28 June 2018
EMA/665778/2018

Variation assessment report

Invented name: OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0041

Marketing authorisation holder (MAH): Bristol-Myers Squibb Pharma EEIG

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List of abbreviations

ADA	Anti Drug Antibody
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMS	Bristol-Meyers Squibb
cHL	classical Hodgkin Lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated antigen 4
DBL	Data Base Lock
DMFS	Distant Metastasis Free Survival
dMMR	mismatch repair deficient
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicine Agency
EORTC	European Organisation for Research end Treatment Cancer
EQ-5D	EuroQol European Quality of Life-5 Dimensions
ESMO	European Society for Medical Oncology
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
HR	Hazard ratio
HRQoL	Health Related Quality of Life
IEC	Independent Ethics Committee
IFNα	Interferon-α
IHC	Immunohistochemistry
IMAE	Immune-mediated Adverse Event
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
MAH	Marketing Authorisation holder
MAPK	Mitogen-activated protein kinase
MCID	Minimally Clinically Important Difference
MedDRA	Medical Dictionary or Regulatory Activities
MRI	Brain Magnetic Resonance
MSI-H	Microsatellite Instability High
NAb	Neutralizing Antibody

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD-1	Programmed death-1
PDCO	Paediatric Committee
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PEG-IFN	Pegylated Interferon
PI	Product information
PIP	Paediatric Investigation Plan
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-C30	EORTC Quality of Life Questionnaire version 3.0
RCC	Renal cell carcinoma
RFS	Recurrence Free Survival
RMP	Risk Management Plan
RT	Radiation Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Head and Neck Cancer
SmPC	Summary of Product Characteristics
SNLB	Sentinel lymph node biopsy
SNP	Single nucleotide polymorphism
TSH	Thyroid-Stimulating Hormone
UC	Urothelial Carcinoma
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WPAI:GH	Work Productivity and Activity Impairment: General Health

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 6 October 2017 an application for a variation.

The following variation was requested:

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

Extension of Indication to include adjuvant treatment of adults and adolescents 12 years of age and older with completely resected Stage III and IV melanoma for OPDIVO; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from the pivotal Study CA209238. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the PI. The RMP version 12.0 has also been submitted. The MAH also took the opportunity to revise the due dates for two Category 4 studies (CA209172 and CA209171) to a later date.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0064/2014 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

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

Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Start of procedure:	28 October 2017
CHMP Co-Rapporteur Assessment Report	22 December 2017
PRAC Rapporteur Assessment Report	3 January 2018
PRAC members comments	4 January 2018
Updated PRAC Rapporteur Assessment Report	5 January 2018
PRAC Outcome	11 January 2018
CHMP members comments	15 January 2018
Updated CHMP Co-Rapporteur(s) (Joint) Assessment Report	18 January 2018
1st Request for Supplementary Information	25 January 2018
MAH submission	22 February 2018
Restart of procedure:	26 February 2018
CHMP Co-Rapporteur responses Assessment Report	28 March 2018
PRAC Rapporteur responses Assessment Report	28 March 2018
PRAC members comments	4 April 2018
Updated PRAC Rapporteur responses Assessment Report	5 April 2018
PRAC Outcome	12 April 2018
CHMP members comments	16 April 2018
Updated CHMP Co-Rapporteur responses Assessment Report	20 April 20148
2nd Request for Supplementary Information	26 April 2018
MAH submission	29 May 2018
Restart of procedure:	30 May 2018
PRAC Rapporteur responses Assessment Report	5 June 2018
PRAC members comments	6 June 2018
Updated PRAC Rapporteur responses Assessment Report	n/a
CHMP Co-Rapporteur responses Assessment Report	13 June 2018
PRAC Outcome	14 June 2018
SAG experts meeting to address questions raised by the CHMP (Annex 2)	18 June 2018
CHMP members comments	18 June 2018
Updated CHMP Co-Rapporteur responses Assessment Report	21 June 2018
CHMP Opinion	28 June 2018

2. Scientific discussion

2.1. Introduction

Nivolumab (Opdivo, BMS-936558, MDX-1106, ONO-4538) binds to the programmed death-1 (PD-1) T-cell membrane receptor and thereby blocks its interaction with PD ligand 1 (PD-L1) and PD ligand 2 (PD-L2).

Nivolumab is currently approved in the United States, European Union, Japan and several other countries. The approved dose and schedule of nivolumab monotherapy for all approved indications in the EU is 3 mg/kg administered as an intravenous (IV) infusion over 60 minutes every 2 weeks (Q2W).

The approved indications for nivolumab include:

- Advanced (unresectable or metastatic) melanoma in adults, as monotherapy, approved on 19 Jun 2015;
- Locally advanced or metastatic squamous-cell non-small cell lung cancer (NSCLC) after prior chemotherapy in adults, as monotherapy, approved on 20 Jul 2015;
- Locally advanced or metastatic non-squamous NSCLC after prior chemotherapy, as nivolumab monotherapy, approved on 04 Apr 2016;
- Advanced renal cell carcinoma after prior therapy, as nivolumab monotherapy, approved on 04 Apr 2016;
- Advanced (unresectable or metastatic) melanoma with nivolumab in combination with ipilimumab, approved on 11 May 2016;
- Relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin in adults, as monotherapy, approved on 13 Oct 2016;
- Squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy, as monotherapy, approved on 28 April 2017;
- Locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy, as monotherapy, approved on 2 June 2017.

Stage III and Stage IV Resectable Melanoma

The European incidence of malignant Melanoma varies from 3-5/100 000/year in Mediterranean countries to 12-25 /100 000-year in Nordic Countries, and this incidence is still rising[1].

For early-stage melanoma, surgical resection is the standard treatment and is world-wide associated with an excellent long-term survival prognosis for stage I (98%) and stage II (90%). However, patients with stage III disease, who have regional involvement at diagnosis, are at higher risk of recurrence after locoregional resections. Stage IIIA patients (according to AJCC 7th edition) have a primary tumour without ulceration and 1-3 micrometastases in the nodes while Stage IIIB and C have an ulcerating primary tumour and/or macrometastases in the nodes. The risk of recurrence increases with increasing disease stage. The overall 5-year RFS for stage IIIA, IIIB, and IIIC patients has been shown to be approximately 63%, 32%, and 11%[2] . In the US, 5-year survival rates are 78%, 59% and 40% respectively (American Cancer Society). Based on literature, recurrences in stage III melanoma are mostly likely to occur within 3 years[3].

The Stage IV survival rates are around 15-20%. Due to the increase in the use of newly approved drugs (PD-1 inhibitors, CTLA-4 inhibitors and targeted BRAF and/or MEK inhibitors) for systemic treatment of patients with unresectable and stage IV disease, these numbers might be an underestimation. Currently the staging of melanoma is based on the American Joint Committee on

[1] Dummer R, Hauschild A, Lindenblatt N, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5:v126-32.
[2] Romano E, Scordo M, Dusza SW, et al. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol 2010;28:3042-7. 10.1200/JCO.2009.26.2063
[3] Leiter J Am Acad Dermatol 2010; Romano JCO 2012; Meyers Ann Surg Oncol 2009; Tas Melanoma Research 2017

Cancer (AJCC) 8th edition criteria. However, at the time when the pivotal trial CA209238 was recruiting patients, patients were staged using the 7th edition. The main differences in the updated 8th edition are in relation to the N categorization of regional lymph node status and nodal disease terminology. The term micrometastasis has been replaced by "clinically occult disease" as detected by sentinel lymph node biopsy (SLNB). Macrometastasis has been replaced by "clinically detected disease." In-transit or satellite node metastasis or microsatellite metastasis with satellite nodes was formerly listed simply as N3, in the new system there are subcategories for N3 based upon the number of metastatic nodes involved. As a result there are now four pathologic Stage III groups rather than three, and as such the new classifications for stage IIIA, IIIB and IIIC now include different criteria for T (size of the tumours) and N (number of nodes involved) and as a result are not identical as to the same groups that were used for the staging for the entry criteria into the to the same trial CA209238 (Figure 1).

AJCC 7th edition

Pathologic Staging[4]			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N1b	M0
	T1-4a	N2b	M0
	T1-4a	N2c	M0
IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4b	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

AJCC 8th edition

Pathologic Staging[4]			
0	Tis	N0	M0
IA	T1a	N0	M0
	T1b	..	..
IB	T2a	..	..
IIA	T2b	M0	M0
	T2a	..	..
IIB	T3b	..	..
	T4a	..	..
IIC	T4b	..	..
IIIA	T1-2a	N1a	M0
	T1-2a	N2a	..
IIIB	T0	N1b-c	M0
	T1-2a	N1b-c	..
	T1-2a	N2b	..
	T2b-3a	N1a-2b	..
IIIC	T0	N2b-c	M0
	T0	N3b-c	..
	T1a-3a	N2c-3c	..
	T3b-4a	Any N	..
	T4b	N1a-2c	..
IIID	T4b	N3a-c	M0
IV	Any T	Any N	M1

Figure 1: Pathological staging of melanoma according to the AJCC 7th and 8th edition

The schematics below outline the changes in the criteria that result in re-staging of patients per the 8th edition.

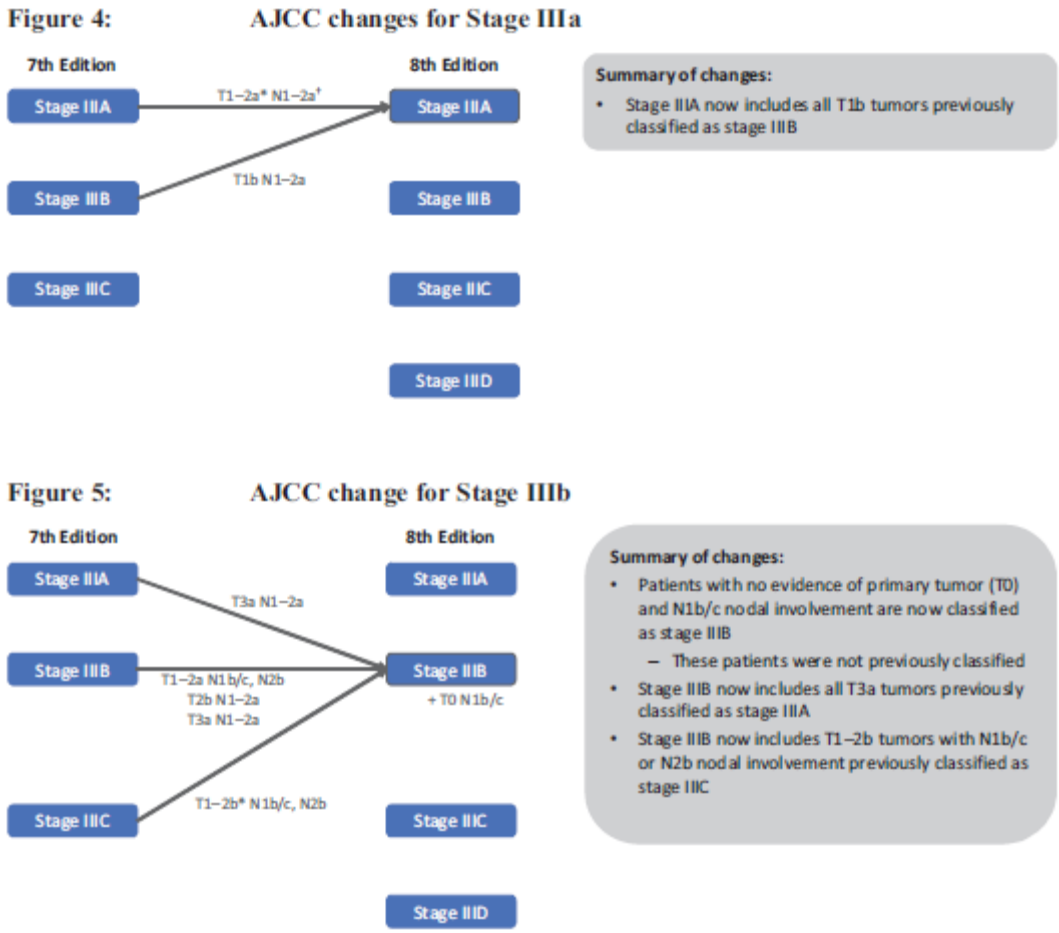


Figure 2: Comparison between the AJCC 7th and 8th edition for melanoma Stage III

Adjuvant Treatments for Stage III and Stage IV Resectable Melanoma

To reduce the risk of relapse, Stage III and IV patients are candidates for adjuvant treatment after complete surgical treatment which has removed all detectable disease. Currently, there are limited adjuvant treatment options for Stage III and Stage IV resectable melanoma. Standard treatment described in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines include interferon-α, pegylated interferon therapy and ipilimumab. Although ipilimumab is recommended as adjuvant treatment in the ESMO guideline, ipilimumab is not approved for adjuvant treatment of melanoma in the EU. The standard of care after complete surgical resection differs per EU country. Observation of the lesions and low dose interferon are both used as standard of care in the EU[4].

Interferon-α

High-dose interferon-α (IFNα) is approved in the US and in the EU as adjuvant therapy in patients who are free of disease after surgery but are at high risk of systemic recurrence, e.g., patients with primary or recurrent (clinical or pathological) lymph node involvement. A recent meta-analysis involving fifteen trials showed that EFS was significantly improved with IFN-α (hazard ratio [HR] = 0.86, CI 0.81-0.91; P < 0.00001), as was OS (HR = 0.90, CI 0.85-0.97; P = 0.003). The absolute differences in EFS at 5 and 10 years were 3.5% and 2.7%, and for OS were 3.0% and 2.8% respectively in favour

[4] Svedman FC, Pillas D, Taylor A, Kaur M, Linder R, Hansson J. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe – a systematic review of the literature. Clinical Epidemiology. 2016;8:109-122

of IFN-α with specifically patients with ulcerated tumours obtaining benefit from IFN-α [5]. However, the size of interferon benefit in terms of disease-free survival and OS is relatively small given the toxicities observed, including acute constitutional symptoms, chronic fatigue, myelosuppression, and neurologic and psychologic effects.

Pegylated Interferon

Pegylated IFNα was developed to decrease the frequency with which IFNα is administered while maintaining high exposure levels. The efficacy is similar to high dose IFNα, but a higher percentage of patients receiving PEG-IFN discontinued treatment due to toxicity.

Ipilimumab

Ipilimumab, a fully human, IgG1 monoclonal antibody that blocks CTLA-4, is approved for the treatment of metastatic melanoma in the EU. However, ipilimumab is not approved for the adjuvant treatment of melanoma. It is approved in the US for this indication based on a clinical trial EORTC 18071 (CA184029) that showed positive efficacy OS data based on the 10 mg/kg schedule in patients with Stage III disease. In the placebo controlled trial with stage III melanoma patients (IIIA 20%, IIIB 44% and IIIC 36%) the RFS was significantly better with ipilimumab compared with placebo (five-year RFS 40.8 versus 30.3 percent, HR 0.76, 95% CI 0.64-0.89) and the median RFS for ipilimumab was 27.6 months (95% CI 19.3-37.2) versus 17.1 months (95% CI 13.6-216) placebo[6,7]. Also, DMFS was significantly better with ipilimumab compared with placebo (five-year DMFS 48.3 versus 38.9 percent, HR 0.76, 95% CI 0.64-0.92) as well as overall survival (five-year overall survival 65.4 versus 54.4 percent, HR 0.72, 95% CI 0.58-0.88, p = 0.001). This benefit was seen despite the use of various systemic therapies in patients who subsequently developed recurrent disease.

The dose of ipilimumab used in the adjuvant EORTC 18071 trial was 10 mg/kg, which is different than the dose approved to treat metastatic melanoma (3 mg/kg). There is evidence that 10 mg/kg is associated with increased toxicity.[8] Toxicity associated with adjuvant ipilimumab was significant. Adverse events of any grade were observed in 98.7% of patients treated with ipilimumab, including 54.1% with grade 3 or 4 adverse events (compared to 91.1% and 26.2% for placebo respectively). The most common Grade 3-4 immune-related adverse events (irAEs) in the ipilimumab arm (and placebo arm) were gastrointestinal (16.1% vs 0.8%), hepatic (10.8% vs 0.2%), and endocrine (7.9% vs 0.2%). 53.3% of subjects discontinued treatment with ipilimumab due to AEs (51.0% due to drug-related AEs). The overall types of events were consistent with those observed in advanced melanoma. However, the rate of adverse events with ipilimumab in the context of adjuvant therapy is higher than that observed with the same dose in a pooled analysis involving patients with advanced melanoma[9, 10, 11]. Treatment-related deaths in patients treated with ipilimumab were due to colitis, myocarditis, and multi-organ failure associated with Guillain-Barré syndrome. Quality of life was assessed using the EORTC Quality of Life Questionnaire version 3.0 (QLQ-C30). There was a statistically significant decrease in global health status both during and after induction therapy, but the

[5] Ives NJ, Suciu S, Eggermont AMM, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis. Eur J Cancer. 2017 Sep;82:171-183
[6] Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015; 16:522
[7] Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med 2016; 375:1845
[8] Tarhini AA, Lee SJ, Hodi FS, et al. A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma (U.S. Intergroup E1609): Preliminary safety and efficacy of the ipilimumab arms (abstract 9500). 2017 American Society of Clinical Oncology annual meeting.
[9] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711-23
[10] Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517-26
[11] Wolchek JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010; 11: 155-64

difference did not exceed the clinically relevant threshold of 10 points (difference in means of approximately -4 when comparing ipilimumab to placebo)[12].

Adjuvant treatments under investigation

Low-dose (3mg/kg) Ipilimumab

A phase III trial in the adjuvant setting compared ipilimumab at two different doses (the 10 mg/kg dose or 3 mg/kg dose) with high-dose IFN (E-1609, NCT01274338). An unplanned exploratory analysis based on a 3.1 year follow-up of 773 concurrently randomized patients showed that toxicity was lower with the 3 mg/kg schedule compared with the 10 mg/kg schedule (all grade 3-4 adverse events 36.6% versus 56.5% and grade 3-4 immune-related adverse events 18.8% versus 34.0%). Moreover, there was no difference in the three-year RFS (42.3 and 42.6 percent, respectively, HR 1.0), but longer follow-up is required.

Dabrafenib plus trametinib (BRAF V600 mutation only): In a phase III trial, 870 patients with completely resected BRAF V600 mutation-positive stage III melanoma were randomly assigned to the combination of dabrafenib (150 mg twice a day) plus trametinib (2 mg once a day) or to matching placebos for 12 months[13] . The median follow-up was 2.8 years, with a minimum 2.5 years. Relapse-free survival, the primary endpoint of the trial, was significantly longer with dabrafenib plus trametinib compared with placebo (three-year rate 58% versus 39%, HR 0.47, 95% CI 0.39-0.58). At the time of analysis, median RFS had not yet been reached in the combination-therapy group (95% CI, 44.5 months to not reached) and was 16.6 months (95% Ci, 12.7 to 22.1) in the placebo group. Overall survival, while not statistically significant, was prolonged with the targeted therapy (three-year rate 86% versus 77%, HR 0.57, 95% CI 0.42-0.79). The safety profile of the combination therapy was consistent with that observed in patients with metastatic melanoma.

Vemurafenib (BRAF V600E mutation only): BRIM8 was a randomised, double-blind, placebo-controlled, 2-cohort study that placed 498 adult patients with fully resected stage IIC, IIIA, or IIIB melanoma into cohort 1 and patients with stage IIIC melanoma to cohort 2. Both cohorts were randomly assigned to vemurafenib at 960 mg twice daily or placebo for 52 weeks[14] . In cohort 2 no significant improvements in DFS and Distant metastasis-free survival (DMFS) were detected. In contrast, in cohort 1, substantial improvement in DFS was seen when comparing adjuvant vemurafenib (28.7% events) versus placebo (45.9% events). The median time to event was 'not estimated' for vemurafenib versus 36.9 months for placebo (HR 0.54; 95% CI 0.37, 0.78 (p = 0.0010)). Overall, the safety profile of adjuvant vemurafenib was consistent with previous data and no new safety signals were observed.

Pembrolizumab: A phase III trial comparing pembrolizumab with placebo has completed accrual for patients with high-risk stage III melanoma following complete resection (NCT02362594). At a median follow-up of 15 months, pembrolizumab showed a RFS benefit over placebo (1-year rate of recurrence-free survival, 75.4% [95% confidence interval {CI}, 71.3 to 78.9] vs. 61.0% [95% CI, 56.5 to 65.1]; hazard ratio for recurrence or death, 0.57; 98.4% CI, 0.43 to 0.74; P<0.001)[15].

In addition, a phase III cooperative group trial (NCT02506153, Southwest Oncology Group S1404) comparing pembrolizumab with high-dose interferon or high-dose ipilimumab is ongoing in patients with high-risk stage III or IVA disease following complete resection.

[12] Coens C, Suciu S, Chiarion-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol 2017; 18:393

[13] Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med 2017; 377:1813

[14] Lewis K, Maio M, Demidov L, et al. BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients with completely resected, BRAF V600+ melanoma at high risk for recurrence (abstract LBA7). Presented at the 2017 European Society of Medical Oncology meeting.

[15] Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018; 378:1789

About the application:

The current submission concerns the extension of the indication for nivolumab monotherapy for the adjuvant treatment of adult and adolescent patients 12 years of age and older with completely resected Stage III and IV melanoma. The recommended dose and schedule of nivolumab monotherapy is the same as that approved for melanoma, NSCLC, and renal cell carcinoma monotherapy: 3 mg/kg IV infusion over 60 minutes Q2W. Treatment duration is until disease recurrence or unacceptable toxicity for up to 1 year.

The MAH applied for the following indication:

“OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with completely resected Stage III and IV melanoma.”

The final agreed indication is as follows:

“OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1).”

The recommended dose of OPDIVO is 3 mg/kg nivolumab administered intravenously over 60 minutes every 2 weeks.

For adjuvant therapy, the maximum treatment duration with OPDIVO is 12 months.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

The applicant has provided a justification for not performing an environmental risk assessment. As nivolumab is a protein composed of natural amino acids, proteins are expected to biodegrade in the environment and not pose a significant risk. Therefore, nivolumab is exempt from preparation of an Environmental Risk Assessment as per the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” (EMEA/CHMP/SWP/4447/00).

2.2.2. Discussion on non-clinical aspects

Nivolumab and the product excipients do not pose a significant risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The lack of non-clinical data is acceptable as the indication relates to the same disease as the approved indication. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of nivolumab. Considering the above data, nivolumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical study

Study #/Type	Study Objective	Study Design	Treatment Cohorts	# of Treated Subjects	Study Population
NIVOLUMAB MONOTHERAPY					
CA209238 Efficacy, Safety	To compare the efficacy, as measured by recurrence free survival (RFS), provided by nivolumab versus ipilimumab	Phase 3, randomized (1:1), double-blind study of nivo vs ipi	Active dosing regimens: Nivo group: nivo 3 mg/kg IV Q2W Ipi group: ipi 10 mg/kg Q3W for 4 doses then Q12W starting at Wk 24	N=905 Treated (452 nivo and 453 ipi)	Completely resected Stage IIIb/c or Stage IV melanoma in adults and adolescents ≥15 years of age

2.3.2. Pharmacokinetics

The nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics, drug-drug interaction potential, QT prolongation potential, and dose selection for phase 2/3 studies has been well characterized previously in the initial marketing authorization dossier.

The basis of this submission is the phase 3 study CA209238, in which nivolumab 3 mg/kg as adjuvant therapy was compared with ipilimumab 10 mg/kg with the primary endpoint of RFS in subjects with completely resected Stage IIIb/c or Stage IV melanoma. An updated popPK analysis and immunogenicity results from study CA209238 is presented.

-Pharmacokinetics – popPK analysis

The popPK analysis included in this submission focused on the evaluation of adjuvant treatment of melanoma versus treatment of advanced melanoma. The popPK analysis performed to support this submission characterized the PK of nivolumab in 1773 subjects with solid tumours, including advanced melanoma (N=565) and in the setting of adjuvant treatment of melanoma (N=448). Data from the following studies were included in the current popPK analysis (MDX1106-01, MDX1106-03, ONO4538-01 (multiple tumour types), CA209017, CA209057, CA209063 (NSCLC), ONO-4538-02, CA209037, CA209066 (advanced melanoma), and CA209238 (adjuvant treatment of melanoma). Sparse data sampling was conducted in study CA209238 (adjuvant treatment of melanoma): week 1 day1 and week 7 day 1 pre-dose and end-of-infusion, week 13, 23, and 35 pre-dose.

The PK of nivolumab in subjects with solid tumours and cHL was previously characterized by a popPK analysis where nivolumab PK was described initially by a stationary model, in which nivolumab CL was constant with respect to time, and then by a time-varying CL model.

The Final Model was a two-compartment, zero-order IV infusion with stationary CL for the setting of adjuvant treatment of melanoma and time-varying CL (sigmoidal-Emax function) for advanced melanoma, NCSLC 2L+ and the other tumour types. The model included a proportional residual error model, with random effect on CL, VC, VP and Emax and correlation of random effect between CL and VC. The final model also contained baseline BWT, eGFR, PS, sex, race and tumour type on CL and baseline BWT and sex on VC. Baseline covariates were incorporated into the final model using functional relationships.

The geometric mean baseline CL for advanced melanoma was 10.6 mL/h (after the first dose) and reached a steady-state value of 7.94 mL/h (Table 2). Table 1 shows that the geometric mean CL for in the setting of adjuvant treatment of melanoma was constant at 6 mL/h. The percent difference in CL at baseline between adjuvant treatment of melanoma and advanced melanoma was approximately 40%, and over time the percent difference decreased to approximately 20% at steady state.

Table 1: **Summary Statistics of Individual PK Parameters for Subjects with adjuvant treatment for melanoma (n=448, popPK analysis)**

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Baseline Clearance (mL/h)	6.24(1.83)	6.00(29.3)	5.91(1.62,17)
Steady State Clearance (mL/h)[a]	6.24(1.83)	6.00(29.3)	5.91(1.62,17)
Volume of the Central Cmt (L)	3.62(1.12)	3.39(30.9)	3.64(0.108,6.9))
Volume of the Peripheral Cmt (L)	2.98(0.893)	2.85 (29.9)	2.90(0.837,7.91)
Volume of Distribution (L)[b]	6.60(1.56)	6.42(23.6)	6.47(2.49,12.3)
Alpha Half-life (hr)	36.2(9.43)	34.7(26.1)	36.0(2.14,68.8)
Beta Half-life (day)	33.6(10.9)	32.4(32.6)	33.0(10.9,170)

[a] steady state clearance is the same as baseline clearance for adjuvant melanoma

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

Table 2: **Summary Statistics of Individual PK Parameters for Advanced Melanoma Subjects (n=565, popPK analysis)**

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Baseline Clearance (mL/h)	11.4(4.66)	10.6(40.9)	10.6(3.04,36.8)
Steady State Clearance (mL/h)	8.82(5.63)	7.94(63.8)	7.83(0.862,99)
Volume of the Central Cmt (L)	3.98(1.17)	3.79(29.5)	3.87(0.448,8.49))
Volume of the Peripheral Cmt (L)	2.91(1.21)	2.78 (41.6)	2.78(1.06,21.8)
Volume of Distribution (L)[a]	6.89(1.75)	6.70(25.4)	6.63(3.47,25.5)
Alpha Half-life (hr)	36.9(7.98)	36.0(21.6)	36.5(8.23,70)
Beta Half-life (day)	27.9(16.5)	25.8(59.1)	25.9(3.37,252)

[a] Volume of Distribution (L) at steady-state = Volume of the Central Cmt (L) + Volume of the Peripheral Cmt (L)
Analysis Directory: /global/pkms/data/CA/209/238/prd/ppk/final

Table 3 shows that subjects with adjuvant treatment of melanoma had a range of 13% to 45% higher predicted dose-normalized exposures relative to the advanced melanoma subjects across exposure measures (after the first dose and at steady state).

Table 3: **Summary Statistics of Individual Measures of Dose Normalized Nivolumab Exposure for Subjects with Adjuvant Melanoma and Advanced Melanoma treatment Q2W (popPK analysis)**

Parameter	Adjuvant Melanoma (N=448)	Advanced Melanoma (n=530)	
	Geometric Mean (%CV)	Geometric Mean (%CV)	% Diff[a] (%)
Dose-Normalized C_{min1} [(µg/mL)/(mg/kg)]	8.24(19.7)	5.87(27.0)	40.4
Dose-Normalized C_{max1} [(µg/mL)/(mg/kg)]	22.4(135)	19.7(50.4)	13.7
Dose-Normalized C_{avg1} [(µg/mL)/(mg/kg)]	11.5(20.5)	9.31(22.4)	23.5
Dose-Normalized C_{minss} [(µg/mL)/(mg/kg)]	31.9(30.3)	22(64.3)	45.0
Dose-Normalized C_{maxss} [(µg/mL)/(mg/kg)]	55.5(62.3)	42.9(44.6)	29.4
Dose-Normalized C_{avgss} [(µg/mL)/(mg/kg)]	39.2(26.4)	28.8(52.6)	36.1

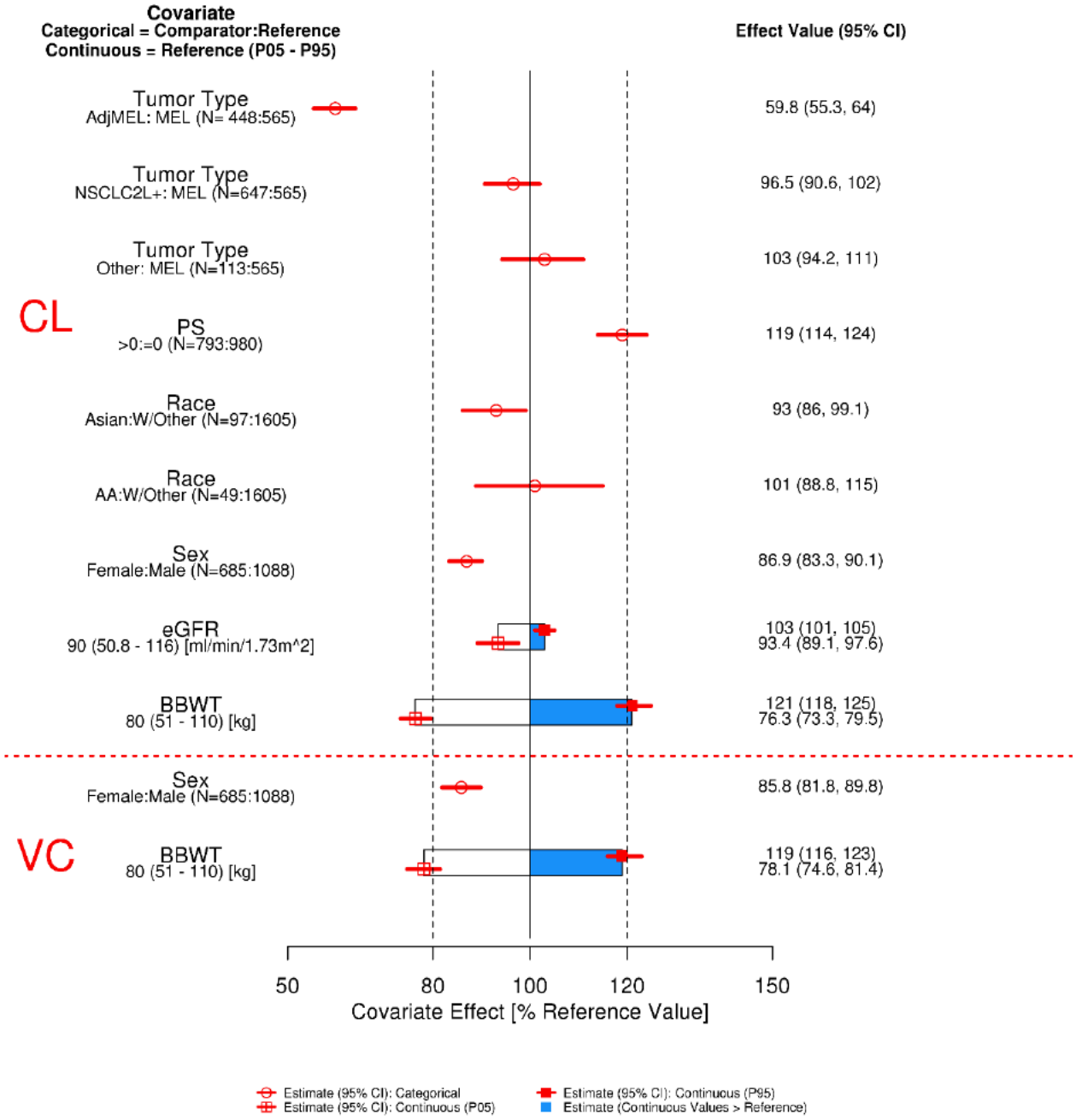
[a] Calculated as $(Geo.Mean_{AdjMEL} - Geo.Mean_{MEL})/Geo.Mean_{MEL}*100$

Analysis Directory: /global/pkms/data/CA/209/238/prd/ppk/final

Program Source: Analysis Directory/R/scripts/exposure-summary.r

Source: Analysis Directory/R/export/AdjMEL_MEL_ExposureSummary_FinalTable.csv

In addition to including tumour type in the popPK model, the model also included effects of baseline body weight, baseline eGFR, performance status, sex, and race on CL; and baseline body weight and sex on VC. These covariates were from the previously established popPK model, and were included in this analysis to describe nivolumab concentration-time data in subjects upon adjuvant treatment of melanoma.



