25 February 2016
EMA/246304/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0002

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADA: anti-drug antibody

AE: adverse event

AE-DC/D: adverse event leading to discontinuation or death

ALK: anaplastic lymphoma kinase

BMS: Bristol-Myers Squibb

BOR: best overall response

BSC: best supportive care

C_{avgss}: time-averaged steady-state concentration

CHMP: Committee for Medicinal Products for Human Use

CI: confidence interval

CMH: Cochran-Mantel-Haenszel

CR: complete response

CSR: clinical study report

DMC: data monitoring committee

DOR: duration of response

ECOG: Eastern Cooperative Oncology Group

ECL: electrochemiluminescence

eCTD: electronic Common Technical Document

EGFR: epidermal growth factor receptor

EU: European Union

FDA: Food and Drug Administration

HR: hazard ratio

IHC: immunohistochemistry

IV: intravenous(ly)

LCSS: Lung Cancer Symptom Scale

LDH: lactate dehydrogenase

MA: marketing authorization

MAA: Marketing Authorization Application

NSCLC: non-small cell lung cancer

NSQ: non-squamous

ORR: objective response rate

OS: overall survival

PD-1: programmed death-1

PD-L1: programmed death-ligand 1

PFS: progression-free survival

PK: pharmacokinetic

PPK: population pharmacokinetics

PR: partial response

Q2W: every two weeks

RECIST: Response Evaluation Criteria in Solid Tumours

SAE: serious adverse event

SD: stable disease

SmPC: Summary of Product Characteristics

SQ: squamous

TKI: tyrosine kinase inhibitor

TTR: time to response

US: United States

UTD: unable to determine

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 July 2015 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment as monotherapy of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults based on study CA209057. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, SmPC section 4.8 has been revised with updated combined clinical trial exposure numbers to reflect inclusion of studies in non-squamous NSCLC and advanced melanoma. In addition, the MAH took the opportunity to align the annexes with the latest QRD template version 9.1 and to implement minor editorial changes. A revised RMP version 3.0 was provided as part of the application.

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/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

In the EU, the clinical development program in NSCLC was the subject of 2 Committee for Medicinal Products for Human Use (CHMP) Scientific Advices with final advice letters received in January 2012 and July 2012, respectively. The questions were focused on the design of the 2 Phase 3 clinical studies (studies CA209017

in SQ NSCLC, and CA209057 in NSQ NSCLC), with regard to target population, comparator and endpoints. The outcome of the advice will be further discussed in the context of the results of these 2 studies.

1.2. Steps taken for the assessment of the product

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

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

Assessment Timetable

Timetable	Actual dates
Start of procedure	25 July 2015
CHMP Rapporteur Assessment Report	25 September 2015
CHMP Co-Rapporteur Assessment Report	21 September 2015
PRAC Rapporteur Assessment Report	25 September 2015
PRAC members comments	30 September 2015
Updated PRAC Rapporteur Assessment Report	1 October 2015
PRAC Outcome	8 October 2015
CHMP members comments	12 October 2015
CHMP Rapporteurs Joint Assessment Report	15 October 2015
Request for Supplementary Information (RSI)	22 October 2015
Submission of responses	23 November 2015
CHMP Rapporteurs Joint response Assessment Report	4 January 2016
PRAC Rapporteur response Assessment Report	4 January 2016
Comments from PRAC	N/A
Updated PRAC Rapporteur response Assessment Report	N/A
PRAC outcome	14 January 2016
SAG Oncology meeting	14 January 2016
Comments from CHMP	20 January 2016
Updated CHMP Rapporteurs Joint response Assessment Report	22 January 2016
Oral Explanation	26 January 2016
2nd RSI	28 January 2016
Submission of responses	01 February 2016
CHMP Rapporteurs Joint response Assessment Report	12 February 2016
PRAC Rapporteur response Assessment Report	N/A
Comments from PRAC	N/A
Updated PRAC Rapporteur response Assessment Report	N/A
PRAC outcome	N/A

Timetable	Actual dates
Comments from CHMP	18 February 2016
Updated CHMP Rapporteurs Joint response Assessment Report	19 February 2016
CHMP Opinion	25 February 2016

2. Scientific discussion

2.1. Introduction

Opdivo (nivolumab) is a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. The PD-1 receptor is a key regulator of T-cell activity that has been shown to control tumour-specific inhibition of T-cell responses to tumours. Engagement of the PD-1 co-inhibitory receptor on activated T cells through programmed death ligands 1 and 2 (PD-L1 and PD-L2) results in inhibition of T-cell proliferation, survival and cytokine secretion.

Opdivo is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that potentiates in vitro T-cell responses through dual ligand blockade of PD-L1 and PD-L2, and does not mediate antibody-dependent cell-mediated cytotoxicity (ADCC). Expression of PD-L1 and PD-L2 by malignant cells or other cells, including immune cells, allows multiple tumour types to evade immune-mediated destruction. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Problem statement

Lung cancer has been among the most common cancers in the world for several decades. The 2012 worldwide estimates of cancer incidence and mortality by GLOBOCAN, indicate a total of 1.8 million new lung cancer cases and 1.6 million lung cancer related deaths, accounting for 13.0% of all cancer cases (except non-melanoma skin cancers) and 19.4% of all cancer deaths (except non-melanoma skin cancers). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2013, the estimated number of lung cancer related deaths is 159,480 in the United States (Siegel et al 2013) and 269,610 in the European Union (Malvezzi et al 2013).

The two most prevalent sub-types of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) accounts for approximately 75% to 85% of all NSCLC and squamous cell (epidermoid) carcinoma accounting for approximately 15% to 25% of all NSCLC (~230,000 to 380,000 cases)[1,2].

Tobacco use is the most important risk factor for lung cancer, with up to 80% of lung cancer patients reporting a history of tobacco use. Approximately 10% to 30% of NSQ NSCLC occurs in patients with a never smoker history and show a correlation with the presence of an activating EGFR mutation or other genetic alteration[3].

[1] Brambilla E, Travis WD. Lung cancer. In: World Cancer Report, Stewart BW, Wild CP (Eds). World Health Organization, Lyon 2014.
[2] Schrump DS, Carter D, Kelsey CR, et al. Non-Small Cell Lung Cancer. Cancer: Principles and Practice of Oncology. 9th Edition. 2011. (Chapter 75).
[3] Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012. Sep. 27;489(7417):519-25.

In addition to the high mortality associated with NSCLC, a high proportion of patients experience severe morbidity as a result of local and metastatic spread of disease.

In treatment-naive NSCLC patients, platinum-based chemotherapy continues to be the standard of care. Overall, the prognosis for previously treated NSCLC after failure of platinum-based chemotherapy is poor for all histological subtypes, including NSQ NSCLC, and treatment options are limited. In this setting, docetaxel has been a standard treatment for the last 15 years. However, only a small fraction of patients benefit from docetaxel, with historical response rates of 3.3% - 15.5%, median OS of 6 to 10 months and 1-year OS rates of approximately 30 to 40%. Overall, this group of patients only has an overall survival (OS) of about 8 months after progression from platinum agents. Patients with tumours that have mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) are candidates for target-therapy agents. However, once resistance to tyrosine kinase inhibitors (TKIs) occurs, the patients who have EGFR mutations or ALK translocations will have a rapid disease progression.

Therefore, NSQ NSCLC remains a disease with high burden and unmet medical need, and new agents that have meaningful clinical efficacy in this subtype are required.

The proposed and recommended indication is as follows: Opdivo as monotherapy is indicated for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

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

2.2.2. Discussion and conclusion on non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study Type	Study Identifier/Report Location (Study Status)	Study Objective	Study Design	Treatment Cohorts	No. of Treated Subjects (No. of Nivolumab-treated subjects)	Study Population
Efficacy, Safety	CA209057/ Module 5.3.5.1 (study completed, final report available)	To compare the OS of nivolumab to docetaxel	Phase 3, open-label randomized study of nivolumab vs docetaxel	Randomized in 1:1 ratio to: Nivolumab - 3 mg/kg IV Q2W Docetaxel - 75mg/ m² IV Q3W	555 (287)	Subjects with metastatic or recurrent NSQ NSCLC who had experienced disease progression during or after prior platinum-based chemotherapy. This study also included subjects who had EGFR mutations or ALK translocations who may have had disease progression after the use of a TKI and platinum-based chemotherapy.

Abbreviations: ALK: anaplastic lymphoma kinase, BMS: Bristol-Myers Squibb, IV: intravenous, EGFR: epidermal growth factor receptor, No: number, NSCLC: non-small cell lung cancer, NSQ: non-squamous, OS: overall survival, Q2W: every 2 weeks; Q3W: every 3 weeks.

2.3.2. Pharmacokinetics

No new clinical pharmacology studies are included in this submission.

An update to the nivolumab PPK and E-R analyses was performed to enable an assessment of the potential effects of intrinsic and extrinsic factors on nivolumab PK and to assess exposure-response in the SQ and NSQ NSCLC population from the CA209017 and CA209057 studies.

Additionally, an integrated immunogenicity analysis across the solid tumour patient population was performed to assess the effect of immunogenicity on the safety and efficacy of nivolumab.

Dose and schedule of nivolumab (3 mg/kg every 2 weeks), is the same as already approved for nivolumab monotherapy in adults with locally advanced or metastatic squamous NSCLC or advanced (unresectable or metastatic) melanoma.

Methods

The population pharmacokinetic analysis dataset included subjects from the following 9 studies, for whom nivolumab serum concentration data were available (N=1,314): three Phase 1 studies (MDX1106-01, ONO-4538-01, and MDX1106-03), three Phase 2 studies (CA209010, ONO-4538-02, and CA209063), and three Phase 3 studies (CA209037, CA209017, and CA209057). These studies were selected based on their inclusion in a previous nivolumab PPK analysis, with the addition of data from CA209017 and CA209057 to further characterise the PK of nivolumab in subjects with advanced SQ or NSQ NSCLC.

Nivolumab concentration time data were well described by the previously developed linear, 2-compartment, zero-order input intravenous (IV) infusion model with first-order elimination.

Bioanalytical methods used for quantifying nivolumab serum concentrations in the development program are cross-validated, and hence allowed merging of the exposure data for PPK analysis.

Absorption

A summary of the individual PK parameter estimates obtained from the final popPK model is provided. No differences were noted in nivolumab CL or exposure in subjects with different tumour types (SQ NSCLC versus NSQ NSCLC versus melanoma), thus tumour type was not found to be a clinically relevant predictor of nivolumab PK.

Table 1: Summary Statistics of Individual PK Parameters of nivolumab (n=1314)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
CL (L/h)	0.0101 (0.00487)	0.00922 (48.1)	0.00904 (0.00129,0.0466)
VC (L)	4.02 (1.13)	3.87 (28)	3.89 (0.78,9.16)
VP (L)	3.98 (1.88)	3.69 (47.3)	3.71 (0.776,28.3)
VSS (L)	8 (2.36)	7.71 (29.5)	7.71 (2.58,31.3)
T-HALFα (h)	40.9 (9.81)	39.7 (24)	40.5 (12.5,88.7)
T-HALFβ (d)	28.9 (25)	26.2 (86.7)	25.9 (4.76,724)

CL: clearance; VC: volume of the central compartment; VP: volume of the peripheral compartment; VSS: volume of distribution at steady-state; T-HALFα: alpha half-life; T-HALFβ: beta half-life; SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; n: number of subjects.

Source: /global/pkms/data/CA/209/C09/prd/ppk/sd/Cognigen

A summary of the individual measures of exposure of nivolumab in patients with NSCLC enrolled in Studies CA209017, and CA209057 (receiving 3 mg/kg Q2W) as estimated by popPK analysis is shown in the table below.

Table 2: Summary Statistics of Individual Measures of Nivolumab Exposure for Subjects with NSCLC (studies CA209017 and CA209057 (3 mg/kg Q2W) (n=405)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Cmin1 [mcg/mL]	17.9 (5.61)	17.1 (31.3)	17.3 (3.36,58.7)
Cminss [mcg/mL]	59.9 (25.1)	54.7 (41.9)	55.5 (3.86,197)
Cmaxss [mcg/mL]	124 (39.5)	119 (31.8)	117 (49.1,344)
Cavgss [mcg/mL]	78 (27.8)	73.3 (35.6)	73.6 (14.8,238)

Cmin1: post-dose 1 trough serum concentration; Cminss: trough serum concentration at steady-state; Cmaxss: peak serum concentration at steady-state; Cavgss: time-averaged serum concentration at steady-state; SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; n: number of subjects

Source: /global/pkms/data/CA/209/C09/prd/ppk/sd/Cognigen.

Distribution

Mean Vss of all subjects in the popPK analysis was 7.7 L (CV=29.5%).

Elimination

Mean clearance of nivolumab of all subjects in the popPK analysis was 0.092 L/hour (CV=48%) and elimination half-life (t1/2) 26 days (CV=87%).

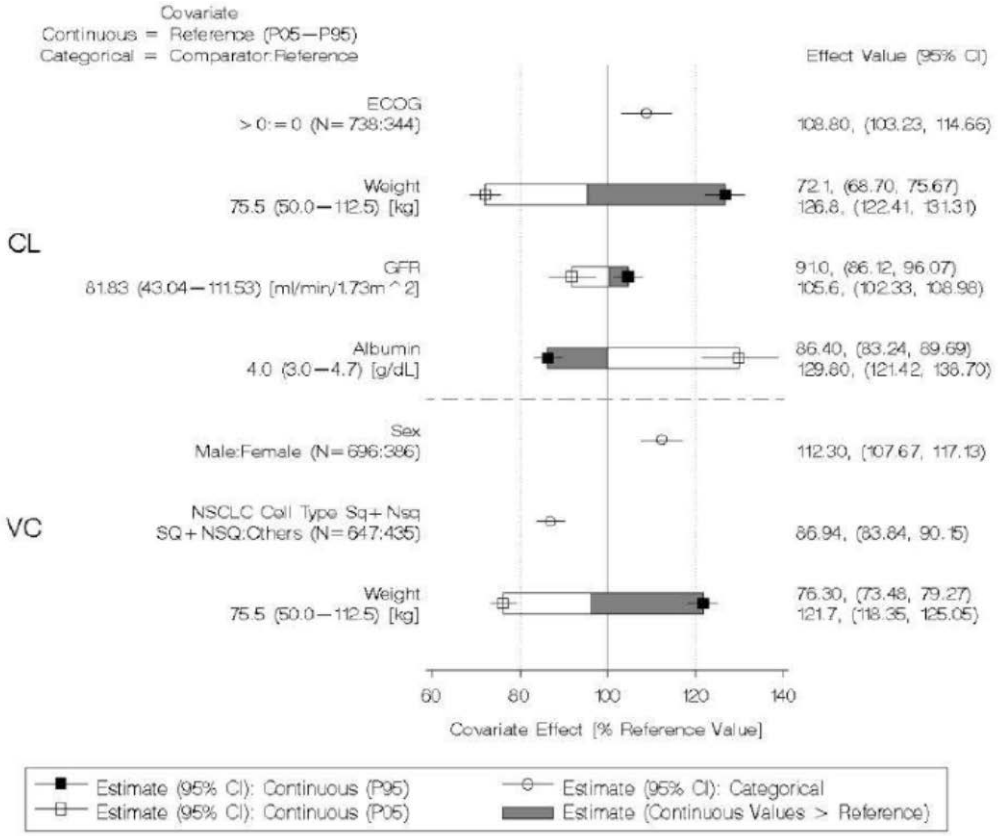
Dose proportionality and time dependencies

As indicated with the popPK analysis for the MAH in melanoma and SQ-NSCLC, pharmacokinetics of nivolumab was dose proportional over the dose range 0.1 mg/kg-10 mg/kg and no unexpected accumulation was observed.

