nivolumab and/or nivolumab + ipilimumab combination therapy should be further explored, specifically:	30 September 2015
1. To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy. These analyses will be conducted in studies CA209037 and CA209066 in patients with advanced melanoma.	
2. 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 monotherapy: studies CA209038 and CA209066	30 September 2017
- Melanoma combination (with ipilimumab): studies CA209038, CA209067 and CA209069	31 March 2019
- NSCLC: studies CA209017, CA209057 and CA209026	31 March 2018
- RCC: studies CA209025 and CA209009	31 March 2018
In addition, levels of myeloid-derived suppressor cells in circulation will be explored in study CA209038.	
3. To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies (CA209009, CA209038 and CA209064).	31 March 2017
4. To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in studies CA209066, CA209057 and CA209025.	30 June 2018
5. To further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in studies CA209009, CA209038 and CA209064.	30 September 2017

APPENDIX 1

DIVERGENT POSITION DATED 1 April 2016

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Opdivo indicated for the following indication:

> 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 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 observed benefit in PFS for the combination therapy in comparison to nivolumab and ipilimumab is considered promising. However, the PFS benefit was only seen in a subset of patients with low PD-L1 receptor expression, whereas a substantial part of the patients (i.e. patients with PD-L1 expression in more than 1% of the tumour cells) had no PFS benefit by combination therapy in comparison to nivolumab monotherapy alone. Selection of the patients who might benefit from combination therapy, is hampered by uncertainties in the validity and usability of available assays to determine PD-L1 expression levels, resulting in a considerable, undefined number of patients being treated unnecessarily.

This should be considered against a substantial increase in toxicity resulting in a low tolerability of the combination treatment by patients with an increase in grade 3-4 AEs of almost 20% (68.8% vs 40.5% for combination therapy and nivolumab monotherapy, respectively) and a discontinuation rate of more than 30% (43% vs 11.6% for combination therapy and nivolumab monotherapy, respectively). In my opinion, only a demonstrated clinical benefit in terms of OS would justify the use of this highly toxic combination of ipilimumab and nivolumab compared to the use nivolumab alone.

In summary, the overall benefit-risk balance for Opdivo in the above claimed indication is considered negative due to:

1) the high toxicity of the combination therapy,

2) the lack of OS data that demonstrates long term benefit of combination therapy above nivolumab monotherapy,

3) the substantial part of the study population who obtained no PFS benefit, without a valid and usable test to identify these patients

Overall, for these reasons, we have a negative opinion recommending the granting of a marketing authorisation for Opdivo in the above claimed indication.

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Pieter de Graeff

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 Romaldas Mačiulaitis