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

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

Note 3: Reference subject is white/others male age=65 yr, PS=0, eGFR=90 ml/min/1.73m^2 and body weight=80kg, subject with normal hepatic function with advanced melanoma. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value. AA under race indicates African American.

Confidence Interval values are taken from bootstrap calculations (500 successful out of a total of 500)

Analysis -Directory: /global/pkms/data/CA/209/238/prd/ppk/final/

R-Program Source: Analysis-Directory/R/scripts/ cov-eff-plot-FinalModel.r'

Source: Analysis-Directory/R/plots/a-model3-cov-eff-plot.png

Figure 3: Covariate Effects on popPK Model Parameters adjuvant treatment of melanoma (Final Model)

2.3.3. Immunogenicity

The incidence of immunogenicity was 2.3% (10/426 subjects) following nivolumab monotherapy. Three subjects (0.7%) were persistent positive in the nivolumab group. No subjects were neutralizing ADA (NAb) positive following nivolumab administration.

In an analysis of selected AEs (hypersensitivity/infusion reaction), nivolumab ADA occurrence did not seem to have an impact on safety: of the 13 subjects with a selected adverse event of hypersensitivity/infusion reaction, only 1/10 nivolumab ADA positive subjects and 12/416 nivolumab ADA negative subjects in the nivolumab group experienced AEs in the hypersensitivity/infusion reaction category.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetic data were collected in Study CA209238. Based on popPK analysis, clearance (CL) of nivolumab was lower in subjects with adjuvant treatment of melanoma (6 ml/h) compared to advanced melanoma subjects (10.6 ml/h) and this did not vary over time. Hence, nivolumab exposure (Cave) at steady-state was approximately 40% higher in subjects with adjuvant treatment of melanoma compared to advanced melanoma. The lower and constant CL for subjects with adjuvant treatment of melanoma is consistent with the previous hypothesis that nivolumab CL is related to disease state. Patients suitable for adjuvant treatment are relatively healthier than advanced melanoma subjects as the first population is considered disease-free prior to randomization for treatment. In advanced melanoma, a decrease in nivolumab CL following treatment was mostly observed in patients with a CR and PR, hence in patients in which disease burden decreases. In CA209238, the performance status of the subjects at baseline was 0 for 91% of the subjects as compared to 64% in advanced melanoma subjects. Therefore, the stationary CL in resected melanoma fits previous observations. Similar to prior analyses, nivolumab CL increased with an increase in baseline body weight and baseline eGFR; and was higher in subjects with PS>0, and in males. Sex, race, and renal function were not clinically relevant predictors of nivolumab clearance (< 20% effect).

The absence of exposure response analysis for efficacy and safety in subjects in the adjuvant treatment setting of melanoma has been sufficiently justified. Previous exposure-response relationships had shown that Cavg,ss was not a significant predictor of death after accounting for nivolumab CL. As in clinical pharmacology studies in the adjuvant treatment setting of melanoma only one nivolumab dose was administered, relationships with Cavg,ss are confounded by nivolumab CL. Nivolumab 3 mg/kg Q2W has been shown to be safe and well tolerated in several other tumour types and previous analyses in advanced melanoma, NSCLC, and RCC patients have shown that AE-DC/D does not increase with Cavg,ss following nivolumab doses of 1 to 10 mg/kg Q2W. The safety profile seems acceptable even though nivolumab exposure was approximately 40% higher in resected melanoma subjects with adjuvant treatment compared to advanced melanoma (see clinical safety).

Incidence of immunogenicity was low (2.3%) in subjects following melanoma resection and adjuvant nivolumab treatment compared to approximately 11% ADA incidence in other tumour types. Subjects with nivolumab ADA continued treatment with clinical benefit from therapy, and there was no trend for presence of ADA to be associated with a reduction in efficacy.

2.3.5. Conclusions on clinical pharmacology

The pharmacokinetic aspects of nivolumab 3 mg/kg every 2 weeks for the adjuvant treatment of melanoma are considered to have been sufficiently well characterised. Nivolumab exposure was approximately 40% higher in patients with adjuvant melanoma compared to advanced melanoma. With available safety data, this higher nivolumab exposure was not clinically meaningful.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The dose and schedule of nivolumab monotherapy (3 mg/kg Q2W) was based upon the analyses of safety, efficacy, and exposure-response data from 306 subjects treated with nivolumab Q2W in the Phase 1 dose-ranging study CA209003.

The ipilimumab dose regimen of 10 mg/kg Q3W x 4 doses evaluated in this study was chosen based upon an analysis of data from 475 subjects randomized (471 treated) with ipilimumab 10 mg/kg Q3W in the Phase 3 study EORTC 18071 (CA184029), which showed an recurrence free survival (RFS) advantage of ipilimumab over placebo. After the initial four doses (induction) of ipilimumab, additional therapy (maintenance) was added based on the theoretical principles of continued re-stimulation of the immune system, consistent with previous studies of immunotherapy in the adjuvant treatment setting of melanoma. However, in study CA209238 the dosing duration was capped at 1 year due to the fact very few subjects received ipilimumab beyond 1 year in the EORTC 18071 study.

2.4.2. Main study

Title: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence.

Methods

Study participants

Key Inclusion criteria

- At least 15 years of age

  Except: where local regulations and/or institutional policies do not allow for subjects < 18 years of age (paediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age.

- All subjects must be either Stage IIIb/c or Stage IV AJCC (7th edition) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. Subjects must have been surgically rendered free of disease with negative margins on resected specimens.
  - If Stage III melanoma (whether Stage IIIb or IIIc) the subjects usually have clinically detectable lymph nodes that are confirmed as malignant on the pathology report and/or ulcerated primary lesions. Subjects who are “N2c” classification with 2-3 metastatic nodes and in transit metastases/satellites without metastatic nodes, or, “N3”classification with any “T” and 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes are eligible. Clinically detectable lymph nodes are defined as:

    (1) a palpable node (confirmed as malignant by pathology)

    (2) a non-palpable but enlarged lymph node by CT scan (at least 15 mm in short axis) and confirmed as malignant by pathology

    (3) a PET scan positive lymph node of any size confirmed by pathology

    (4) evidence of pathologically macrometastatic disease in one or more lymph nodes defined by one or more foci of melanoma at least 1cm in diameter.

  - If Stage IV melanoma, the pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization.

- For CNS lesion(s), documentation provided by a neurosurgeon, indicating that there has been complete resections of CNS lesion(s) suffice as confirmation of negative margins.

- Complete resection of Stage III disease that is documented on the surgical and pathology reports or complete resection of Stage IV disease with margins negative for disease that is documented on the pathology report.
- Complete resection must be performed within 12 weeks prior to randomization
- All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include a CT scan of the neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c or Stage IV disease, and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
- Tumour tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression classification (positive, negative/or indeterminate) as determined by a central lab.
- ECOG performance score of 0 and 1.

Key Exclusion Criteria:

- History of ocular/uveal melanoma.
- Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enrol.
- Subjects with previous non-melanoma malignancies are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include but are not limited to, non-melanoma skin cancers; in situ bladder cancer, in situ gastric cancer, in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ)
- Subjects with a condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
- Prior therapy for melanoma except surgery for the melanoma lesion(s) and/or except for adjuvant radiation therapy (RT) after neurosurgical resection for central nervous system (CNS) lesions and except for prior adjuvant interferon. Specifically subjects who received prior therapy with interferon, anti- PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) are not eligible.

    i) Prior treatment with adjuvant interferon is allowed if completed ≥ 6 months prior to randomization.

Treatments

In subjects randomized to the nivolumab group, nivolumab 3 mg/kg was administered as a 60-minute intravenous (IV) infusion every 2 weeks (Q2W). In subjects randomized to the ipilimumab group, ipilimumab 10 mg/kg was administered as a 90-minute IV infusion every 3 weeks (Q3W) x 4 doses, then 10 mg/kg IV Q 12 weeks starting at Week 24.

First dose must be administered within 3 business days following randomization. When study drugs (ipilimumab or nivolumab) or matched placebos are to be administered on the same day, separate

infusion bags and filters must be used for each infusion. Nivolumab or nivolumab-placebo is to be administered first.

The second infusion will always be the ipilimumab or ipilimumab-placebo study drug, and will start no sooner than 30 minutes after completion of the nivolumab or nivolumab-placebo infusion.

Subjects may be dosed up to ± 3 days before or after the scheduled date if necessary. There should be a minimum of 12 days between 2 nivolumab/nivolumab-placebo administrations. For dosing visits of Week 24, Week 36 and Week 48, subjects may be dosed up to ± 7 days.

Dose reductions and dose delays were not permitted for nivolumab and ipilimumab. Doses of nivolumab and ipilimumab were to be omitted (instead of delayed) based on specific criteria, such as any Grade 2 non-skin drug related adverse events, any grade 3 skin, drug-related event, any grade 3 drug-related laboratory abnormality or any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants omitting the dose of study medication. If the criteria to resume treatment are met within the dosing window (Day 1, Week X ± 3 days, Week 24, Week 36 and Week 48 ± 7 days), then the dose may be given.

Subjects must discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Recurrence (local, regional or distant)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by the MAH
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)

All subjects who discontinue study drug should comply with protocol specified follow-up procedure. If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented.

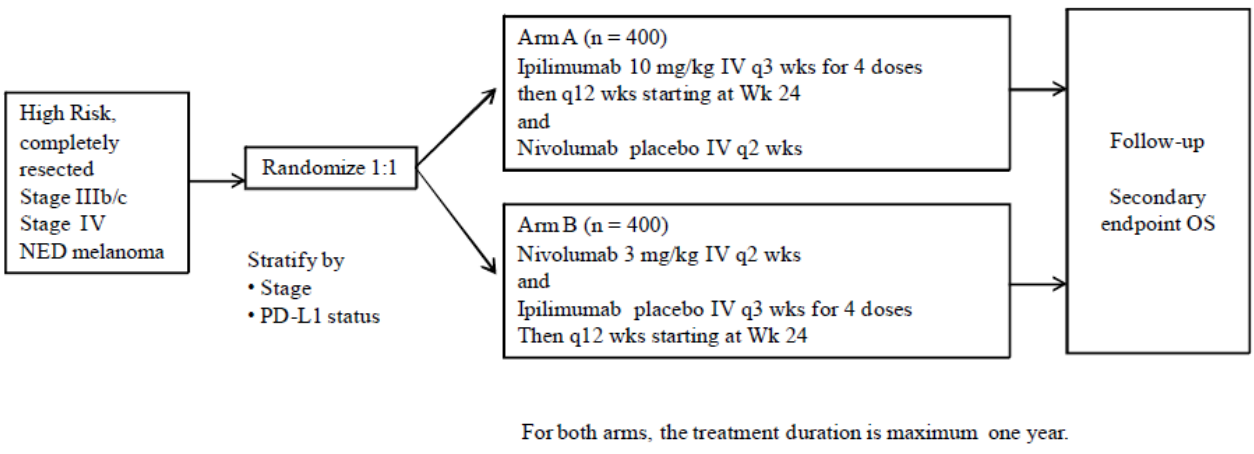


Figure 4: Study Design Schematic

Objectives

Primary Objective

To compare the efficacy, as measured by RFS, provided by nivolumab versus ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV melanoma.

Secondary Objectives

- To compare the OS of nivolumab vs ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV melanoma.
- To assess the overall safety and tolerability of nivolumab and ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV melanoma.
- To evaluate whether PD-L1 expression is a predictive biomarker for RFS.
- To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - 30-item core (QLQ-C30).

Exploratory objectives

- To evaluate distant metastasis-free survival (DMFS) in subjects who are Stage IIIb/c at study entry.
- To evaluate associations between BRAF mutation status and clinical efficacy.
- To explore potential biomarkers associated with clinical efficacy (RFS, DMFS and OS) and/or incidence of adverse events (AEs) of nivolumab by serum, plasma, tumor tissue and peripheral blood mononuclear cells [PBMCs]) in comparison to clinical outcomes.
- To assess the effect of natural genetic variation (single nucleotide polymorphisms [SNPs]) in select genes including, but not limited to, programmed death receptor-1 (PD-1), PD-L1, programmed cell death ligand 2 (PD-L2) and cytotoxic T lymphocyte associated antigen-4 (CTLA4) on clinical endpoints and/or the incidence of AEs.
- To characterize the pharmacokinetics and explore exposure-response relationships (if appropriate) with respect to safety and efficacy.
- To characterize the immunogenicity of nivolumab and ipilimumab.
- To assess changes in health status and work and activity impairment in treatment groups using the EuroQol European Quality of Life-5 Dimensions (EQ-5D) and the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire, respectively.

Outcomes / endpoints

Primary Endpoint

Recurrence Free Survival (RFS): RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first. Subjects will be assessed for recurrence (until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects) by CT or MRI as follows:

1. Screening
2. Treatment Period: Every 12 weeks (± 7 days) from first dose of study drug through 12 months (relative to the first dose of study drug)
3. Follow-up Period:

a) Every 12 weeks (± 7 days) through 12 months for subjects who discontinued early from treatment (relative to the first dose of study drug)

b) Every 12 weeks (± 14 days) if > 12 months through 24 months (relative to the first dose of study drug)

c) Every 6 months (± 4 weeks) if > 24 months through and up to Year 5 (relative to the first dose of study drug)

Secondary Endpoints

- *AEs, SAEs, deaths, laboratory abnormalities:* Safety and tolerability were measured by the incidence of AEs, serious adverse events (SAEs), deaths, and laboratory abnormalities. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. AEs and laboratory values were graded for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- *RFS endpoint by PD-L1:* The PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay co-developed by BMS and DAKO North America (Carpinteria, CA US) using a rabbit anti-human PD-L1 antibody (clone 28-8; Epitomics Inc, Burlingame, CA US) was used to assess PD-L1 expression in tumour samples. PD-L1 expression missing: no available tumour biopsy specimen for PD-L1 evaluation. PD-L1 expression: the percent of tumour cells demonstrating plasma membrane PD-L1 staining of any intensity in a minimum of 100 evaluable tumor cells using the Dako PD-L1 IHC 28-8 pharmDx assay. Quantifiable: an available tumour biopsy specimen and the number of viable tumour cells is ≥ 100 and percentage of tumour PD-L1 expression is ≥ 0%. Indeterminate: tumour cell membrane staining hampered for reasons attributed to the biology of the tumour biopsy specimen and not because of improper sample preparation or handling. Not evaluable: tumour biopsy specimen was not optimally collected or prepared (eg, PD-L1 expression is neither quantifiable nor indeterminate).
- *HRQoL/QLQ-C30*: The QLQ-C30 (Version 3) has 30 items divided among 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and 6 single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Two item measuring overall health status and quality of life are graded on a 7-point Likert scale, while all remaining items are graded on a 4-point scale: 1 (not at all) to 4 (very much).

Exploratory Endpoints

- *AEs leading to discontinuation and dose modification, select AEs, IMAEs, and other events of special interest*: Safety and tolerability was further measured by the incidence of AEs leading to discontinuation, AEs leading to dose modification, select AEs, immune-mediated AEs (IMAEs), and other events of special interest. Select AE analyses included incidence, time-to-onset, and time-to-resolution.
- *DMFS*: DMFS was programmatically determined based on the first date of distant metastasis provided by the investigator and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause) whichever occurred first.
- *RFS, DMFS, and OS*: Consistency of treatment effects in BRAF mutation status (BRAF mutant, BRAF wildtype) and RFS and DMFS (a forest plot of RFS and DMFS un-stratified hazard ratio and 95% confidence interval (CI) were produced). To evaluate associations between BRAF mutation status and clinical efficacy (RFS, DMFS and OS not included in this Interim CSR).
- *Serum ADA and neutralizing ADA response to nivolumab and ipilimumab*: Human serum samples from nivolumab- and ipilimumab-treated subjects were evaluated for the presence of ADA at PPD Inc. (Richmond, VA) using validated immunoassay methods (Method ICDIM 140 and Method ICDIM 14)6,7 and neutralizing activity at BMS (Princeton NJ) using validated functional cell-based assays (Method 15400 and Method 15818).

- *EQ-5D responses*: The EQ-5D descriptive system is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and severe health problems. The EQ-5D visual analog scale (VAS) recorded the subject's self-rated health state on a 100-point vertical VAS (0 = worst imaginable health state; 100 = best imaginable health state).
- *WPAI:GH*: The Work Productivity and Activity Impairment questionnaire: General Health (WPAI:GH) is a patient-reported quantitative assessment 6-item questionnaire yielding 4 different types of scores: percent work time missed due to health, percent impairment while working due to health, percent overall work impairment due to health and percent activity impairment due to health.

Sample size

The primary objective of the study was to compare RFS between the treatment arms in all randomised subjects. The sample size was calculated to compare RFS between subjects randomised to receive nivolumab vs. ipilimumab. RFS was evaluated for a treatment effect at an overall alpha level of 0.05 (two-sided) with approximately 85% power. The number of events and power were calculated assuming a delayed treatment effect and cure fraction. Approximately 800 subjects total were to be randomised to the two treatment arms in a 1:1 ratio. Taking into account the actual AJCC disease stage distribution (about 80% of Stage III subjects and 20% of Stage IV subjects), higher cure rates, and some early drop-out, the original planned 507 events might not be reached by the final RFS analysis. Therefore, approximately 450 RFS events were anticipated at the final RFS analysis, ensuring at least 85% power to detect a hazard ratio of 0.75 with an overall type I error of 0.05 (two-sided). An interim analysis of RFS was added via protocol amendment 4 months before execution to take place after all subjects had a minimum of 18 months of follow-up. Approximately 350 RFS events were anticipated at this analysis. The stopping boundary at the interim analysis is derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

Randomisation

After initial eligibility was established and the informed consent obtained, subjects were enrolled into the study via an Interactive Voice Response System (IVRS). In order to be randomized, a subject must have had a PD-L1 expression classification (positive, negative or indeterminate) as determined by the Central Laboratory. PD-L1 status (positive [based on 5% level] vs negative/indeterminate) was used as a stratification factor.

Once enrolled in the IVRS, subjects who met all eligibility criteria were randomized by IVRS in a 1:1 ratio to the nivolumab group or the ipilimumab group. Using a permuted block design, with stratification by PD-L1 status (the result of PD-L1 positive vs PD-L1 negative/indeterminate was entered by the central laboratory vendor and both the site and the BMS study team remained blinded to the result) and disease stage (Stage Stage IIIb/c, Stage IV M1a-M1b or Stage IV M1c) at screening.

Blinding (masking)

This was a double blinded study. Upon recurrence of disease and treatment discontinuation of each subject, investigators may be unblinded to the subject's treatment assignment via the Interactive Voice Response System (IVRS) to inform the appropriate subsequent treatment. The Sponsor's central protocol team will remain blinded to treatment assignment.

The randomization call was performed by the unblinded pharmacy site staff.

Statistical methods

Discrete variables were tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment. Continuous variables were summarized by treatment using the mean, standard deviation, median, minimum and maximum values. Time to event distributions were estimated using Kaplan-Meier techniques. This was done for endpoints of RFS and DMFS. Median survival times, along with 95% CIs, were constructed based on a log-log transformed CI for the survivor function S(t). Rates at fixed time points were derived from the Kaplan-Meier estimate and corresponding confidence interval were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t). Analyses were conducted using a two-sided log-rank test stratified by PD-L1 status and Stage at screening in randomized subjects. The hazard ratio of nivolumab to ipilimumab, and its associated CI, were obtained by fitting a stratified Cox model with the treatment group variable as the sole covariate using stratification factor information recorded in the IVRS.

The primary RFS analyses were conducted using a two-sided log-rank test stratified by PD-L1 status and Stage at screening in randomized subjects. The hazard ratio and corresponding two sided 97.56 % CI (adjusted for the interim analysis) was estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. To evaluate PD-L1 expression as a predictive biomarker, a Cox proportional hazards model was used to test the interaction between PD-L1 expression (positive vs negative) and treatment arm for the RFS endpoint. Additionally, RFS was analysed within each PD-L1 expression subgroup (positive and negative) including hazard ratios with corresponding confidence intervals. These analyses were descriptive and not adjusted for multiplicity.

Multiplicity if RFS will be statistically significant (at the RFS interim with minimum 18 months follow-up, added via protocol amendment 18, or at the original RFS final analysis with minimum 36 months), OS will be tested at the OS interim which is at the time of the final RFS analysis (minimum 36 months follow-up) or at the OS final analysis with a minimum of 48 months follow-up. Separate Lan-DeMets alpha spending functions with O'Brien-Fleming boundaries for RFS and OS will be used.

Censoring rules for RFS

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of randomization	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-melanoma primary cancer reported prior or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-melanoma primary cancer	Censored

Figure 5: Censoring Scheme for Primary Definition RFS

Censoring rules for DMFS

A subject who had disease at baseline was considered to have an event on the day of randomisation. A subject who died without reported distant metastasis was considered to have had distant metastasis on the date of death. For subjects who remained alive and distant metastasis-free, DMFS was censored on the date of last evaluable disease assessment. For those subjects who remained alive and had no recorded post-randomization disease assessment, DMFS was censored on the day of randomization.

Sensitivity analyses for RFS

The sensitivity analyses using the Kaplan-Meier method, stratified Cox proportional hazards model, and stratified log-rank test included:

- Unstratified RFS
- RFS stratified by PD-L1 status and disease stage per eCRF/clinical database (instead of IVRS, primary analysis)
- RFS accounting for assessment on/after subsequent therapy or on/after second non-melanoma primary cancer
- RFS accounting for missing disease assessment prior to RFS event
- RFS accounting for subjects lost to follow-up
- RFS for subjects with no relevant deviations

One of the sensitivity analyses of RFS ('RFS accounting for assessment on/after subsequent therapy or on/after second non-melanoma primary cancer') will investigate the first RFS event without censoring for subsequent therapy or non-melanoma primary cancer. Other sensitivity analyses investigated the impact of stratification based on CRF instead of IVRS, of not stratifying, of having a relevant protocol deviation, of missing >2 visits, and of lost-to-follow up.

Overall Survival

Per protocol, the first OS analysis (formal interim analysis) will take place when all subjects have a minimum follow-up of 3 years (ie, LPLV of Nov-2018) and the final OS analysis will be performed 4 years after last patient randomisation.

PFS2

An evaluation on PFS2 was conducted based on the evaluation of data collected on outcomes at the end of next line treatment. Progression-free survival on next line systemic therapy was defined as time from randomization to the earliest event which is either end date of next-line subsequent systemic therapy OR death from any cause, and to last known alive date in case of no event (ie, censor) meaning either (1) no subsequent systemic therapy and no death OR (2) subsequent systemic therapy but no end date available and no death.

Results

Participant flow

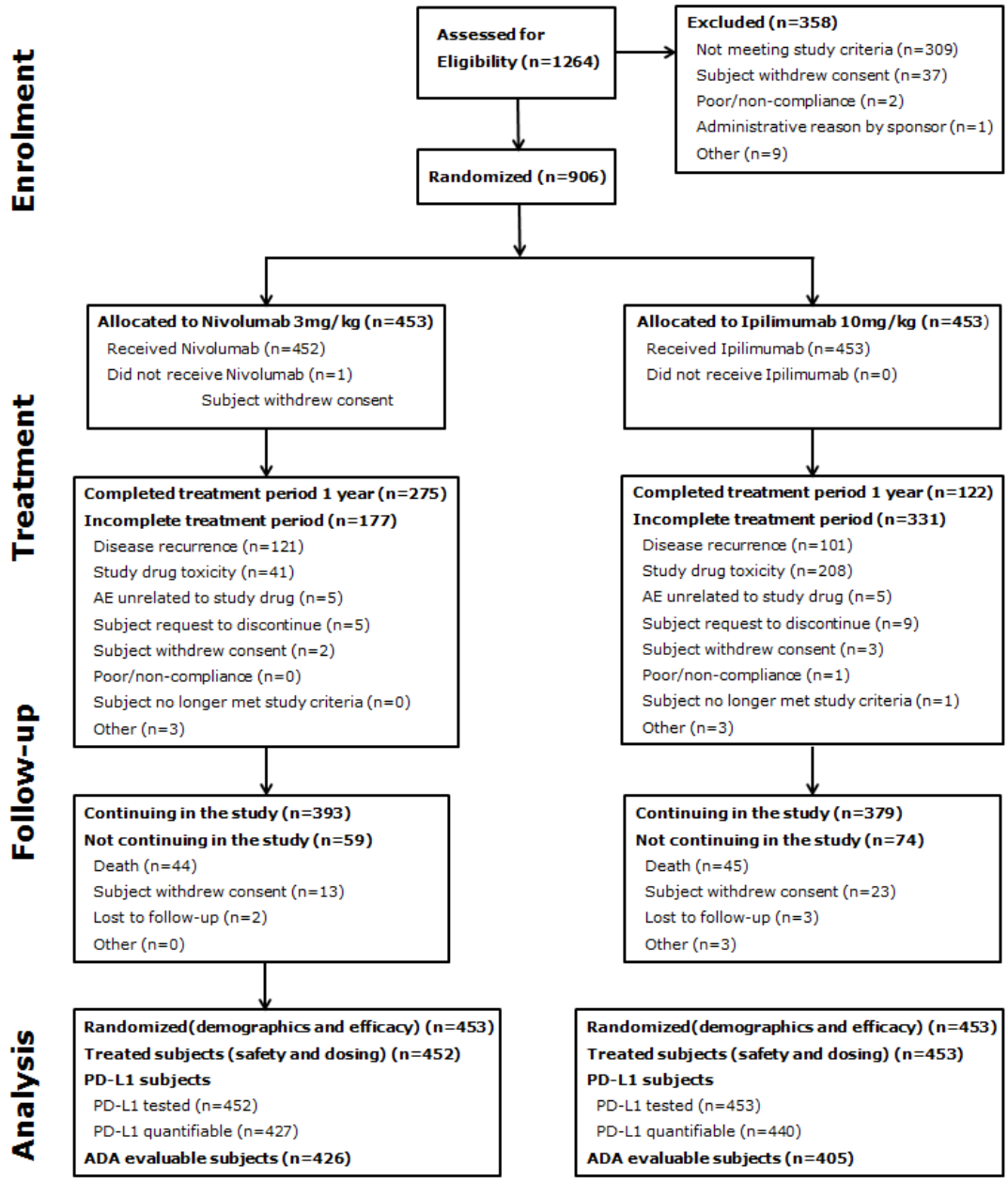


Figure 6: Participant Flow

Recruitment

The enrollment period lasted 6 months (16-Mar-2015 to 23-Sep-2015). The first patient first visit date was 16-Mar-2015 and the last patient first treatment date was 30-Nov-2015. This study is ongoing, and the last patient last visit date for this interim analysis was 15-May-2017. The clinical database lock was on 12-Jun-2017 (including the PD-L1 biomarker database lock), and a staggered lock for disease diagnosis data on 26-Jun-2017.

906 subjects were randomized at 130 sites in 25 countries (Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Finland, France, Greece, Hungary, Ireland, Italy, Japan, Republic of Korea, Netherlands, Norway, Poland, Romania, South Africa, Spain, Sweden, Switzerland, Taiwan, United Kingdom, and the United States of America); Of the 906 randomized subjects, 523 (57.7%) were in Europe, 257 (28.4%) were in North America, and 126 (13.9%) were in Rest of World.

Of the 906 subjects randomized (453 to nivolumab, 453 to ipilimumab), 905 (99.9%) were treated (452 with nivolumab, 453 with ipilimumab).

Conduct of the study

The original protocol for this study was dated 11-Nov-2014. Six global amendments and 12 country-specific amendments were issued for this study, and are summarized in Table 4. In addition, 1 administrative letter was issued for this study (21-Jan-2015) included a clarification that survival follow-up visit should take place 3 months after Follow-up Visit 2.