Special populations

Nivolumab concentration time data were well described by the previously developed linear, 2-compartment, zero-order input intravenous (IV) infusion model with first-order elimination. Consistent with previous findings, WT, sex, ECOG, and eGFR were covariates on nivolumab PK parameters. In addition, baseline

serum albumin appeared to be a covariate for CL and cell type/ histology was found to influence VC. The magnitude of the effect of covariates on CL, accounting for uncertainty, was within the ±20% boundaries for all covariates, except body weight and serum albumin. With dosing of nivolumab on an mg/kg basis, nivolumab exposure was comparable across the range of body weight (34-162 kg), justifying the dosing per body weight. Baseline serum albumin appears to be a potentially important covariate for CL, as a decrease in baseline serum albumin from the median to the 5th percentile value (4 g/dL and 3 g/dL, respectively) isassociated with a >20% (29.8%) increase in CL. Thus, both body weight and serum albumin appear to be clinically relevant covariates on nivolumab PK. No differences were noted in nivolumab CL or exposure in subjects with different tumour types (SQ NSCLC versus NSQ NSCLC versus 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 female, ECOG=0, eGFR=80 mL/min/1.73m^2, serum albumin=4 g/dL, body weight=80kg, and other cell type/histology. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Source: /global/pkms/data/CA/209/C09/prd/ppk/sd/Cognigen (KIWI Run ID 133614)

Figure 1: Covariate Effects on popPK Model Parameters

2.3.3. Pharmacodynamics

Exposure response analyses for efficacy and safety were conducted using data from completed studies in patients with advanced or metastatic NSQ NSCLC (MDX1106-03 and CA209057). PopPK model-predicted time-averaged steady-state concentration (C_{avgss}) was used as the measure of nivolumab exposure. Overall survival was used as the efficacy measure, and time to first adverse event leading to discontinuation or death (AE-DC/D) was used as the safety measure.

Exposure-Response Efficacy Analysis

The nivolumab E-R relationship of efficacy for this analysis was characterised for OS in 354 previously treated patients with advanced or metastatic NSQ NSCLC in Studies MDX1106-03 (nivolumab doses 1, 3 and 10 mg/kg), and CA209057 (nivolumab 3 mg/kg). The E-R analysis of efficacy was characterised with respect to OS by a Cox proportional-hazards model that incorporated the effects of covariates that may modulate the E-R relationship.

The predictor variables with a significant effect on OS were ECOG status, PD-L1 status, line of treatment, nivolumab CL, body weight, and baseline LDH (95% CI of effect did not include 1).Nivolumab Cavgss and all the other predictor variables evaluated (prior maintenance therapy, EGFR mutation status, smoking status, sex, baseline albumin, baseline tumour size and age) were not a significant predictor of OS (95% CI of effect included 1).

The first sensitivity analysis (excluding the effect of CL) was performed to assess the potential confounding effect of nivolumab CL on the estimated effects of C_{avgss}. In this analysis, the ECOG status, PD-L1 status, line of therapy, and baseline LDH are still identified as significant predictor of OS (95% CI of effect did not include 1), which is consistent with that found from the full model.After removing CL effect, nivolumab Cavgss and baseline albumin became significant predictor of OS (95% CI of effect did not include 1), and subjects with higher exposure or higher baseline albumin appeared to have better OS. Body weight was not a significant predictor of OS in this model.

The second sensitivity analysis was performed to evaluate the impact of tumour shrinkage at Week 8 (TSW8) on OS. This variable was not included in the full model, as approximately 25% of subjects did not have tumour shrinkage data available at Week 8 for analysis. In this sensitivity analysis, the effect of TSW8 was significant on OS. Risk of death appeared to be higher in subjects with lower tumour shrinkage at Week 8 and higher baseline tumour size. ECOG status, PD-L1 status, and line of therapy were not significant predictors of OS after including effect of tumour shrinkage.

The third sensitivity analysis was performed to evaluate the impact of time averaged concentration over the first dosing interval (C_{avg1}) replacing C_{avgss} in the full model including the effect of clearance. There was no change in the effect of predictors on OS in this model when compared to the full model, and C_{avg1} was not a significant predictor of OS.

Table 3: Parameter Estimates of exposure response OS (Full Model) for NSQ NSCLC (BMS-936558 report)

Predictor[a]	Estimate	SE	RSE%	Hazard Ratio Coefficient[b] (95% CI)
log(Cavgss)[c] [μg/mL]	-0.0864	0.157	-181	0.917 (0.675, 1.25)
Age [yr]	0.00692	0.00756	109	1.01 (0.992, 1.02)
Body Weight [kg]	-0.021	0.00563	-26.8	0.979 (0.968, 0.99)
LDH [XULN][d]	0.774	0.157	20.3	2.17 (1.59, 2.95)
log(Clearance) [L/h][e]	1.68	0.279	16.6	5.35 (3.09, 9.23)
Baseline tumor size [mm]	-0.00244	0.00137	-56	0.998 (0.995, 1)
Albumin [g/dL]	-0.319	0.169	-53	0.727 (0.522, 1.01)
ECOG	0.347	0.167	48.2	1.41 (1.02, 1.96)
Sex	-0.0135	0.157	-1160	0.987 (0.726, 1.34)
Line of therapy	0.432	0.171	39.6	1.54 (1.1, 2.15)
Smoking status	-0.0258	0.186	-721	0.975 (0.676, 1.4)
EGFR mutation (unknown)	-0.232	0.219	-94.7	0.793 (0.516, 1.22)
EGFR mutation (wildtype)	-0.268	0.209	-78.2	0.765 (0.507, 1.15)
Prior maintenance therapy	-0.00516	0.154	-2980	0.995 (0.736, 1.35)
PD-L1 (≥1%)	-0.406	0.165	-40.6	0.666 (0.482, 0.92)
PD-L1 (unknown)	0.182	0.171	93.8	1.2 (0.858, 1.68)

[a] reference values: ECGO=0, sex=Male, line of therapy=2nd line, PD-L1 status <1%, prior maintenance therapy = none, EGFR mutation status = mutant, smoking status = current/former

[b] increase in hazard for every unit increase in continuous predictor variables, or hazard relative to reference values of categorical predictor variables

[c] Cavgss was log transformed. log(Cavgss) increases by one unit for approximately 2.7-fold increase in Cavgss

[d] LDH was log transformed. log transformed LDH increase by one unit for approximately 2.7-fold increase in LDH

[e] CL was log transformed. log transformed CL increase by one unit for approximately 2.7-fold increase in CL

Exposure-Response Analysis for Safety in NSCLC

Assessment of the relationship between nivolumab exposure and safety was performed with data from 648 subjects with SQ and NSQ NSCLC with respect to Adverse events (excluding disease progression) leading to nivolumab discontinuation or death (AE-DC/D). The E-R relationship was characterised by a semi-parametric CPH model, and included assessments of the modulatory effect of covariates on the E-R relationship. The Cavgss was used as the measure of nivolumab exposure. This measure of exposure represents the overall average of nivolumab exposure within each subject. Furthermore, other summary measures of exposure (such as Cminss and Cmaxss) are highly correlated with Cavgss.

The risk of AE-DC/D did not increase with Cavgss produced by doses ranging from 1 to 10 mg/kg nivolumab in NSCLC patients. The risk of AE-DC/D was higher in patients with ECOG > 0 or who received 2 or more previous therapies, relative to patients with ECOG = 0 and those receiving second line therapy. The risk of AE-DC/D increased with decreasing baseline body weight, and serum albumin; and the risk increased with increasing baseline LDH.

Table 4: Parameter Estimates of exposure-response (Adverse events (excluding disease progression) leading to nivolumab discontinuation or death (AE-DC/D)) - Full Model

Predictor[a]	Estimate	SE[b]	RSE%[c]	Hazard Ratio Coefficient (95% CI)[d]
log(Cavgss)	-0.201	0.151	75.5	0.818 (0.608, 1.1)
Age [yr]	-0.00819	0.00918	112	0.992 (0.974, 1.01)
Baseline Body Weight [kg]	0.00714	0.0054	75.6	1.01 (0.997, 1.02)
log(LDH)	0.476	0.191	40.2	1.61 (1.11, 2.34)
Baseline Serum Albumin [g/dL]	-0.702	0.174	24.8	0.495 (0.352, 0.697)
Sex (Male:Female)	-0.301	0.197	65.4	0.74 (0.503, 1.09)
ECOG (>0:0)	0.824	0.245	29.8	2.28 (1.41, 3.69)
Histology (SQ:NSQ)	-0.0358	0.186	520	0.965 (0.67, 1.39)
Line of Therapy (>2L:2L)	0.478	0.179	37.5	1.61 (1.13, 2.29)
Disease Stage (Stage IV: Stage II/III/IIIb)	-0.0996	0.256	257	0.905 (0.548, 1.49)

a log(Cavgss) and log(LDH) increase by 1 unit for approximately 2.7-fold increase in Cavgss and LDH, respectively. The units of Cavgss and LDH are [ug/mL] and [xULN], respectively

b SE: Standard Error

c RSE: Relative Standard Error = (100* SE/Estimate)

d For continuous valued predictors (log-transformed Cavgss, age, baseline body weight, baseline serum albumin, and log-transformed LDH), the HR represents the change in hazard for a 1 unit increase in the value of the predictor. Note that log-transformed values of predictors increase by 1 unit for every 2.7-fold increase in the value of the predictor.

Immunogenicity

A pooled analysis of nivolumab ADA assessments was performed with data available from the following BMS-sponsored studies for NSCLC and melanoma in which ADA was assessed by the current sensitive and drug tolerant assay (ICDIM 140 V1.00/V2.02): CA209037, CA209063, CA209066, CA209017, CA209057 and CA209067 (nivolumab monotherapy arm).

Of 1037 subjects who were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) and evaluable for the presence of anti-drug antibodies (ADA), 128 subjects (12.3%) tested positive for treatment-emergent ADA. Of those who were ADA positive, only 1 subject (0.1% of the total) was persistent positive, and neutralizing antibodies were detected in 9 subjects (0.9% of the total). The safety profiles of these 9 subjects were examined and determined to be no different than those observed in ADA negative subjects. There were no acute infusion reactions, hypersensitivity events, or new or additional AEs observed in subjects with neutralizing antibodies. Neutralizing antibodies were not detectable in subsequent ADA assessments in 8/9 of these subjects; one of the subjects with neutralizing ADA had a subsequent assessment that was ADA positive with a lower titer and neutralizing antibody positive.

Table 5: Summary of Nivolumab Antibody Assessments Using Method ICDIM 140V1.00/V2.02 Following Nivolumab 3 mg/kg every 2 weeks - 16 Week Definition for Persistent Positive

	Number of Patients (%)						
	CA209063 (N=101)	CA209037 (N=181)	CA209066 (N=107)	CA209017 (N=109)	CA209057 (N=251)	CA209067 (N=288)	Pooled Summary (N=1037)
Baseline ADA Positive	11 (10.9)	9 (5.0)	3 (2.8)	8 (7.3)	18 (7.2)	10 (3.5)	59 (5.7)
ADA Positive	12 (11.9)	13 (7.2)	6 (5.6)	21 (19.3)	43 (17.1)	33 (11.5)	128 (12.3)
Persistent Positive	0	0	0	1 (0.9)	0	0	1 (0.1)
Only Last Sample Positive	8 (7.9)	9 (5.0)	2 (1.9)	4 (3.7)	12 (4.8)	10 (3.5)	45 (4.3)
Other Positive	4 (4.0)	4 (2.2)	4 (3.7)	16 (14.7)	31 (12.4%)	23 (8.0)	82 (7.9)
Neutralizing ADA Positive	0	2 (1.1)	0	3 (2.8)	3 (1.2%)	1 (0.3)	9 (0.9)
ADA Negative	89 (88.1)	168 (92.8)	101 (94.4)	88 (80.7)	208 (82.9)	255 (88.5)	909 (87.7)

Source:
For CA209063 and CA209037 see Appendix 1
For CA209066 refer to Table S.7.10 in the Clinical Study Report[7]
For CA209017 refer to Table S.7.10a in the Clinical Study Report[2]
For CA209057 refer to Table S.7.10a in the Clinical Study Report[3]
For CA209067 refer to Table 8.13.1-1 in the Clinical Study Report[8]

A total of 9/1037 subjects (0.9%) were positive for neutralizing antibodies. In the majority of the neutralizing ADA-positive subjects, the presence of neutralizing antibodies was transient and did not recur in subsequent samples. The majority of subjects with neutralizing antibodies continued treatment with benefit from therapy. There was no evidence of loss of efficacy in subjects with neutralizing antibodies.

A total of 51 subjects experienced hypersensitivity reactions/infusion reactions and were evaluable for the presence of ADA. Of the 51 evaluable subjects, 48 (94.1%) were negative for nivolumab ADA and 3 subjects (5.9%) were positive for ADA. No association was established between the presence of ADA and hypersensitivity or infusion reactions.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics of nivolumab was similar in subjects with different tumour types (SQ NSCLC versus NSQ NSCLC versus melanoma). Body weight was an important covariate of nivolumab pharmacokinetics, justifying dosing based on mg/kg body weight. Further, nivolumab clearance increased with decreasing baseline serum albumin (approximately 30% increase for the median versus 5th percentile of serum albumin values). Although the mechanistic link is not entirely clear, serum albumin has also been shown to affect the clearance of other antibodies.