Table 4: Summary of Changes to Protocol CA209238

Document (Sites)	Date	Summary of Change
Amendment 01 (All)	03-Dec-2014	Permitted the collection and storage of blood samples for use in future exploratory pharmacogenetic research at all sites that permit pharmacogenetic studies to be conducted..
Amendment 02 (ZA)	14-Jan-2015	In accordance with recommendations from the Medicines Control Council of South Africa, human immunodeficiency virus (HIV) testing was added at Screening and as an Exclusion Criteria to ensure HIV positive subjects were not included in the study.
Amendment 03 (GD, IT)	05-Feb-2015	Local regulatory requirements in Greece and Italy do not permit subjects < 18 years of age.
Amendment 04 (JP)	12-Feb-2015	Local regulatory requirements for Japanese sites were added.
Amendment 05 (AR)	19-Feb-2015	Based on a request from the Argentinean health authority, study drug should be permanently discontinued in case of pregnancy and subjects <18 years of age are excluded from participation.
Amendment 06 (SE)	06-Mar-2015	In response to the Swedish Medical Products Agency, (MPA) and in line with guidelines from European Clinical Trial Facilitation Group (CTFG) dated 15-Sep-2014, the contraception methods listed in Section 3.3.1.3 of the protocol about Highly Effective Methods of Contraception and Less Effective Methods of Contraception were not amended.
Amendment 07 (TR)	06-Mar-2015	Subjects < 18 years of age were excluded from the study.
Amendment 08 (#10, 14, 16, 26, 95, 123, 126, 157)	18-Mar-2015	Based on a request from the Western IRB, study drug should be permanently discontinued in case of pregnancy.
Amendment 09 (All)	02-Apr-2015	Clarifications to inclusion/exclusion criteria were made including that the inclusion of adolescents may not be appropriate per local regulations. A new requirement regarding additional sample collection (serum, and biopsy of affected organ) for biomarker analysis was added. Typographical errors were corrected and references were updated.
Amendment 10 (NO)	02-Apr-2015	In response to Norwegian Medicines Agency (NOMA) and in line with guidelines from European Clinical Trial Facilitation Group (CTFG) dated 15-Sep-2014, "Male condoms with spermicide" was removed from the list of "Highly effective methods of contraception" and added to the list of "Less effective methods of contraception".
Amendment 11 (#21)	22-Apr-2015	Western IRB requested a statement at this site be added that in case of pregnancy, the study drug should be permanently discontinued.
Amendment 12 (#0017)	17-Jun-2015	In response to a request from the Washington University Institution Review Board, the requirement of an optional biopsy occurring at a Grade 3 drug-related AE and/or laboratory abnormalities was removed from the protocol.
Amendment 13 (#0189)	23-Jul-2015	Western IRB requested a statement at this site be added that in case of pregnancy, the study drug should be permanently discontinued.
Amendment 14 (RO)	23-Jul-2015	Per Health Authority request, the procedure for obtaining Informed Consent from adolescent patients was added.
Amendment 15 (All)	06-Aug-2015	Incorporated the definition of immune-mediated adverse events (IMAEs), AE management algorithms, clarified follow-up of laboratory toxicities and

		IMAEs, revised discontinuation criteria, definition for RFS, added censoring rules for primary analysis, and clarified survival follow-up.
Amendment 16 (All)	24-Feb-2016	Provided a greater window for the dosing visits in order to allow more flexibility, clarified the prohibited and/or restricted treatments and the timing of follow-up Visit 1 in case of discontinuation, and updated the acceptable methods of contraception to be consistent with the most recent version of BMS standard operating procedure (SOP).
Amendment 17 (All)	04-Aug-2016	Added a laboratory test (ACTH) to be consistent with the latest update of the ipilimumab Investigator's Brochure (IB) V19, more information on surveillance scan requirements when a patient starts a new systemic therapy, an update in the treatment management algorithms to be consistent with the updated nivolumab IB V15, updates to the acceptable methods of contraception in order to be consistent with the most recent version of BMS SOP and IB V15 and some additional clarifications.
Amendment 18 (All)	26-Jan-2017	Added an interim analysis, the ipilimumab mechanism of action, the name and contact information of the new Medical Monitor, and confirmation that development of Anti-Drug Antibody (ADA) will also be evaluated for subjects receiving ipilimumab.

Protocol deviations

Relevant protocol deviations (significant protocol deviations that could potentially affect the interpretability of study results) were reported in 3.6% of subjects (2.6% nivolumab and 4.6% ipilimumab) see Table 5. The most common relevant protocol deviation at study entry was that the last intervention demonstrating the subjects was free of disease was more than 13 weeks prior to randomisation, affecting 0.9% of subjects in the nivolumab group and 2.6% of subjects in the ipilimumab group.

The most common relevant protocol deviation during the treatment period was receipt of concurrent anti-cancer therapy, affecting 3 (0.7%) subjects in the nivolumab group and 3 (0.7%) subjects in the ipilimumab group.

Relevant protocol deviations were predefined in the SAP.

Table 5: Relevant Protocol Deviations - Study CA209238

	Number of Subjects (%)		
	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N = 906
SUBJECTS WITH AT LEAST ONE DEVIATION	12 (2.6)	21 (4.6)	33 (3.6)
AT ENTRY			
THE LAST INTERVENTION DEMONSTRATING THE SUBJECT IS FREE OF DISEASE IS MORE THAN 13 WEEKS PRIOR TO RANDOMIZATION	4 (0.9)	12 (2.6)	16 (1.8)
NO HISTOLOGICALLY DOCUMENTED STAGE IIIB OR STAGE IIIC OR STAGE IV MELANOMA AS PER AJCC STAGING	4 (0.9)	0	4 (0.4)
DOCUMENTED/CONFIRMED DISEASE AT BASELINE	1 (0.2)	2 (0.4)	3 (0.3)
SUBJECT RECEIVED PRIOR SYSTEMIC ANTI-CANCER THERAPY	0	4 (0.9)	4 (0.4)
ON-STUDY			
SUBJECTS RECEIVING ANTI-CANCER THERAPY WHILE ON STUDY THERAPY	3 (0.7)	3 (0.7)	6 (0.7)

Baseline data

Baseline demographic and disease characteristics are found in Table 6 and Table 7.

Table 6: Baseline Demographic Characteristics - Study CA209238 (All Randomized Subjects)

	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N = 906
AGE (YEARS)			
N	453	453	906
MEAN	54.4	53.6	54.0
MEDIAN	56.0	54.0	55.0
MIN , MAX	19 , 83	18 , 86	18 , 86
Q1 , Q3	45.0 , 65.0	43.0 , 65.0	44.0 , 65.0
STANDARD DEVIATION	13.34	13.50	13.42
AGE CATEGORIZATION (%)			
< 65	333 (73.5)	339 (74.8)	672 (74.2)
>= 65 AND < 75	103 (22.7)	101 (22.3)	204 (22.5)
>= 75	17 (3.8)	13 (2.9)	30 (3.3)
>= 65	120 (26.5)	114 (25.2)	234 (25.8)
GENDER (%)			
MALE	258 (57.0)	269 (59.4)	527 (58.2)
FEMALE	195 (43.0)	184 (40.6)	379 (41.8)
RACE (%)			
WHITE	425 (93.8)	434 (95.8)	859 (94.8)
BLACK OR AFRICAN AMERICAN	0	0	0
ASIAN	25 (5.5)	18 (4.0)	43 (4.7)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.2)	0	1 (0.1)
OTHER	2 (0.4)	1 (0.2)	3 (0.3)
ETHNICITY (%)			
HISPANIC OR LATINO	6 (1.3)	8 (1.8)	14 (1.5)
NOT HISPANIC OR LATINO	215 (47.5)	208 (45.9)	423 (46.7)
NOT REPORTED	232 (51.2)	237 (52.3)	469 (51.8)
GEOGRAPHIC REGION (%)			
US AND CANADA	126 (27.8)	131 (28.9)	257 (28.4)
WESTERN EUROPE	227 (50.1)	226 (49.9)	453 (50.0)
EASTERN EUROPE	40 (8.8)	30 (6.6)	70 (7.7)
ASIA	24 (5.3)	17 (3.8)	41 (4.5)
AUSTRALIA	34 (7.5)	44 (9.7)	78 (8.6)
ROW	2 (0.4)	5 (1.1)	7 (0.8)

Source: Table S.3.1

Table 7: Baseline Disease Characteristics - Study CA209238 (All Randomized Subjects)

	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N = 906
PERFORMANCE STATUS (ECOG) [%]			
0	413 (91.2)	405 (89.4)	818 (90.3)
1	40 (8.8)	48 (10.6)	88 (9.7)
TIME FROM SURGICAL RESECTION TO RANDOMIZATION (WEEKS)			
N	453	453	906
MEAN	8.8	9.1	9.0
MEDIAN	9.0	9.7	9.3
MIN , MAX	0 , 15	0 , 35	0 , 35
Q1 , Q3	6.9 , 11.3	7.0 , 11.6	7.0 , 11.3
STANDARD DEVIATION	2.63	3.20	2.93
< 3	5 (1.1)	17 (3.8)	22 (2.4)
3- < 6	60 (13.2)	49 (10.8)	109 (12.0)
6- < 9	156 (34.4)	126 (27.8)	282 (31.1)
9- < 12	180 (39.7)	180 (39.7)	360 (39.7)
12- < 15	50 (11.0)	76 (16.8)	126 (13.9)
15- < 18	2 (0.4)	3 (0.7)	5 (0.6)
18- < 21	0	1 (0.2)	1 (0.1)
>= 21	0	1 (0.2)	1 (0.1)
CRF DISEASE STAGE AT STUDY ENTRY			
STAGE IIIB	163 (36.0)	148 (32.7)	311 (34.3)
STAGE IIIC	204 (45.0)	218 (48.1)	422 (46.6)
STAGE IV	82 (18.1)	87 (19.2)	169 (18.7)
OTHER[a]	2 (0.4)	0	2 (0.2)
NOT REPORTED	2 (0.4)	0	2 (0.2)
TUMOR ULCERATION STATUS IN STAGE III SUBJECTS			
ABSENT	201 (44.4)	216 (47.7)	417 (46.0)
PRESENT	153 (33.8)	135 (29.8)	288 (31.8)
NOT REPORTED	15 (3.3)	15 (3.3)	30 (3.3)
LYMPH NODE INVOLVEMENT IN STAGE III SUBJECTS			
MICROSCOPIC	125 (27.6)	134 (29.6)	259 (28.6)
MACROSCOPIC	219 (48.3)	214 (47.2)	433 (47.8)
NOT REPORTED	25 (5.5)	18 (4.0)	43 (4.7)
CLASSIFICATION OF NODES IN STAGE III SUBJECTS			
IN TRANSIT MET/SATELLITES W/O MET NODES	85 (18.8)	75 (16.6)	160 (17.7)
MATTED NODES	63 (13.9)	67 (14.8)	130 (14.3)
IN TRANSIT MET/SATELLITES W/ MET NODES	82 (18.1)	86 (19.0)	168 (18.5)
NOT REPORTED	139 (30.7)	138 (30.5)	277 (30.6)
M-STATUS IN STAGE IV SUBJECTS			
M1A	50 (11.0)	51 (11.3)	101 (11.1)
M1B	12 (2.6)	15 (3.3)	27 (3.0)
M1C WITH BRAIN METASTASES	6 (1.3)	6 (1.3)	12 (1.3)
M1C WITHOUT BRAIN METASTASES	14 (3.1)	15 (3.3)	29 (3.2)
MELANOMA SUBTYPE			
MUCOSAL	16 (3.5)	13 (2.9)	29 (3.2)
CUTANEOUS	388 (85.7)	378 (83.4)	766 (84.5)
ACRAL	16 (3.5)	17 (3.8)	33 (3.6)
OCULAR/UVEAL	0	0	0
OTHER	33 (7.3)	45 (9.9)	78 (8.6)
TUMOR ORIGIN			
PRIMARY	241 (53.2)	215 (47.5)	456 (50.3)
RECURRENT	208 (45.9)	235 (51.9)	443 (48.9)
NOT REPORTED	4 (0.9)	3 (0.7)	7 (0.8)
BASELINE LDH 1			
<= ULN	413 (91.2)	411 (90.7)	824 (90.9)
> ULN	32 (7.1)	37 (8.2)	69 (7.6)
NOT REPORTED	8 (1.8)	5 (1.1)	13 (1.4)
BASELINE LDH 2			
<= 2*ULN	445 (98.2)	446 (98.5)	891 (98.3)
> 2*ULN	0	2 (0.4)	2 (0.2)
NOT REPORTED	8 (1.8)	5 (1.1)	13 (1.4)
CRF PD-L1 STATUS 1			
< 1%	140 (30.9)	133 (29.4)	273 (30.1)
>= 1%	287 (63.4)	307 (67.8)	594 (65.6)
INDETERMINATE	25 (5.5)	13 (2.9)	38 (4.2)
UNEVALUABLE/NOT REPORTED	1 (0.2)	0	1 (0.1)
CRF PD-L1 STATUS 2			
< 5%	275 (60.7)	286 (63.1)	561 (61.9)
>= 5%	152 (33.6)	154 (34.0)	306 (33.8)
INDETERMINATE	25 (5.5)	13 (2.9)	38 (4.2)
UNEVALUABLE/NOT REPORTED	1 (0.2)	0	1 (0.1)
CRF PD-L1 STATUS 3			
< 10%	321 (70.9)	335 (74.0)	656 (72.4)
>= 10%	106 (23.4)	105 (23.2)	211 (23.3)
INDETERMINATE	25 (5.5)	13 (2.9)	38 (4.2)
UNEVALUABLE/NOT REPORTED	1 (0.2)	0	1 (0.1)
B-RAF MUTATION STATUS			
MUTANT	187 (41.3)	194 (42.8)	381 (42.1)
WILDTYPE	197 (43.5)	214 (47.2)	411 (45.4)
NOT REPORTED	69 (15.2)	45 (9.9)	114 (12.6)

a Subjects with Disease Stage IIIa
Source: Table S.3.2 (physical measurements), Table S.3.3 (other baseline characteristics), Table S.3.4 (baseline disease characteristics)

Numbers analysed

The all-randomized population was the primary population used for the primary efficacy analysis and the all-treated population was the primary population for safety analyses. A description of the analysis populations is provided in Table 8.

Table 8: Analysis Populations - Study CA209238

Population	Nivolumab 3 mg/kg N	Ipilimumab 10 mg/kg N	Total N
Enrolled subjects: All subjects who signed an ICF and were registered into the IVRS. This is the population for pre-treatment disposition.	NA	NA	1264
Randomized subjects: All enrolled subjects who were randomized. This is the population for baseline demographics and efficacy analyses.	453	453	906
Treated subjects: All randomized subjects who received at least one dose of study drug. This is the population for the safety and dosing evaluation.	452	453	905
PD-L1 subjects			
PD-L1 tested subjects: All randomized subjects who had a tumor biopsy specimen assessed for PD-L1 expression	452	453	905
PD-L1 evaluable subjects: All PD-L1 tested subjects with quantifiable PD-L1 expression. See definitions of baseline and quantifiable PD-L1 expression in Table 3.5-1.	427	440	867
Immunogenicity (ADA evaluable) subjects: All nivolumab- and ipilimumab-treated subjects with baseline and at least 1 post-baseline assessment for ADA	426	405	831

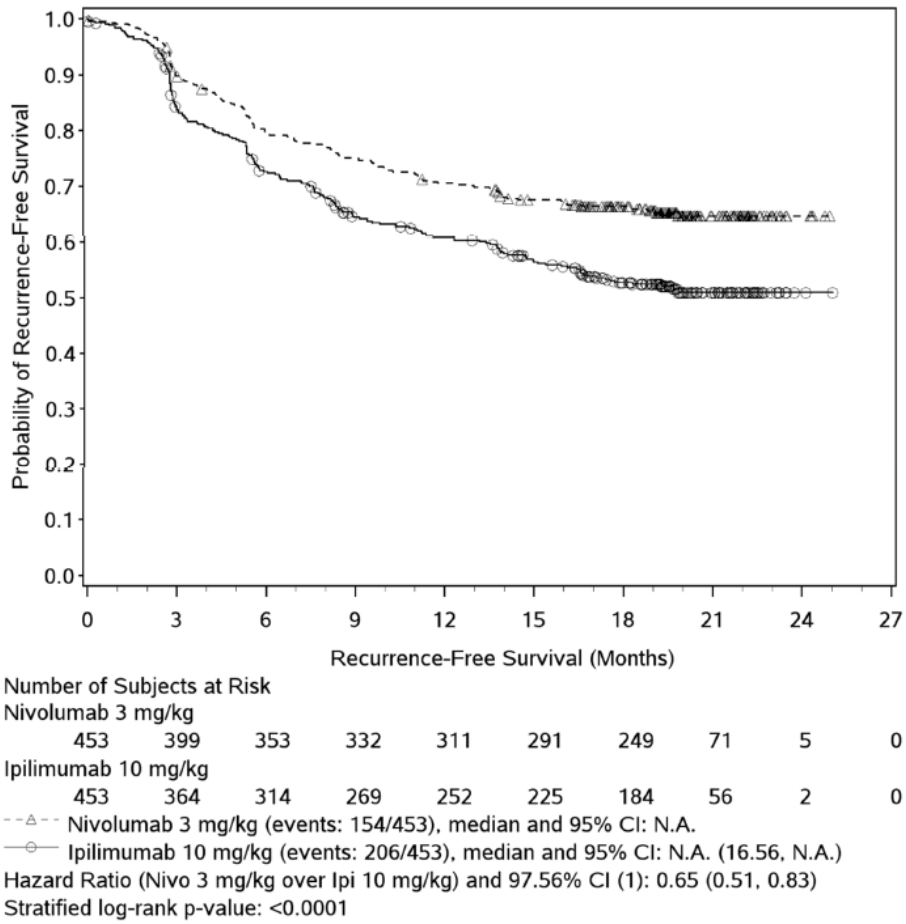
Abbreviations: NA - not applicable

Outcomes and estimation

Primary Endpoint – Recurrence-free Survival

As of the data cut-off for this interim analysis, 360 of the planned 450 RFS evens (80% information fraction) has occurred. The critical hazard ratio for 80% information fraction is 0.78 and p< 0.0244 (two-sided) was needed for statistical significance at this interim. At the time of the database lock, 299 (66.0%) subjects in the nivolumab group and 247 (54.5%) subjects in the ipilimumab group were censored. Among those censored, none were still on treatment, and most were in follow-up (286 [63.1%] in the nivolumab group and 215 [47.5%] in the ipilimumab group.

The primary analysis in all randomized subjects demonstrates a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51,0.83; stratified log-rank p < 0.0001) in completely resected Stage IIIb/c or Stage IV melanoma.



Statistical model for hazard ratio and p-value: Stratified Cox proportional hazards model and stratified log-rank test.

Symbols represent censored observations

Figure 7: Kaplan-Meier Recurrence-free Survival Plot - Study CA209238 (All Randomized Subjects)

Minimum follow-up (last subject's last randomization date of 30-Nov-2015 to clinical cut-off date of 15-May-2017) for all randomized subjects was approximately 18 months. Time from last disease assessment date to clinical data cut-off date (ie, currentness of follow-up) was within 3 months for 431 (95.1%) subjects in the nivolumab group and 418 (92.3%) subjects in the ipilimumab group. 2.2% of the patient in the ipilimumab group had a currentness of follow-up of ≥18 months and <24 months, compared to 0.9% in the nivolumab group.

Recurrence Free Survival - Updated analyses with a minimal follow-up of 24 months

The following analyses are based on approximately 6 months additional follow-up, ie, a minimum follow-up of about 24 months. The number of RFS events increased from 154 to 171 in the nivoluamab group (an increase with 17 events) and from 206 to 221 in the ipilimumab group (an increase with 15 events).

The updated analyses show a median RFS of 30.75 months for nivolumab vs 24.08 months for ipilimumab HR = 0.66 [95% CI: 0.54, 0.81]. It should be noted that the median provided is unstable due to low number of patients and censoring with 24 months of follow-up.

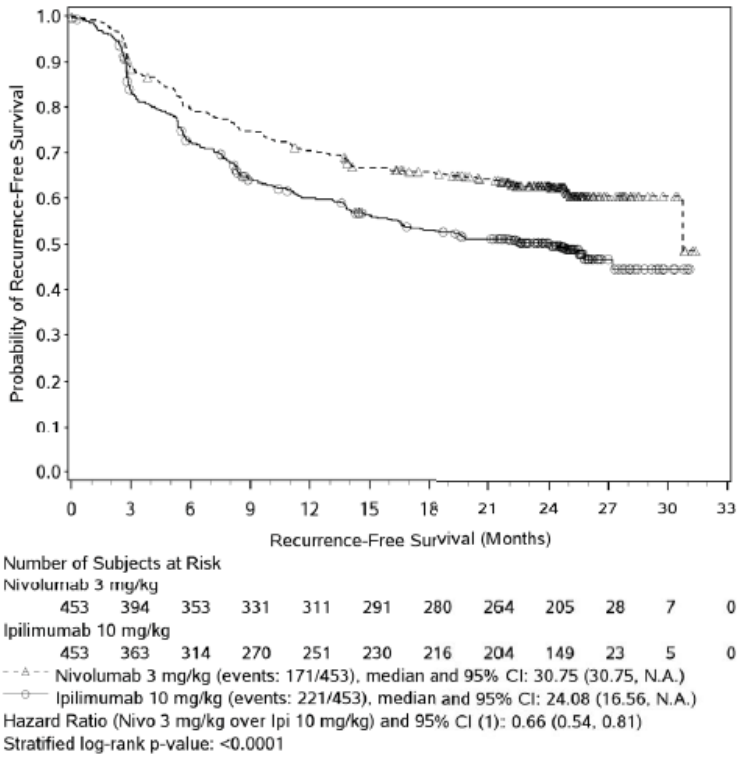


Figure 8: K-M plot of Recurrence-Free Survival with minimum 24 months follow-up - Study CA209238 (All Randomised subjects)

RFS rates are presented in Table 9.

Table 9: Recurrence-free Survival Rates - Study CA209238 (All Randomized Subjects)

RFS Rate (Two-Sided 95% CI)	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Difference in RFS Rates (Two-Sided 95% CI)
6-MONTH	79.6 (75.6, 83.1)	72.4 (68.0, 76.4)	7.2 (3.2, 13.5)
12-MONTH	70.4 (65.9, 74.4)	60.0 (55.2, 64.5)	10.4 (5.8, 16.5)
18-MONTH	65.8 (61.2, 70.0)	53.0 (48.1, 57.6)	12.8 (7.9, 19.0)
24-MONTH	62.6 (57.9, 67.0)	50.2 (45.3, 54.8)	12.5 (7.7, 18.4)
30-MONTH	60.4 (55.4, 65.0)	44.4 (37.6, 50.9)	16.0 (9.7, 23.8)

Based on Kaplan-Meier Estimates
Based on December 2017 data
Program Source: /gbs/prod/clin/programs/ca/209/238/csria05/rpt/adhoc/eursi/20180410/rt-ef-rfsratesd-v01.sas 13-APR-2018 16:29

Secondary efficacy endpoint – Baseline PD-L1 Expression and RFS

As of database lock, 452/453 randomized subjects in the nivolumab group had a tumour tissue sample collected at baseline and 453/453 subjects in the ipilimumab group. 67.9% of the samples in the nivolumab group came from a metastatic site compared to 77.7% of the ipilimumab group. The majority of the metastatic samples was derived from the lymph nodes. 867 (95.7%) had quantifiable PD-L1 expression and 38 (4.2%) did not have quantifiable PD-L1 expression (all 38 subjects were indeterminate, 37 due to high melanin content and 1 due to high background). The proportion of subjects with quantifiable PD-L1 expression at baseline was similar between the nivolumab (94.3%)

and ipilimumab (97.1%) groups. Almost all subjects (99.1%) had a tumour specimen in which immune cells were present (99.5% nivolumab and 98.6% ipilimumab).

An analysis of the risk of recurrence for nivolumab vs ipilimumab at all pre-defined expression levels of ≥1%, ≥5%, and 10% is shown in Figure 9. See Figure 10, Figure 11 and Figure 12for RFS Kaplan-Meier plots using the PD-L1 expression cut-offs of 1%, 5% and 10%.

The study was not powered to detect interactions, but the p-value for the interaction term was 0.1765 (cut-off 5%).

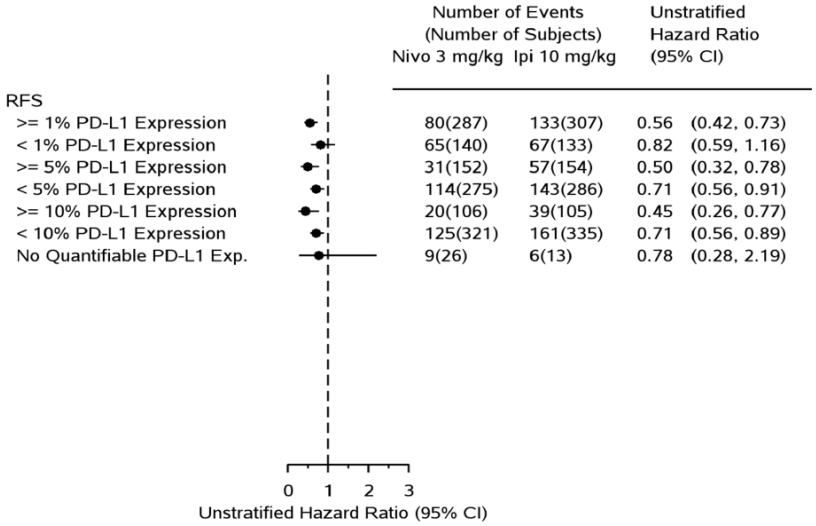
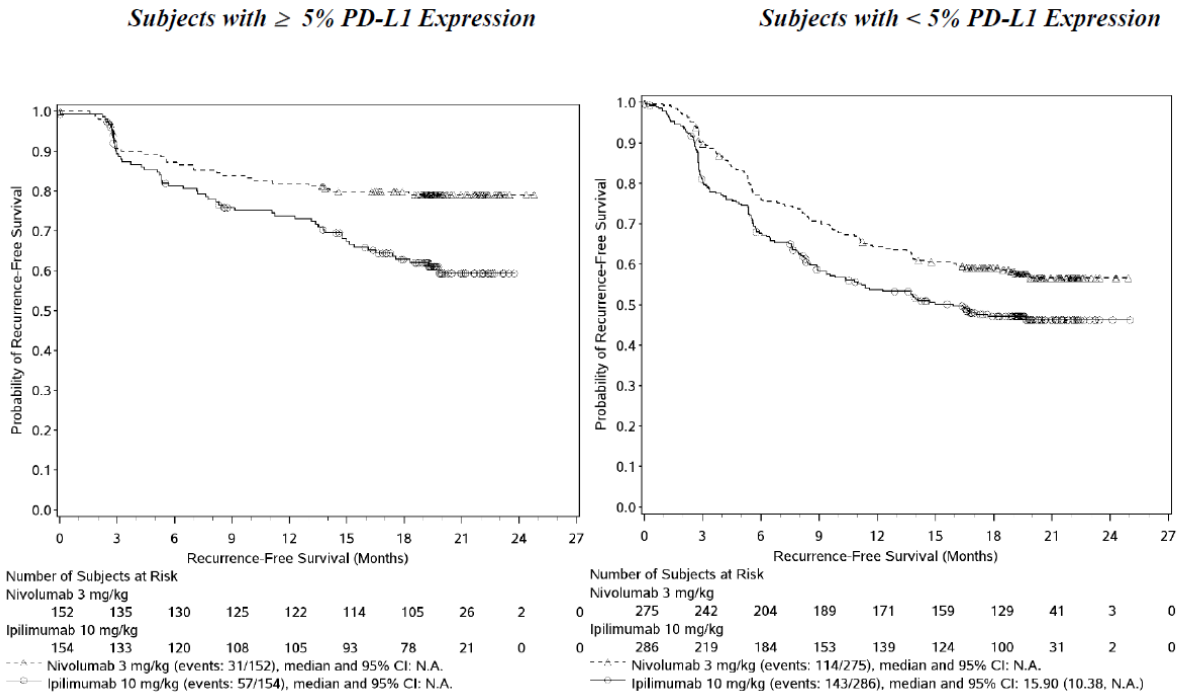


Figure 9: Forest Plot of Recurrence-free Survival - Hazard Ratios by PD-L1 Expression Level – Study CA209238 (All Randomized Subjects)



Symbols represent censored observations.

Figure 10: Kaplan-Meier Plot of Recurrence-Free Survival by PD-L1 Expression Level (5% Cutoff) – Study CA209238 (All Randomized Subjects)

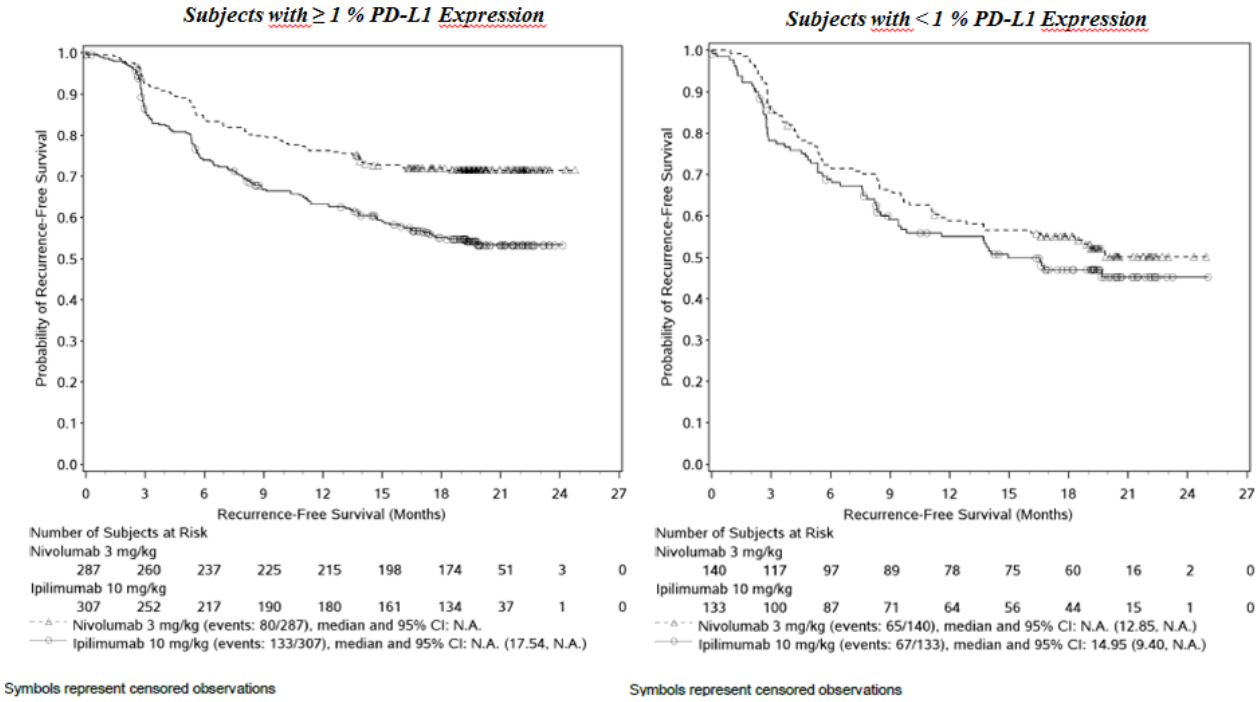


Figure 11: Kaplan-Meier Plot of Recurrence-Free Survival by PD-L1 Expression Level (1% Cutoff) – Study CA209238 (All Randomized Subjects)

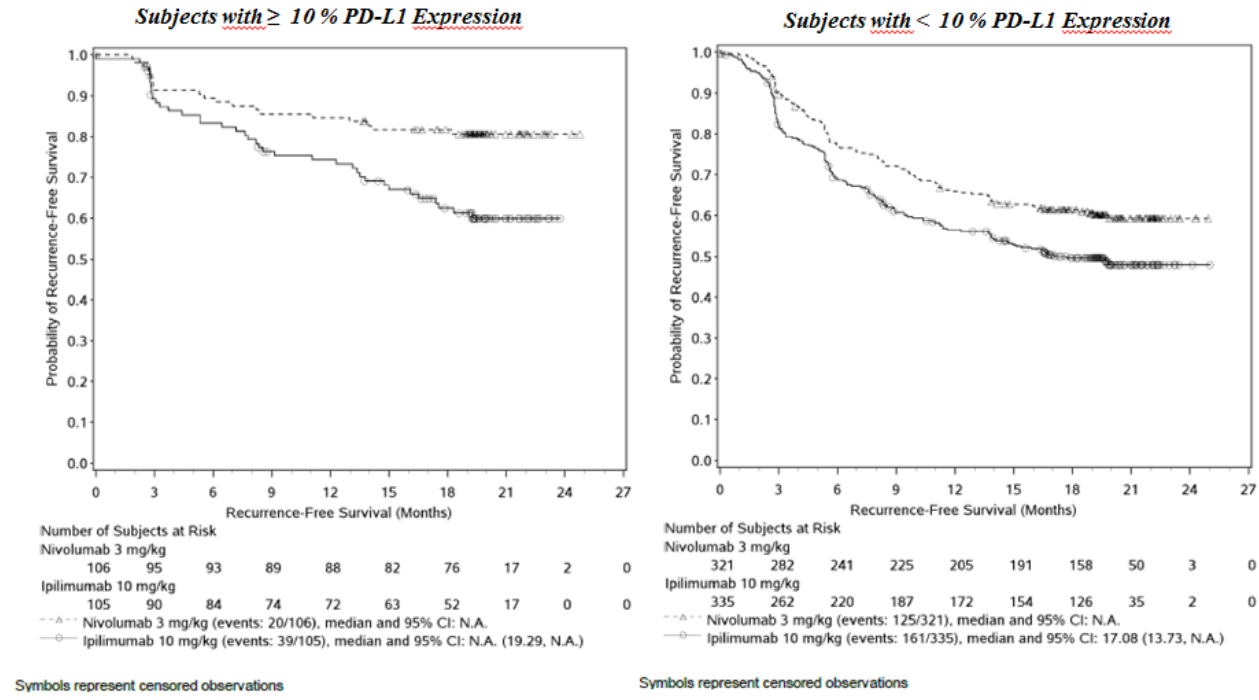
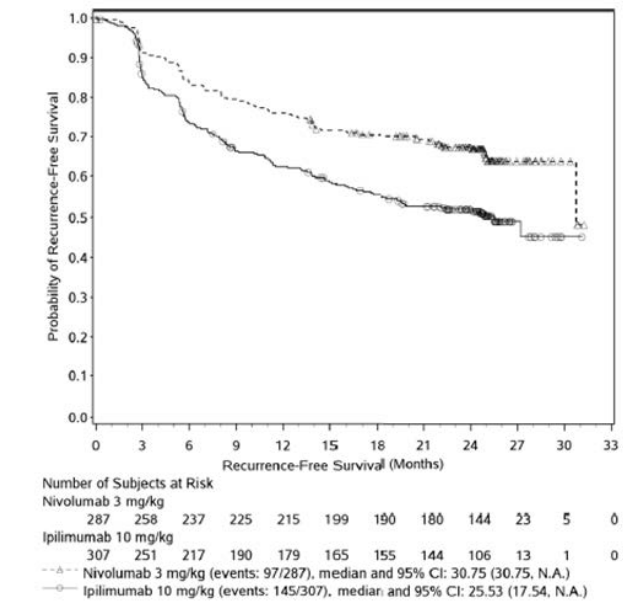


Figure 12: Kaplan-Meier Plot of Recurrence-Free Survival by PD-L1 Expression Level (10% Cutoff) – CA209238 (All Randomized Subjects)

Baseline PD-L1 Expression and RFS - Updated Analyses with a minimal follow-up of 24 months

Updated results for RFS based on tumour PD-L1 expression are presented below.