In full model, the effect of SQ or NSQ NSCLC on CL or VC was within 20 % in comparison to other tumor types. Although the combined effect of the SQ and NSQ histologies is retained in the final model, the impact is not clinically significant. Therefore, the final model-predicted nivolumab exposures (Cmin1, Cminss, Cmaxss and Cavgss) are similar even if SQ/NSQ were included in the final model.

Nivolumab CL, ECOG status, baseline LDH, baseline body weight, PD-L1 expression status (≥1%), line of therapy, and tumour shrinkage at Week 8 were significant predictors of OS in previously treated NSQ NSCLC subjects. Nivolumab clearance was a significant factor. This may be due to the CL of nivolumab being reflective of the disease severity of subjects - serum albumin, ECOG status, baseline LDH were significant factors of nivolumab clearance - and therefore the effect is redistributed among other predictors that are indicative of disease state when CL is excluded from the model. This finding is consistent with previous results, where no relation between nivolumab exposure and observed response in NSCLC and melanoma was apparent.

The applicant discussed the issue of Nivolumab exposure (Cavgss) as a significant predictor of OS in previously treated SQ/NSQ NSCLC subjects, taking into account the potential confounding effect of predictors (CL and Weight) on the estimated effects of Cavgss. The applicant has justified that the parameter estimates were robust, as the correlations between the parameter estimates (e.g., Cavgss, CL and bodyweight) in the full model were all well below 0.9. The correlation coefficient among the parameter estimates of Cavgss, CL and body weight obtained from the full model were less than|0.6|, indicating that the full model was not over-parameterized and that the effects of allcovariates are relatively independent. The effects of Cavgss and CL could both be adequately estimated in the same model, as the analysis dataset includes subjects who received nivolumab over a dose range of 1 to 10 mg/kg, even though most of the data are for subjects who received 3mg/kg. In addition, model evaluation also showed that the Kaplan-Meier curves were in good agreement with the CPH model predictions for different studies and doses, indicating anadequate model performance over a range of exposures.

Risk of AEs leading to treatment discontinuation or death was higher in subjects with ECOG >0, line of therapy >2, and increasing baseline LDH and the risk of AE-DC/D increased with decreasing baseline body weight, and baseline serum albumin. All of the factors are either directly or indirectly associated with the overall health status of the patient. Risk of AEs leading to treatment discontinuation or death did not increase with C_{avgss} resulting from nivolumab doses of 1 to 10 mg/kg in SQ and NSQ NSCLC subjects.The results of this analysis are consistent with an earlier analysis of exposure safety analysis in melanoma and SQ NSCLC.

The choice of AE-DC/D as a compiled indicator of safety could have an impact on the lack of significance of C_{avgss} as predictor of safety. The applicant has submitted the distribution of nivolumab exposure (Cavgss) presented by patients with and without the most common grade 3+ nivolumab-relaed AEs (pneumonitis, fatigue, lymphopenia and diarrhea) showing that there is no marked difference between the exposure distributions. However, the number of subjects with the events are low (N= 4 to 13), and hence not considered adequate for a model-based analysis.

In the time-varying exposure intensity, subjects who remain on study for longer duration of time tend to have lower CL, and therefore have Cavg values higher than the group of all treated subjects. The applicant has justified that the nivolumab exposure-response for safety is flat over the 1 to 10 mg/kg dose range and doses up to 10 mg/kg are well tolerated; the higher Cavg for patients who remain on treatment is not considered to pose a safety risk due to higher exposure. Also, patients with low CL stay on study longer which suggests that they tolerate nivolumab treatment well. Hence, a change in dosing frequency is not considered appropriate based on the benefits of uniform prescribing information for all patients receiving nivolumab.

Nivolumab has low immunogenic potential. Of 1037 subjects who were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) and evaluable for the presence of anti-drug antibodies (ADA), 128 subjects (12.3%) tested positive for treatment-emergent ADA. Of those who were ADA positive, only 1 subject (0.1% of the total) was persistent positive, and neutralizing antibodies were detected in only 9 subjects (0.9% of the total). The safety profiles of persistent positive or neutralizing positive subjects were no different than those in other subjects. There was no evidence of loss of efficacy in subjects with neutralizing antibodies.

2.3.5. Conclusions on clinical pharmacology

Pharmacokinetics, exposure response relationship and immunogenicity of nivolumab has been sufficiently investigated for the extension of the indication of nivolumab 3 mg/mg every 2 weeks for treatment of locally advanced or metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC).

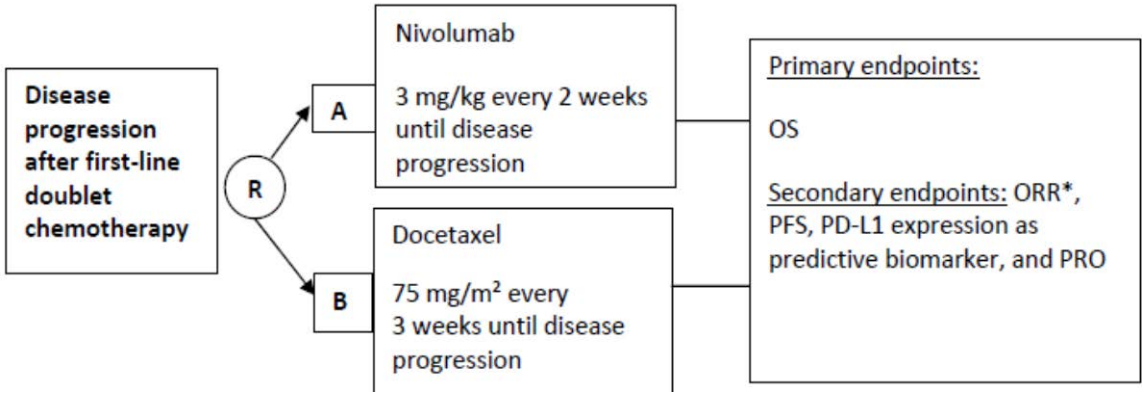
2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The dose and posology used are the same as for the squamous NSCLC indication. No new data has been submitted with this application.

2.4.2. Main study

Study CA209057: An open-label randomised phase III trial of nivolumab versus docetaxel in previously treated metastatic non-squamous non-small cell lung cancer (NSCLC)



R = randomization; * Objective Response (by RECIST v1.1) as determined by investigator.
Source: Protocol (Appendix 1.1)

Figure 2: Study Design Schematic

Methods

Study participants

This study included adult subjects with metastatic or recurrent non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy. It also included subjects who had EGFR mutations or ALK (CD246) translocations and may have had disease progression after the use of a TKI and platinum doublet-based chemotherapy.

Inclusion and exclusion criteria were similar to those in study CA209017, which included SQ-NSCLC patients; some modifications related to the NSQ-NSCLC population were also made.

Key inclusion criteria were:

1. Subjects ≥ 18 years of age with advanced Stage IIIB/ Stage IV non-squamous NSCLC or recurrent/ progressive disease.
2. ECOG performance status of ≤ 1
3. Subjects must have had measurable disease
4. Subjects who received study therapy after acceptable prior therapy as specified below:
    a. Subjects who received study therapy as second line of treatment
        i. Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

Continuous or switch maintenance therapy following platinum doublet-based chemotherapy was considered as first-line therapy.

b. Subjects who received study therapy as third line of treatment:

   i. Subjects who received an EGFR TKI (erlotinib, gefitinib, or experimental) in addition to a platinum doublet-based chemotherapy must have had a tumour with a known activating EGFR mutation.

   ii. Subjects who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum doublet-based chemotherapy must have had a tumour with a known ALK-translocation.

5. An FFPE tumour tissue block or unstained slides of tumour sample (archival or recent) must have been available for biomarker evaluation.

Key exclusion criteria were:

1. Subjects with untreated CNS metastases.
2. Subjects with carcinomatous meningitis.
3. Any serious or uncontrolled medical disorder or active infection with hepatitis or human immunodeficiency virus that may have been reactivated.
4. Other active malignancy requiring concurrent intervention.
5. Subjects with previous malignancies
6. Subjects with a condition requiring systemic treatment with either corticosteroids.
7. Subjects with active, known or suspected autoimmune disease.
8. Prior treatment with docetaxel.
9. Subjects with interstitial lung disease that was symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

Treatments

Subjects received one of the following treatments:

Nivolumab group: nivolumab at 3 mg/kg Q2W by IV infusion. Dosing calculations were to be based on the body weight.

Docetaxel group: docetaxel at 75mg/m^2 Q3W by IV infusion. Dosing calculations were to be based on body surface area.

No premedications were recommended for initiation of dosing of nivolumab. Premedication with corticosteroids were to be given to subjects randomised to the docetaxel treatment group per the USPI and SmPC; institutional standard regimens for steroid premedication consistent with (or equivalent to) recommendations contained within the docetaxel label were also allowed.

Dose reductions were not permitted for nivolumab but were permitted for docetaxel for subjects who experienced docetaxel-related events of febrile neutropenia, neutrophils < 500 cell/mm^3 for > 7 days, severe or cumulative cutaneous reactions, or other Grade 3/4 non-haematological toxicities during docetaxel treatment.

Dose delays were permitted in both groups. Dose delays of < 6 weeks were permitted, with longer delays allowed for completion of steroid tapers to manage drug-related AEs, or for non-drug- related reasons if approved by the Medical Monitor.

Subjects were treated until progression, unacceptable toxicity, or other protocol-defined reasons.

Objectives

Primary Objective

- To compare the OS of nivolumab to docetaxel in subjects with non-squamous NSCLC after failure of prior platinum-based chemotherapy

Secondary Objectives

- To compare the ORR of nivolumab versus docetaxel
- To compare PFS of nivolumab versus docetaxel
- To evaluate whether PD-L1 expression is a predictive biomarker for OS and ORR
- To evaluate the proportion of subjects exhibiting disease-related symptom improvement by12 weeks, as measured by the LCSS, in nivolumab and docetaxel treatment groups
- Other exploratory objectives were assessment of safety, PK, health status (using EQ-5D index) characterisation of immunogenicity.

Outcomes / endpoints

Primary endpoint

- Overall survival (OS).

Key Secondary endpoints

- Investigator assessed ORR using RECIST v 1.1.
- PFS as determined by the investigator using RECIST v1.1 criteria, or death due to any cause.
- DOR and TTR, as determined by the investigator.
- OS and ORR based on PD-L1 status at baseline.

Radiographic tumour response were assessed at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days) for the first year of treatment, then every 12 weeks after the first year of treatment until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, or withdrawal of consent.

PD-L1 tumour membrane expression levels were evaluated using an automated immunohistochemistry (IHC) assay using a rabbit-ant-human PD-L1 antibody. PD-L1 expression was defined as the percent of tumour cells demonstrating plasma membrane PD-L1 staining in a minimum of 100 evaluable tumour cells per this validated DAKO PD-L1 IHC assay.

Sample size

The final analysis of OS was planned to take place after 442 deaths were observed among 574 randomised subjects. One interim analysis of OS was planned after at least 380 deaths (86% of total deaths required for final analysis) had been observed.

The OS distribution was assumed exponential for the docetaxel group, while for the nivolumab group, a long-term survival and delayed onset of benefit were assumed, as observed in patients treated with the immuno-oncology drug ipilimumab in recent Phase 3 studies.

Piecewise mixture model assumptions were as follows: a 4-month delayed separation of curves between docetaxel and nivolumab treatment groups, an exponential distribution for docetaxel (8 month median OS), an 18% 'cure' rate (long-term survival) in the nivolumab treatment group, and an 8 month median OS for 'non-cured' nivolumab subjects. The piecewise mixture distribution for nivolumab had an overall 9.8 months median OS for all randomised nivolumab subjects. HRs between nivolumab and docetaxel group followed the following pattern: Months 0-4: HR=1; Month 6: HR=0.71; Month 12: HR= 0.59; Month 24: HR=0.34; Month 36: HR=0.15. Simulations were performed using Power Analysis & Sample Size Software7 to assess power and timing of interim and final OS analyses.

Randomisation

Subjects who met all eligibility criteria were randomised by IVRS in a 1:1 ratio to the nivolumab group or the docetaxel group, with stratification by prior use of maintenance vs. no maintenance therapy and second-line vs. third-line therapy. Subjects were enrolled regardless of PD-L1 expression status, and PD-L1 expression status was not a stratification factor.

Blinding (masking)

This was an open-label study.

Statistical methods

Discrete variables were tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages in the tables were rounded and, therefore, may not always sum to 100%. Continuous variables were summarized by treatment group (with total) using the mean, SD, median, minimum and maximum values.

Time-to-event distributions (i.e., OS, PFS, and DOR) were estimated using K-M techniques.

Median survival time along with 95% CI were constructed based on log-log transformed CI for the survivor function S(t). Rates at fixed time points (e.g., OS at 6 months) were derived from the K-M estimate and corresponding CI was derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t).

Unless otherwise specified, a stratified log-rank test was performed to test the comparison between time to event distributions (e.g., PFS and OS).

Unless otherwise specified, the stratified HR between 2 treatment groups along with CI was obtained by fitting a stratified Cox model with the treatment group variable as unique covariate.

The difference in rates between the two treatment groups along with their two-sided 95% CI were estimated using the following CMH method of weighting, adjusting for the stratification factors.

The associated odds-ratio was to be derived. P-values from sensitivity analyses were for descriptive purpose only and there were no multiplicity adjustment for these analyses.

OS was compared between the two treatment groups using a two-sided, log-rank test stratified (per IVRS) by maintenance vs. no maintenance therapy, and second-line vs. third-line therapy. The HR and the corresponding 100(1-α) % CI (adjusted for the interim) were estimated in a stratified Cox proportional hazards model using randomised group as a single covariate. The OS curves for each treatment group were estimated using the K-M product-limit method. Two-sided, 95% CIs for median OS were constructed based on a log-log transformed CI for the survivor function S(t).

Survival rates at 6, 12, 18, 24, 36, 48 months and at 5 years were to be estimated using K-M estimates on the OS curve for each randomised group. Minimum follow-up must have been$\geq$ time point to generate the rate. For this study report, survival rates at 6 and 12 months were estimated. The associated two-sided 95%

CIs were calculated using the Greenwood's formula for variance derivation and on log-log transformation applied on the survivor function S(t).

PFS for each treatment group was estimated using K-M product limit method and graphically displayed. A two-sided 95% CI for median PFS was constructed based on a log-log transformed CI for the survivor function S(t).