Symbols represent censored observations
Based on December 2017 data.
Source : Figure S.10.7

Figure 13: Kaplan-Meier Plot of Recurrence-Free Survival by PD-L1 Expression Level (5% Cutoff) – Study CA209238 (All Randomized Subjects)

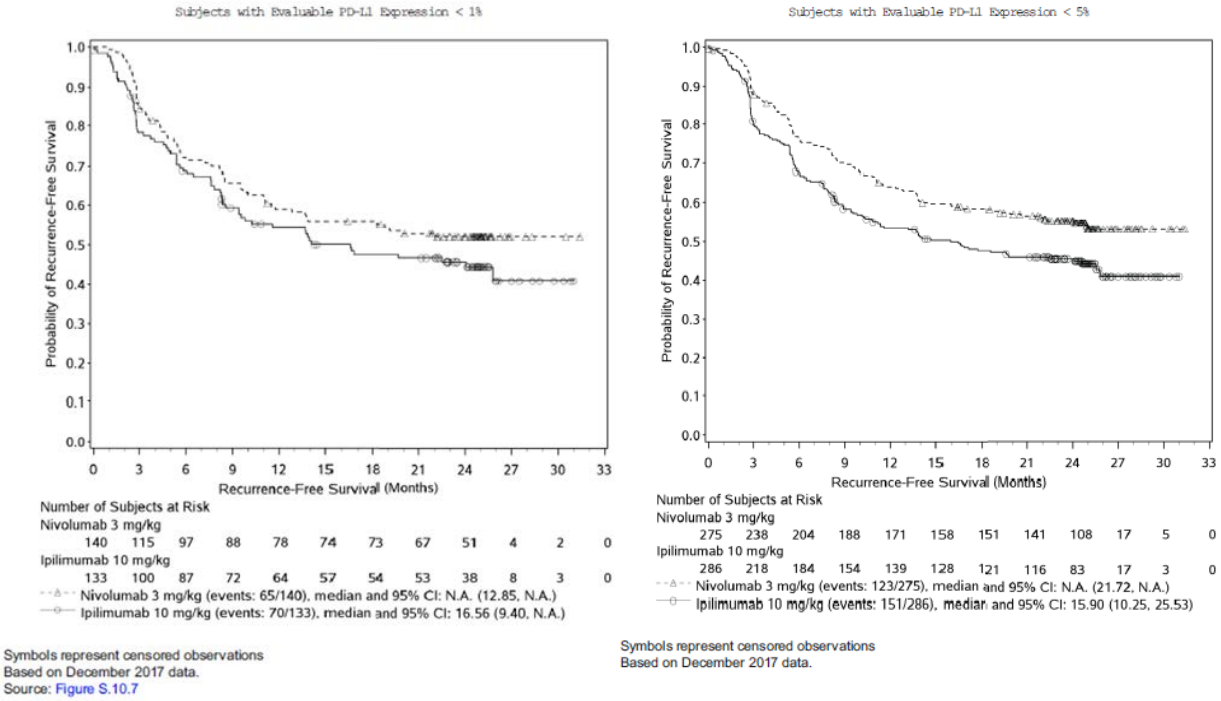


Figure 14: Kaplan-Meier Plot of Recurrence-Free Survival by PD-L1 Expression Level (1% Cutoff) – Study CA209238 (All Randomized Subjects)

Exploratory Endpoint – Distant Metastasis-free Survival

In all randomised subjects with Stage III disease (n = 369 in the nivolumab group and n = 366 in the ipilimumab group), median DMFS was not reached in either group. A benefit is suggested for Nivolumab over ipilimumab HR = 0.73 [95%CI: 0.55, 0.95]; stratified log-rank p = 0.0204) Figure 16.

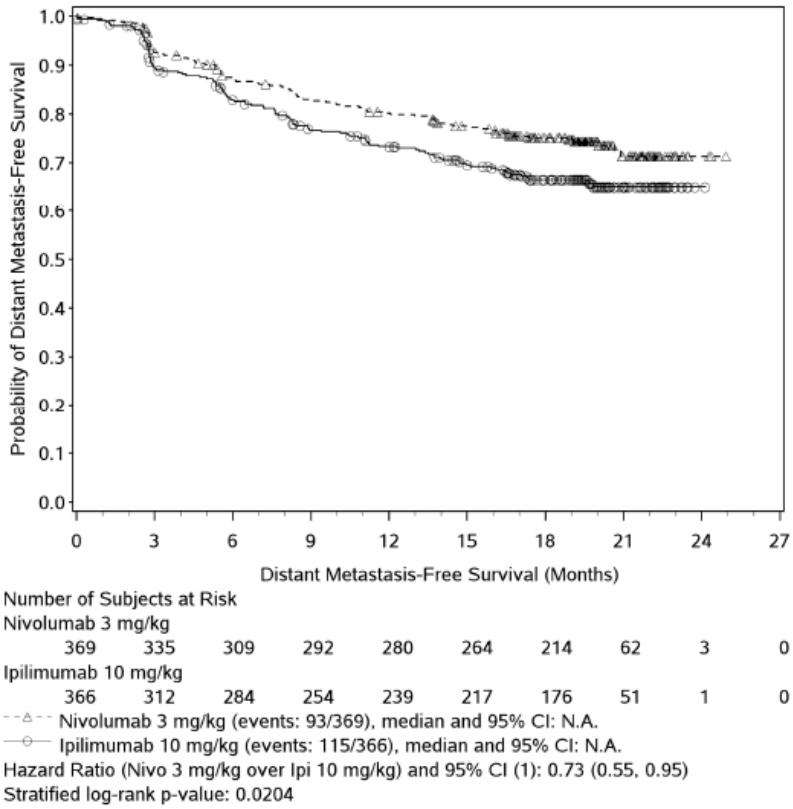


Figure 15: Kaplan-Meier Plot of Distant Metastasis-Free Survival in patients with Stage III Disease – Study CA209238 (All Randomized Subject)

DMFS rates for the nivolumab group and the ipilimumab group at 6 months were 87.5% vs 82.9%, 80.2% vs 73.4% at 12 months, and 75.1% vs 66.6% at 18 months, respectively . At the time of the database lock, 276/369 (74.8%) subjects in the nivolumab group and 251/366 (68.6%) subjects in the ipilimumab group were censored for DMFS. Among those censored, most were in follow-up (264 [71.5%] in the nivolumab group and 234 [63.9%] in the ipilimumab group).

Distant Metastasis-free Survival - Updated analyses with a minimal follow-up of 24 months

In the subgroup of all randomized subjects with Stage III disease, median DMFS was not reached, HR = 0.76 [95% CI: 0.59, 0.98; stratified log-rank p = 0.0340].

The DMFS rate at 24 months was 70.5% in the nivolumab group and 63.7% for ipilumumab group (Figure 17.

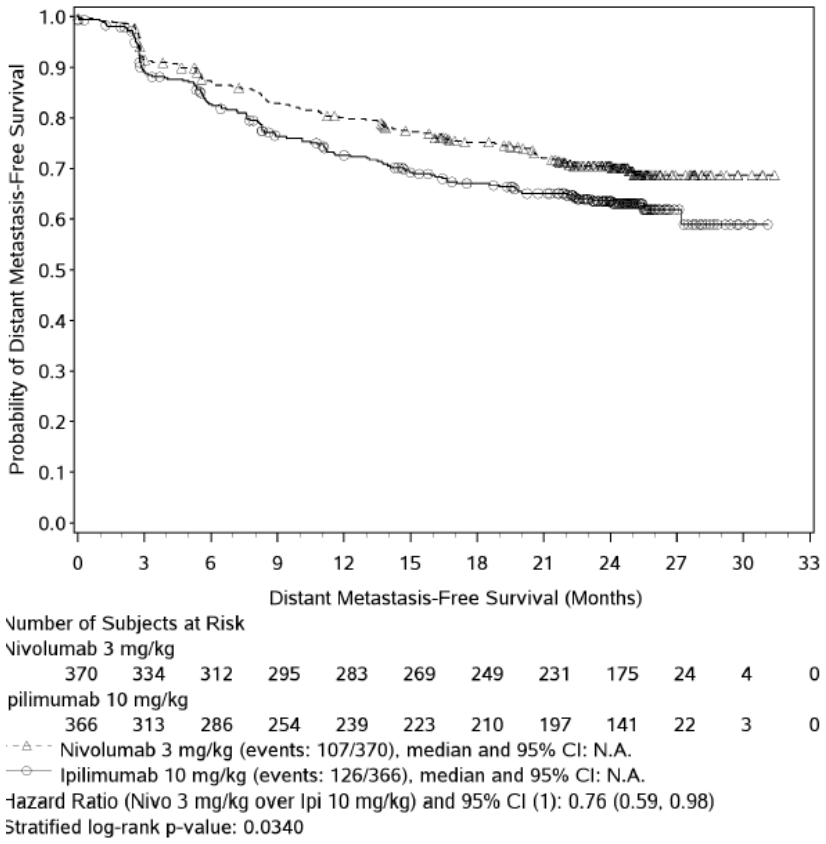


Figure 16: Kaplan-Meier Plot of Distant Metastasis-Free Survival in patients with Stage III Disease – Study CA209238 24 months minimum follow-up (All Randomized Subject)

DMFS by PD-L1 expression - Updated analysis with a minimal follow-up of 24 months

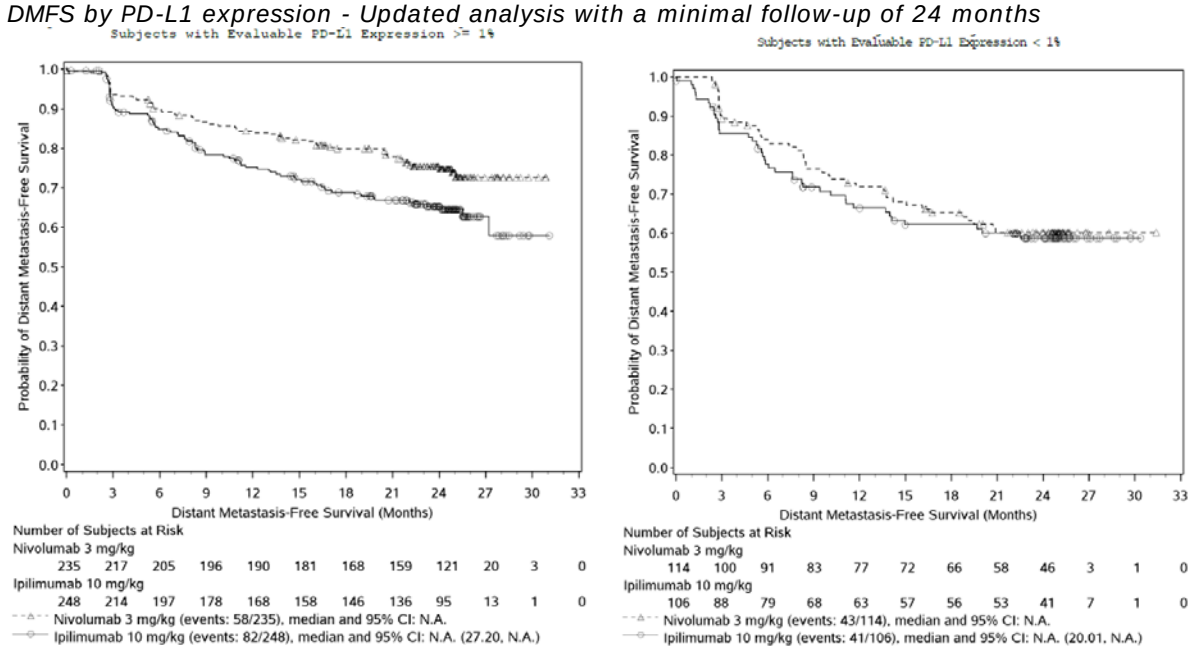


Figure 17: Kaplan-Meier Plot of Distant Metastasis-Free Survival by PD-L1 Expression Level (1% Cutoff) – Study CA209238 (All Randomized Subjects)

Health-related Quality of Life – Secondary and exploratory Endpoints

EORTC General Cancer Module (QLQ-C30) – secondary endpoint
The EORTC QLQ-C30 is the most commonly used quality-of-life instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales, and a global health/quality of life scale. Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline. A difference of 10 points on a 100 point scale between the two treatment arms is considered clinically relevant, based on the work of Osoba et al (Osoba, 1998).

Questionnaire completion rates at baseline were 97.8% (443/453) in the nivolumab group and 96.0% (435/453) in the ipilimumab group. Calculated as a percentage of subjects on study or in follow-up, completion rates for the nivolumab and ipilimumab groups met or exceeded 86.4% and 84.0%, respectively, at all assessments through 49 weeks. Completion rates for Follow-up Visits 1 and 2 for the nivolumab and ipilimumab groups met or exceeded 76.3% and 71.7%, respectively.

At baseline, mean EORTC QLQ-C30 summary scores for All Randomized subjects were comparable between treatment groups (no statistical test performed). Quality of life through Week 49 as measured by the EORTC QLQ-C30 Global Health Status (as well as for the individual functioning or symptom scales) remained stable in both treatment groups, with no mean change score from baseline reaching the minimal important difference for the patient (i.e. mean change ≥10 points) at any time point for either treatment group.

Patient-reported General Health Status (EQ-5D)
The EQ-5D-3L5 is a generic multi-attribute health-state classification system. The respondent's self-described health state can be converted into a utility score representing the societal desirability of his/her own health. In addition, the EQ-5D includes a VAS allowing a respondent to rate his/her health on a scale ranging from 0–100, with a MCID for mean change score from baseline of 0.08 for the EQ 5D utility score and of 7 for the EQ 5D VAS (Pickard, 2007).

Questionnaire completion rates for the EQ-5D at baseline were 98.0% (444/453) of subjects in the nivolumab group and 96.9% (439/453) of subjects in the ipilimumab group completed the EQ-5D and met or exceeded 86% and 85%, respectively, at all assessments through 49 weeks of follow up, and met or exceeded 77.2 and 73.5 at follow-up visits.

At baseline, mean EQ-5D utility index scores and EQ-5D VAS for All Randomized subjects were comparable between treatment groups (no statistical test performed). The EQ-5D utility index scores and EQ-5D VAS remained stable in both treatment groups, with no mean change score from baseline reaching the MID for the patient at any time point for either treatment group.

WPAI:GH - Exploratory Endpoint
The WPAI:GH is a six-item questionnaire yielding four different scale scores. The questionnaire was created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, work productivity and daily activity impairment attributable to general health. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. WPAI:GH does not have an MIC established yet. Currently, one-half the standard deviation (SD) of scores at baseline was used as an estimate of MID for each of the WPAI:GH scales.

Questionnaire completion rates at baseline were 93.2% (422/453) in the nivolumab group and 94.3% (427/453) in the ipilimumab group. Calculated as a percentage of subjects on study or in follow-up, completion rates for the nivolumab and ipilimumab groups met or exceeded 83.8% and 80.8%,

respectively, at all assessments through 49 weeks, and met or exceeded 74% and 69.8% at follow-up visits.

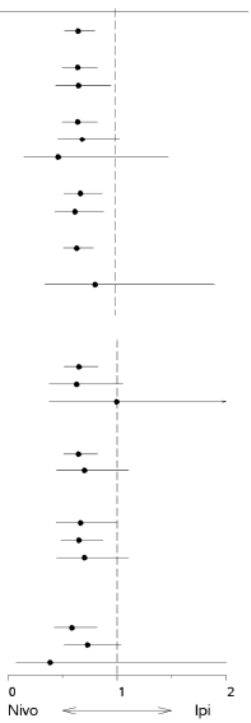
At baseline, mean WPAI:GH summary scale scores for All Randomized subjects were comparable between treatment groups (no statistical tests). Considering one-half of the standard deviation at baseline no clinically meaningful deterioration or improvement was observed at any time point for either treatment group for any scale.

Ancillary analyses

RFS in pre-defined subsets

The unstratified HRs for RFS favoured nivolumab over ipilimumab in pre-defined subgroups, with the exception of the small subgroup of subjects with mucosal melanoma (nivolumab group n = 16 and ipilimumab group n = 13), Stage IV M1c (nivolumab group n = 20 and ipilimumab group n = 21), and ulceration present plus microscopic lymph node involvement (nivolumab group n = 66 and ipilimumab group n = 69) at 18 months follow-up.

		Nivolumab 3 mg/kg		Ipilimumab 10 mg/kg		Unstratified
	N	N of events (N of subjects)	mRFS (95% CI)	N of events (N of subjects)	mRFS (95% CI)	Hazard Ratio (95% CI)
Overall	906	154 (453)	N.A.	206 (453)	N.A. (16.56, N.A.)	0.66 (0.53, 0.81)
Age Category I						
< 65	672	106 (333)	N.A.	147 (339)	N.A. (17.38, N.A.)	0.65 (0.51, 0.84)
>= 65	234	48 (120)	N.A. (18.79, N.A.)	59 (114)	16.10 (9.56, N.A.)	0.66 (0.45, 0.97)
Age Category II						
< 65	672	106 (333)	N.A.	147 (339)	N.A. (17.38, N.A.)	0.65 (0.51, 0.84)
>= 65 and < 75	204	43 (103)	N.A. (16.07, N.A.)	52 (101)	16.10 (9.56, N.A.)	0.70 (0.47, 1.05)
>= 75	30	5 (17)	N.A. (10.81, N.A.)	7 (13)	16.76 (4.21, N.A.)	0.47 (0.15, 1.50)
Gender						
Male	527	99 (258)	N.A.	133 (269)	16.62 (13.50, N.A.)	0.68 (0.53, 0.88)
Female	379	55 (195)	N.A.	73 (184)	N.A. (19.29, N.A.)	0.63 (0.44, 0.89)
Race						
White	859	141 (425)	N.A.	195 (434)	N.A. (16.56, N.A.)	0.65 (0.52, 0.80)
Black	0	0 (0)		0 (0)		
Asian	43	12 (25)	19.84 (6.70, N.A.)	10 (18)	14.08 (5.75, N.A.)	0.82 (0.35, 1.93)
Other	4	1 (3)	N.A. (2.76, N.A.)	1 (1)	5.78 (N.A., N.A.)	
Stage Category I (CRF)						
Stage IIIb/IIIc	733	120 (367)	N.A.	163 (366)	N.A. (16.56, N.A.)	0.65 (0.52, 0.83)
Stage IV M1a-M1b	128	25 (62)	N.A. (11.53, N.A.)	35 (66)	13.73 (7.62, N.A.)	0.63 (0.38, 1.05)
Stage IV M1c	41	8 (20)	N.A. (5.19, N.A.)	8 (21)	N.A. (8.54, N.A.)	1.00 (0.37, 2.66)
Not Reported	2	1 (2)	N.A. (9.69, N.A.)	0 (0)		
Stage Category II (CRF)						
Stage III	735	120 (369)	N.A.	163 (366)	N.A. (16.56, N.A.)	0.65 (0.51, 0.82)
Stage IV	169	33 (82)	N.A. (15.90, N.A.)	43 (87)	16.76 (8.54, N.A.)	0.70 (0.45, 1.10)
Not Reported	2	1 (2)	N.A. (9.69, N.A.)	0 (0)		
Stage Category III (CRF)						
Stage IIIb	311	41 (163)	N.A.	54 (148)	N.A.	0.67 (0.44, 1.00)
Stage IIIc	422	79 (204)	N.A.	109 (218)	16.62 (9.82, N.A.)	0.65 (0.49, 0.87)
Stage IV	169	33 (82)	N.A. (15.90, N.A.)	43 (87)	16.76 (8.54, N.A.)	0.70 (0.45, 1.10)
Other	2	0 (2)	N.A.	0 (0)		
Not Reported	2	1 (2)	N.A. (9.69, N.A.)	0 (0)		
Stage III: Ulceration						
Absent	417	58 (201)	N.A.	94 (216)	N.A. (16.10, N.A.)	0.59 (0.42, 0.82)
Present	288	60 (153)	N.A.	64 (135)	19.68 (10.38, N.A.)	0.73 (0.51, 1.04)
Not Reported	30	2 (15)	N.A.	5 (15)	N.A. (10.35, N.A.)	0.39 (0.07, 2.00)



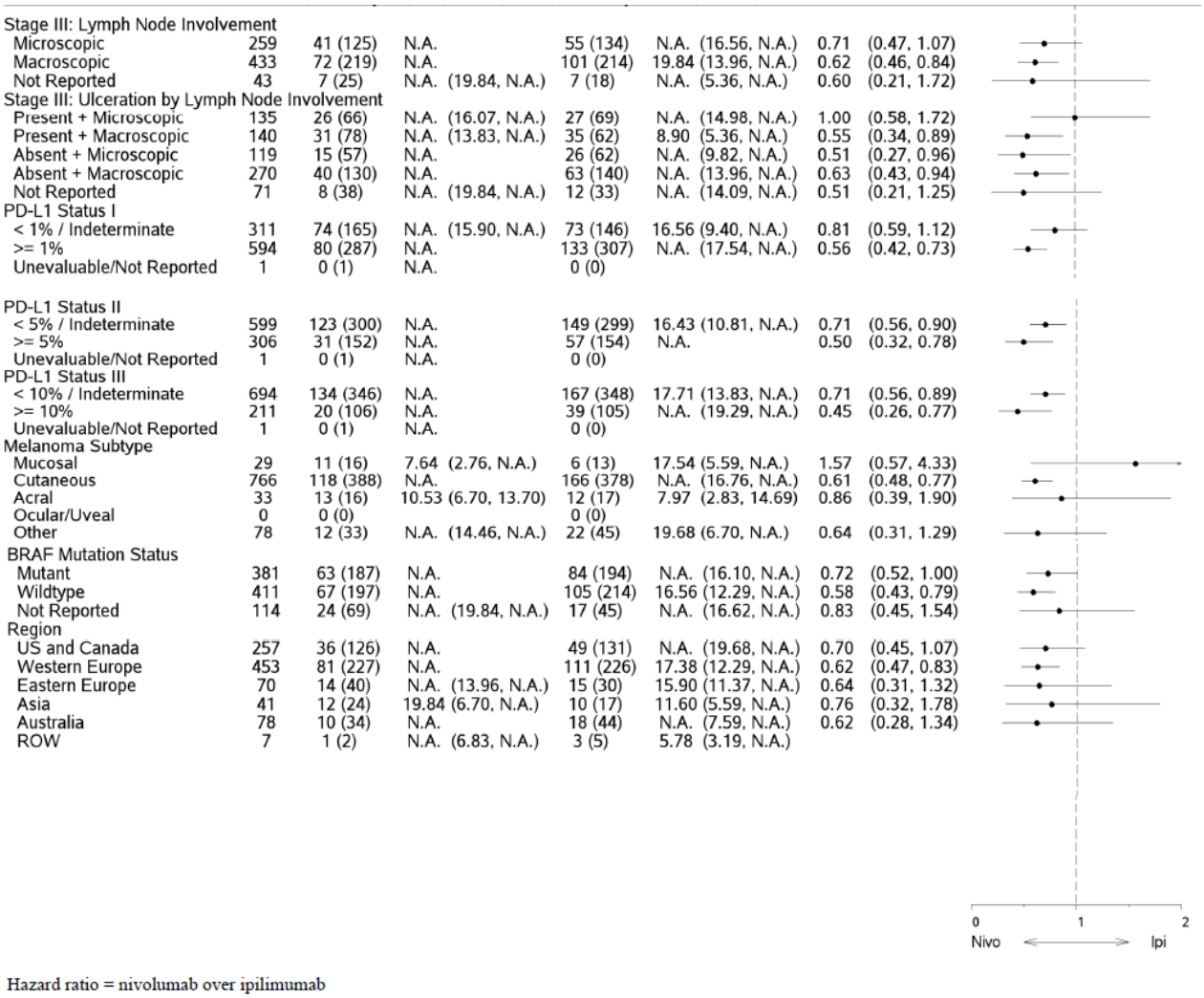


Figure 18: Forest Plot of Treatment Effect on Recurrence-free Survival in Pre-Defined Subsets – Study CA209238 (All Randomized Subjects)

DMFS in Subgroup Analyses

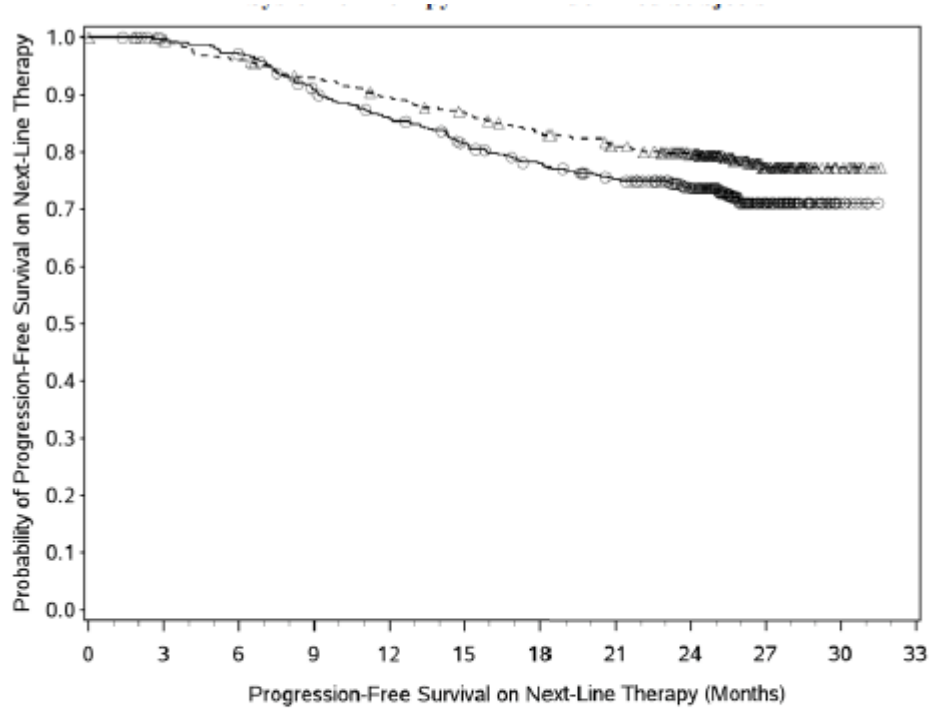
The unstratified HRs for DMFS favoured nivolumab over ipilimumab in pre-defined subgroups among most of the randomised subjects with Stage III disease, with the exception of 4 subgroups. The 2 smaller subsets including patients with mucosal melanoma (HR 2.36; 95% CI: 0.62, 8.90; n = 15 in the nivolumab group and n = 11 in the ipilimumab group) and subjects from Eastern Europe (HR 0.87; 95% CI: 0.26, 2.84; nivolumab n = 35, ipilimumab n = 17) had wide CIs that encompassed 1.0. In addition, the analyses of the ulceration present plus microscopic lymph node involvement (HR 1.03; 95% CI: 0.57, 1.88; nivolumab group n = 66 and ipilimumab group n = 69) and PD-L1 status < 1%/ Indeterminate (HR 0.95; 95% CI: 0.63, 1.43; nivolumab n = 133, ipilimumab n = 118) also had wide CIs that encompassed 1.0.

OS

At the time of the present database lock (December 2017), only 111 deaths have occurred (about 37% of the protocol-expected number of deaths). These data are immature and prevent definitive conclusions.

PFS2

Progression-free survival on next line systemic therapy for nivolumab vs ipilimumab had an HR = 0.74 [95% CI: 0.57, 0.97]; stratified log-rank p =0.0302.



Number of Subjects at Risk

Nivolumab 3 mg/kg	453	447	431	414	398	385	367	351	316	102	15	0
Ipilimumab 10 mg/kg	453	446	433	401	376	353	334	316	273	94	8	0

Nivolumab 3 mg/kg (events: 96/453), median and 95% CI: N.A.
Ipilimumab 10 mg/kg (events: 121/453), median and 95% CI: N.A.
Hazard Ratio (Nivo 3 mg/kg over Ipi 10 mg/kg) and 95% CI (1): 0.74 (0.57, 0.97)
Stratified log-rank p-value: 0.0302

Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations
Based on December 2017 data.