The comparison of PFS distribution was performed using a stratified log-rank test at two-sided, 5% level. In addition, the stratified HRs between treatment groups were provided along with the 95% CI.

PFS rates at 6, 12, 18, 24, 36, 48 months and at 5 year were also to be estimated using K-M estimates on the PFS curve for each randomised group. For this study report, the PFS rates at 6 and12 months were estimated. Minimum follow-up was to be longer than or equal to time point to generate the rate. The associated two-sided 95% CIs were calculated using the Greenwood's formula.

ORR was computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs and corresponding 95% CI were calculated using CMH methodology and adjusted by the same stratification factors as in primary analysis of OS. A by subject listing of BOR and tumour measurements were provided.

The stratified (source: IVRS) odds ratios (Mantel-Haenszel estimator) between the treatment groups was provided along with the 95% CI. ORR was compared between the treatment groups using a two-sided stratified, CMH test, and 5% alpha level.

Results

Participant flow

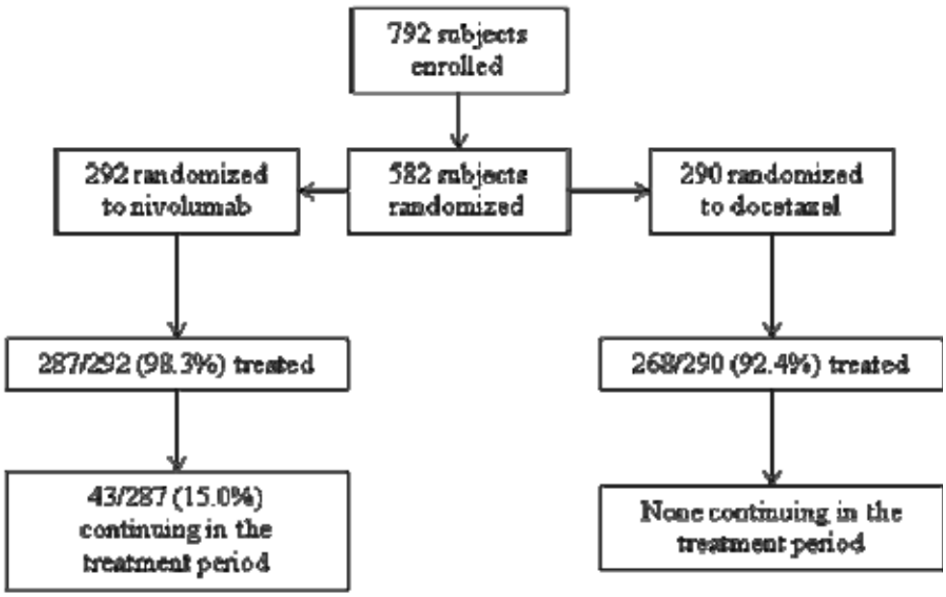


Figure 3: Disposition of Subjects

Recruitment

The enrolment period was from Nov-2012 until Dec-2013. The last subject was randomised on 31-Dec-2013 and last patient's last visit occurred on 05-Feb-2015, providing a minimum follow-up of 13.2 months. The clinical database lock occurred on 18-Mar-2015.

This study was conducted at 112 sites in 22 countries (Argentina, Australia, Austria, Brazil, Canada, Chile, Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Mexico, Norway, Peru, Poland, Romania, Russian Federation, Singapore, Spain, Switzerland, and US). Of the 582 randomised subjects, 269 (46.2%)

were in Europe, 215 (36.9%) were in the US and Canada, and 98 (16.8%) were in the “rest of world”.

Conduct of the study

The sponsor independently reviewed safety data during the study. The review was not done by treatment group in order to maintain blinding.

An independent data monitoring committee was utilized to provide oversight of safety and efficacy considerations, study conduct and risk benefit ratio for the study. The DMC acted in an advisory capacity to BMS.

The DMC met on 16-April 2015 for the formal interim analyses of OS after 413 reported deaths (93.4% of the planned number of events of the final analyses). The DMC confirmed that the pre-specified boundary for significance was crossed, ($p<0.0408$) and noted that there were no new safety signals that would affect continuation of the study. The DMC recommended that patients who were originally randomised to docetaxel to receive subsequent nivolumab therapy as part of a nivolumab extension phase

Changes to the protocol based on the amendments are summarized in the table below.

Table 6: Protocol Amendments

Document	Site(s)	Date of Issue
Amendment No. 01	Site specific: all sites • Permitted the collection and storage of blood samples for use in future exploratory pharmacogenetic research	02-Jul-2012
Amendment No. 02	Country-specific - all sites in Brazil • Updated Post Study Access to Therapy	02-Jul-2012
Amendment No. 03	VOID	
Amendment No. 04	Country-specific - all sites in France • Updated protocol to clarify the following information for all enrolled CA209057 subjects in France: length of contraceptive use required, inclusion of recommended management algorithms for suspected pulmonary toxicity, diarrhea/colitis, suspected hepatoxicity, suspected endocrinopathy, and nephrotoxicity, reference text in the protocol indication the location of safety management guidelines, addition of urinalysis at screening, and notification of change in BMS medical monitor	07-Jan-2013
Amendment No. 05	Site specific: all sites • Updated the Summary of Safety section in the protocol to include new preliminary reproductive toxicology data that was distributed as a Non-clinical Expedited Safety Report and included changes to the guidance on contraception. This revision applied to all subjects.	11-Mar-2013
Amendment No. 06	Site specific: all sites • Modified the trial to require confirmation of objective response per RECIST 1.1 criteria. This modification was in response to a request of the US Food and Drug Administration. This amendment additionally included the following changes to the protocol: • Clarification of the target population, • Extension of OS analyses to 5 years beyond the primary OS analysis, • Collection of PRO information during the survival phase, • Modification of the secondary objective related to analysis of efficacy data by PD-L1 expression status and update of LCSS evaluation by 12 weeks, • Modification of the tumor assessment schedule for non-progressing subjects who initiate a subsequent anticancer therapy, • Addition of Nivolumab Safety Algorithms as Appendix #3 • Inclusion of additional biomarker sampling • Inclusion of additional safety information on nivolumab for opportunistic infections related to immunosuppression • Inclusion of "nivolumab" throughout the protocol, as the approved generic name for BMS-936558 • Minor, additional clarifications and typographical revisions throughout the protocol.	17-Jul-2013
Amendment No. 07	Site specific: all sites • Modified the OS analysis relating to number of required events and timing of interim and final analyses. These changes were made to address observations of long-term survival and delayed onset of benefit in studies with immuno-oncology drugs. This amendment additionally included the following changes to the protocol: • Updated sections on Pharmacokinetic - Immmunogenicity and PD-L1 Protein Expression Assessments to reflect testing methods • Clarified the guidance for use of on-study palliative radiation • Clarified the docetaxel dose modification due to docetaxel-related events • Updated methods for secondary endpoint • Clarified the assay used to evaluate PD-L1 expression • Clarified the method used for the CI of the median • Clarified the DMC review and evaluation of the interim analysis of OS • Corrected typographical errors	14-Jan-2014
Amendment No. 08	Site specific: all sites • Modified the protocol based on the recommendations of the DMC, to provide a mechanism for eligible subjects originally randomized to the docetaxel treatment group to receive subsequent nivolumab therapy as part of a nivolumab extension phase • Modifications to the Time and Events Schedule for nivolumab subjects were incorporated	22-Apr-2015

Source: Appendix 1.1.

Relevant protocol deviations were reported in 7.4% of subjects. The most common deviations at entry were

for subjects who had received inadequate prior lines of therapy (5.1% nivolumab and 5.2% docetaxel).

Baseline data

In Study CA209057, 582 patients were randomised (1:1), 292 patients in the nivolumab group and 290 in the docetaxel group. Most of the patients received treatment (287 and 268 patients, for nivolumab and docetaxel, respectively).

Table 7: Baseline Demographic Characteristics - All Randomised Subjects (Study CA209057)

	Nivolumab 3 mg/kg N = 292	Docetaxel N = 290	Total N = 582
AGE (YEARS)			
N	292	290	582
MEAN	60.9	62.3	61.6
MEDIAN	61.0	64.0	62.0
MIN , MAX	37 , 84	21 , 85	21 , 85
STANDARD DEVIATION	9.27	9.75	9.53
AGE CATEGORIZATION (%)			
< 65	184 (63.0)	155 (53.4)	339 (58.2)
>= 65 AND < 75	88 (30.1)	112 (38.6)	200 (34.4)
>= 75 AND < 85	20 (6.8)	21 (7.2)	41 (7.0)
>= 85	0	2 (0.7)	2 (0.3)
>= 75	20 (6.8)	23 (7.9)	43 (7.4)
>= 65	108 (37.0)	135 (46.6)	243 (41.8)
GENDER (%)			
MALE	151 (51.7)	168 (57.9)	319 (54.8)
FEMALE	141 (48.3)	122 (42.1)	263 (45.2)
RACE (%)			
WHITE	267 (91.4)	266 (91.7)	533 (91.6)
BLACK OR AFRICAN AMERICAN	7 (2.4)	9 (3.1)	16 (2.7)
ASIAN	9 (3.1)	8 (2.8)	17 (2.9)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.3)	0	1 (0.2)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (0.3)	1 (0.2)
OTHER	8 (2.7)	6 (2.1)	14 (2.4)
ETHNICITY (%)			
HISPANIC OR LATINO	19 (6.5)	16 (5.5)	35 (6.0)
NOT HISPANIC OR LATINO	135 (46.2)	141 (48.6)	276 (47.4)
NOT REPORTED	138 (47.3)	133 (45.9)	271 (46.6)

Most subjects had a result of prior EGFR driver mutation testing reported by the investigator (72.5%). Of these subjects, 19.4% (82/422 tested) were found to harbour an EGFR mutation. Results of other driver mutation testing reported included: K-RAS gene mutation, MET receptor, and ALK translocation. The K-RAS gene mutational status and the ALK translocation status were known for 31.8% and 45.4% of the subjects, respectively. Of these subjects, most were found to be wildtype (K-RAS: 123/185 [66.5%], ALK translocation not detected: 243/264 [92.0%]). Most subjects (> 97%) did not have their MET receptor status reported.

All randomised subjects (except 1 docetaxel subject) had tumour samples collected at pre-study (baseline). Most subjects had a quantifiable PD-L1 status at pre-study (baseline) (78.2%).

Table 8: Baseline Disease Characteristics and Tumour Assessments - All Randomised Subjects (Study CA209057)

	Nivolumab 3 mg/kg N = 292	Docetaxel N = 290	Total N = 582
DISEASE STAGE			
STAGE IIIB	20 (6.8)	24 (8.3)	44 (7.6)
STAGE IV	272 (93.2)	266 (91.7)	538 (92.4)
TIME FROM INITIAL DIAGNOSIS (YEARS)			
N	292	290	582
MEDIAN (MIN - MAX)	0.82 (0.2 - 8.4)	0.82 (0.0 - 8.5)	0.82 (0.0 - 8.5)
TIME FROM INITIAL DIAGNOSIS (%)			
< 1 YEAR	176 (60.3)	174 (60.0)	350 (60.1)
1- < 2 YEARS	77 (26.4)	78 (26.9)	155 (26.6)
2- < 3 YEARS	19 (6.5)	22 (7.6)	41 (7.0)
3- < 4 YEARS	11 (3.8)	7 (2.4)	18 (3.1)
4- < 5 YEARS	3 (1.0)	2 (0.7)	5 (0.9)
>= 5 YEARS	6 (2.1)	7 (2.4)	13 (2.2)
CELL TYPE			
ADENOCARCINOMA	268 (91.8)	273 (94.1)	541 (93.0)
LARGE CELL CARCINOMA	7 (2.4)	7 (2.4)	14 (2.4)
BRONCHO-ALVEOLAR CARCINOMA	5 (1.7)	0	5 (0.9)
OTHER	12 (4.1)	10 (3.4)	22 (3.8)
EGFR MUTATION STATUS			
ANY EGFR GENE MUTATION			
POSITIVE	44 (15.1)	38 (13.1)	82 (14.1)
NOT DETECTED	168 (57.5)	172 (59.3)	340 (58.4)
NOT REPORTED	80 (27.4)	80 (27.6)	160 (27.5)
ALK TRANSLOCATION STATUS			
ANY ALK GENE TRANSLOCATION			
POSITIVE	13 (4.5)	8 (2.8)	21 (3.6)
NOT DETECTED	113 (38.7)	130 (44.8)	243 (41.8)
NOT REPORTED	166 (56.8)	152 (52.4)	318 (54.6)
MET RECEPTOR STATUS			
POSITIVE	2 (0.7)	3 (1.0)	5 (0.9)
NEGATIVE	6 (2.1)	5 (1.7)	11 (1.9)
NOT REPORTED	284 (97.3)	282 (97.2)	566 (97.3)
K-RAS MUTATION STATUS			
ANY K-RAS GENE MUTATION			
POSITIVE	28 (9.6)	34 (11.7)	62 (10.7)
NOT DETECTED	60 (20.5)	63 (21.7)	123 (21.1)
NOT REPORTED	204 (69.9)	193 (66.6)	397 (68.2)
SUBJECTS WITH AT LEAST ONE LESION [b] (%)	291 (99.7)	288 (99.3)	579 (99.5)
SITE OF LESION [a,b] (%)			
ADRENAL GLAND	58 (19.9)	55 (19.0)	113 (19.4)
ASCITES	3 (1.0)	1 (0.3)	4 (0.7)
BONE	86 (29.5)	75 (25.9)	161 (27.7)
BONE MARROW	0	1 (0.3)	1 (0.2)
CENTRAL NERVOUS SYSTEM	34 (11.6)	34 (11.7)	68 (11.7)
CHEST WALL	5 (1.7)	5 (1.7)	10 (1.7)
EFFUSION	40 (13.7)	36 (12.4)	76 (13.1)
ESOPHAGUS	2 (0.7)	1 (0.3)	3 (0.5)
KIDNEY	11 (3.8)	8 (2.8)	19 (3.3)
LIVER	72 (24.7)	60 (20.7)	132 (22.7)
LUNG	254 (87.0)	251 (86.6)	505 (86.8)
LYMPH NODE	154 (52.7)	159 (54.8)	313 (53.8)
MEDIASTINUM	25 (8.6)	21 (7.2)	46 (7.9)
ORAL CAVITY	0	1 (0.3)	1 (0.2)
OTHER	20 (6.8)	25 (8.6)	45 (7.7)
PANCREAS	0	2 (0.7)	2 (0.3)
PELVIS	5 (1.7)	2 (0.7)	7 (1.2)
PERICARDIUM	11 (3.8)	3 (1.0)	14 (2.4)
PERITONEUM	8 (2.7)	8 (2.8)	16 (2.7)
PLEURA	35 (12.0)	34 (11.7)	69 (11.9)
SKIN/SOFT TISSUE	9 (3.1)	7 (2.4)	16 (2.7)
SPLEEN	10 (3.4)	3 (1.0)	13 (2.2)
VISCERAL, OTHER	2 (0.7)	3 (1.0)	5 (0.9)
NOT REPORTED	0	1 (0.3)	1 (0.2)
NUMBER OF SITES WITH AT LEAST ONE LESION [b] (%)			
1	44 (15.1)	46 (15.9)	90 (15.5)
2	81 (27.7)	85 (29.3)	166 (28.5)
3	88 (30.1)	86 (29.7)	174 (29.9)
4	42 (14.4)	43 (14.8)	85 (14.6)
>=5	36 (12.3)	28 (9.7)	64 (11.0)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	290 (99.3)	287 (99.0)	577 (99.1)
SITE OF TARGET LESION [a] (%)			
ADRENAL GLAND	53 (18.2)	50 (17.2)	103 (17.7)
BONE	5 (1.7)	5 (1.7)	10 (1.7)
CHEST WALL	3 (1.0)	2 (0.7)	5 (0.9)
ESOPHAGUS	0	1 (0.3)	1 (0.2)
KIDNEY	7 (2.4)	7 (2.4)	14 (2.4)
LIVER	61 (20.9)	52 (17.9)	113 (19.4)
LUNG	237 (81.2)	234 (80.7)	471 (80.9)
LYMPH NODE	83 (28.4)	106 (36.6)	189 (32.5)
MEDIASTINUM	17 (5.8)	11 (3.8)	28 (4.8)
OTHER	12 (4.1)	17 (5.9)	29 (5.0)
PANCREAS	0	2 (0.7)	2 (0.3)
PELVIS	1 (0.3)	1 (0.3)	2 (0.3)
PERICARDIUM	3 (1.0)	1 (0.3)	4 (0.7)
PERITONEUM	1 (0.3)	3 (1.0)	4 (0.7)
PLEURA	10 (3.4)	8 (2.8)	18 (3.1)
SKIN/SOFT TISSUE	7 (2.4)	5 (1.7)	12 (2.1)
SPLEEN	6 (2.1)	2 (0.7)	8 (1.4)
VISCERAL, OTHER	2 (0.7)	3 (1.0)	5 (0.9)
NOT REPORTED	0	1 (0.3)	1 (0.2)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)			
N	290	287	577
MEDIAN (MIN - MAX)	71.5 (10 - 298)	70.0 (12 - 219)	71.0 (10 - 298)
CNS METASTASIS			
YES	34 (11.6)	34 (11.7)	68 (11.7)
NO	258 (88.4)	256 (88.3)	514 (88.3)
SMOKING STATUS			
CURRENT/FORMER	231 (79.1)	227 (78.3)	458 (78.7)
NEVER SMOKED	58 (19.9)	60 (20.7)	118 (20.3)
UNKNOWN	3 (1.0)	3 (1.0)	6 (1.0)
PERFORMANCE STATUS (ECOG) [%]			
0	84 (28.8)	95 (32.8)	179 (30.8)
1	208 (71.2)	193 (66.6)	401 (68.9)
2	0	0	0
3	0	1 (0.3) [c]	1 (0.2)
4	0	0	0
NOT REPORTED	0	1 (0.3)	1 (0.2)

a Subjects may have had lesions at more than one site. b Included both target and non-target lesions. c The ECOG PS for Subject was 1 on Day -9. He developed Grade 3 pericardial effusion on Day -4; his pre-treatment ECOG PS on Day 1 was 3

Previous and Subsequent Treatments

Most patients in both treatment groups had not received prior maintenance therapy (60.0% per CRF and 56.4% per IVRS) and were receiving study drug as second-line therapy (88.5% per CRF and 87.5% per IVRS). There was 1 subject in the nivolumab group who received study drug as first-line therapy (subsequent to neo-adjuvant therapy):

- All subjects received a prior platinum doublet-based therapy.
- Less than 10% of the subjects in each treatment group had received a prior EGFR TKI regimen, and < 1% of subjects had received a prior ALK inhibitor.
- The majority of subjects (62.5%) completed their most recent prior systemic regimen within 3 months and most (82.3%) within 6 months, of randomization.
- Most subjects had prior surgery (72.0%); 47.6% of subjects had received prior radiotherapy.

Subsequent systemic anti-cancer therapy was received by 42.1% of nivolumab subjects and 49.7% of docetaxel subjects. The most frequently used subsequent systemic therapy was chemotherapy in both the nivolumab group (37.7%) and the docetaxel group (34.5%). Sixty-six subjects randomised to nivolumab (22.6%) received subsequent treatment with docetaxel. Six subjects in the docetaxel group received subsequent therapy with immunotherapy, 5 of whom received an anti-PD1 pathway agent: MPDL3280A (2 subjects) and EDI4736, nivolumab, and pembrolizumab (1 subject each). Subsequent ALK/EGFR TKIs were received by 11.0% of nivolumab subjects and 22.1% of docetaxel subjects, of which erlotinib was the most common in both groups (6.5% and 17.2%, respectively).

Numbers analysed

The primary datasets used are the all randomised population for the primary efficacy analysis and the all treated population for the safety analyses. A description of all analysis populations is presented in the table below.

Table 9: Analysis Populations - Study CA209057

Population	Nivolumab Group N	Docetaxel Group N	Total N
All enrolled subjects: All subjects who signed an ICF and were registered into the IVRS.	NA	NA	792
All randomized population: All subjects who were randomized to any treatment group in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, outcome research and PD-L1expression.	292	290	582
All treated population: All subjects who received at least one dose of nivolumab or docetaxel. This is the primary dataset for analyses for dosing and safety.	287	268	555
Response-evaluable subjects: Randomized subjects whose change in the sum of diameters of target lesions was assessed (ie, target lesion measurements were made at baseline and at least one on-study tumor assessment).	233	231	464
PD-L1 quantifiable subjects: All randomized subjects with quantifiable PD-L1 expression at baseline	231	224	455
Immunogenicity subjects: All nivolumab-treated subjects with baseline and at least one post-baseline assessment for ADA	251	NA	251

Source: Table S.2.5 (enrolled), Table S.2.6 (randomized and treated), Figure S.5.16 (response-evaluable), Table S.10.13 (PD-L1 quantifiable), Table S.7.10A (immunogenicity)

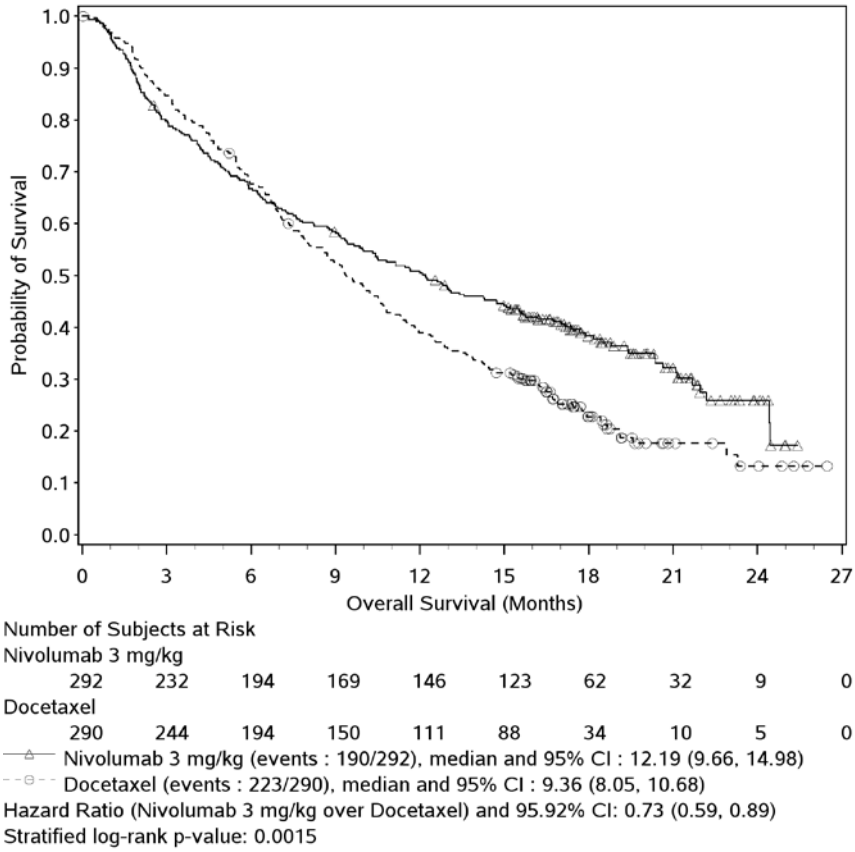
Outcomes and estimation

Primary endpoint: Overall survival

Table 10: Overall survival results - Study CA209057

Efficacy Parameter	Nivolumab N = 292	Docetaxel N = 290
PRIMARY ENDPOINT		
Overall Survival		
Events, n (%)	190 (65.1)	223 (76.9)
Stratified Log-rank Test p-value[a,b]	0.0015	
HR (95.92% CI)[c]	0.73 (0.59, 0.89)	
Median (95% CI) (Months)[d]	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate at 12 Months (95% CI)	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)

a Log-rank test stratified by prior maintenance therapy (yes/no) and line of therapy (2nd line/3rd line) as entered into the IVRS.
b The boundary for statistical significance required the p-value to be less than 0.0408.
c Stratified Cox proportional hazard model. The HR is nivolumab over docetaxel.
d Median was computed using the K-M method.



Symbols represent censored observations.

The boundary for statistical significance requires the p-value to be less than 0.0408.

Figure 4: Kaplan-Meier Overall Survival Plot - All Randomised Subjects - CA209057

Secondary endpointsl

Progression free survival

There was no statistically significant difference in PFS per RECIST v1.1 observed in subjects randomised to the nivolumab group vs the docetaxel group (HR=0.92 [95% CI: 0.77, 1.11]; stratified log-rank test p-value = 0.3932).

Table 11: Progression free survival results - Study CA209057

Efficacy Parameter	Nivolumab N = 292	Docetaxel N = 290
Progression-free Survival		
Events, n (%)	234 (80.1)	245 (84.5)
Stratified Log-rank Test p-value[a]	0.3932	
HR (95% CI)[c]	0.92 (0.77, 1.11)	
Median (95% CI) (Months)[d]	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate at 12 Months (95% CI)	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)

a Log-rank test stratified by prior maintenance therapy (yes/no) and line of therapy (2nd line/3rd line) as entered into the IVRS.
c Stratified Cox proportional hazard model. The HR is nivolumab over docetaxel.
d Median was computed using the K-M method.

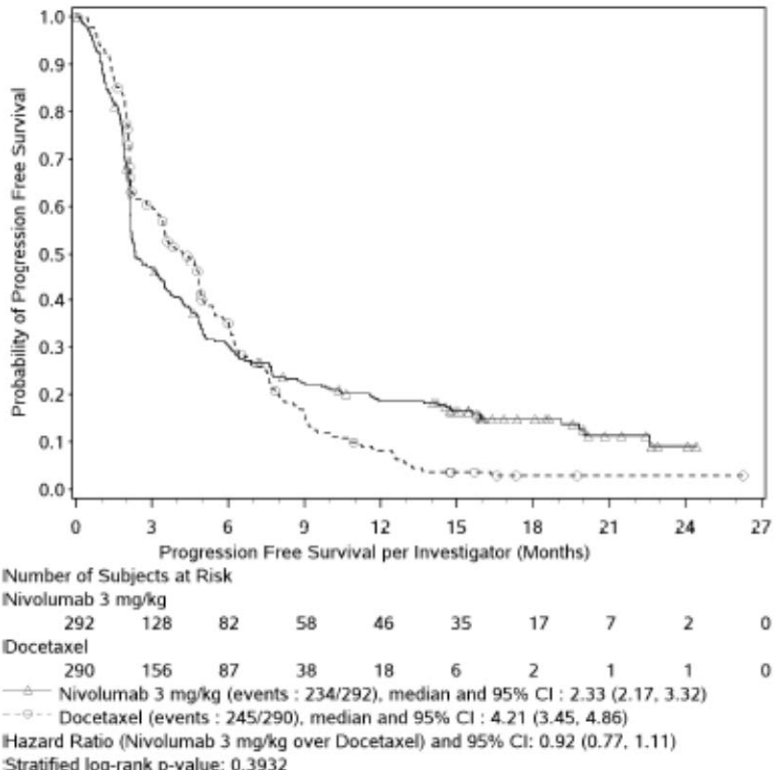


Figure 5: Kaplan-Meier Plot of Progression-free Survival - All Randomised Subjects in CA209057

Objective response rate

The investigator-assessed confirmed ORR using RECIST v1.1 criteria higher in the nivolumab group than in the docetaxel group.