Figure 19: K-M plot of Progression-Free Survival on next-line systemic therapy - Study CA209238 (All Randomised Subjects)

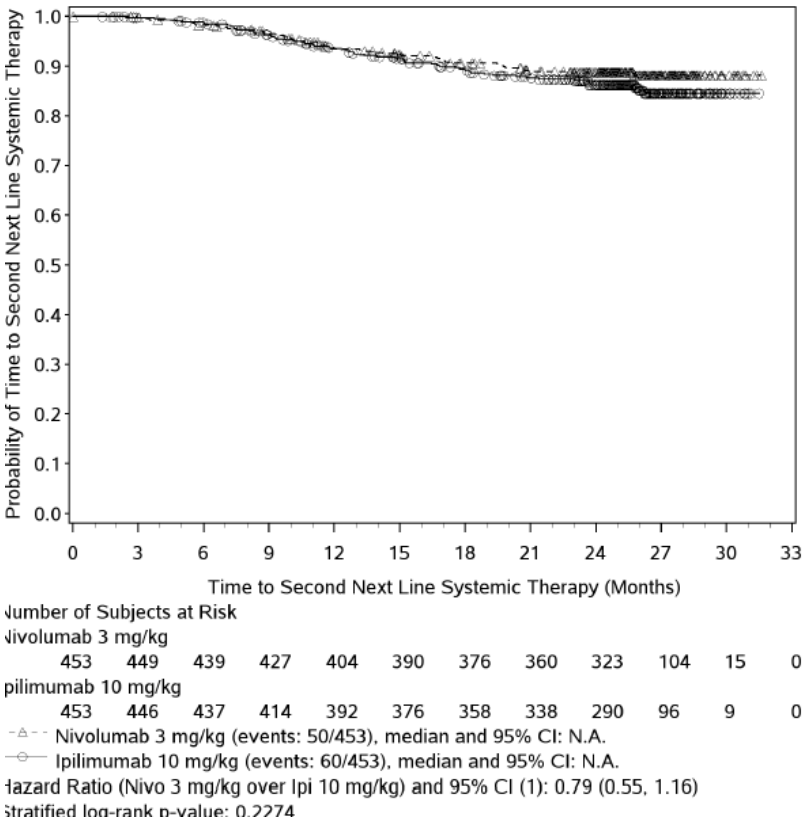


Figure 20: K-M plot of time to next-line systemic therapy - Study CA209238 (All Randomised Subjects)

Table 10: Subsequent Cancer Therapy Summary - All Randomized Subjects

Subsequent Treatment in CA209238[a]	Nivolumab (N = 453)	Ipilimumab (N = 453)
Any subsequent therapy	141 (31.1%)	151 (33.3%)
Subsequent Radiotherapy	26 (5.7%)	27 (6.0%)
Subsequent Surgery	73 (16.1%)	68 (15%)
Any Systemic Treatment	100 (22.1%)	151 (33.3%)
Immunotherapy	60 (13.2%)	119 (26.3%)
Anti-PD-1	1 (0.2%)	2 (0.4%)
Anti-CTLA4	1 (0.2%)	1 (0.2%)
Ipilimumab/Nivolumab	2 (0.4%)	1 (0.2%)
Ipilimumab[b]	43 (9.5%)	18 (4.0%)
Nivolumab[b]	20 (4.4%)	52 (11.5%)
Pembrolizumab	13 (2.9%)	72 (15.9%)
BRAF Inhibitor[c]	44 (9.7%)	44 (9.7%)
MEK/NRAS Inhibitor[c]	35 (7.7%)	45 (9.9%)
BRAF in combination with MEK/RAS Inhibitor	3 (0.7%)	1 (0.2%)
Other Systemic Cancer Therapy - experimental drugs	10 (2.2%)	9 (2.0%)
Other Systemic Cancer Therapy - chemotherapy	28 (6.2%)	3 (6.6%)
Unassigned	2 (0.4%)	1 (0.2%)

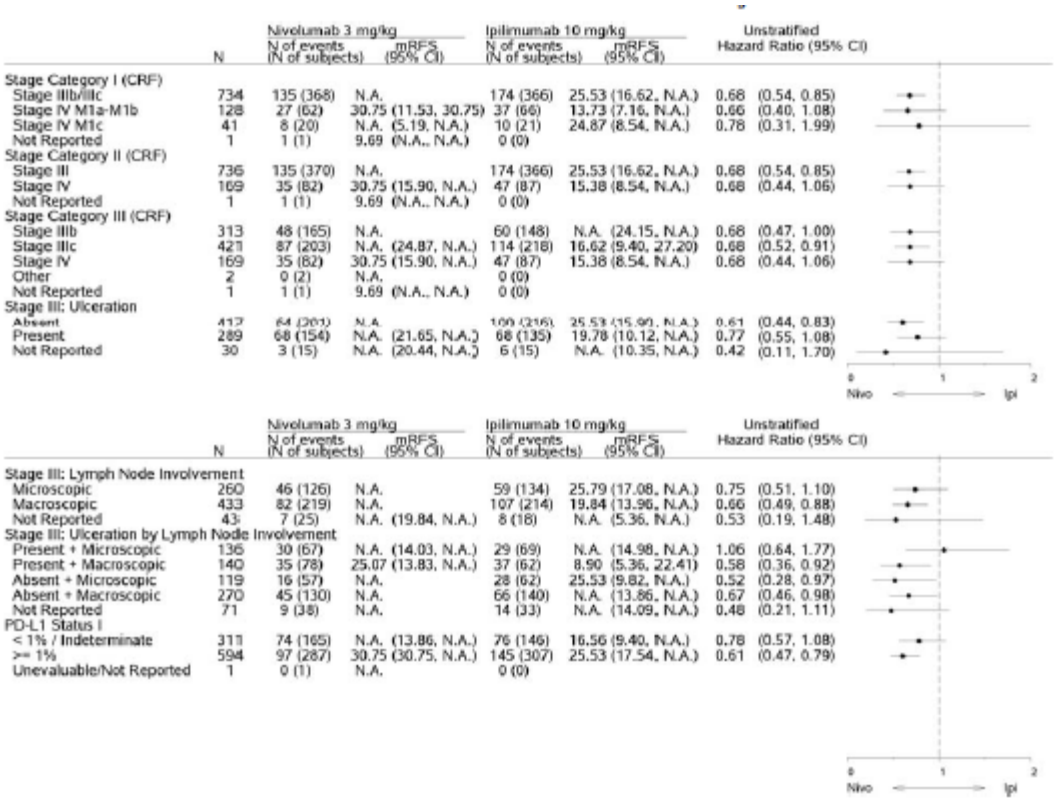
[a]Patients may have received more than one type of subsequent therapy and more than one agent within each type

[b]May include additional patients treated with nivolumab/ipilimumab combination

[c]May include additional patients treated with BRAF in combination with MEK/RAS inhibitor

Reclassification of disease staging according to the new AJCC 8th edition

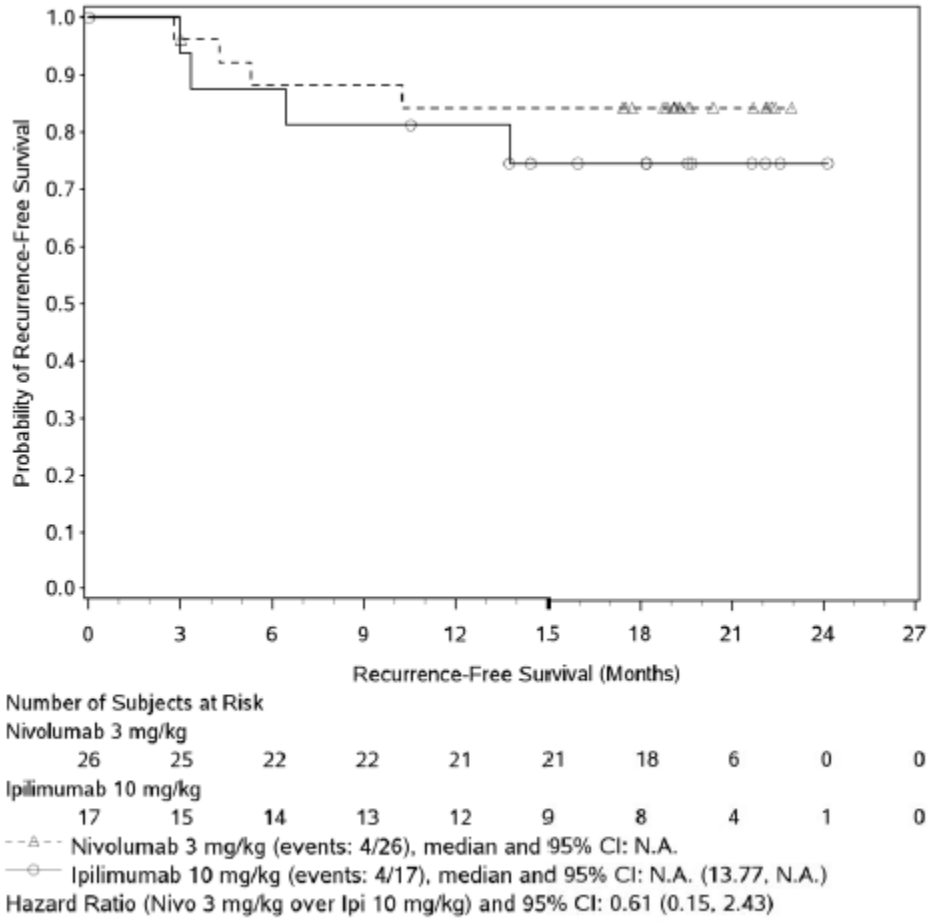
In a pre-defined subgroup analyses for patients with nonulcerated, micrometastatic disease (n=119), nivolumab had an HR of 0.52 vs. ipilimumab. In the AJCC 7th edition, many of these patients would have been considered Stage IIIb solely based on a mitotic rate ≥1/mm2, whereas in the AJCC 8th edition staging would be IIIa as mitotic rate is no longer a T staging criteria. Patients who met with the criteria of 4 or more metastatic nodes or matted nodes would be excluded from the 119 patients since such patients are considered stage IIIc/IIId.



Based on December 2017 data

Figure 21: Forest Plot of treatment on updated Recurrence-Free Survival in pre-defined subsets - Study CA209238 (All Randomised Subjects)

Patients with non-ulcerated, micrometastatic disease who were defined as Stage IIIb subjects per AJCC 7th Edition would be considered Stage IIIa subjects per AJCC 8th Edition. For these subjects (N=43), the HR of nivolumab over ipilimumab was 0.61 based on June 2017 database lock with a minimum follow-up of 18 months. With a minimum follow-up of 24 months, one more subject in the ipilimumab group had an event and the HR of nivolumab over ipilimumab was 0.50 (95% CI: 0.13, 1.85).



Symbols represent censored observations

Figure 22: K-M Plot of Recurrence-Free Survival in Subjects with Stage IIIb/other stage disease and microscopic LN involvement and no ulceration - Study CA209238 (All Randomised SUbjects)

RFS for PD-L1 expression by site of origin

The impact of sample origin on RFS was analysed for the PDL-1 expression subgroups. There was a total of 905/906 randomized subjects that had a tumor tissue sample collected at baseline with the majority (72.8%) of samples being from a metastatic site and 23.6% from a primary site. Slightly more subjects in the ipilimumab group (77.7%) had tissue collected from a metastatic site compared to nivolumab subjects (67.9%). 867 (95.7%) had quantifiable PD-L1 expression and 38 (4.2%) did not have quantifiable PD-L1 expression (all 38 subjects were indeterminate, 37 due to high melanin content and 1 due to high background). The proportion of subjects with quantifiable PD-L1 expression at baseline was similar between the nivolumab (94.3%) and ipilimumab (97.1%) groups.

RFS results are presented below for all randomised (Primary site and Metastatic site) (Figure 25) and by PD-L1 expression level at cutoff level of 5% (Figure 26 and Figure 27) and cutoff level of 1% (Figure 28 and Figure 29).

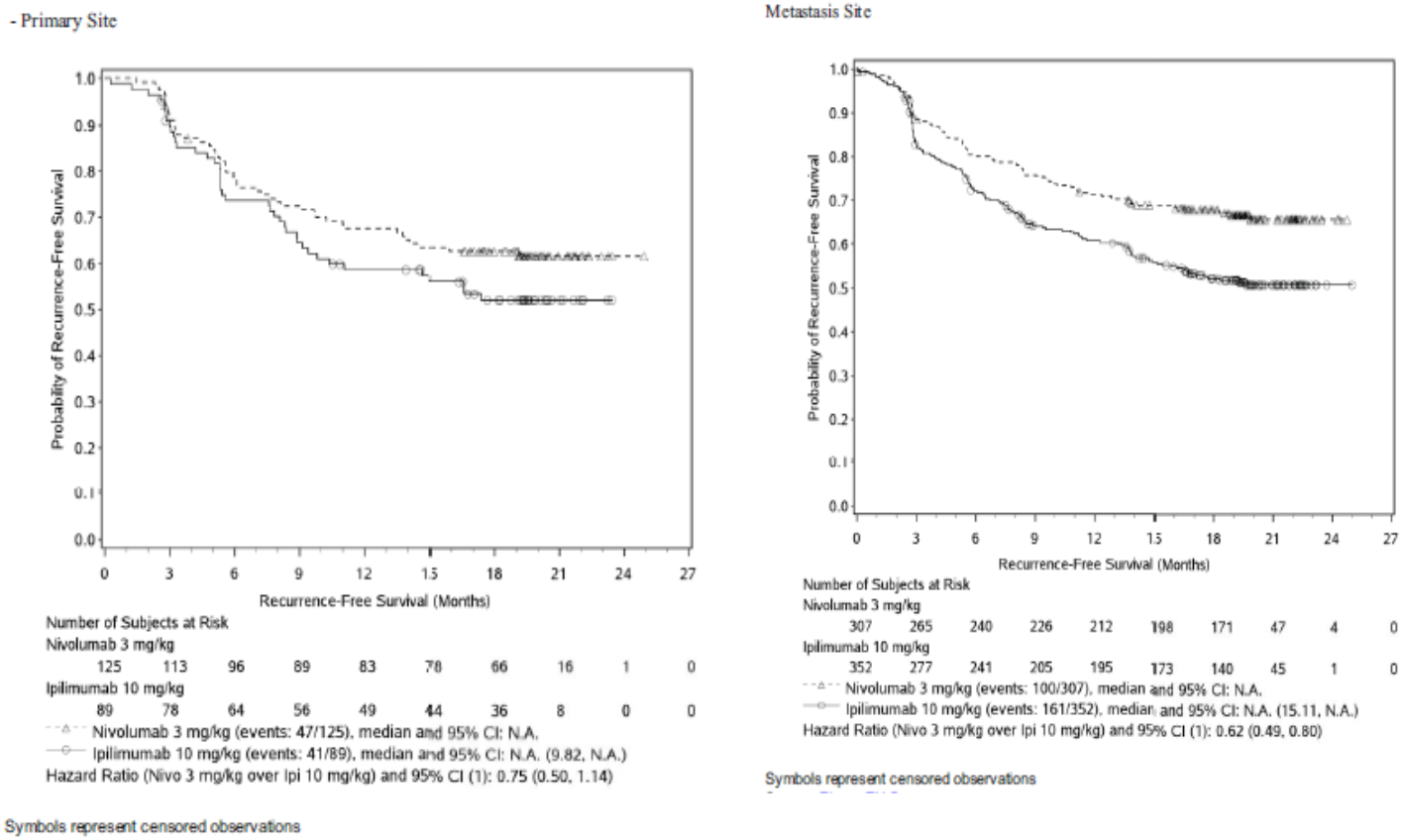
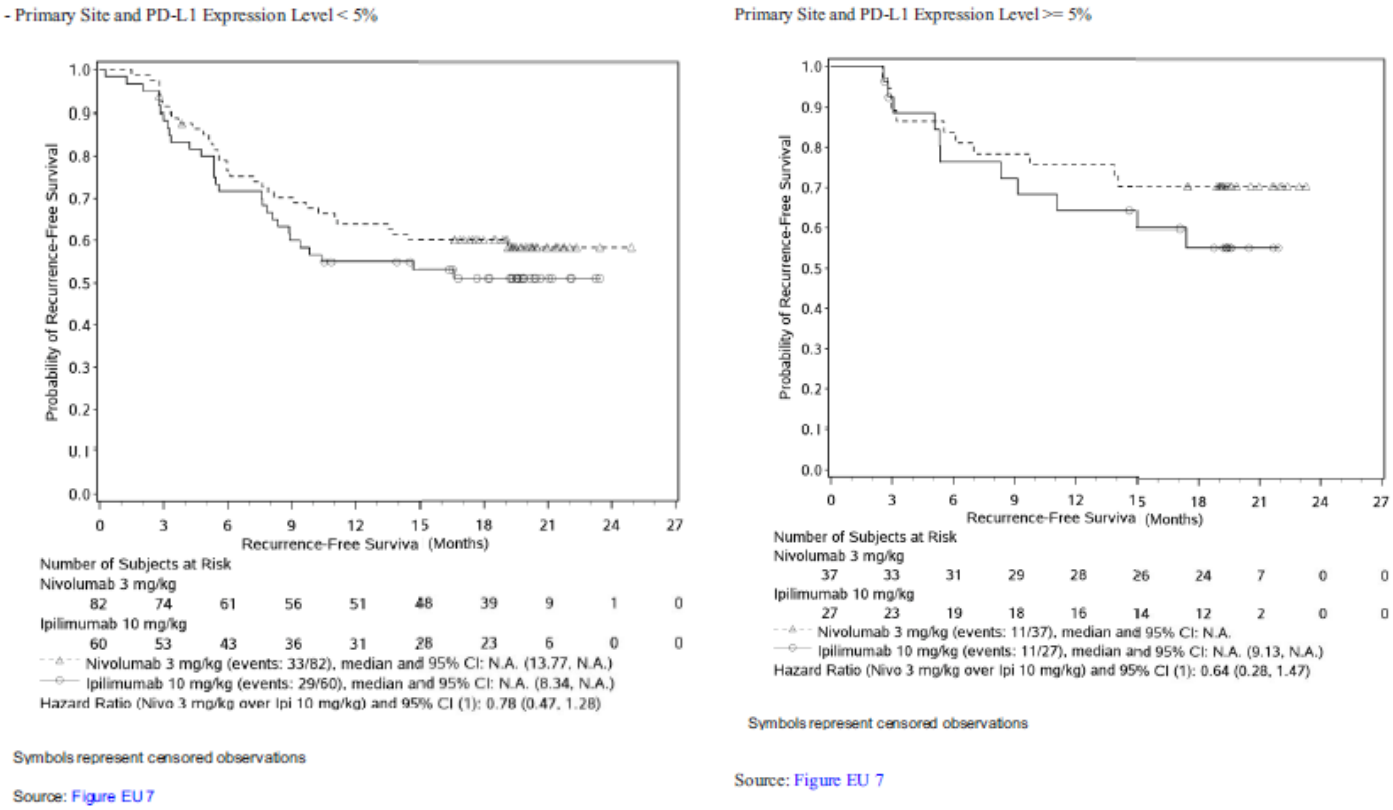


Figure 23: Kaplan- Meier Plot of Recurrence-Free Survival by Sample Origin - Study CA209238 (All Randomised Subjects)



Source: Figure EU 7

Figure 24: Kaplan-Meier Plot of Recurrence-Free Survival for Primary site and PD-L1 expression level cutoff 5% - Study CA209238 (All Randomised Subjects)

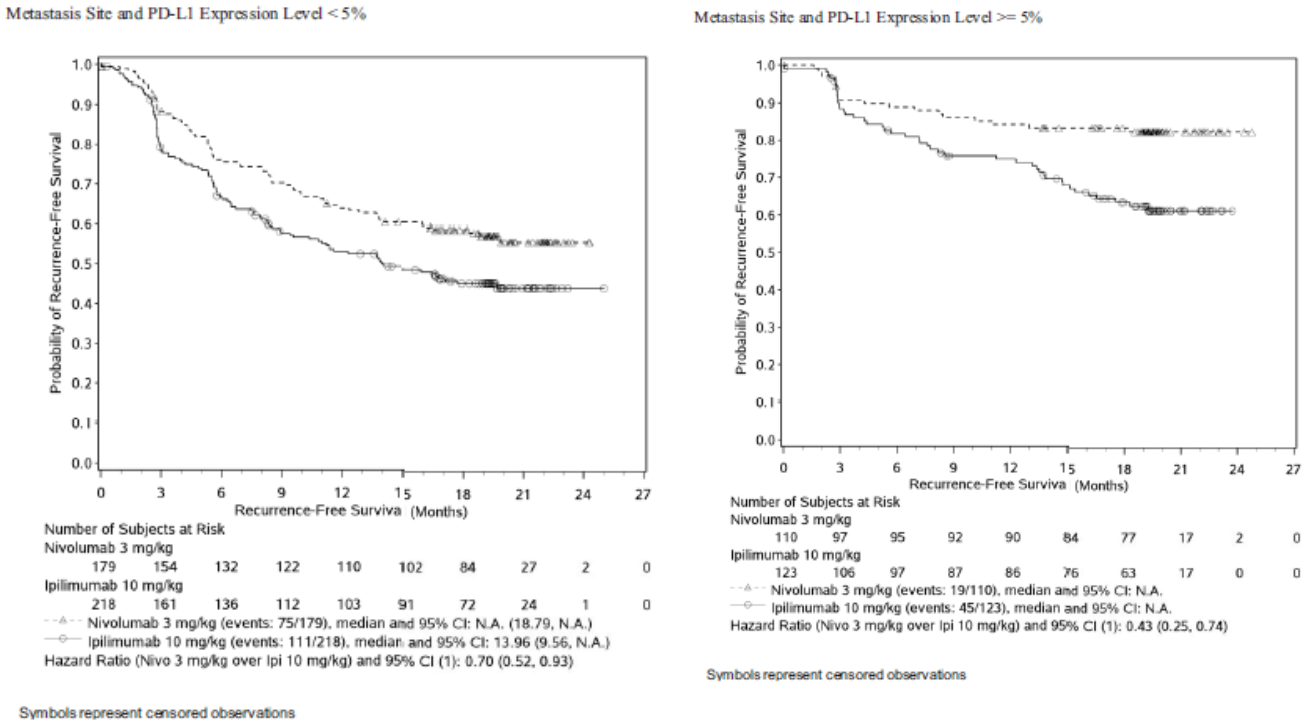


Figure 25: Kaplan-Meier Plot of Recurrence-Free Survival for Metastatic site and PD-L1 expression level cutoff 5% - Study CA209238 (All Randomised Subjects)

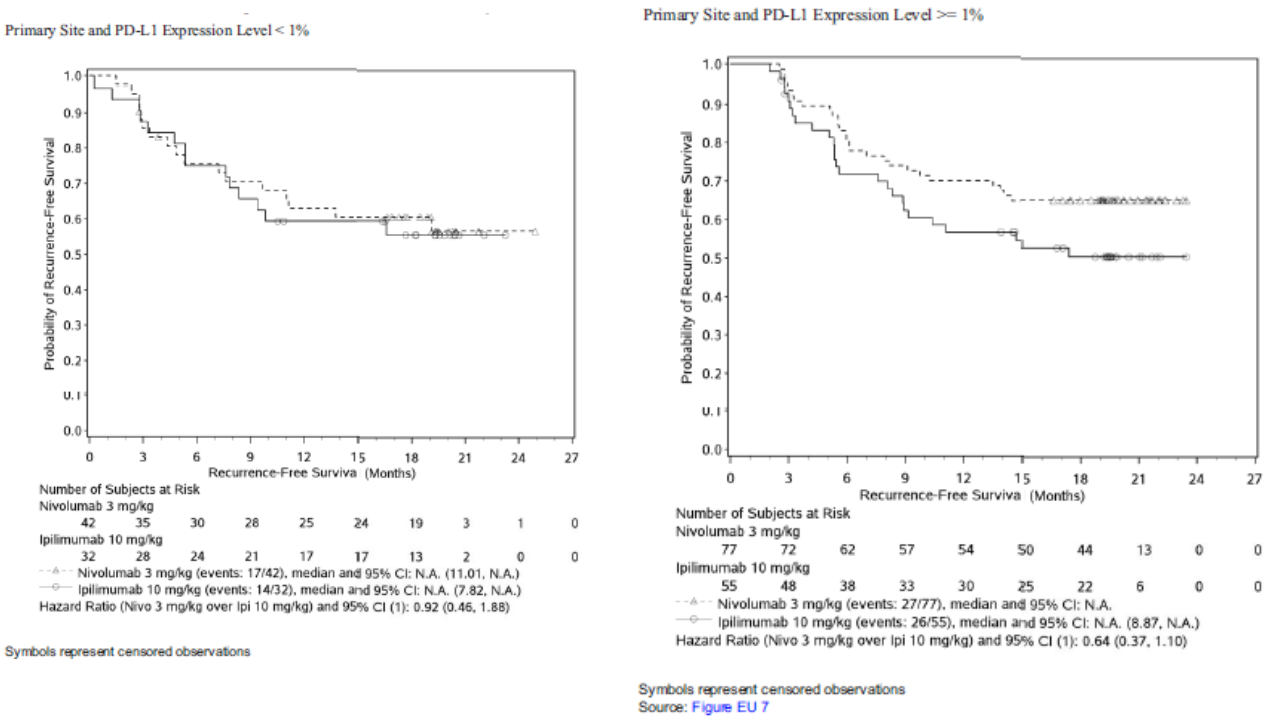


Figure 26: Kaplan-Meier Plot of Recurrence-Free Survival for Primary site and PD-L1 expression level cutoff 1% - Study CA209238 (All Randomised Subjects)

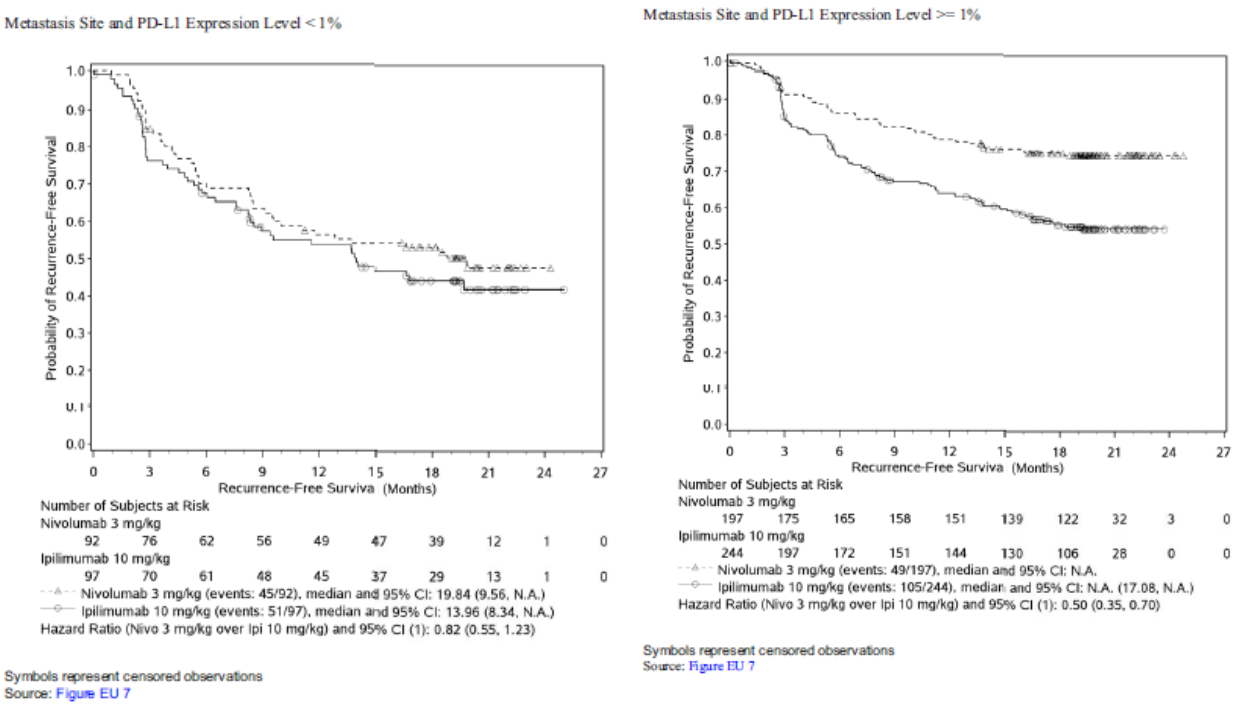


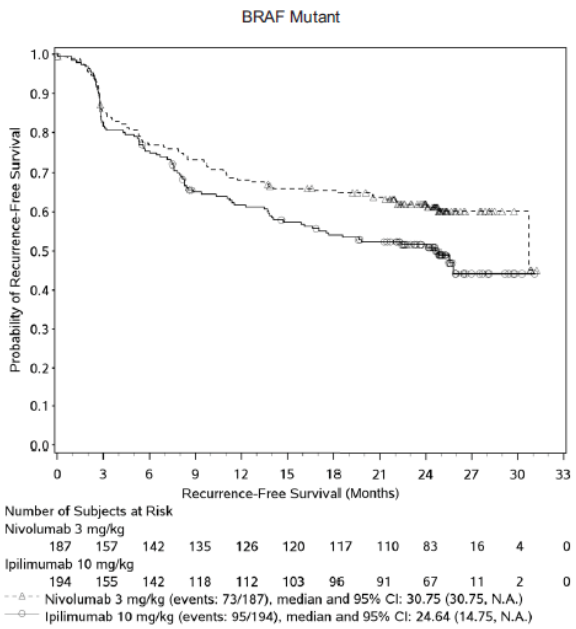
Figure 27: Kaplan-Meier Plot of Recurrence-Free Survival for Metastatic site and PD-L1 expression level cutoff 1% - Study CA209238 (All Randomised Subjects)

RFS and DMFS by BRAF mutation

Among all randomized subjects, 381 (42.1%) subjects were BRAF V600 mutation positive, 409 (45.1%) subjects were BRAF wild type; and for 116 (12.8%) subjects BRAF status was unknown. There were 2 subjects who were considered BRAF wildtype in the original analysis that are now considered with BRAF mutated. There were 39% of BRAF mutant patients (73/187) with nivolumab and 49% (95/194) with ipilimumab with events (HR=0.73; 95%CI (0.54, 0.99) and in BRAF wild type patients 37.1% (73/197) with nivolumab and 50.5% (107/212) with ipilimumab had an event (HR=0.61; 95%CI (0.45, 0.82).

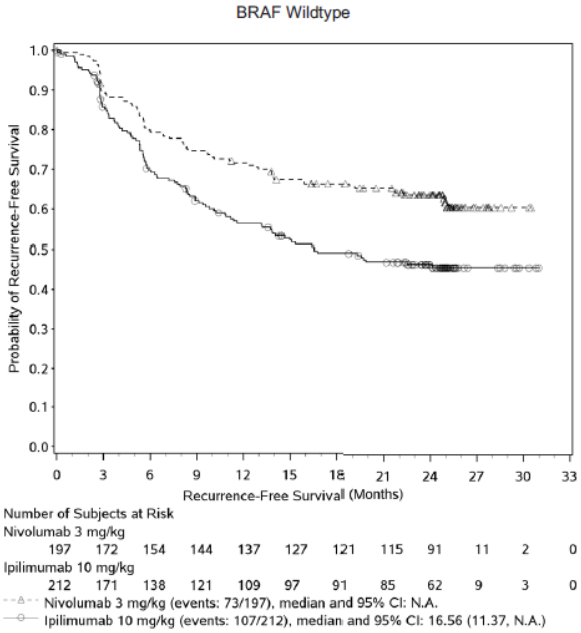
Updated results with a minimal follow up of 24 months are shown in Figure 30

Figure 16: Kaplan-Meier Plot of Updates Recurrence-Free Survival by BRAF Status - All Randomized Subjects



Symbols represent censored observations
Based on December 2017 data.

Figure 16: Kaplan-Meier Plot of Updates Recurrence-Free Survival by BRAF Status - All Randomized Subjects



Symbols represent censored observations
Based on December 2017 data.

Figure 28: Kaplan-Meier Plot of Recurrence-Free Survival by BRAF mutation status - Study CA209238 (All Randomised Subjects)

RFS rates are presented in Table 12.

Table 11: Recurrence-Free Survival by BRAF mutation status - Study CA209238 (All Randomised Subjects)

	All Randomized Subjects	
Survival Rate (95% CI)	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453
MUTANT		
6-MONTH	76.8 (70.1, 82.3)	75.3 (68.5, 80.8)
12-MONTH	68.2 (60.9, 74.3)	61.8 (54.4, 68.3)
18-MONTH	65.4 (58.1, 71.8)	54.0 (46.6, 60.9)
24-MONTH	61.9 (54.4, 68.5)	51.7 (44.2, 58.6)
WILDTYPE		
6-MONTH	79.9 (73.5, 84.9)	69.7 (62.8, 75.5)
12-MONTH	71.6 (64.6, 77.4)	56.4 (49.2, 63.0)
18-MONTH	66.3 (59.2, 72.5)	49.0 (41.8, 55.8)
24-MONTH	63.5 (56.2, 69.8)	46.2 (39.1, 53.0)

Based on Kaplan-Meier Estimates
Based on December 2017 data.