Table 12: Best Overall Response per Investigator - All Randomised Subjects in CA209057

	Nivolumab 3 mg/kg N = 292	Docetaxel N = 290
BEST OVERALL RESPONSE (RECIST 1.1, CONFIRMATION OF RESPONSE REQUIRED):		
COMPLETE RESPONSE (CR)	4 (1.4)	1 (0.3)
PARTIAL RESPONSE (PR)	52 (17.8)	35 (12.1)
STABLE DISEASE (SD)	74 (25.3)	122 (42.1)
PROGRESSIVE DISEASE (PD)	129 (44.2)	85 (29.3)
UNABLE TO DETERMINE (UTD)	33 (11.3)	47 (16.2)
NEVER TREATED	5 (1.7)	22 (7.6)
WRONG CANCER DIAGNOSIS	0	0
DEATH PRIOR TO DISEASE ASSESSMENT	25 (8.6)	19 (6.6)
EARLY DISCONTINUATION DUE TO TOXICITY	0	1 (0.3)
OTHER	3 (1.0)	5 (1.7)
OBJECTIVE RESPONSE RATE (1)	56/292 (19.2%)	36/290 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	6.8%	
(95% CI)	(0.9, 12.7)	
ESTIMATE OF ODDS RATIO (3, 4)	1.68	
(95% CI)	(1.07, 2.64)	
P-VALUE (5)	0.0246	

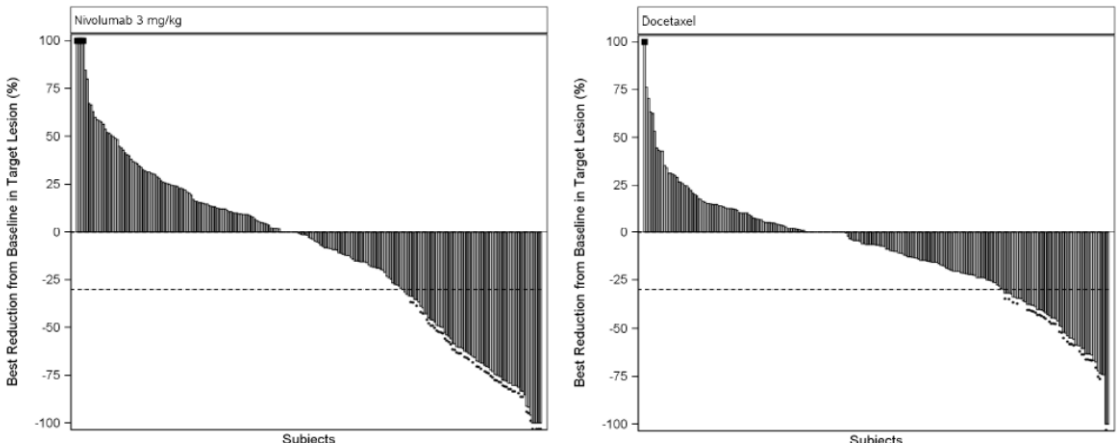
(1) CR+PR, confidence interval was based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (nivolumab - docetaxel) was based on the Cochran-Mantel-Haenszel method of weighting.
(3) Stratified by prior maintenance therapy (yes vs no) and line of therapy (2L vs 3L) at randomization as entered into the IVRS.
(4) Strata adjusted odds ratio (nivolumab over docetaxel) used the Mantel-Haenszel method.
(5) Two-sided p-value was from a stratified Cochran-Mantel-Haenszel test.
Source: refer to Table 7.3-1 of the CA209057 Final CSR

Table 13: Time to Objective Response and Duration of Response per Investigator - All Responders in CA209057

	Nivolumab 3 mg/kg N = 56	Docetaxel N = 36
TIME TO OBJECTIVE RESPONSE (MONTHS)		
NUMBER OF RESPONDERS	56	36
MEAN	2.62	2.97
MEDIAN	2.10	2.61
MIN, MAX	1.2, 8.6	1.4, 6.3
Q1, Q3	1.97, 3.33	2.04, 3.55
STANDARD DEVIATION	1.195	1.228
DURATION OF OBJECTIVE RESPONSE (MONTHS)		
MIN, MAX (A)	1.8, 22.6+	1.2+, 15.2+
MEDIAN (95% CI) (B)	17.15 (8.38, N.A.)	5.55 (4.40, 6.97)
N EVENT/N RESP (%)	27/56 (48.2)	31/36 (86.1)

(A) Symbol + indicates a censored value.
(B) Median was computed using the Kaplan-Meier method.
Source: refer to Table 7.3.2-1 of the CA209057 Final CSR

The reductions in target lesion tumour burden are reflected in the figure below.



Subjects with target lesion at baseline and at least one evaluable target lesion assessment on-study= 233 (nivolumab) and 231 (docetaxel)
Negative/positive value means maximum tumour reduction/minimum tumour increase.
Best reduction was based on evaluable target lesion measurements up to progression or start subsequent therapy date, excluding on-treatment palliative
radiotherapy of non-target bone lesions or CNS lesions.
Horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response.
*: Responder per RECIST1.1 criteria, a confirmation of the response was required.
A square symbol represents % change truncated to 100%.

Figure 6: Waterfall Plot of Best Reduction from Baseline in Sum of Diameters of Target Lesions per Investigator -All Response-evaluable Subjects in CA209057

At the time of database lock, the proportion of responders with on-going response (as of the last tumour assessment before censoring) was greater in the nivolumab group (29/56, 51.8%) than in the docetaxel group (5/36, 13.9%).

Ancillary analyses

Efficacy by PD-L1 Expression

Sample with quantifiable PD-L1 expression were provided by 78.2% of randomised subjects.

Table 14: Overall Frequency of PD-L1 Expression at Baseline - All Randomised Subjects in CA209057

Population PD-L1 Expression Category	Nivolumab 3 mg/kg N = 292	Docetaxel N = 290	Total N = 582
OVERALL	292	290	582
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	231 (79.1)	224 (77.2)	455 (78.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	123/231 (53.2)	123/224 (54.9)	246/455 (54.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	108/231 (46.8)	101/224 (45.1)	209/455 (45.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	95/231 (41.1)	86/224 (38.4)	181/455 (39.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	136/231 (58.9)	138/224 (61.6)	274/455 (60.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10%	86/231 (37.2)	79/224 (35.3)	165/455 (36.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10%	145/231 (62.8)	145/224 (64.7)	290/455 (63.7)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE (N(%))	61 (20.9)	66 (22.8)	127 (21.8)

Source: refer to Table 7.5.1-1 of the CA209057 Final CSR

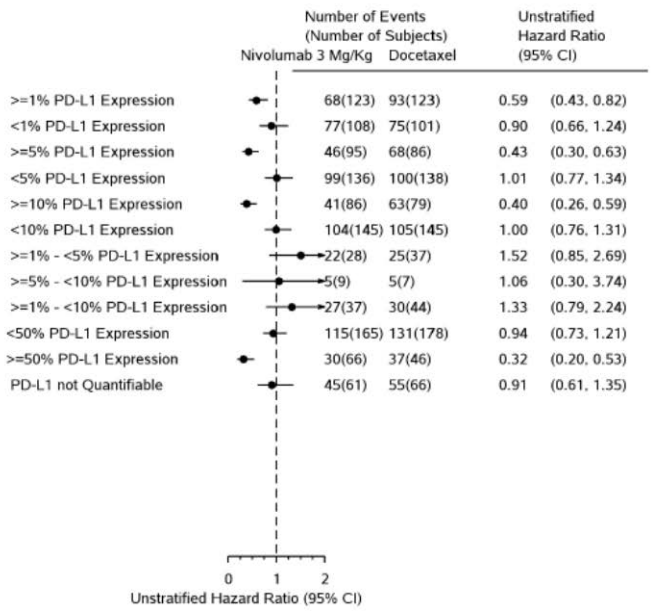
Efficacy outcomes

In subjects with tumour PD-L1 expression levels ≥1%, ≥5%, and ≥10%, the nivolumab group showed improved OS, ORR, and PFS compared with the docetaxel group across expression levels, as reflected in the OS and PFS K-M curves

In subjects with tumour PD-L1 expression levels <1%, <5%, and <10%, there were no clinically relevant differences in OS, ORR, and PFS in the nivolumab group compared with the docetaxel group across expression levels, as reflected in the OS and PFS K-M curves.

APPENDIX 1: PLOT OF OVERALL SURVIVAL HAZARD RATIOS BY PD-L1 EXPRESSION INTERVAL

(1) All Randomized Subjects



(2) All Randomized Subjects Who Were Alive At Month 3

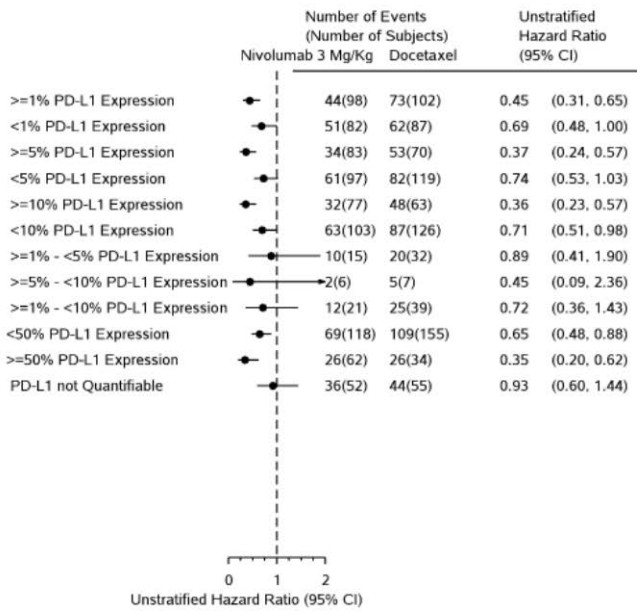
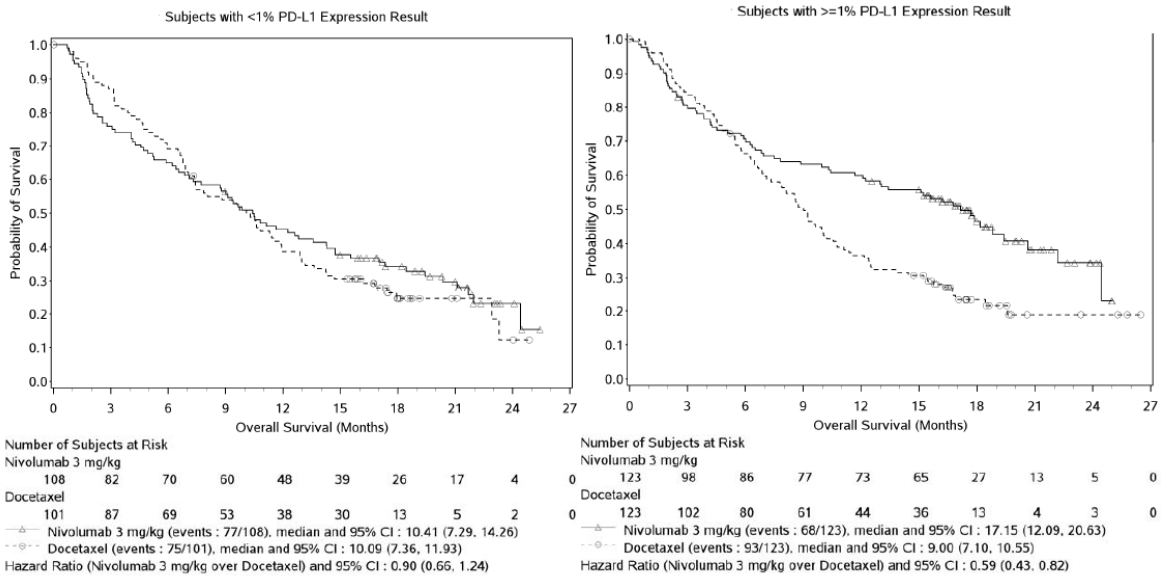


Figure 7: Plot of OS Hazard Ratios by PD-L1 Expression Level at Baseline - All Randomised Subjects CA209057

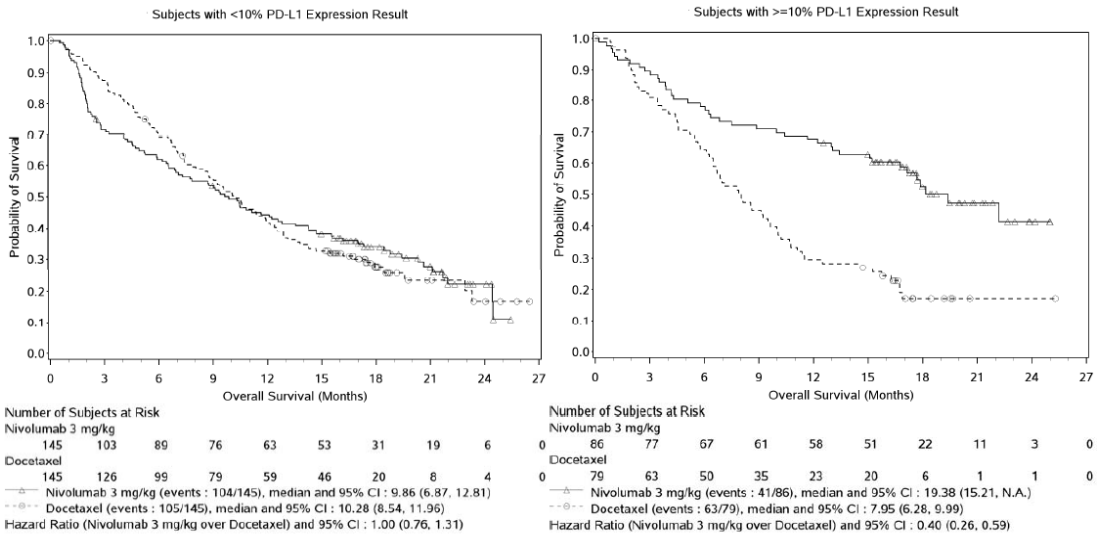
Table 15: OS by PD-L1 Expression Level at Baseline - All Randomised Subjects CA209057

	nivolumab	docetaxel	
PD-L1 Expression	**Number of events (number of patients)**		**Unstratified Hazard Ratio (95% CI)**
<1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥1% to <10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥10% to <50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)

[a]Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharma Dx assay was not analytically validated at the 10% or 50% expression levels

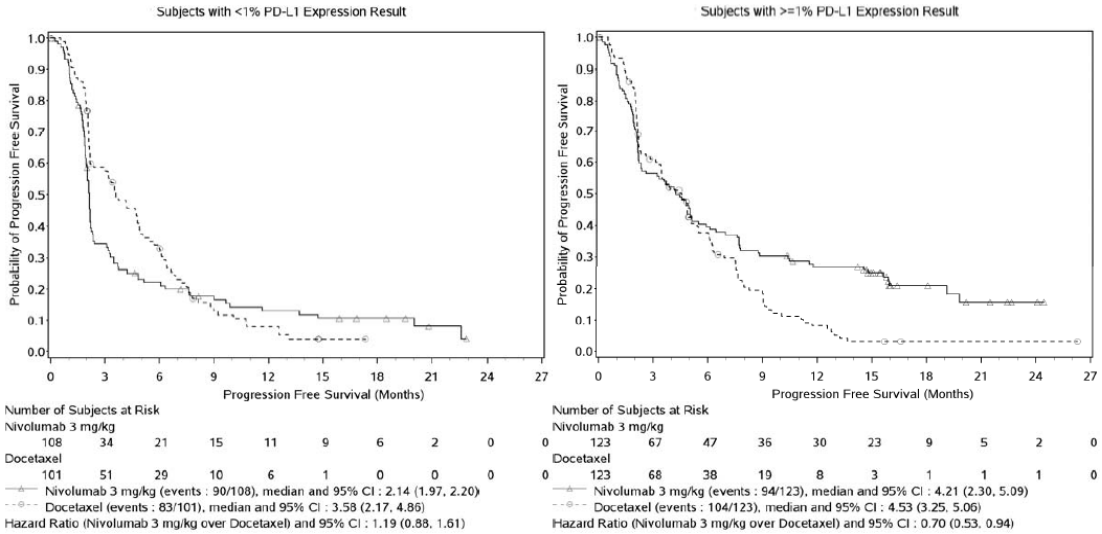


Symbols represent censored observations.