DMFS results showed that in BRAF mutant patients, there were 30.2% (45/149) events with nivolumab and 35.8% (58/162) events with ipilimumab (HR=0.76; 95%CI (0.52, 1.13)) and in BRAF wild type patients 31.0% (49/158) had events with nivolumab and 35.8% (59/165) with ipilimumab (HR=0.76; 95%CI (0.52, 1.11)).

DMFS results by BRAF status are presented in Figure 31.

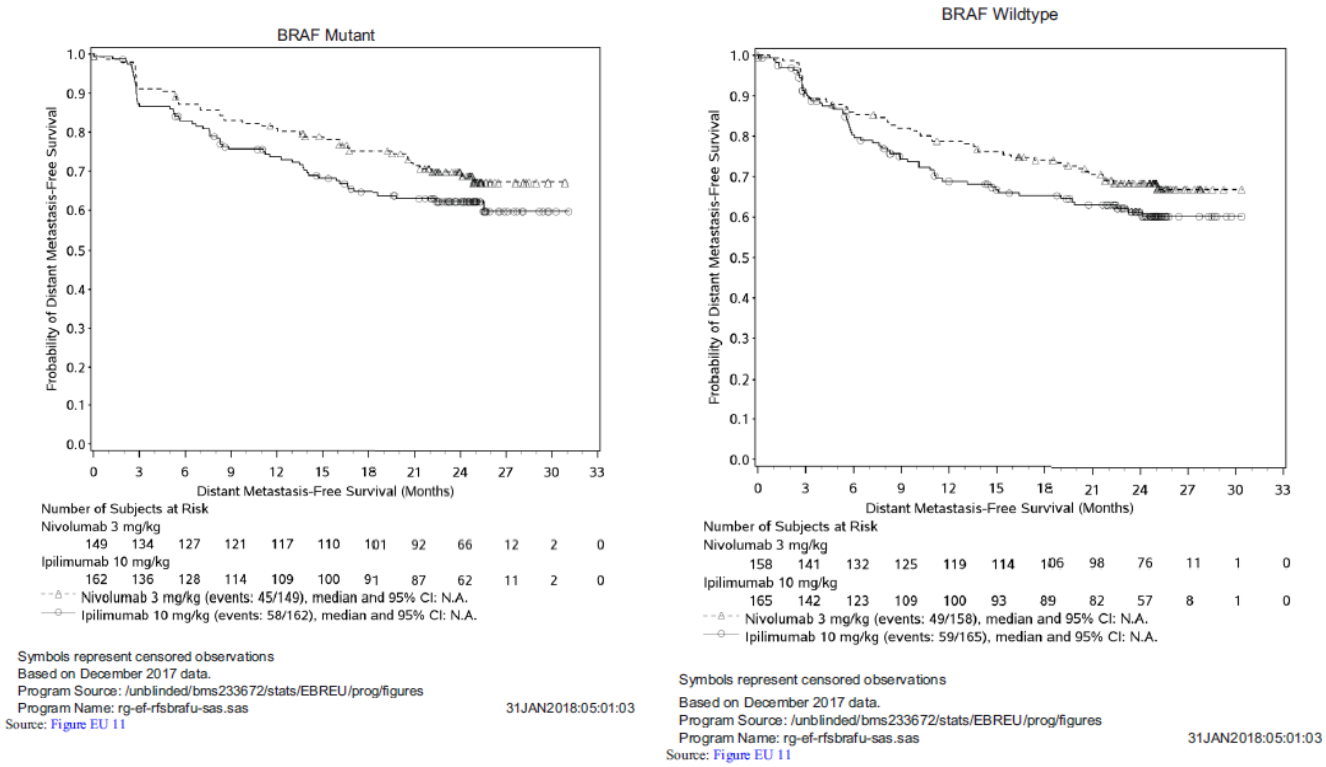


Figure 29: Kaplan-Meier Plot of Recurrence-Free Survival by BRAF Status - Study CA209238 (All Randomised Subjects with Stage III Disease)

Updated results for 24 months DMFS rates are presented in Table 13.

Table 12: Distant Metastasis-Free Survival rates by BRAF mutation Status - CA209238 (All Randomised Subjects)

Survival Rate (95% CI)	Nivolumab 3 mg/kg N = 370	Ipilimumab 10 mg/kg N = 366
MUTANT		
6-MONTH	87.1 (80.5, 91.5)	82.8 (75.9, 87.9)
12-MONTH	80.9 (73.5, 86.4)	73.6 (65.9, 79.8)
18-MONTH	75.2 (67.3, 81.4)	64.7 (56.6, 71.7)
24-MONTH	69.7 (61.4, 76.6)	62.5 (54.2, 69.7)
WILDTYPE		
6-MONTH	86.0 (79.5, 90.5)	80.3 (73.1, 85.7)
12-MONTH	78.7 (71.4, 84.4)	68.8 (60.9, 75.5)
18-MONTH	74.1 (66.4, 80.3)	65.3 (57.1, 72.3)
24-MONTH	68.3 (60.2, 75.1)	61.2 (52.8, 68.6)

Based on Kaplan-Meier Estimates
Based on December 2017 data.

Summary of main study

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

Table 13: Summary of Efficacy for trial CA209238

Title: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence			
Study identifier	CA209238		
Design	A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	5 years not applicable not applicable	
Hypothesis	Treatment with adjuvant nivolumab monotherapy will have clinical activity in subjects with completely resected Stage IIIb/c or Stage IV melanoma		
Treatments groups	Nivolumab 3 mg/kg		Nivolumab 3 mg/kg, max 1 year, n=453
	Ipilimumab 10 mg/kg		Ipilimumab 3mg/kg, max 1 year, n=453
Endpoints and definitions	Primary endpoint	RFS	RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first.

	Secondary endpoint	RFS endpoint by PD-L1	RFS evaluated by baseline PD-L1 expression (5% tumour cell membrane expression: the percent of tumour cells demonstrating plasma membrane PD-L1 staining of any intensity in a minimum of 100 evaluable tumour cells using the Dako PD-L1 IHC 28-8 pharmDx assay.).
	Exploratory endpoint	DMFS	DMFS was programmatically determined based on the first date of distant metastasis provided by the investigator and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause) whichever occurred first.
Database lock	Following the initial database lock in Jul-17, a subsequent database lock occurred in Dec-17, which allowed all subjects to have a minimum of 24 months follow-up after first dose of study therapy. Data from this later database lock was submitted and assessed and is also reflected in the SmPC		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All randomized subjects with a minimum follow-up of 24 months		
Descriptive statistics and estimate variability	Treatment group	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg
	Number of subject	n=453	n=453
	RFS		
	Events, n (%)	171 (37.7)	221 (48.8)
	Median, months	30.75[a]	24.08
	95% CI	(30.75, N.A.)	(16.56, N.A.)
	HR	0.66	
	97.56% CI	(0.54, 0.81)	
	Stratified log rank p-value	< 0.0001	
	Rate at 12 months, %	70.4	60.0
	95% CI	(65.9, 74.4)	(55.2, 64.5)
	Rate at 18 months, %	65.8	53.0
	95% CI	(61.2, 70.0)	(48.1, 57.6)
	Rate at 24 months, %	62.6	50.2

	95% CI	(57.9, 67.0)	(45.3, 54.8)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	All randomized subjects with a minimum follow-up of 24 months		
	RFS by PD-L1 expression		
	Subjects with ≥ 5% PD-L1, n (%)	152 (33.6)	154 (34.0)
	Median, months	30.75	27.20
		(30.75, N.A)	(22.41, N.A)
	Unstratified HR	0.54	
		(0.36, 0.81)	
	Subjects with < 5% PD-L1, n (%)	275 (60.7)	286 (63.1)
	Median, months	N.A.	15.90
		(21.72, N.A)	(10.25, 25.53)
	Unstratified HR	0.73	
		(0.57, 0.92)	
	Subjects with Non-quantifiable PD-L1, n (%)	26 (5.7)	13 (2.9)
	Median, months	N.A.	N.A.
		(6.70, N.A.)	(4.76, N.A.)
	Unstratified HR	0.79	
		(0.28, 2.22)	
Analysis description	**Exploratory Analysis**		
Analysis population and time point description	All randomized subjects with Stage III disease at study entry with a minimum follow-up of 18 months		
	Exploratory Endpoint (DMFS)		
	Events/number of subjects, n/N (%)	107/370 (28.9)	126/366 (34.4)
	Median, months	N.A.	N.A.
		(N.A., N.A)	(N.A., N.A)

	Unstratified HR	0.76	
		(0.59, 0.98)	
	Stratified log rank p-value	0.0340	
	Rate at 12 months, %	80.1	72.7
	95% CI	(75.6, 83.8)	(67.6, 77.0)
	Rate at 18 months, %	75.2	67.1
	95% CI	(70.3, 79.3)	(61.8, 71.8)
	Rate at 24 months, %	70.5	63.7
	95% CI	(65.4, 75.0)	(58.2, 68.6)

[a] It should be noted that the median provided is unstable due to low number of patients and censoring with 24 months of follow-up

Clinical studies in special populations

Elderly patients

Patients ≥65 years old comprised 26.5% of the nivolumab group and 25.5% of the ipilimumab group, whereas patients ≥75 years old comprised 3.8% and 2.9% respectively. Table 15 summarises the RFS in the elderly patients.

Table 14: Recurrence-Free Survival in Elderly Patients

	Age 65-74		Age 75-86	
	Nivolumab	Ipilimumab	Nivolumab	Ipilimumab
patients number/total number (%)	103/453 (22.7%)	101/453 (22.3%)	17/453 (3.8%)	13/453 (2.9%)
Events/patient number (%)	43/103 (41.7%)	52/101 (51.5%)	5/17 (29.4%)	7/13 (53.8%)
Median, months	N.A.	16.10	N.A.	16.76
	(16.07, N.A)	(9.56, N.A.)	(10.81, N.A.)	(4.21, N.A.)
Unstratified HR	0.70		0.47	
	(0.47, 1.05)		(0.15-1.50)	

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study

(CA209238). The study included adult patients, who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7th edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumour PD-L1 status. Patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomisation) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomised to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomisation was stratified by tumour PD-L1 expression (≥ 5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumour assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

In this adjuvant setting, it is not expect that patients are treated until disease progression as many patients at low and high risk are cured even without systemic treatment after complete resection. Hence, the decision was made to limit the duration of study therapy of both ipilimumab and nivolumab for study CA209238 to 1 year maximum duration based on prior experience with immunotherapies (interferon and ipilumumab). This is acceptable as it is possible that the optimal treatment duration could be shorter than currently proposed but no further data has been provided to support a shorter dosing regimen.

Ipilimumab, although not approved for adjuvant treatment of melanoma in the EU, was used as the comparator for this study. According to the guidelines, the comparator should be the best available, evidence-based and widely used treatment and therefore, the comparator is acceptable, considering that such active treatments can be used in the EU. In addition, ipilimumab appears to have similar RFS rates in trials CA184029 and CA209238 with the 1-year RFS rates of 63.5% and 60.5% respectively, which is reassuring from the perspective of consistency of the treatment effect, even taking into account that the patient populations are slightly different.

The use of RFS as primary endpoint is an accepted clinical endpoint for adjuvant treatment in many tumour types (eg breast, CRC) and also would apply to melanoma, as long as there is no detrimental effect observed for OS. It is yet unknown whether there is a positive correlation between RFS and OS and if higher rates of RFS will lead to an increase in OS in patients that have recurrent disease in the long term. There is some data that appears to suggest that a delay in recurrent disease may prolong OS, however, further long term data is needed to make any firm conclusion.

In accordance with the guideline for the evaluation of anticancer medicinal products in man the trial is set up to include patients representative of those likely to be treated with the experimental compound in clinical practice. Overall, the inclusion and exclusion criteria are considered to be appropriate.

Baseline characteristics were generally balanced between the two groups. The median age was 55 years (range: 18-86), 58% were men, and 95% were white. Baseline ECOG performance status score was 0 (90%) or 1 (10%). The majority of patients had AJCC Stage III disease (81%), and 19% had

Stage IV disease. Forty-eight percent of patients had macroscopic lymph nodes and 32% had tumour ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and; 13% BRAF were status was unknown. For tumour PD-L1 expression, 34% of patients had PD-L1 expression ≥ 5% and 62% had < 5% as determined by clinical trial assay. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

The number of elderly patients was balanced between the treatment groups. Patients ≥65 years old comprised 26.5% of the nivolumab group and 25.5% of the ipilimumab group. The number of patients ≥75 years low with 17 (3.8%) and 13 (2.9%) patients in the nivolumab and ipilimumab arms, respectively. It is of note that the trial inclusion criteria also included adolescents 15 year an above but no patient within this age demographic was enrolled.

Via protocol amendment 18, an interim analysis for RFS was added during the study, only 4 months in advance. In general, interim analyses for PFS-like endpoints are not recommended (EMA/CHMP/27994/2008/Rev.1) however, this was taken into account in the calculation of the alpha spending and is not considered to have an impact on the validity or interpretability of the results. It is possible that there might have been some informative censoring when subjects withdrew consent or lost to follow-up or had the category other. As there were 154 RFS events in the nivolumab arm and 206 in the ipilimumab arm, it is considered unlikely that this will affect the final conclusion on RFS.

In general, the conduct of the study did not raise any serious concerns and there were no imbalances during randomization and in the different stratification groups which could have introduced any important biases in the analyses of the primary efficacy parameters.

Efficacy data and additional analyses

Primary Endpoint – Recurrence-Free Survival

The study met its primary endpoint in all randomized subjects. The trial demonstrated a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with the ipilimumab 10 mg/kg arm with HR of 0.66 (95% CI: 0.54,0.81; stratified log-rank p < 0.0001).

RFS rates were higher in the nivolumab group than in the ipilimumab group at 6 months (79.6% vs 72.4%), at 12 months (70.4% vs 60.0%), at 18 months (65.8% vs 53.0%), at 24 month (62.6% vs 50.2%) and at 30 months (60.4% vs 44.4%). Minimum follow-up was approximately 24 months. OS was not mature at the time of this analysis. A separation of the Kaplan-Meier curves is shown. The difference in RFS rate between the nivolumab group and ipilimumab group is increasing over time 7.2%, 10.4%, 12.8%, 12.5% and 16.0% at 6, 12, 18, 24 and 30 months, respectively. Although the treatment was stopped at 12 months, the separation of the curves seems to continue over time and appears to stabilise. It is unlikely that the trend will change after further follow up as most patients in stage IIB/C and IV at high risk of recurrence will have relapsed within 3 years.

There is some evidence from the literature that RFS may be a surrogate for OS[16]. The studies used in this modelling approach were performed at the time that the treatment landscape in the advanced melanoma setting did not include immunotherapies.. However, no long-term efficacy data were presented for the trial CA209238. A descriptive analysis of the immature OS was presented showing no detriment. As the efficacy assessment in terms of OS is based partially on the assumption that the surrogate endpoints (RFS and DMFS) may lead to an improvement on OS in the long term, it would be important to confirm the impact of the intervention on clinical outcome or disease progression. Therefore, the final RFS/DMFS analysis is expected to be performed in 2019 and the final OS analysis

[16] Stefan Suciu, Alexander M. M. Eggermont, Paul Lorigan, John M. Kirkwood, Svetomir N. Markovic, Claus Garbe, David Cameron, Srividya Kotapati, Tai-Tsang Chen, Keith Wheatley, Natalie Ives, Gaetan de Schaetzen, Achmad Efendi, Marc Buyse; Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II–III Melanoma Adjuvant Therapy, JNCI: Journal of the National Cancer Institute, Volume 110, Issue 1, 1 January 2018, djx133,

is expected to be performed in 2020. The final study report of the RFS, DMFS and OS should be submitted for assessment.

Secondary efficacy endpoint – Correlation between RFS and Baseline PD-L1 Expression, BRAF mutation status

RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease. The results (with a minimal of 24 months follow-up) of the analysis of RFS by PD-L1 tumour expression showed that in patients with tumour expression ≥1%, ≥5%, ≥10% the HR was 0.61 (95%CI 0.47, 0.79), 0.54 (95%CI 0.36, 0.81) and 0.54 (95%CI 0.33, 0.87) suggesting that PD-L1 expression results in lower risk of recurrence in nivolumab treated group compared to ipilimumab treated group. However, in patients with tumours <1%, the HR was 0.78 (95%CI 0.57, 1.08) with KM curves almost overlapping suggesting that patients treated with nivolumab may not have an advantage in terms of benefit over ipilimumab treatment and that nivolumab is at least as effective as ipilimumab in patients with PD-L1 expression <1%.

Furthermore, in the analyses provided by the applicant, PD-L1 expression is defined using the percentage of tumour cells demonstrating plasma membrane PD-L1 staining of any intensity. Efficacy in melanoma patients treated with PD-1 inhibitors might also be related to PD-L1 expression on tumour-associated inflammatory cells[17] . To understand the value of PD-L1 expression in the tumour and on the infiltrating immune cells it is essential to analyse PD-L1 expression on the infiltrating immune cells as well to correlate the expression of PD-L1 on the infiltrating inflammatory cells (and the PD-L1 expression on both tumour cells and inflammatory cells) with efficacy. There is uncertainties with respect to the efficacy of a nivolumab in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence. Therefore, the MAH has committed to investigate the predictive value of biomarkers for the efficacy of nivolumab, which has been included as condition to the MA in Annex IID.

Subgroup analyse for BRAF WT vs V600 mutation showed that there was no effect of BRAF mutation on the RFS or DMFS in patients treated with either nivolumab or ipilimumab.

Exploratory Endpoint – Distant Metastasis-free Survival

There was a favourable DMFS shown for nivolumab compared to ipilimumab with HR = 0.76 (95% CI: 0.59, 0.98; stratified log-rank p = 0.0340). The DMFS rate at 24 months was also favourable in the nivolumab group 70.5% compared to 63.7% for ipilumumab group. DMFS is an exploratory endpoint, however it is supportive of the overall effect on RFS and the clinical benefit of nivolumab as adjuvant treatment of melanoma. From a clinical perspective, as melanoma is generally considered to be incurable when distant metastasis are present, a prolonged period free of distant metastasis, could be considered as a more clinically relevant representative for long-term clinical benefit, rather than RFS.

Subgroup analyses

In general, the subgroup analyses for both RFS and DFMS were consistent with the overall population. For some subgroups, the unstratified HR for RFS did not favour nivolumab over ipilimumab, but this was mainly due to small sample size with large variations and therefore, not clinically meaningful.

In addition, LDH expression is a strong prognostic factor in (metastatic) melanoma. No subgroup analysis was performed on LDH expression. Over 90% of the subject had normal LDH expression. Therefore, the subgroup of patients with high LDH is very small and no conclusions can be made.

Multivariate analysis of RFS

In a multivariate analysis of RFS, the treatment effect when adjusted for age (≥ 65 years vs < 65 years), gender (male vs female), baseline ECOG performance status (PS) (1 vs 0), disease stage

[17] Harriet M. Kluger, Christopher R. Zito, Gabriela Turcu, Marina K. Baine, Hongyi Zhang, Adebowale Adeniran, Mario Sznol, David L. Rimm, Yuval Kluger, Lieping Chen, Justine V. Cohen and Lucia B. Jilaveanu. PD-L1 Studies Across Tumor Types, Its Differential Expression and Predictive Value in Patients Treated with Immune Checkpoint Inhibitors, Clin Cancer Res August 1 2017 (23) (15) 4270-4279; DOI: 10.1158/1078-0432.CCR-16-3146

(Stage IIIc vs Stage IIIb, Stage IV vs Stage IIIb, and other vs Stage IIIb), PD-L1 status (≥5% vs < 5%; indeterminate vs < 5%), and time from surgical resection to randomization (≥ 6 weeks vs < 6 weeks) was consistent with the primary RFS analysis (data not shown).

Progression-free survival on next line systemic therapy

A post-hoc analysis of PFS2 showed an improvement on next line systemic therapy with nivolumab 3 mg/kg as adjuvant therapy compared with ipilimumab 10 mg/kg (HR = 0.74 [95% CI: 0.57, 0.97]; stratified log-rank p =0.0302). Assuming that next-line therapy is mainly given when recurrence occurs, it is likely that the time to next-line therapy is in favour of nivolumab compared to ipilimumab, as the nivolumab patients have a longer time until recurrence (HR=0.60 [95% CI: 0.46,0.77). No difference is seen in time to second next-line systemic therapy between the two treatment groups, although no firm conclusions can be drawn due to a low number of events and extensive censoring.

Extrapolation to patients stage IIIA

The trial included only adult patients with Stage IIIB, IIIC and IV (as per the AJCC 7th edition), but the initially requested indication also included patients with Stage IIIA and adolescents. Keeping the new AJCC 8th edition in mind, the current trial included patients with a wide range of prognostic estimates (including patients in the "new" category IIIA) Therefore, the wording of the indication became a more general wording without the mentioning of specific disease stages.

Extrapolation to adolescents

The MAH initially requested an indication that included adolescent from 12 years and older, in line with the inclusion criteria of the protocol . However, only adult patients of 18 years and older were enrolled in the trial. As no data has been generated in this patient population with early signs of disease, a similar PK and safety profile cannot be assumed in adjuvant melanoma for this patient population event taking account the argument that disease characteristics for stage III-IV melanoma between adolescents and adults might be comparable. Therefore, the indication was restricted to adult patients only.

Quality of Life

With regard to all 3 questionnaires (EORTC QLQ-C30, EQ-5D and WPAI:GH) at baseline, the scores were comparable between treatment groups (not statistically tested). Although reduction in the mean change score from baseline as seen, none were reaching the MID for the patient at any time point for either treatment group. For the QLQ-C30 also no clinically meaningful difference in score were detected for the individual functioning or symptom scales in both treatment groups (SmPC section 5.1).

Additional expert consultation

Upon request from the Committee for Human Medicinal Products (CHMP), this SAG meeting was convened on 18 June 2018 in the context of an extension of indication procedure. The following questions were addressed by the experts:

1. What is the clinical relevance of the improvement in RFS when seen in light of the results of the analyses of the secondary endpoints, eg dMFS, having in mind:

- **that available OS data are descriptive and limited;**
- **the standard of care in the EU is observation;**
- **ipilimumab has shown an OS benefit as adjuvant treatment for melanoma at a time that checkpoint inhibitors were not available.**

The SAG agreed that RFS is considered a reliable and clinically relevant endpoint in this setting of adjuvant treatment of stage III melanoma. This is in concordance with the EMA anticancer guidelines. The relevance also in the melanoma setting is justified on the basis of delaying distant metatstases, which is associated with very poor prognosis. It is acknowledged that a fraction of distant metastases are still amenable to surgery (e.g., small cutaneous or lymph-node recurrence) but the majority carry a very poor prognosis (e.g., CNS metastasis).

The effect on RFS was, in addition, supported by an effect on DMFS. The effect in terms of RFS was larger compared to interferon or iplilimumab (both of which are sometimes used as adjuvant

treatments). PFS2 data are also supportive showing that an important detriment in subsequent treatments and OS is unlikely.

Nivolumab increases the efficacy compared to ipilimumab (already an improvement compared to no adjuvant treatment) and the former is associated with a better toxicity profile.

From a biological point of view, it is likely that a better effect can be achieved when the tumor load is smaller as in the adjuvant setting compared to the metastatic setting (this paradigm has been verified in a number of solid tumors for chemotherapy) and data from another PD-1 inhibitor, pembrolizumab showed a consistent (and somewhat larger) effect in stage IIIA patients. From a mechanism of action point of view, immunotherapy may also be more active early on in the disease before the development of subclones that may escape immunological surveillance, potentially also associated with higher degree of tumour heterogeneity in the macrometastatic setting.

The question of whether treating earlier in the adjuvant setting is better than treating later in the metastatic setting is often raised when introducing treatments at earlier stages of disease. Although there are no data to compare the two strategies, from a patient preference point of view, spending longer time recurrence and distance metastasis-free is very likely to be more valuable than spending longer time in the metastatic setting. Also, given the pace of discovery, this may also increase the chances of more effective treatments becoming available before reaching the metastatic setting.

There was some discussion about whether the effect observed could be extrapolated to the current stage IIIA classification (TNM classification version 8) that includes better prognosis patients than those treated in the study (version 7). Although there were diverging views, the prevalent view was that the effects observed could be extrapolated to the new staging system. Any uncertainty about treating lower-risk patients should be part of the patient-physician discussion, including other risk factors and co-morbidities.

2. Please discuss the possible impact of adjuvant treatment with nivolumab on the efficacy of subsequent post-progression therapy.

The SAG agreed unanimously that based on the results of PFS2, it is unlikely that treatment with nivolumab in the adjuvant setting hampers the efficacy of subsequent treatments.

3. Is the safety profile of the proposed treatment regimen acceptable for the intended patient population?

Yes, the safety profile is acceptable in compared to other adjuvant treatments in other solid tumours (e.g., breast cancer; colorectal cancer) and compared to treatments in melanoma that have been studied and are sometimes used, like interferon and ipilimumab. Although rare severe toxicity is possible, including endocrine, CNS and lung toxicity, no fatalities were reported for nivolumab in the present study. The toxicity is also acceptable in relative terms given the effect on RFS observed, and overall the benefit-risk balance is therefore judged to be positive.

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy data based on statistically significant RFS suggests a clinically meaningful benefit of nivolumab on adjuvant treatment compared to ipilimumab in high risk, completely resectable Stage IIIb/c and IV melanoma subjects of 18 years of age and older. RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease. These data are supported by the subgroup analyses as well as DMFS and PFS2. As OS is still immature, it is not clear whether this prolongation in RFS and DMFS will translate into a long-term survival benefit but the evidence so far accumulated, though immature, suggests no detrimental effect on OS. As the staging of the disease has changed and the studied population is different than the

patient population described in the updated strata for stage IIIB/C and IV, the proposed indication has been amended to reflect the intended population at high risk of recurrence i.e. in patients with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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

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

- To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1 (on tumour- and tumour associated immune cells), PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, Tumour mutational burden) as predictive of nivolumab adjuvant therapy efficacy. This will be provided for the approved indications:
    - Adjuvant treatment of melanoma (monotherapy): study CA209238
- The MAH should submit the final OS data for study CA209238: A Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma. Due 4Q2020.

The CHMP considers the following measure is required as a post-authorisation measure to address issues related to efficacy:

- RFS/DMFS PAM: The MAH committed to provide the updated RFS/DMFS data with a minimal follow-up of 36 months as soon as it is available. Due 4Q2019. This should be reflected in a PAM.

2.5. Clinical safety

Introduction

The current safety data have been provided from the individual phase II and III studies across the various indications, such as non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), head and neck cancer (SCCHN) and urothelial carcinoma (UC).

The known safety profile of nivolumab includes fatigue, gastrointestinal complaints (including diarrhoea and nausea), and multiple immune-related AEs, including immune-related pneumonitis, colitis, hepatitis, nephritis, rash, and endocrinopathies (including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis).

New safety data presented in this application come from the pivotal Study CA209238. The all-treated population in the pivotal study, which are all randomized subjects who have received at least one dose of study drug, was the primary population for safety analyses. This population included 452 patients in the nivolumab group and 453 patients in the ipilimumab group. At the time of the Interim analysis (12 June 2017), the minimum follow-up period was approximately 18 months. Safety and tolerability were measured by the incidence of AEs, serious adverse events (SAEs), deaths, and laboratory abnormalities. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. AEs and laboratory values were graded for severity according to the National Cancer Institute

(NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Also safety and tolerability were further quantified by the incidence of AEs leading to discontinuation, AEs leading to dose modification, select AEs, immune-mediated AEs (IMAEs), and other events of special interest.

Patient exposure

The proportion of treated subjects who received ≥ 90% of the planned dose intensity was 86.3% in the nivolumab group and 80.1% in the ipilimumab group. 94.9% of treated subjects in both groups received first dose of treatment within 3 days of randomization. The median number of doses received was 24.0 (range: 1 - 26) in the nivolumab group and 4.0 (range: 1 - 7) in the ipilimumab group. The median duration of therapy was 11.50 months in the nivolumab group and 2.73 months in the ipilimumab group. After approximately 3 weeks, the proportion of subjects still on therapy was higher at every time point in the nivolumab group than in the ipilimumab group.

For dose omissions, 35.4% of subjects in the nivolumab group and 19.6 % in the ipilimumab group had a dose omission (Table 15). Primary reason for dose omission was AEs in both groups. Relatively more subjects in the nivolumab arm compared to the ipilimumab arm had dose omissions; however, relatively more subjects in the ipilimumab arm had dose omissions due to AEs. More subjects in the nivolumab arm had dose omission due to other reasons.

Table 15: Dose omission of Study Therapy - All Treated Subjects

	Nivolumab 3 mg/kg N = 452	Ipilimumab 10 mg/kg N = 453
DOSE OMISSION		
SUBJECTS WITH AT LEAST ONE OMITTED DOSE (%)	160 (35.4)	89 (19.6)
NUMBER OF OMITTED DOSES PER SUBJECT (%)		
0	292 (64.6)	364 (80.4)
1	77 (17.0)	73 (16.1)
2	36 (8.0)	13 (2.9)
3	30 (6.6)	3 (0.7)
>= 4	17 (3.8)	0
TOTAL NUMBER OF OMITTED DOSES	325	108
REASON FOR OMITTED DOSE (A)		
ADVERSE EVENT	195 (60.0)	77 (71.3)
OTHER	108 (33.2)	24 (22.2)
NOT REPORTED	22 (6.8)	7 (6.5)

For infusion interruptions, 2.4% of subjects in the nivolumab group and 4.0% in the ipilimumab group had an infusion interruption. Of the subjects who required an infusion interruption, most had 1 infusion interrupted in both groups.

For infusion rate reductions, 3.8% of subjects in the nivolumab group and 3.1% in the ipilimumab group had an infusion rate reduction. Of the subjects who required an infusion interruption, most had only 1 infusion rate reduction in both groups.

Concomitant Therapy

Most subjects (91.8% nivolumab and 95.6% ipilimumab) received concomitant non-study medications. Immune-modulating concomitant medications were administered for management of AEs in 45.1% and 79.2% of subjects in the nivolumab and ipilimumab groups, respectively. Systemic corticosteroids were the most common type of immune-modulating medication administered (31.6% of nivolumab subjects and 70.2% of ipilimumab subjects). Immunosuppressive agents such as infliximab were administered to fewer subjects in the nivolumab arm (1.8%) than in the ipilimumab arm (10.2%). Pre-medication with systemic corticosteroids was administered to 1.3% of treated subjects in both groups. Dermatological preparation of corticosteroids were administered equally in nivolumab and ipilimumab subjects (23.9% vs 29.6% respectively).

Adverse events

Any grade adverse events were reported in 96.9% of subjects in the nivolumab group and 98.5% of subjects in the ipilimumab group (Table 16). In the nivolumab group, the most frequently reported AEs were fatigue (42.7%), diarrhoea (36.9%), pruritus (28.1%), rash (25.4%), headache (23.5%), and nausea (23.0%). In the ipilimumab group, the most frequently reported AEs were diarrhoea (54.5%), fatigue (40.8%), pruritus (36.9%), rash (33.1%), headache (31.3%), nausea (28.0%), and pyrexia (21.2%).

Grade 3-4 AEs were reported in 25.4% of subjects in the nivolumab group and 55.2% of subjects in the ipilimumab group (Table 16). In the nivolumab group, the most frequently reported Grade 3-4 AEs were lipase increased (4.9%), diarrhoea (2.4%), and amylase increased (2.4%). In the ipilimumab group, the most frequently reported Grade 3-4 AEs were diarrhoea (10.6%), colitis (7.7%), and alanine aminotransferase (ALT) increased (6.2%). A similar AE pattern was seen in subjects with extended follow-up (100 days after last dose).

Table 16: Adverse Events by Worst CTC Grade Reported in ≥ 10% of Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 452			Ipilimumab 10 mg/kg N = 453		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	438 (96.9)	115 (25.4)	0	446 (98.5)	250 (55.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	302 (66.8)	7 (1.5)	0	320 (70.6)	18 (4.0)	0
FATIGUE	193 (42.7)	3 (0.7)	0	185 (40.8)	4 (0.9)	0
ASTHENIA	72 (15.9)	1 (0.2)	0	70 (15.5)	7 (1.5)	0
PYREXIA	32 (7.1)	0	0	96 (21.2)	5 (1.1)	0
GASTROINTESTINAL DISORDERS	289 (63.9)	20 (4.4)	0	337 (74.4)	92 (20.3)	0
DIARRHOEA	167 (36.9)	11 (2.4)	0	247 (54.5)	48 (10.6)	0
NAUSEA	104 (23.0)	1 (0.2)	0	127 (28.0)	0	0
ABDOMINAL PAIN	53 (11.7)	0	0	73 (16.1)	4 (0.9)	0
CONSTIPATION	46 (10.2)	0	0	40 (8.8)	0	0
VOMITING	37 (8.2)	2 (0.4)	0	65 (14.3)	2 (0.4)	0
COLITIS	10 (2.2)	3 (0.7)	0	46 (10.2)	35 (7.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	280 (61.9)	8 (1.8)	0	313 (69.1)	29 (6.4)	0
PRURITUS	127 (28.1)	0	0	167 (36.9)	5 (1.1)	0
RASH	115 (25.4)	5 (1.1)	0	150 (33.1)	16 (3.5)	0
RASH MACULO-PAPULAR	26 (5.8)	0	0	52 (11.5)	9 (2.0)	0
INFECTIONS AND INFESTATIONS	208 (46.0)	12 (2.7)	0	160 (35.3)	25 (5.5)	0
VIRAL UPPER RESPIRATORY TRACT INFECTION	52 (11.5)	0	0	25 (5.5)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	200 (44.2)	4 (0.9)	0	181 (40.0)	7 (1.5)	0
ARTHRALGIA	87 (19.2)	2 (0.4)	0	59 (13.0)	2 (0.4)	0
MYALGIA	63 (13.9)	1 (0.2)	0	31 (6.8)	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	182 (40.3)	9 (2.0)	0	203 (44.8)	19 (4.2)	0
HEADACHE	106 (23.5)	2 (0.4)	0	142 (31.3)	9 (2.0)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	178 (39.4)	6 (1.3)	0	164 (36.2)	8 (1.8)	0
COUGH	82 (18.1)	0	0	78 (17.2)	0	0
INVESTIGATIONS	129 (28.5)	36 (8.0)	0	174 (38.4)	69 (15.2)	0
ALT INCREASED	33 (7.3)	5 (1.1)	0	81 (17.9)	28 (6.2)	0
AST INCREASED	28 (6.2)	2 (0.4)	0	71 (15.7)	20 (4.4)	0
ENDOCRINE DISORDERS	93 (20.6)	5 (1.1)	0	97 (21.4)	20 (4.4)	0
HYPOTHYROIDISM	52 (11.5)	1 (0.2)	0	34 (7.5)	2 (0.4)	0
HYPOPHYSITIS	7 (1.5)	2 (0.4)	0	49 (10.8)	11 (2.4)	0
METABOLISM AND NUTRITION DISORDERS	85 (18.8)	4 (0.9)	0	123 (27.2)	26 (5.7)	0
DECREASED APPETITE	38 (8.4)	0	0	63 (13.9)	1 (0.2)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.2a

Late-Emergent Adverse Events

Late-emergent drug-related AEs were defined as drug-related AEs with an onset date > 100 days after the last dose of study therapy. Late emergent drug-related AEs were reported in 16 (3.5%) subjects in the nivolumab group, including 3 (0.7%, diarrhea, pneumonitis, diabetic ketoacidosis) with Grade 3-4 events, and 22 (4.9%) subjects in the ipilimumab group, including 6 (1.3%; diarrhoea, colitis, rash, adrenocortical insufficiency, increased lipase, bone marrow failure, immune thrombocytopenic purpura) with Grade 3-4 events. No events were reported in >1% of subjects in either treatment group.

Drug-Related Adverse Events

Any-grade drug-related AEs were reported in 85.2% of subjects in the nivolumab group and 95.8% of subjects in the ipilimumab group, and the pattern is similar to the all causality AEs. In the nivolumab group, the most frequently reported drug-related AEs were fatigue (34.5%), diarrhoea (24.3%), and pruritus (23.2%). In the ipilimumab group, the most frequently reported drug-related AEs were diarrhoea (45.9%), pruritus (33.6%), fatigue (32.9%), rash (29.4%), and nausea (20.1%).

Grade 3-4 drug-related AEs were reported in 14.4% of subjects in the nivolumab group and 45.9% of subjects in the ipilimumab group. In the nivolumab group, Grade 3-4 drug-related AEs reported in ≥ 1% of subjects were lipase increased (4.2%), amylase increased (2.0%), diarrhoea (1.5%), ALT increased (1.1%), and rash (1.1%).

In the ipilimumab group, Grade 3-4 drug-related AEs reported in ≥ 1% of subjects were diarrhoea (9.5%), colitis (7.5%), ALT increased (5.7%), AST increased (4.2%), lipase increased (3.5%), rash (3.1%), hypophysitis (2.4%), rash maculo-papular (2.0%), headache (1.5%), GGT increased (1.3%), transaminases increased (1.3%), hepatitis (1.3%), and pruritus, amylase increased, and autoimmune colitis (all 1.1%).

A similar drug-related AE pattern was seen in subjects with extended follow-up (100 days after last dose).

When incidence rates were exposure-adjusted, the AE rate was lower in the nivolumab group than in the ipilimumab group (1264.7 vs 2267.7 incidence rate per 100 person years).

Serious adverse event / deaths / other significant events

The overall frequencies of SAEs and drug-related SAEs were lower in the nivolumab group than in the ipilimumab group. Drug-related SAEs consisted mainly of events in the System Organ Class (SOCs) of Gastrointestinal and Endocrine Disorders in both treatment groups.

SAEs were reported in 17.5% of subjects in the nivolumab group and 40.4% of subjects in the ipilimumab group (Table 17). Grade 3-4 SAEs were reported in 10.6% and 31.8% of subjects in the nivolumab and ipilimumab groups, respectively. In the nivolumab group, the most frequently reported SAEs were melanoma recurrent (1.8%) and cellulitis (1.5%). In the ipilimumab group, the most frequently reported SAEs were diarrhoea (7.7%) and colitis (7.1%).

Drug-related SAEs were reported in 5.3% of subjects in the nivolumab group and 31.1% of subjects in the ipilimumab group. Grade 3-4 drug-related SAEs were reported in 3.3% and 24.5% of subjects in the nivolumab and ipilimumab groups, respectively. In the nivolumab group, the most frequently reported drug-related SAEs were diarrhoea and pneumonitis (0.7% each). In the ipilimumab group, the most frequently reported drug-related SAEs were diarrhea and colitis (7.1% each).

The frequency of serious adverse events (all causality and drug-related) in subject with Extended follow-up (100 days after last dose) is somewhat higher. In general, more events were seen occurring in the ipilimumab group than in the nivolumab group.

Table 17: SAEs by Worst CTC Grade Reported in ≥ 1% of Subject - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 452			Ipilimumab 10 mg/kg N = 453		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	79 (17.5)	48 (10.6)	0	183 (40.4)	144 (31.8)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	25 (5.5)	14 (3.1)	0	11 (2.4)	5 (1.1)	0
MELANOMA RECURRENT	8 (1.8)	4 (0.9)	0	2 (0.4)	1 (0.2)	0
INFECTIONS AND INFESTATIONS	13 (2.9)	10 (2.2)	0	27 (6.0)	21 (4.6)	0
CELLULITIS	7 (1.5)	6 (1.3)	0	3 (0.7)	3 (0.7)	0
GASTROINTESTINAL DISORDERS	8 (1.8)	4 (0.9)	0	79 (17.4)	64 (14.1)	0
DIARRHOEA	4 (0.9)	3 (0.7)	0	35 (7.7)	24 (5.3)	0
COLITIS	1 (0.2)	0	0	32 (7.1)	27 (6.0)	0
AUTOIMMUNE COLITIS	0	0	0	5 (1.1)	5 (1.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (1.5)	3 (0.7)	0	8 (1.8)	6 (1.3)	0
PNEUMONITIS	3 (0.7)	0	0	5 (1.1)	4 (0.9)	0
ENDOCRINE DISORDERS	5 (1.1)	3 (0.7)	0	21 (4.6)	15 (3.3)	0
HYPOPHYSITIS	2 (0.4)	2 (0.4)	0	14 (3.1)	10 (2.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.9)	2 (0.4)	0	15 (3.3)	5 (1.1)	0
PYREXIA	2 (0.4)	0	0	9 (2.0)	2 (0.4)	0
HEPATOBILIARY DISORDERS	3 (0.7)	3 (0.7)	0	16 (3.5)	14 (3.1)	0
HEPATITIS	0	0	0	5 (1.1)	4 (0.9)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.18a

Deaths

As of the 12-Jun-2017 database lock, the immature data show no detriment between the arms. Disease progression was the most common cause of death for both groups (both arms 9.1%). There were no deaths occurring within 30 days of last dose for either group and the proportion of deaths occurring within 100 days of last dose was low for both groups.

No deaths in the nivolumab group and 2 (0.4%) deaths in the ipilimumab group were attributed to study drug toxicity by the investigator. One patient died due to colitis 127 day after last dose of ipilimumab and one patient died due to medullary aplasia 203 days after last dose of ipilimumab.

Three patients treated with nivolumab died due to other reasons; cerebral haemorrhage, sepsis, and septic shock. In the ipilimumab group 2 patients died due to other reasons; general conditions worsening– and septic shock with multi-organ failure and pneumococcal pneumonia.

Select adverse events

Endocrine events

The endocrine select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders. Endocrine select AEs (all-causality, by worst CTC grade) were reported in 106 (23.5%) subjects in the nivolumab group and 106 (23.4%) subjects in the ipilimumab group.

In the nivolumab group, 102 (22.6%) subjects had endocrine select AEs that were considered to be drug-related by the investigator. In the ipilimumab group, 96 (21.2%) subjects had endocrine select AEs that were considered to be drug-related by the investigator. The most commonly reported drug-related event in the nivolumab group was hypothyroidism (10.8%) and in the ipilimumab group was hypophysitis (12.4%). The majority of the drug-related endocrine events were Grade 1-2 (93.6% and 83.5% for nivolumab and ipilimumab respectively); 7 (1.5%) subjects in the nivolumab group and 19 (4.2%) subjects in the ipilimumab group had Grade 3-4 events. Endocrine drug-related select AEs (any grade) led to permanent discontinuation of nivolumab in 3 subjects (0.7%; 2 had Grade 3-4 events) and of ipilimumab in 27 subjects (6.0%; 12 subjects had Grade 3-4 events).

The median time to onset of all grade drug-related endocrine AEs was 8.21 weeks in the nivolumab group, and 8.93 weeks in the ipilimumab group. 17 subjects (16.7%) and 65 subjects (67.7%) received immune modulating medication for any grade drug-related endocrine select AEs in the nivolumab and ipilimumab groups, respectively. 8 (7.8%) subjects in the nivolumab group and 35 (36.5%) subjects in the ipilimumab group were treated with high-dose corticosteroids for a median duration of 3.14 and 2.57 weeks, respectively.

Overall, 52.9% of subjects in the nivolumab group and 42.7% of subjects in the ipilimumab group with drug-related endocrine select AEs resolved; median time to resolution was approximately 48 weeks in the nivolumab group and was not available in the ipilimumab group.

Gastrointestinal Events

Gastrointestinal select AEs (all-causality, any grade) were reported in 172 (38.1%) subjects in the nivolumab group and 256 (56.5%) subjects in the ipilimumab.

114 (25.2%) subjects in the nivolumab group and 219 (48.3%) subjects in the ipilimumab group had GI select AEs that were considered to be drug-related by the investigator. Most drug-related events were Grade 1-2 (92.7% and 74.2% for nivolumab and ipilimumab respectively); 9 (2.0%) subjects in the nivolumab group and 76 (16.8%) subjects in the ipilimumab group had Grade 3-4 events. GI drug-related select AEs (any grade) led to permanent discontinuation of nivolumab in 12 subjects (2.7%; 8 had Grade 3-4 events) and of ipilimumab in 84 subjects (18.5%; 66 subjects had Grade 3-4 events).

The median time to onset of drug-related GI select AEs was 7.71 weeks in the nivolumab group and 4.43 weeks in the ipilimumab group. 24 subjects (21.1%) and 137 subjects (62.6%) received immune modulating medication for any grade drug-related GI select AEs in the nivolumab and ipilimumab groups, respectively. 17 subjects (14.9%) in the nivolumab group and 113 subjects (51.6%) in the ipilimumab group were treated with high-dose corticosteroids for a median duration of 2.86 and 4.0 weeks, respectively.

Overall, 95.6% of subjects in the nivolumab group and 97.3% of subjects in the ipilimumab group with drug-related GI select AEs resolved; median time to resolution was 2.43 weeks in the nivolumab group and 3.14 weeks in the ipilimumab group.

Hepatic Events

Hepatic select AEs (all-causality, any grade) were reported in 50 subjects (11.1%) in the nivolumab group and 116 subjects (25.6%) in the ipilimumab group.

41 (9.1%) subjects in the nivolumab group and 96 (21.2%) subjects in the ipilimumab group had hepatic select AEs considered to be drug-related by the investigator. Most drug-related events were Grade 1-2 (83.7 % and 66.2% for nivolumab and ipilimumab respectively); 8 (1.8%) subjects in the nivolumab group and 49 (10.8%) subjects in the ipilimumab group had Grade 3-4 events. Hepatic drug-related select AEs (any grade) led to permanent discontinuation of nivolumab in 3 subjects (0.7%; 2 had Grade 3-4 events) and of ipilimumab in 34 subjects (7.5%; 31 subjects had Grade 3-4 events).

The median time to onset of drug-related hepatic select AEs was 12.29 weeks in the nivolumab group and 8.14 weeks in the ipilimumab group. 12 subjects (29.3%) and 40 subjects (41.7%) received immune modulating medication for any grade drug-related hepatic select AEs in the nivolumab and ipilimumab groups, respectively. 12 subjects (29.3%) in the nivolumab group and 33 subjects (34.4%) in the ipilimumab group were treated with high-dose corticosteroids for a median duration of 2.64 and 4.29 weeks, respectively.

Overall, 85.4% of subjects in the nivolumab group and 87.5% of subjects in the ipilimumab group with drug-related hepatic select AEs resolved; median time to resolution was 6.14 weeks in the nivolumab group and 4.43 weeks in the ipilimumab group.

Pulmonary Events

Pulmonary select AEs (all-causality, any grade) were reported in 6 (1.3%) subjects in the nivolumab group and 12 (2.6%) subjects in the ipilimumab group.

6 subjects (1.3%) in the nivolumab group and 11 subjects (2.4%) in the ipilimumab group had pulmonary select AEs considered to be drug-related by the investigator. Most drug-related events were Grade 1-2 (100 % and 77.3% for nivolumab and ipilimumab respectively); no subjects in the nivolumab group and 4 (0.9%) subjects in the ipilimumab group had Grade 3-4 events. Pulmonary drug-related select AEs (any grade) led to permanent discontinuation of nivolumab in 2 subjects (0.4%; none had Grade 3-4 events) and of ipilimumab in 7 subjects (1.5%; 4 subjects had Grade 3-4 events)

The median time to onset of drug-related pulmonary select AEs was 7.79 weeks in the nivolumab group and 10.0 weeks in the ipilimumab group. 6 subjects (100%) and 10 subjects (90.9%) received immune modulating medication for any grade drug-related pulmonary select AEs in the nivolumab and ipilimumab groups, respectively. 6 subjects (100%) in the nivolumab group and 9 subjects (81.8%) in the ipilimumab group were treated with high-dose corticosteroids for a median duration of 3.86 and 2.29 weeks, respectively.

Overall, 83.3% of subjects in the nivolumab group and 100% of subjects in the ipilimumab group with drug-related pulmonary select AEs resolved; median time to resolution was 15.14 weeks in the nivolumab group and 3.71 weeks in the ipilimumab group.

Renal Events

Renal select AEs (all-causality, any grade) were reported in 13 (2.9%) subjects in the nivolumab group and 17 (3.8%) subjects in the ipilimumab group.

6 subjects (1.3%) in the nivolumab group and 7 subjects (1.5%) in the ipilimumab group had renal select AEs that were considered to be drug-related by the investigator. All events were Grade 1-2. It should be noted that 3/6 subject in the nivolumab group had acute kidney injury as an adverse event. Drug-related renal select AEs (any grade) led to permanent discontinuation of nivolumab in 1 subject (0.2%) and of ipilimumab in 1 subject (0.2%)

The median time to onset of drug-related renal select AEs was 14.21 weeks in the nivolumab group and 9.71 weeks in the ipilimumab group. 1 subject (16.7%) in the nivolumab group and no subjects in the ipilimumab group received immune modulating medication for any grade drug-related renal select AEs. No subjects were treated with high-dose corticosteroids. Overall, 66.7% of subjects in the nivolumab group and 57.1% of subjects in the ipilimumab group with drug-related renal select AEs resolved; median time to resolution was 10.5 weeks in the nivolumab group and 52.71 weeks in the ipilimumab group.

Skin Events

Skin select AEs (all-causality, any grade) were reported in 243 subjects (53.8%) in the nivolumab group and 294 subjects (64.9%) in the ipilimumab group. 201 subjects (44.5%) in the nivolumab group and 271 subjects (59.8%) in the ipilimumab group had skin select AEs considered to be drug-related by the investigator. The most frequently reported drug-related events in both groups were pruritus, rash, and rash maculo-papular. Most of the drug-related events were Grade 1-2 (97.6% and 90.9% for nivolumab and ipilimumab respectively); 5 (1.1%) subjects in the nivolumab group and 27 (6.0%) subjects in the ipilimumab group had Grade 3-4 events. Drug-related skin select AEs (any

grade) led to permanent discontinuation of nivolumab in 2 subjects (0.4%; 1 subject had a Grade 3-4 event) and of ipilimumab in 8 subjects (1.8%; 7 subjects had Grade 3-4 events).

The median time to onset of drug-related skin select AEs was 8.43 weeks in the nivolumab group and 2.57 weeks in the ipilimumab group. 73 subjects (36.3%) and 128 subjects (47.2%) received immune modulating medication for any grade drug-related skin select AEs in the nivolumab and ipilimumab groups, respectively. 2 subjects (1.0%) in the nivolumab group and 24 subjects (8.9%) in the ipilimumab group were treated with high-dose corticosteroids for a median duration of 7.86 and 2.07 weeks, respectively.

Overall, 66.7% of subjects in the nivolumab group and 73.8% of subjects in the ipilimumab group with drug-related skin select AEs resolved; median time to resolution was 22.14 weeks in the nivolumab group and 9.29 weeks in the ipilimumab group.

Hypersensitivity/Infusion Reactions

Hypersensitivity/infusion reactions (all-causality, any grade) were reported in 14 subjects (3.1%) in the nivolumab group and 10 subjects (2.2%) in the ipilimumab group. 11 subjects (2.4%) in the nivolumab group and 9 subjects (2.0%) in the ipilimumab group had infusion reaction events that were considered to be drug-related by the investigator. All of the drug-related events were Grade 1-2 except 1 (0.2%) Grade 3-4 event of bronchospasm in the nivolumab group; none led to permanent discontinuation of study drug.

The median time to onset of drug-related hypersensitivity/infusion reaction select AEs was 3.29 weeks in the nivolumab group and 6.14 weeks in the ipilimumab group. 2 subjects (18.2%) in the nivolumab group and 2 subjects (22.2%) in the ipilimumab group received immune modulating medication for any grade drug-related hypersensitivity/infusion reaction select AEs. 1 subject (9.1%) in the nivolumab group and 1 subject (11.1%) in the ipilimumab group were treated with high-dose corticosteroids for a median duration of 2.29 and 0.29 weeks, respectively. Overall, 90.9% of subjects in the nivolumab group and 100% of subjects in the ipilimumab group with drug-related hypersensitivity/infusion reaction select AEs resolved; median time to resolution was 0.14 weeks in both groups.

Immune mediated adverse events (IMAE)

IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (ie, with extended follow up). These analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. Endocrine IMAEs included the among others the categories of adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus.

Overall, the majority of IMAEs in the nivolumab group were Grade 1-2. In the Ipilimumab group the majority of patient with IMAEs in the Diarrhea/Colitis and Hepatitis were Grade 3-4. Grade 3-4 IMAEs in the rash, diarrhea/colitis, hepatitis, and hypophysitis categories were less frequently reported (at least 2% difference between treatment groups) in the nivolumab group than in the ipilimumab group; other categories (grade 3-4) were reported at similar frequencies. The most frequently reported IMAE categories (any grade events) were rash (16.2%) and hypothyroidism/thyroiditis (13.9%) in the nivolumab group and diarrhea/colitis (31.8%) and rash (23.2%) in the ipilimumab group. The most frequently reported IMAE categories (Grade 3-4 events) were diarrhea/colitis (2.0%) and hepatitis (2.0%) in the nivolumab group and diarrhoea/colitis (17.2%) and hepatitis (7.5%) in the ipilimumab group.

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

Table 18: Frequency of reporting IMAE categories - All Treated Subjects

	All Grades (percentage of group (%))		3-4 Grade (percentage of group (%))	
	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg
Adrenal insufficiency	7	**19**	0.4	1.3
Hypophysitis	2	**14**	0.4	**4.2**
Hypothyroidism/Thyroiditis	**13.9**	9.1	0.2	0.7
Hyperthyroidism	**8.6**	4.9	0.2	0.4
Diabetes Mellitus	0.9	1.8	0.8	0.4
Diarrhoea/Colitis	6.4	**31.8**	2	**17.2**
Hepatitis	3.3	**9.5**	2	**7.5**
Pneumonitis	1.8	2.6	0	0.9
Nephritis and Renal Dysfunction	0.7	0.2	0.2	0
Rash	16.2	**23.2**	0.7	**4.8**
Hypersensitivity/Infusion Reactions	0.2	0.4	0	0

Bold: Increase in frequency > 2% compared to the other treatment group.

Other events of special interest (OESIs)

OESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, and uveitis.

In the nivolumab group, OESIs within 100 days of last dose of nivolumab were reported as follows:

- 4 subjects with pancreatitis
- 3 subjects with uveitis

In the ipilimumab group, OESIs within 100 days of last dose of ipilimumab were reported as follows:

- 1 subject with a Guillain-Barré Syndrome event (Miller Fisher Syndrome)
- 3 subjects with pancreatitis
- 4 subjects with uveitis
- 1 subject with encephalitis
- 3 subjects with a myositis event (1 with dermatomyositis, 1 with myositis, 1 with polymyositis)

In the nivolumab group, all EOSIs resolved as of data base lock (DBL). In the ipilimumab group, all OESIs resolved, with the exception of an event of Grade 4 drug-related Miller Fisher Syndrome and Grade 2 drug-related dermatomyositis. Among both treatment groups, the following OESI categories had no reported events: myasthenic syndrome, demyelination, myocarditis, and rhabdomyolisis.

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 in the nivolumab and ipilimumab groups. No Grade 3-4 hematologic abnormalities were reported in ≥1% of subjects in either treatment group.

The most prominent shit from baseline was an increase in grade (from 0 to 1-2 or from 1 to 2) for leukocytes and lymphocytes after nivolumab treatment.

Serum Chemistry

Liver function tests

In the nivolumab and ipilimumab groups, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2.

- In the nivolumab group, there were no Grade 3-4 hepatic abnormalities reported in ≥ 5% of subjects. 73.6% and 69.1% ware grade 0 for AST and ALT, respectively.
- In the ipilimumab group, the only Grade 3-4 hepatic abnormalities reported in ≥ 5% of subjects were increased ALT (8.6% Grade 3; 3.2% Grade 4) and increased aspartate aminotransferase (AST) (7.2% Grade 3; 1.4% Grade 4). 69.1% and 56.5% were grade 0 for AST and ALT, respectively.

The overview of on-treatment laboratory abnormalities is provided in Table 19.

Table 19: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects

	Nivolumab 3 mg/kg N = 452	Ipilimumab 10 mg/kg N = 453
	N = 447	N = 444
ALT OR AST > 3XULN	20 (4.5)	68 (15.3)
ALT OR AST > 5XULN	8 (1.8)	53 (11.9)
ALT OR AST > 10XULN	4 (0.9)	28 (6.3)
ALT OR AST > 20XULN	2 (0.4)	14 (3.2)
	N = 447	N = 439
TOTAL BILIRUBIN > 2XULN	3 (0.7)	7 (1.6)
	N = 447	N = 439
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	0	5 (1.1)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	0	5 (1.1)

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Source: Table S.7.6-SI

Kidney function tests

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

In both groups, reported abnormalities in creatinine (increases) were all Grade 1 or 2 (15.4% and 14.4% for nivolumab and ipilimumab respectively). No Grade 3 or 4 abnormalities were reported.

Thyroid Function Tests

The majority of subjects in both groups had normal thyroid-stimulating hormone (TSH) levels at baseline and throughout the treatment period. The proportion of subjects with TSH increases (> ULN) was higher in the nivolumab group than the ipilimumab group (28.0 vs 15.1%, respectively).

Electrolytes

In the nivolumab and ipilimumab groups, most subjects had normal electrolyte levels during the treatment reporting period, and the frequency of these normal electrolyte levels are similar in the two

treatment groups. In both groups, abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity.

- In the nivolumab group, there were no Grade 3-4 abnormalities in electrolytes reported in ≥ 2% of subjects.
- In the ipilimumab group, the only Grade 3-4 abnormalities in electrolytes reported in ≥ 2% of subjects were hyponatremia (2.5% Grade 3, 0.7% Grade 4) and hypokalemia (1.6% Grade 3; 0.5% Grade 4).

Pancreas Function Tests

In the nivolumab and ipilimumab groups, the majority of subjects had normal amylase and lipase values during the treatment reporting period, and the frequency of subjects with normal levels were similar between the two treatment groups. In both groups, abnormalities in amylase and lipase (increases) during treatment were primarily Grade 1-2.

- In the nivolumab group, the only Grade 3-4 abnormality reported in ≥ 5% of subjects was increased lipase (4.7% Grade 3; 2.7% Grade 4).
- In the ipilimumab group, the only Grade 3-4 abnormality reported in ≥ 5% of subjects was increased lipase (7.1% Grade 3; 1.4% Grade 4).

Immunogenicity Results - Exploratory Endpoint

There was low incidence of immunogenicity when nivolumab and ipilimumab were administered as monotherapy in the adjuvant setting. The incidence of subjects being ADA positive was 2.3% (10/426 subjects) and 0.7% (3/405 subjects) following nivolumab and ipilimumab monotherapy. Three subjects (0.7%) were persistent positive in the nivolumab group. No subjects were neutralizing ADA (NAb) positive following either nivolumab or ipilimumab administration. As of the time of the interim analysis, 28 samples from subjects that were positive for ADA in the nivolumab arm were not included in the NAb analyses as they were shipped to the analyzing lab following the database lock. However, these samples have since been analyzed, and all were NAb negative. ADA titers were low ranging from 1 to 8 following nivolumab and 1 to 64 following ipilimumab.

Table 20: Summary of Anti-drug Antibody Assessments - All Nivolumab or Ipilimumab Treated Subject with Baseline and at Least One Post-Baseline Assessment

	Number of Subjects (%)	
	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg
	Nivolumab N = 426	Ipilimumab N = 405
BASELINE ADA POSITIVE	27 (6.3)	18 (4.4)
ADA POSITIVE	10 (2.3)	3 (0.7)
PERSISTENT POSITIVE	3 (0.7)	0
NOT PP - LAST SAMPLE POSITIVE	1 (0.2)	2 (0.5)
OTHER POSITIVE	6 (1.4)	1 (0.2)
NEUTRALIZING ADA POSITIVE	0	0
ADA NEGATIVE	416 (97.7)	402 (99.3)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart; Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint; Other Positive: Not PP but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Source: Table S.7.10

Safety in special populations

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

- A greater frequency of drug-related any-grade AEs was reported in the ≥75 age group (94.1%) vs the <65 age group (85.8%) and also vs the ≥65 and < 75 age group (81.6%); however, a lower frequency of drug-related Grade 3-4 AEs were reported in the ≥75 age group (5.9% vs 12.7% and 21.4%).
- A greater frequency of all-causality and drug-related AEs was reported in White subjects (97.4% and 86.4%) vs Asian subjects (87.5% and 66.7%).
- A greater frequency of drug-related AEs was reported in US and Canada (93.6%) vs Western Europe (82.8%), Eastern Europe (77.5%), or Asia (66.7%).

Discontinuation due to adverse events

Discontinuation of study therapy
As of the 12-Jun-2017 database lock, all subjects in both treatment groups had discontinued study treatment. Primary reason for treatment discontinuation was treatment completion (ie, completed protocol-specified maximum treatment duration of 1 year) in the nivolumab group (60.8% vs 26.9% in the ipilimumab group) and study drug toxicity in the ipilimumab group (45.9% vs 9.1% in the nivolumab group). Discontinuation due to disease recurrence was 26.8% in the nivolumab group and 22.3% in the ipilimumab group.

Discontinuation due to Adverse Events
The overall frequencies of all-causality AEs leading to discontinuation were lower in the nivolumab group than in the ipilimumab group.

AEs leading to discontinuation were reported in 9.7% of subjects in the nivolumab group and 42.6% of subjects in the ipilimumab group (Table 21). Grade 3-4 AEs leading to discontinuation were reported in 4.6% and 30.9% of the subjects in the nivolumab and ipilimumab group, respectively. In the nivolumab group, the most frequently reported AEs leading to discontinuation were diarrhea (7 subjects, 1.5%) and colitis (5 subjects, 1.1%). In the ipilimumab group, the most frequently reported AEs leading to discontinuation were also diarrhea (46 subjects, 10.2%) and colitis (37 subjects, 8.2%).

Drug-related AEs leading to discontinuation were reported in 7.7% of subjects in the nivolumab group and 41.7% of subjects in the ipilimumab group. Grade 3-4 drug-related AEs leading to discontinuation were reported in 3.5% and 30.0% of the subjects in the nivolumab and ipilimumab group, respectively. In the nivolumab group, the most frequently reported drug-related AEs leading to discontinuation were diarrhea (7 subjects, 1.5%) and colitis (5 subjects, 1.1%). In the ipilimumab group, the most frequently reported drug-related AEs leading to discontinuation were diarrhea (45 subjects, 9.9%) and colitis (37 subjects, 8.2%).