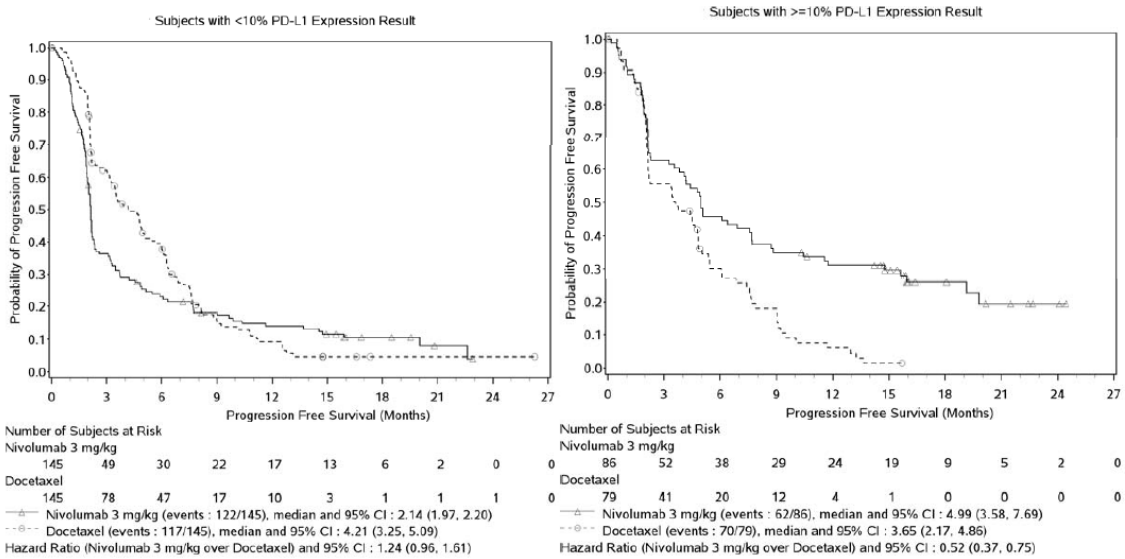


Symbols represent censored observations.

Figure 8: Kaplan-Meier Plot of OS by baseline PD-L1 expression (1 and 10 % Expression Level) - All Randomised Subject CA902057



Symbols represent censored observations.



Symbols represent censored observations.

Figure 9: Kaplan-Meier Plot of PFS by baseline PD-L1 expression (1 and 10 % Expression Level) - All Randomised Subjects CA209057

Higher ORRs were observed with nivolumab versus docetaxel across pre-defined expression levels ≥1%, ≥5%, and ≥10%, (range: 30.9% to 37.2% versus 12.2% to 12.8%), with non-overlapping CIs. Median DOR was longer with nivolumab (16.0 months) versus docetaxel (5.6 months) across PD-L1 expression levels.

For patients with no PD-L1 expression, objective response rates were similar, although numerically higher with docetaxel versus nivolumab, with overlapping CIs. Among responders, median DOR was longer with nivolumab (18.3 months) versus docetaxel (5.6 months) for patients with no PD-L1 expression.

Table 16: ORR by pre-treatment PD-L1 expression status at baseline - CA209057

PD-L1 Expression	nivolumab	docetaxel	
	ORR by tumour PD-L1 expression		Odds Ratio (95% CI)
<1%	10/108 (9.3%)	15/101 (14.9%)	0.59 (0.22, 1.48)
	95% CI: 4.5, 16.4	95% CI: 8.6, 23.3	
≥1%	38/123 (30.9%)	15/123 (12.2%)	3.22 (1.60, 6.71)
	95% CI: 22.9, 39.9	95% CI: 7.0, 19.3	
≥1% to <10%[a]	6/37 (16.2%)	5/ 44 (11.4%)	1.51 (0.35, 6.85)
	95% CI: 6.2, 32.0	95% CI: 3.8, 24.6	
≥10% to <50%[a]	5/20 (25.0%)	7/33 (21.2%)	1.24 (0.26, 5.48)
	95% CI: 8.7, 49.1	95% CI: 9.0, 38.9	
≥50%[a]	27/66 (40.9%)	3/46 (6.5%)	9.92 (2.68, 54.09)
	95% CI: 29.0, 53.7	95% CI: 1.4, 17.9	

[a] Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharma Dx assay was not analytically validated at the 10% or 50% expression levels

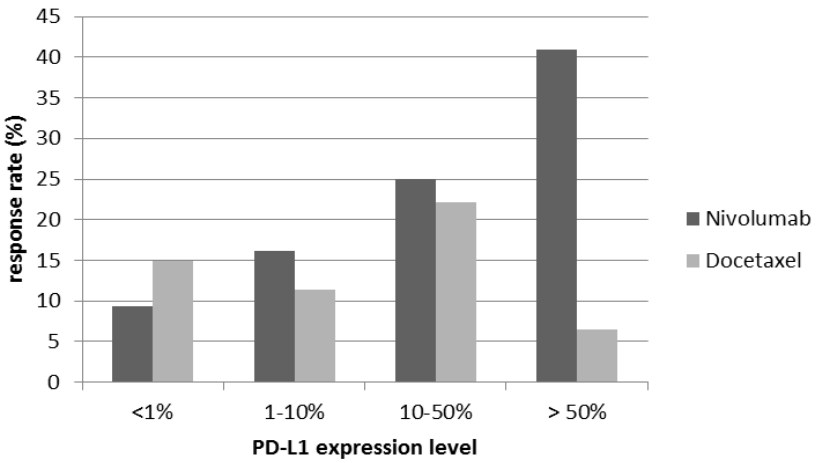


Figure 10: The overall response by baseline PD-L1 expression level - CA209057

Risk of early death

The higher number of early deaths (i.e within 3 months) compared to docetaxel was of concern during the assessment. Baseline characteristics were investigated to identify factors that could explain this outcome.

- Nivolumab vs docetaxel

In the docetaxel group, the early death (OS≤3 months) subgroup had a higher proportion of subjects with ECOG PS 0 (27.3% docetaxel vs. 8.5% nivolumab), 4 sites with at least 1 lesion (27.3% docetaxel vs. 15.3% nivolumab), and best response of PR or CR to the most recent prior systemic therapy (25.0% docetaxel vs. 13.6% nivolumab), as compared to subjects in the nivolumab early death subgroup (Table 17).

This suggests that, although prognostic factors were balanced between the groups at baseline, subjects with these more favorable disease attributes had a higher likelihood of experiencing a death event in the docetaxel group within the first 3 months of treatment relative to the nivolumab group. Importantly, as mentioned, sample sizes in the early death subgroups are small (OS ≤3 months; n = 59 nivolumab, n = 44 docetaxel) and preclude definitive conclusions.

Table 17: Key baseline characteristics by early death status, nivolumab vs docetaxel - CA209057

	NIVOLUMAB			DOCETAXEL		
	Early Death <=3 Months N = 59	Early Death >3 to <=6 Months N = 38	No Early Death N = 195	Early Death <=3 Months N = 44	Early Death >3 to <=6 Months N = 49	No Early Death N = 197
PERFORMANCE STATUS (ECOG) [%]						
0	5 (8.5)	8 (21.1)	71 (36.4)	12 (27.3)	5 (10.2)	78 (39.6)
1	54 (91.5)	30 (78.9)	124 (63.6)	30 (68.2)	44 (89.8)	119 (60.4)
REGION						
US/CANADA	15 (25.4)	12 (31.6)	78 (40.0)	19 (43.2)	22 (44.9)	69 (35.0)
EUROPE	34 (57.6)	18 (47.4)	83 (42.6)	19 (43.2)	23 (46.9)	92 (46.7)
REST OF WORLD	10 (16.9)	8 (21.1)	34 (17.4)	6 (13.6)	4 (8.2)	36 (18.3)
NUMBER OF SITES WITH AT LEAST ONE LESION (A) (%)						
1	5 (8.5)	4 (10.5)	35 (17.9)	4 (9.1)	2 (4.1)	40 (20.3)
2	13 (22.0)	12 (31.6)	56 (28.7)	9 (20.5)	16 (32.7)	60 (30.5)
3	16 (27.1)	9 (23.7)	63 (32.3)	12 (27.3)	19 (38.8)	55 (27.9)
4	9 (15.3)	9 (23.7)	24 (12.3)	12 (27.3)	6 (12.2)	25 (12.7)
>=5	15 (25.4)	4 (10.5)	17 (8.7)	6 (13.6)	5 (10.2)	17 (8.6)
PRIOR MAINTENANCE THERAPY (CRF)						
YES	20 (33.9)	13 (34.2)	89 (45.6)	13 (29.5)	17 (34.7)	81 (41.1)
NO	39 (66.1)	25 (65.8)	106 (54.4)	31 (70.5)	32 (65.3)	116 (58.9)
ON STUDY LINE OF THERAPY (CRF) (B)						
SECOND LINE	48 (81.4)	33 (86.8)	175 (89.7)	39 (88.6)	44 (89.8)	176 (89.3)
THIRD LINE	11 (18.6)	5 (13.2)	19 (9.7)	5 (11.4)	5 (10.2)	21 (10.7)
OTHER	0	0	1 (0.5)	0	0	0
BEST RESPONSE TO MOST RECENT PRIOR SYSTEMIC THERAPY						
CR OR PR	8 (13.6)	8 (21.1)	57 (29.2)	11 (25.0)	10 (20.4)	47 (23.9)
SD	17 (28.8)	13 (34.2)	73 (37.4)	7 (15.9)	13 (26.5)	76 (38.6)
PD	34 (57.6)	16 (42.1)	61 (31.3)	24 (54.5)	24 (49.0)	68 (34.5)
UNKNOWN/NOT REPORTED	0	1 (2.6)	4 (2.1)	2 (4.5)	2 (4.1)	6 (3.0)
TIME FROM COMPLETION OF MOST RECENT PRIOR SYSTEMIC THERAPY REGIMEN TO RANDOMIZATION						
< 3 MONTHS	46 (78.0)	26 (68.4)	109 (55.9)	33 (75.0)	41 (83.7)	109 (55.3)
3-6 MONTHS	8 (13.6)	6 (15.8)	45 (23.1)	6 (13.6)	3 (6.1)	47 (23.9)
> 6 MONTHS	5 (8.5)	6 (15.8)	41 (21.0)	5 (11.4)	5 (10.2)	41 (20.8)
SITE OF LESION (A) (C) (%)						
BONE	26 (44.1)	13 (34.2)	47 (24.1)	11 (25.0)	13 (26.5)	51 (25.9)
LIVER	20 (33.9)	7 (18.4)	45 (23.1)	15 (34.1)	14 (28.6)	31 (15.7)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	50 (84.7)	24 (63.2)	157 (80.5)	33 (75.0)	39 (79.6)	152 (77.2)
PD-L1 EXPRESSION >= 1%	24/50 (48.0)	12/24 (50.0)	87/157 (55.4)	20/33 (60.6)	21/39 (53.8)	82/152 (53.9)
PD-L1 EXPRESSION < 1%	26/50 (52.0)	12/24 (50.0)	70/157 (44.6)	13/33 (39.4)	18/39 (46.2)	70/152 (46.1)
PD-L1 EXPRESSION >= 5%	12/50 (24.0)	10/24 (41.7)	73/157 (46.5)	15/33 (45.5)	15/39 (38.5)	56/152 (36.8)
PD-L1 EXPRESSION < 5%	38/50 (76.0)	14/24 (58.3)	84/157 (53.5)	18/33 (54.5)	24/39 (61.5)	96/152 (63.2)
PD-L1 EXPRESSION >= 10%	9/50 (18.0)	10/24 (41.7)	67/157 (42.7)	15/33 (45.5)	13/39 (33.3)	51/152 (33.6)
PD-L1 EXPRESSION < 10%	41/50 (82.0)	14/24 (58.3)	90/157 (57.3)	18/33 (54.5)	26/39 (66.7)	101/152 (66.4)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE (N(%))	9 (15.3)	14 (36.8)	38 (19.5)	11 (25.0)	10 (20.4)	45 (22.8)
EGFR MUTATION STATUS						
ANY EGFR GENE MUTATION						
POSITIVE	11 (18.6)	6 (15.8)	27 (13.8)	9 (20.5)	5 (10.2)	24 (12.2)
NOT DETECTED	35 (59.3)	22 (57.9)	111 (56.9)	23 (52.3)	29 (59.2)	120 (60.9)
NOT REPORTED	13 (22.0)	10 (26.3)	57 (29.2)	12 (27.3)	15 (30.6)	53 (26.9)

(A) Includes both target and non-target lesions
(B) Derived as number of lines of prior therapy for advanced, metastatic or recurrent disease received + 1.
(C) Subjects may have lesions at more than one site
Source: Table EU.6e and Table EU.6f (baseline physical measurements), Table EU.6g and Table EU.6h (other baseline characteristics), Table EU.6i and Table EU.6j (baseline EGRF, ALK, MET, and K-RAS status), Table EU.6k and Table EU.6l (prior cancer therapies), Table EU.6m and Table EU.6n (PD-L1 expression), and Table EU.6o and Table EU.6p (pre-treatment tumor assessments).

- Nivolumab group: early death (OS <3 months vs. OS >6 months)

In the subgroup of nivolumab subjects with early death (OS < 3 months), as compared with the subgroup of nivolumab subjects with no early death, the factors with at least a 10% difference between subgroups included:

- a higher proportion of subjects with ECOG PS of 1 (91.5% vs. 63.6%), region Europe (57.6% vs. 42.6%), ≥5 sites with at least 1 lesion (25.4 vs. 8.7%), completion of most recent therapy < 3 months prior to randomization (78 vs. 55.9%), no prior maintenance therapy (66.1 vs. 54.4%), PD as best response to most recent prior systemic therapy (57.6 vs. 31.3%, prior radiation therapy (54 vs. 44.1%), bone (44.1 vs. 24.1%) or liver (33.9 vs. 23.1%) involvement at baseline.
- a lower proportion of subjects in the US/Canada region (25.4 vs. 40.0%), or best response of PR or CR to the most recent prior systemic therapy (13.6 vs. 29.2%).