Table 21: Adverse Events Leading to Discontinuation by Worst CTC Grade Reported in ≥ 1% of Subject - All Treated subject

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 452			Ipilimumab 10 mg/kg N = 453		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	44 (9.7)	21 (4.6)	0	193 (42.6)	140 (30.9)	0
GASTROINTESTINAL DISORDERS	16 (3.5)	10 (2.2)	0	89 (19.6)	69 (15.2)	0
DIARRHOEA	7 (1.5)	5 (1.1)	0	46 (10.2)	29 (6.4)	0
COLITIS	5 (1.1)	3 (0.7)	0	37 (8.2)	31 (6.8)	0
INVESTIGATIONS	4 (0.9)	1 (0.2)	0	32 (7.1)	27 (6.0)	0
ALANINE AMINOTRANSFERASE INCREASED	2 (0.4)	1 (0.2)	0	16 (3.5)	14 (3.1)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.2)	0	0	13 (2.9)	10 (2.2)	0
ENDOCRINE DISORDERS	3 (0.7)	2 (0.4)	0	27 (6.0)	12 (2.6)	0
HYPOPHYSITIS	0	0	0	19 (4.2)	7 (1.5)	0
HEPATOBILIARY DISORDERS	2 (0.4)	2 (0.4)	0	16 (3.5)	14 (3.1)	0
HEPATITIS	0	0	0	7 (1.5)	6 (1.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.4)	0	0	12 (2.6)	4 (0.9)	0
PNEUMONITIS	2 (0.4)	0	0	7 (1.5)	4 (0.9)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.23

Post marketing experience

Not applicable.

2.5.1. Discussion on clinical safety

Safety data were presented for all subjects included in the pivotal study who received at least one dose of study drug (n=452 for nivolumab and n=453 for ipilimumab). The patient population in this trial has no or very low disease burden and is in general good health. Therefore, it should be expected that the toxicity observed in these subjects who do not have disease symptoms is most likely drug-related and not disease-related.

The majority of subjects, 86.3% of the subjects in the nivolumab and 80.1% of the subjects in the ipilimumab group, received ≥90% of the planned dose intensity, and a medium duration of therapy of 11.50 and 2.73 months respectively (intended treatment period of 12 months). The omission rate is higher in the nivolumab group compared to the ipilimumab group. This is likely caused by the fact that more doses of nivolumab are given. Total number of omitted doses divided by the total number of doses received indicates that 3.7% (325/8871) in the nivolumab group and 5.8% (108/1863) in the ipilimumab of the total amount of doses are omitted. In addition, the amount of administered immune-modulating concomitant medication for the management of AEs is higher in subjects in the ipilimumab group. This suggests a more severe toxicity profile in the patients treated with ipilimumab.

The currently described adverse events are known AEs with regard to nivolumab treatment. Any grade adverse events occurred at the same frequency as with ipilimumab (96.9% vs 98.5%, respectively). In the nivolumab group, the most frequently reported AEs were fatigue (42.7%), diarrhoea (36.9%), pruritus (28.1%), rash (25.4%), headache (23.5%), and nausea (23.0%). In the ipilimumab group, the most frequently reported AEs were diarrhoea (54.5%), fatigue (40.8%), pruritus (36.9%), rash (33.1%), headache (31.3%), nausea (28.0%), and pyrexia (21.2%). However, less grade 3-4 events occurred in the nivolumab group compared to the ipilimumab group (25.4% vs 55.2%, respectively). The toxicity in the adjuvant setting is similar to the toxicity reported in the advanced setting, but with slightly higher frequencies of AEs detected in the adjuvant setting. However, the incidence of grade 3-

4 AEs was not substantially different and certainly not consistently higher, for adjuvant melanoma than for other tumour types and treatment settings.

Drug-related AEs were reported less frequently in the nivolumab group than in the ipilimumab group (85.2% vs 95.8%, respectively). Grade 3-4 drug-related AEs were reported three times less frequent in the nivolumab group compared to the ipilimumab group (14.4%% and 45.9%). In the dataset of nivolumab 3 mg/kg as monotherapy for the adjuvant treatment of melanoma (n = 452), the most frequent adverse reactions (≥ 10%) were fatigue (46%), rash (29%), diarrhoea (24%), pruritus (23%), nausea (15%), arthralgia (13%), musculoskeletal pain (11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The number of patients with drug-related all grade select AEs is lower (gastrointestinal, 25.2% vs 48.3%; hepatic, 9.1% vs 21.2% and skin, 44.5% vs 59.8%) or equal (endocrine, 22.6% vs 21.2%) in the nivolumab group compared to the ipilimumab groups. Fewer patients were treated with immune modulation medication in the nivolumab group compared to the ipilimumab group. The specific endocrine disorders is differentially distributed between the nivolumab and the ipilimumab group. For nivolumab the most commonly reported drug-related events in the nivolumab group ware hypothyroidism (10.8%) and hyperthyroidism (8.0%) and in the ipilimumab group was hypophysitis (12.4%) and hypothyroidism (6.8%).

The overall frequencies of SAEs (17.5% vs 40.4%) and drug-related SAEs (5.3% vs 31.1%) were lower in the nivolumab group than in the ipilimumab group. Grade 3-4 drug-related SAEs were reported in approximately 3.3% in the nivolumab groups, while a 24.5% of the subjects in the ipilimumab group experienced Grade 3-4 drug-related SAEs. Per category, the frequency is in general equal or lower in the nivolumab group. To be noted, SEAs in the category “neoplasm benign, malignant and unspecified (incl cysts and polyps)” occur more often in the nivolumab group. However, these events are categorized as non-drug related. The incidence of grade 3-4 AEs and of SAEs was clearly lower in the nivolumab monotherapy arm than in the ipilimumab arm and a better safety profile for nivolumab compared to ipilimumab can be concluded.

As of the 12-Jun-2017 database lock, a similar number of subjects died in both treatment groups, with disease progression as the most common cause of death.

Immune mediated adverse events

The majority of the IMAEs in the nivolumab group are grade 1-2, while in the ipilimumab group the majority are grade 3-4. Only the grade 1-2 IMAEs on hypothyroidism/thyroiditis and hyperthyroidism occur more often in the nivolumab group (13.9% and 8.6% vs 9.1% and 4.9% respectively), while grade 3-4 IMAEs in the rash (Niv: 0.7%; Ipi: 4.8%), diarrhoea/colitis (Niv 2%: ; Ipi: 17.2%), hepatitis (Niv: 2%; Ipi: 7.5%), and hypophysitis (Niv: 0.4%; Ipi: 4.2%) categories occurred more often in the ipilimumab group. Therefore, the IMAE profile of nivolumab is less severe than that of ipilimumab. In both groups the majority of the events seems manageable by immune-modulation medication, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered.

No clinically meaningful differences were observed for the majority of the laboratory parameters between the two treatment groups. Abnormalities in hepatic parameters occurred more often in the ipilimumab group, while the proportion of subjects with TSH increases (> ULN) was higher in the nivolumab group (Nivo: 28.0 vs Ipi: 15.1%).

There was low incidence of immunogenicity when nivolumab and ipilimumab were administered as monotherapy in the adjuvant setting. Overall, no association was observed between the presence of either nivolumab or ipilimumab antibodies and the occurrence of hypersensitivity and infusion-related reactions.

No significant differences were detected in the frequencies of all-causality and drug-related AEs in the nivolumab group for the subgroups of gender, race, age, and region.

As of the 12-Jun-2017 database lock, all subjects in both treatment groups had discontinued study treatment. For nivolumab, 60.8% of the subjects stopped due to treatment completion, 26.8% due to disease recurrence and 9.1% due to toxicity. For ipilimumab, 26.9% of the subjects stopped due to treatment completion, 22.3% due to disease recurrence and 45.9% due to toxicity. Drug-related AEs leading to discontinuation were reported in 7.7% of subjects in the nivolumab group and 41.7% of subjects in the ipilimumab group.

2.5.2. Conclusions on clinical safety

There were no new safety signals reported during the treatment period and follow up period. The overall safety profile of nivolumab 3 mg/kg for the adjuvant treatment of melanoma (n = 452) was consistent with that established across tumour types for nivolumab monotherapy.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 12.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 12.3 with the following content:

Safety concerns

Table 22 Summary of the Safety Concerns

Important identified risks	Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Cardiac Arrhythmias Complications of allogeneic HSCT following nivolumab therapy in cHL Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Pediatric patients <18 years of age Elderly patients with: − cHL ≥ 65 years of age − SCCHN ≥ 75 years of age Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Use in patients who have undergone influenza vaccination Patients with brain metastases: − Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases − NSCLC – active brain metastases − RCC – any history of or concurrent brain metastases

Pharmacovigilance plan

Table 23 On-going and planned studies in the post-authorisation pharmacovigilance development plan

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

Risk minimisation measures

Table 24 Summary table of Risk Minimisation Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune related skin ARs Other immune-related ARs	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimization measures: • Adverse Reaction Management Guide • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Postmarketing myotoxicity questionnaire (Annex 4) Additional pharmacovigilance activities: • Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cardiac arrhythmias (previously treated melanoma indication, only)	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: • Adverse Reaction Management Guide • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8 Additional risk minimization measures: • Adverse Reaction Management Guide • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Pediatric patients <18 years of age	Routine risk minimization measures: SmPC Section 4.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Two PIPs have been agreed by the EMA
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Elderly patients with: − cHL ≥ 65 years of age − SCCHN ≥ 75 years of age	Routine risk minimization measures: SmPC Sections 4.2, 4.8, and 5.1	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Use in patients who have undergone influenza vaccination	Routine risk minimization measures: Confirmation of a causal or potential relationship between the use of nivolumab and the occurrence of influenza vaccination complications will trigger the update of SmPC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with brain metastases: − Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases − NSCLC – active brain metastases − RCC – any history of or concurrent brain metastases	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

No changes were proposed to the safety concerns, pharmacovigilance plan or to the risk minimisations measures as a result of this extension of indication. This was found acceptable.

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, 5.2 of the SmPC have been updated. Annex II has been updated to reflect new conditions. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

In addition, the previously authorised indication for Opdivo in squamous cell cancer of the head and neck (SCCHN, procedure EMEA/H/C/003985/II/0017) has been further clarified in order to better reflect the target population investigated in the pivotal trial supporting the application.

Clinical oncologists expressed concerns that the previously authorised indication implied that patients in the (neo)adjuvant setting with a platinum-free-interval < 6 months who are still eligible for curative surgery and/or RT could also be treated with Opdivo, which does not have curative intent.

The following wording has therefore been discussed and agreed with the MAH in section 4.1:

"*OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1)"*

In addition, the following wording has been included in section 5.1:

"The study included patients (18 years or older), with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and who have experienced disease …"

The query did not put into question the B/R of the approved indication. The new wording reflects the main inclusion criteria of the patients recruited into the pivotal study. The target population remains the same, and it is a clarification of indication to better describe the population intended to be treated.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Nivolumab is anti-PD1 antibody that binds to the PD-1 receptor on T-cells and thereby blocks the interaction between PD-1 with the ligands PDL-1 and PDL-2. By blocking binding of PD-L1 and PD-L2 to its PD-1 receptor, nivolumab potentiates T cell responses, including anti-tumour response.

3.1.1. Disease or condition

The MAH is applying for an indication in the treatment of adjuvant melanoma in adult patients with involvement of lymph nodes or metastatic disease who have undergone complete resection.

3.1.2. Available therapies and unmet medical need

According to the staging based on the AJCC 7th edition, patients with stage III disease have metastatic nodes, but no distant metastasis. They are at a high risk of recurrence after locoregional resections. Stage IIIA patients have a primary tumour without ulceration and 1-3 micrometastasis in the nodes. While Stage IIIB and C have an ulcerate primary tumour and/or macrometastasis in the nodes. The risk of recurrence increases with increasing disease stage. The overall 5-year RFS for stage IIIA, IIIB, and IIIC patients has been shown to be approximately 63%, 32%, and 11% , and 5-year survival rates are 78%, 59% and 40%, respectively (American Cancer Society). The Stage IV 5-year survival rates are around 15-20%, though this percentage may in reality be higher due to the increase in the use of newly approved drugs for systemic treatment of patients with unresectable and stage IV disease. These new drugs include checkpoint inhibitor immunotherapies, including those that target PD-1 or cytotoxic T-lymphocytes antigen (CTLA-4), and drugs that target the mitogen-activated protein kinase (MAPK) pathway (BRAF and MEK inhibitors and the combination of these drugs).

To reduce the risk of relapse, Stage III and IV patients are candidates for adjuvant treatment after complete surgical treatment.

In the EU, adjuvant treatment with interferon is approved, but due to limited benefit and high toxicity this drug is rarely used in the setting of adjuvant treatment of melanoma. Ipilimumab is approved for the treatment of Stage III resected melanoma in the US but not in the EU.

The standard of care after complete surgical resection differs per EU country. Observation of the lesions and low dose interferon are both used as standard of care in the EU

3.1.3. Main clinical studies

CA209238 is a phase 3, randomised, double-blind study in subjects that had complete resection of stage IIIB/C or stage IV Melanoma and are at high risk of recurrence. Patients are treated with nivolumab 3 mg/kg (every 2 weeks, n=452) or ipilimumab 10 mg/kg (every 3 weeks for 4 doses followed by every 12 weeks starting at week 24, n=453) with a maximum duration of treatment of 1 year and a total follow-up of 5 years. The prognostic covariates, PDL-1 staging and disease staging, were used as stratification factors. The primary endpoint was recurrence-free survival (RFS), secondary endpoints were OS and RFS based on PD-L1 expression, and an exploratory endpoint was distant metastasis-free survival (DMFS).

3.2. Favourable effects

With an initial minimal follow-up of 18 months, the primary endpoint RFS demonstrated a statistically significant improvement in RFS with nivolumab compared to ipilimumab (HR=0.65; 97.56% CI 0.51-0.83; stratified log-rank p < 0.0001). The updated analyses (with a minimal follow-up of 24 months) continued to show a benefit of nivolumab adjuvant therapy over ipilimumab adjuvant therapy with an HR of 0.66 (95% CI: 0.54, 0.81).RFS rates were higher in the nivolumab group than in the ipilimumab group at 6 months (79.6% vs 72.4%, Δ7.2%), at 12 months (70.4% vs 60.0%, Δ10.4%), at 18 months (65.8% vs 53.0%, Δ12.8%), at 24 months (62.6% vs 50.2%, Δ12.5%) and at 30 months (60.4% vs 44.4%, Δ16.0%). The difference in RFS rate between the nivolumab group and ipilimumab group was increasing and remained stable over time. The lower limit of the confidence intervals of the difference in RFS rate are above 0 for every time-period, which points at a numerical advantage of the nivolumab over the ipilimumab arm. The results are considered clinically relevant against an active comparator ipilimumab.

For the secondary endpoint RFS by PD-L1 expression, it was demonstrated that both subjects with higher (≥1%, ≥5%, and ≥10%) and lower (<1%, <5% and <10%) pre-defined PD-L1 expression levels had a lower risk of recurrence for nivolumab vs ipilimumab. Patients with higher PD-L1 expression levels showed a lower risk (HR-range 0.54-0.61) than the patients with lower levels of PD-L1 expression (HR-range 0.71-0.78).

The exploratory endpoint DMFS, demonstrated a superior effect of nivolumab compared to ipilimumab (HR = 0.73 [95%CI: 0.55, 0.95]; stratified log-rank p = 0.0). DMFS rates were higher in the nivolumab group than in the ipilimumab group at 6 months (87.5% vs 82.9%, Δ4.6%), at 12 months (80.1% vs 72.7%, Δ7.4%), at 18 months (75.2% vs 67.1%, Δ8.1%) and at 24 months (70.5% vs 63.7%, Δ6.8%). Superior DMFS was seen consistently for nivolumab compared to ipilimumab at the updated analysis (HR=0.76 [95% CI; 0.59, 0.98; stratified log-rank p = 0.0340]).

As an additional post-hoc analysis, PFS2 data and an improvement in PFS on next line therapy was seen for nivolumab compared to ipilimumab (HR=0.74 [CI:0.57,0.97]; stratified log-rank p = 0.0302).

Although not yet mature, descriptive OS data showed no detrimental effect of nivolumab on survival relative to ipilimumab.

An analysis of the effect of BRAF mutation status on RFS showed no impact in both nivolumab and ipilimumab treated patients.

3.3. Uncertainties and limitations about favourable effects

With the minimal follow-up of 24 months the data is not mature to determine if an increase in RFS and DMFS will translate into a positive impact on OS, and as a result increase the cure rates, or if the treatment will only delay the progression of the disease. RFS does not yet present a plateau in KM curve and RFS has not yet been established as a surrogate endpoint for OS in adjuvant melanoma as it has been demonstrated in other types of tumours (e.g. breast cancer). Although it is reassuring that nivolumab treatment suggest no detriment on OS, the uncertainty remains as to whether patients will have a beneficial treatment effect in the long term and if so, what would be the extent of the magnitude of the treatment effect of nivolumab in patients with resectable disease treated for adjuvant melanoma. As a result, the MAH has committed to submit the final OS analyses as a condition in Annex II and RFS/DMFS as a post-authorisation measure.

There were uncertainties concerning the RFS benefit of patients with PD-L1 expression <1% with nivolumab over ipilimumab, as the separation of the Kaplan-Meier curves was not as clear as in the other PD-L1 expression subgroups and the HR 95% CI encompassed 1.0. The updated analyses confirmed that the effect on RFS and DMFS in patient with low PD-L1 expression is low (RFS) to none (DMFS). The PD-L1 expression is defined using the percentage of PD-L1 staining on tumour cells, while the efficacy might also be related to PD-L1 expression on tumour-associated inflammatory cells (or a combination of both). Whether the expression of PD-L1 on these inflammatory cells is correlated to efficacy in the adjuvant treatment of melanoma remains to be determined. In addition, since the identification of biomarkers, other than PD-L1 expression on tumours, are still lacking that would allow a better selection of the patient population which would be most at risk and would have the best response to treatment, the MAH has committed to further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1 (on tumour- and tumour associated immune cells), PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, Tumour mutational burden) as predictive of nivolumab adjuvant therapy efficacy. This has been included as an obligation in Annex II.

3.4. Unfavourable effects

The safety data of nivolumab monotherapy in adjuvant melanoma is considered similar to nivolumab monotherapy in metastatic melanoma as well as in other tumour types. In general, the ADRs identified in the current trial are consistent with the known ADRs for nivolumab treatment.

In the nivolumab group, the most frequently reported AEs were fatigue (42.7%), diarrhoea (36.9%), pruritus (28.1%), rash (25.4%), headache (23.5%), and nausea (23.0%) and the most frequently reported drug-related AEs were fatigue (34.5%), diarrhoea (24.3%), and pruritus (23.2%).

In the dataset of nivolumab 3 mg/kg as monotherapy for the adjuvant treatment of melanoma (n = 452), the most frequent adverse reactions (≥ 10%) were fatigue (46%), rash (29%), diarrhoea (24%), pruritus (23%), nausea (15%), arthralgia (13%), musculoskeletal pain (11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Any grade adverse events in the nivolumab group occurred with a similar frequency as in the ipilimumab group (96.9% vs 98.5%, respectively). With respect to the drug-related adverse events, fewer adverse events were observed in the nivolumab group (All grade 85.2 vs 95.8% and 3-4 grade 14.4%% and 45.9%, for nivolumab and ipilimumab respectively). Grade 3-4 events occurred less frequently in subject treated with nivolumab compared to ipilimumab (25.4% vs 55.2%, respectively).

The overall frequencies of SAEs (17.5% vs 40.4%) and drug-related SAEs (5.3% vs 31.1%) were lower in the nivolumab group than in the ipilimumab group. Grade 3-4 drug-related SAEs were reported in approximately 3.3% in the nivolumab groups, while 24.5% of the subjects in the ipilimumab group experienced Grade 3-4 drug-related SAEs.

For the categories of gastrointestinal, hepatic, skin and endocrine SOCs,all grade select AEs detected less (gastrointestinal, 25.2% vs 48.3%; hepatic, 9.1% vs 21.2% and skin, 44.5% vs 59.8%) or equal (endocrine, 22.6% vs 21.2%) numbers of drug-related select AEs in the nivolumab group compared to the ipilimumab group.

No deaths in the nivolumab group were attributed to the study drug toxicity.

The majority of the immune-mediated AEs (IMAEs) in the nivolumab group were grade 1-2, while in the ipilimumab group the majority are grade 3-4. Only the grade 1-2 IMAEs on hypothyroidism/thyroiditis and hyperthyroidism occured more often in the nivolumab group (13.9% and 8.6% vs 9.1% and 4.9% respectively), while grade 3-4 IMAEs in the rash (Niv: 0.7%; Ipi: 4.8%), diarrhea/colitis (Niv 2%: ; Ipi: 17.2%), hepatitis (Niv: 2%; Ipi: 7.5%), and hypophysitis (Niv: 0.4%; Ipi: 4.2%) categories occurred more frequently in the ipilimumab group.

Drug-related AEs leading to discontinuation were reported in 7.7% of subjects in the nivolumab group and 41.7% of subjects in the ipilimumab group.

In addition, the amount of administered immune-modulating concomitant medication for the management of AEs is higher in subjects in the ipilimumab group.

3.5. Uncertainties and limitations about unfavourable effects

There were no new safety concerns identified during the conduct of the clinical trial. Hence, there are no uncertainties on the unfavourable effects.

The majority of the immune-mediated AEs (IMAEs) in the nivolumab group were grade 1-2, while in the ipilimumab group the majority are grade 3-4. Only the grade 1-2 IMAEs on hypothyroidism/thyroiditis and hyperthyroidism occured more often in the nivolumab group (13.9% and 8.6% vs 9.1% and 4.9% respectively), while grade 3-4 IMAEs in the rash (Niv: 0.7%; Ipi: 4.8%), diarrhea/colitis (Niv 2%: ; Ipi: 17.2%), hepatitis (Niv: 2%; Ipi: 7.5%), and hypophysitis (Niv: 0.4%; Ipi: 4.2%) categories occurred more frequently in the ipilimumab group. In both groups the majority of the events seemed manageable but required lifelong treatment for thyroid replacement therapy.

Therefore, it is important that the treating physician is able to identify the symptoms rapidly and initiate the administration of immune-modulation medication as soon as possible in order to limit any irreversible damage in this patient population with early stage of the disease that may be cured and have a prolonged lifespan.

There are no data on adjuvant treatment in patients with melanoma with the following risk factors (see sections 4.5 and 5.1):patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications; patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation); patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways); subjects under the age of 18 years. In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis. A warning has been included in the SmPC section 4.4.

3.6. Effects Table

Table 25: Effects Table for nivolumab as adjuvant treatment for completely resected high risk, stage IIIB, IIIC and IV melanoma (data cut-off efficacy: December 2017; safety: 12-Jun-2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	Refs
Favourable Effects						
RFS	Recurrence Free Survival	Median - months	30.75	24.08	HR=0.66 Median of nivolumab not representative	CSR
RFS	Recurrence Free Survival Rate – 24 months	%	62.6	50.2	Stable difference at 18 and 24 months.	CSR
RFS	Recurrence Free Survival < 5% PD-L1	Median - months	N.A.	15.90	HR=0.73	CSR
RFS	Recurrence Free Survival ≥ 5% PD-L1	Median - months	N.A. 30.75	27.20	HR=0.54	CSR
DMFS	Distant Metastasis-free survival	Median - months	N.A.	N.A.	HR=0.76	CSR
DMFS	Distant Metastasis-free survival rate – 24 months	%	70.5	63.7		CSR
Unfavourable Effects						
All AEs	All Causality Adverse events	%	96.9	98.5	No comparison to safety in other tumour types	CSR
All AEs	Drug-related Adverse events	%	85.2	95.8	No comparison to safety in other tumour types	CSR
SAEs	All Causality Serious AEs	%	17.5	404	No comparison to safety in other tumour types	CSR
SAEs	Drug-related Serious AEs	%	5.3	31.1	No comparison to safety in other tumour types	CSR
Discontinu	Drug-related AEs	%	7.7	41.7	No comparison to safety	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	Refs
ations	leading to Discontinuation				in other tumour types	
Fatigue	Most frequent All Causality AEs	%	42.7	40.8	No comparison to safety in other tumour types	CSR
Diarrhoea	Most frequent All Causality AEs	%	36.9	54.5	No comparison to safety in other tumour types	CSR
Pruritus	Most frequent All Causality AEs	%	28.1	36.9	No comparison to safety in other tumour types	CSR
Rash	Most frequent All Causality AEs	%	25.4	33.1	No comparison to safety in other tumour types	CSR
Headache	Most frequent All Causality AEs	%	23.5	31.3	No comparison to safety in other tumour types	CSR

Abbreviations: RFS=Recurrence Free Survival; DMSF= Distant Metastasis Free Survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with Stage III and IV melanoma are at high risk of recurrence and are therefore candidates for adjuvant treatment after complete resection of all detectable disease. In line with Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5), the main goal of adjuvant therapy is to provide long-term benefit in terms of an increase in OS.

The clinical data established a clinically relevant benefit for RFS, the primary endpoint, which was supported by subgroup analysis based on PD-L1 expression and BRAF mutation status. The exploratory endpoint DMFS and PFS2 also showed a favourable effect in favour of nivolumab treatment compared to ipilimumab. Although the data is not mature, the descriptive OS presented showed no detrimental effect so far.

The safety data showed no new safety concerns. The ADRs are considered manageable with the recommendations in the SmPC, early identification and monitoring of immune-related adverse reactions, the use of immunosuppressive agents as well as the additional risk minimization measures.

3.7.2. Balance of benefits and risks

Melanoma is generally considered to be incurable when distant metastases are present. Patients with unresectable and metastatic disease have a poor prognosis usually have a median survival of less than one year. Therefore, a prolonged period of disease- free and metastasis-free that could delay recurrence and/or metastatic progression would be an important clinical benefit for patients that are at high risk of relapsing. The pivotal trial has demonstrated a statistically significant and clinically meaningful benefit of nivolumab adjuvant therapy in terms of RFS, which has shown a 7% gain in RFS in patients that go on to develop metastasis compared to ipilimumab adjuvant therapy. The members of the SAG-O confirmed the relevance of RFS as a clinically relevant endpoint for adjuvant treatment in melanoma. Although only an explorative endpoint, DMFS data provides supportive evidence that suggest a clinical benefit of nivolumab in the long term, that could potentially result into an OS advantage over time. This would be the ultimate goal, however the data is still too immature to reach any firm conclusions.

The safety results confirm the known safety profile of nivolumab, which is acceptable in this asymptomatic patient population as the ADRs are manageable. The overall safety profile of nivolumab 3 mg/kg for the adjuvant treatment of melanoma (n = 452) was consistent with that established across tumour types for nivolumab monotherapy. There is some concern about the over-treatment of patients that will not experience a recurrence (and are cured already without an adjuvant therapy). However, it has been judged that the benefit of delaying progression and in some patients, reaching curative intent, outweighs the safety concerns which are generally manageable. It is recommended that the treating-physicians discuss the long term risks (such as hypothyroidism, endocrinopathies and other autoimmune-related ADRs) with their patients.

3.7.3. Additional considerations on the benefit-risk balance

The trial CA209238 key inclusion criteria included the enrollment of adolescents and adult patients with Stage IIIB, IIIC and IV (per the AJCC 7th edition) histologically confirmed melanoma that is completely surgically resected. However, as the AJCC staging has changed, it may be difficult to define the new patient population that would be representative of the patients that were included in the trial. Hence, the current wording of the indication was modified with a more general wording "….with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection", without the mentioning of specific disease stages. Keeping the new AJCC 8th edition in mind, the current trial included patients with a wide range of prognostic estimates (including a proportion of patients in the "new" category IIIA, primary tumor ≤1.0mm with ulceration with regional lymph nodes involvement, clinically occult or detected (N1-2a)) and hence the indication reflects this distinction.

As there were no data collected in the adolescent population and there is uncertainty concerning the extrapolation of the PK, PD, efficacy and safety data in this patient population, it was not agreed to include adolescents and the indication was restricted to adults only.

3.8. Conclusions

The overall B/R of Opdivo is positive.

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

To understand the value of PD-L1 expression in the tumour and on the infiltrating immune cells it is essential to analyse PD-L1 expression on the infiltrating immune cells as well to correlate the expression of PD-L1 on the infiltrating inflammatory cells (and the PD-L1 expression on both tumour cells and inflammatory cells) with efficacy. There are uncertainties with respect to the efficacy of a nivolumab in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence. Therefore, the MAH has committed to investigate the predictive value of biomarkers for the efficacy of nivolumab, which has been included as condition to the MA in Annex IID.

1. To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1 (on tumour- and tumour associated immune cells), PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, Tumour mutational burden) as predictive of nivolumab adjuvant therapy efficacy. This will be provided for the approved indications:
    - Adjuvant treatment of melanoma (monotherapy): study CA209238

As the efficacy assessment in terms of OS is based partially on the assumption that the surrogate endpoints (RFS and MDSF) may lead to an improvement on OS in the long term, it would be important to confirm the impact of the intervention on clinical outcome or disease progression. Therefore, the final RFS/DMFS analysis is expected to be performed in 2019 and the final OS analysis is expected to be performed in 2020 and the final study report of the RFS, DMFS and OS should be submitted for assessment.

2. The MAH should submit the final OS data for study CA209238: A Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma. , due 4Q2020.

The MAH should submit the final RFS and DMFS data for study CA209238: A Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma. Due 3Q2019.

4. Recommendations

Outcome

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

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

Extension of Indication to include adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from the pivotal Study CA209238. The Package Leaflet is updated in accordance. In addition, the already authorised indication in squamous cell cancer of the head and neck has been further clarified. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the PI. Annex II has been updated to reflect new conditions. The RMP has been updated to version 12.3.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

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

Description	Due date
1. Post authorisation efficacy study (PAES): The MAH should submit the addendum to the CA209205 Final CSR reporting the OS data and data from the discontinuation schedule in Cohort C.	30th June 2021
2. The MAH should submit the final OS data for study CA209238: A Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma.	4Q2020
3. The value of biomarkers to predict the efficacy of nivolumab and/or nivolumab + ipilimumab combination therapy should be further explored, specifically:	
1. To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, etc.) as predictive of nivolumab therapy efficacy. This will be provided for the approved indications: - NSCLC: studies CA209017, CA209057 and CA209026 - RCC: studies CA209025 and CA209009 - UC: studies CA209275 and CA209032.	 30th June 2018 30th June 2018 30th June 2018

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 + ipilimumab combination therapy efficacy in the context of melanoma studies CA209038, CA209067, or CA209069. In addition, levels of myeloid-derived suppressor cells in circulation will be explored in study CA209038.	31st March 2019
3. To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1 (on tumour- and tumour associated immune cells), PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, Tumour mutational burden) as predictive of nivolumab adjuvant therapy efficacy. This will be provided for the approved indications: - Adjuvant treatment of melanoma (monotherapy): study CA209238	31st March 2019
4. To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies (CA209009, CA209038 and CA209064). - The MAH should submit full analytical study methods and validation reports for PD-L1 and PD-L2 assays used in the CA209009, CA209038 and CA209064 studies including discussion on performance characteristics (assay limitations and robustness). Comparison of expression of PD-L1 and PD-L2 in these studies with data reported in literature should also be included - The MAH should provide an update on plans to potentially further investigate immune-cell PD-L2 expression on available clinical study samples (for CA209009, CA209038 and CA209064).	31st December 2017 30th June 2018
5. To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in studies CA209066, CA209057 and CA209025.	30th June 2018
6. To further investigate, in CA209141, the association between improved clinical outcomes to nivolumab and the presence of: - PD-L2 expression - High inflamed phenotype.	30th September 2018 30th September 2018
7. To further explore in UC patients the early identification of those who do / do not respond to treatment with nivolumab, as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of: - Mutational and neoantigen load, PD-L1 expression on tumour- and tumour associated immune cells using validated approaches as feasible.	30th June 2018