Table 18: Key baseline characteristics by early death status – All randomised nivolumab subjects - CA209057

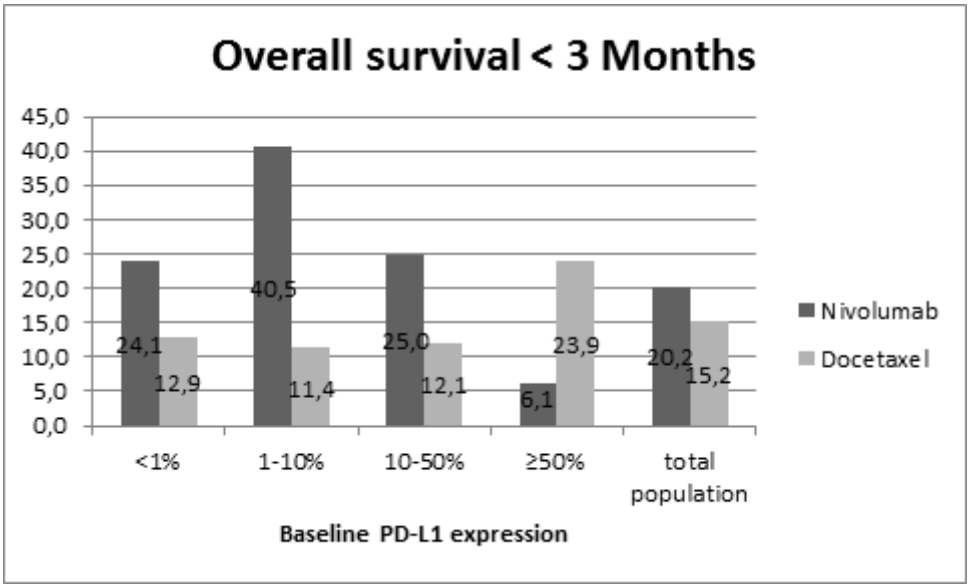
	Early Death <=6 Months N = 97	Early Death <=3 Months N = 59	Early Death >3 to <=6 Months N = 38	No Early Death N = 195	Total N = 292
PERFORMANCE STATUS (ECOG) [%]					
0	13 (13.4)	5 (8.5)	8 (21.1)	71 (36.4)	84 (28.8)
1	84 (86.6)	54 (91.5)	30 (78.9)	124 (63.6)	208 (71.2)
AGE CATEGORIZATION (%)					
< 65	63 (64.9)	40 (67.8)	23 (60.5)	121 (62.1)	184 (63.0)
>= 65 AND < 75	26 (26.8)	16 (27.1)	10 (26.3)	62 (31.8)	88 (30.1)
>= 75 AND < 85	8 (8.2)	3 (5.1)	5 (13.2)	12 (6.2)	20 (6.8)
>= 75	8 (8.2)	3 (5.1)	5 (13.2)	12 (6.2)	20 (6.8)
>= 65	34 (35.1)	19 (32.2)	15 (39.5)	74 (37.9)	108 (37.0)
CNS METASTASIS					
YES	14 (14.4)	6 (10.2)	8 (21.1)	20 (10.3)	34 (11.6)
NO	83 (85.6)	53 (89.8)	30 (78.9)	175 (89.7)	258 (88.4)
SMOKING STATUS					
CURRENT/FORMER	80 (82.5)	49 (83.1)	31 (81.6)	151 (77.4)	231 (79.1)
NEVER SMOKED	17 (17.5)	10 (16.9)	7 (18.4)	41 (21.0)	58 (19.9)
UNKNOWN	0	0	0	3 (1.5)	3 (1.0)
REGION					
US/CANADA	27 (27.8)	15 (25.4)	12 (31.6)	78 (40.0)	105 (36.0)
EUROPE	52 (53.6)	34 (57.6)	18 (47.4)	83 (42.6)	135 (46.2)
REST OF WORLD	18 (18.6)	10 (16.9)	8 (21.1)	34 (17.4)	52 (17.8)
NUMBER OF SITES WITH AT LEAST ONE LESION (A) (%)					
1	9 (9.3)	5 (8.5)	4 (10.5)	35 (17.9)	44 (15.1)
2	25 (25.8)	13 (22.0)	12 (31.6)	56 (28.7)	81 (27.7)
3	25 (25.8)	16 (27.1)	9 (23.7)	63 (32.3)	88 (30.1)
4	18 (18.6)	9 (15.3)	9 (23.7)	24 (12.3)	42 (14.4)
>=5	19 (19.6)	15 (25.4)	4 (10.5)	17 (8.7)	36 (12.3)
PRIOR MAINTENANCE THERAPY (CRF)					
YES	33 (34.0)	20 (33.9)	13 (34.2)	89 (45.6)	122 (41.8)
NO	64 (66.0)	39 (66.1)	25 (65.8)	106 (54.4)	170 (58.2)
ON STUDY LINE OF THERAPY (CRF) (B)					
SECOND LINE	81 (83.5)	48 (81.4)	33 (86.8)	175 (89.7)	256 (87.7)
THIRD LINE	16 (16.5)	11 (18.6)	5 (13.2)	19 (9.7)	35 (12.0)
OTHER	0	0	0	1 (0.5)	1 (0.3)
TYPE OF PRIOR SYSTEMIC THERAPY RECEIVED (C)					
ANY PRIOR SYSTEMIC THERAPY	97 (100)	59 (100)	38 (100)	195 (100)	292 (100)
PRIOR PLATINUM-BASED THERAPY	97 (100)	59 (100)	38 (100)	195 (100)	292 (100)
PRIOR ALK INHIBITORS	1 (1.0)	1 (1.7)	0	0	1 (0.3)
PRIOR EGFR TKI	11 (11.3)	7 (11.9)	4 (10.5)	18 (9.2)	29 (9.9)
OTHER SYSTEMIC CANCER THERAPY - CHEMOTHERAPY	97 (100)	59 (100)	38 (100)	195 (100)	292 (100)
OTHER SYSTEMIC CANCER THERAPY - EXPERIMENTAL DRUGS	6 (6.2)	4 (6.8)	2 (5.3)	17 (8.7)	23 (7.9)
PRIOR SYSTEMIC THERAPY REGIMEN SETTING					
ADJUVANT	7 (7.2)	3 (5.1)	4 (10.5)	14 (7.2)	21 (7.2)
NEO-ADJUVANT	2 (2.1)	2 (3.4)	0	7 (3.6)	9 (3.1)
METASTATIC	96 (99.0)	58 (98.3)	38 (100)	188 (96.4)	284 (97.3)
BEST RESPONSE TO MOST RECENT PRIOR SYSTEMIC THERAPY					
CR OR PR	16 (16.5)	8 (13.6)	8 (21.1)	57 (29.2)	73 (25.0)
SD	30 (30.9)	17 (28.8)	13 (34.2)	73 (37.4)	103 (35.3)
PD	50 (51.5)	34 (57.6)	16 (42.1)	61 (31.3)	111 (38.0)
UNKNOWN/NOT REPORTED	1 (1.0)	0	1 (2.6)	4 (2.1)	5 (1.7)
TIME FROM COMPLETION OF MOST RECENT PRIOR SYSTEMIC THERAPY REGIMEN TO RANDOMIZATION					
< 3 MONTHS	72 (74.2)	46 (78.0)	26 (68.4)	109 (55.9)	181 (62.0)
3-6 MONTHS	14 (14.4)	8 (13.6)	6 (15.8)	45 (23.1)	59 (20.2)
> 6 MONTHS	11 (11.3)	5 (8.5)	6 (15.8)	41 (21.0)	52 (17.8)
PRIOR RADIOTHERAPY					
YES	53 (54.6)	32 (54.2)	21 (55.3)	86 (44.1)	139 (47.6)
NO	44 (45.4)	27 (45.8)	17 (44.7)	109 (55.9)	153 (52.4)
SITE OF LESION (A) (D) (%)					
BONE	39 (40.2)	26 (44.1)	13 (34.2)	47 (24.1)	86 (29.5)
LIVER	27 (27.8)	20 (33.9)	7 (18.4)	45 (23.1)	72 (24.7)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	74 (76.3)	50 (84.7)	24 (63.2)	157 (80.5)	231 (79.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	36/74 (48.6)	24/50 (48.0)	12/24 (50.0)	87/157 (55.4)	123/231 (53.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	38/74 (51.4)	26/50 (52.0)	12/24 (50.0)	70/157 (44.6)	108/231 (46.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	22/74 (29.7)	12/50 (24.0)	10/24 (41.7)	73/157 (46.5)	95/231 (41.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	52/74 (70.3)	38/50 (76.0)	14/24 (58.3)	84/157 (53.5)	136/231 (58.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10%	19/74 (25.7)	9/50 (18.0)	10/24 (41.7)	67/157 (42.7)	86/231 (37.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10%	55/74 (74.3)	41/50 (82.0)	14/24 (58.3)	90/157 (57.3)	145/231 (62.8)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE(N(%))	23 (23.7)	9 (15.3)	14 (36.8)	38 (19.5)	61 (20.9)
EGFR MUTATION STATUS					
ANY EGFR GENE MUTATION					
POSITIVE	17 (17.5)	11 (18.6)	6 (15.8)	27 (13.8)	44 (15.1)
NOT DETECTED	57 (58.8)	35 (59.3)	22 (57.9)	111 (56.9)	168 (57.5)
NOT REPORTED	23 (23.7)	13 (22.0)	10 (26.3)	57 (29.2)	80 (27.4)

(A) Includes both target and non-target lesions
(B) Derived as number of lines of prior therapy for advanced, metastatic or recurrent disease received + 1.
(C) Some subjects may have been treated with more than 1 type of therapy.
(D) Subjects may have lesions at more than one site
The total column includes all subjects randomized to Nivolumab

- Nivolumab vs. docetaxel (according to PD-L1 expression)

The docetaxel group shows a similar death rate across the different baseline groups according to baseline PD-L1 expression. The additional post hoc analyses revealed that for nivolumab patients with a baseline PD-L1 expression <10%, the early death rate was around 25%; this death rate is higher than for docetaxel. In contrast, patients with a PD-L1 expression ≥ 50%, nivolumab shows a low overall early death rate (6.1%,

which is lower than observed with docetaxel 24%).

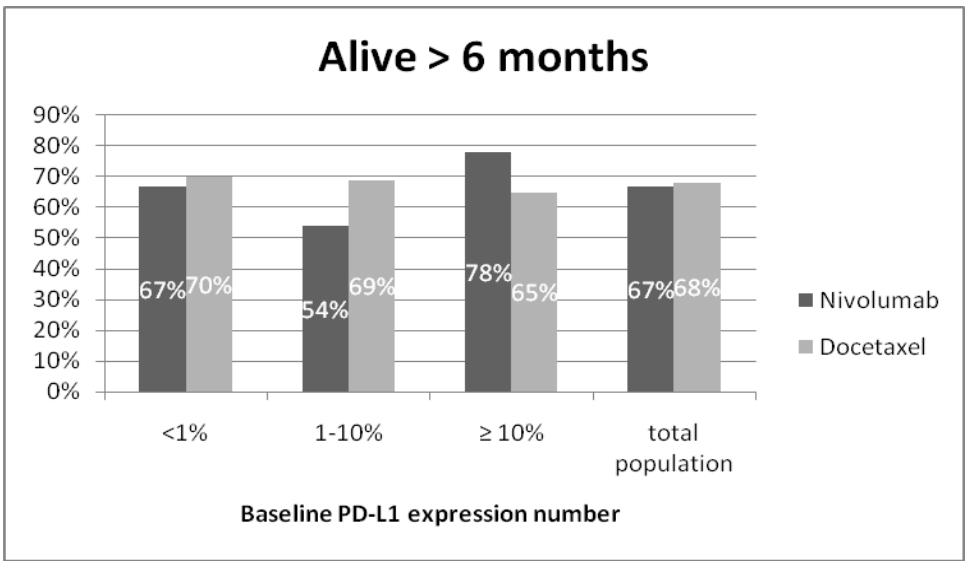


Note: The proportion of patients by PD-L1 expression cut-offs represents those experiencing an early death. The PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels.

Figure 11: Comparison of the early death rate (OS <3 months) between nivolumab and docetaxel according baseline PD-L1 expression- Study CA209057

At 6 months, the overall survival rates between nivolumab and docetaxel are comparable for the patients group with a baseline PD-L1 expression <10%. The patients group with a PD-L1 expression ≥ 10% shows the largest difference in overall survival (OS >6 Month) between nivolumab and docetaxel (78% vs. 65%) favouring nivolumab.

The death rates and survival for the patient group with unquantifiable PD-L1 are comparable to docetaxel (early death rate 15% vs 17%, OS at six months 62% vs 68%)



Note: The proportion of patients by PD-L1 expression cut-offs represents those not experiencing an early death (<= 6 months, not based on Kaplan-Meier estimates). The PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels?

Figure 12: Comparison of the Overall survival rate after 6 months between nivolumab and docetaxel according baseline PD-L1 expression number- Study CA209057

The applicant submitted OS sensitivity analyses of all randomised patients alive at landmark time points (3 months and 6 months).

Table 19: Landmark analyses of the patients alive at start of the study, 3 months and 6 months for both the overall population and those with a PD-L1 expression < 1% - CA209057

	Nivolumab		Docetaxel		
	Events/ number	**Median OS (95% CI)**	**Events/ number**	**Median OS (95% CI)**	**Hazard Ratio (95% CI)**
Overall population					
start study	190/292	12.19 (9.66-14.98)	223/290	9.36 (8.05-10.68)	0.73 (0.59-0.89)
3 months	131/232	17.35 (14.72-20.34)	179/244	11.30 (9.99 -12.75)	0.59 (0.47- 0.74)
6 months	93/194	20.37 (17.87-22.18)	130/194	13.90 (12.16-16.20)	0.51 (0.39- 0.68)
PD-L1 < 1%					
Start study	77/108	10.41 (7.29-14.26)	75/101	10.09 (7.36-11.93	0..90 (0.66-1.24)
3 months	51/ 82	14.72 (11.14-21.09)	62/87	11.40 (9.36 - 13.14)	0.66 (0.45- 0.97)
6 months	39/ 70	19.42 (14.26-21.95)	44/69	13.63 (11.40- 17.45)	0.65 (0.42- 1.01)

The patients population with PD-L1 expression < 1% at the landmark analyses at 3 months, the curves are slightly in favour of nivolumab run parallel up in favour of nivolumab till 6 months, when they split.

The landmark analyses at 6 months shows that they appear to separate at 7 months. The hazard ratio for overall survival shows a considerable improvement from the start (Hazard ratio (0.91) of the study to 3 months (hazard ratio 0.66) with no further improvement from month 3 to 6.

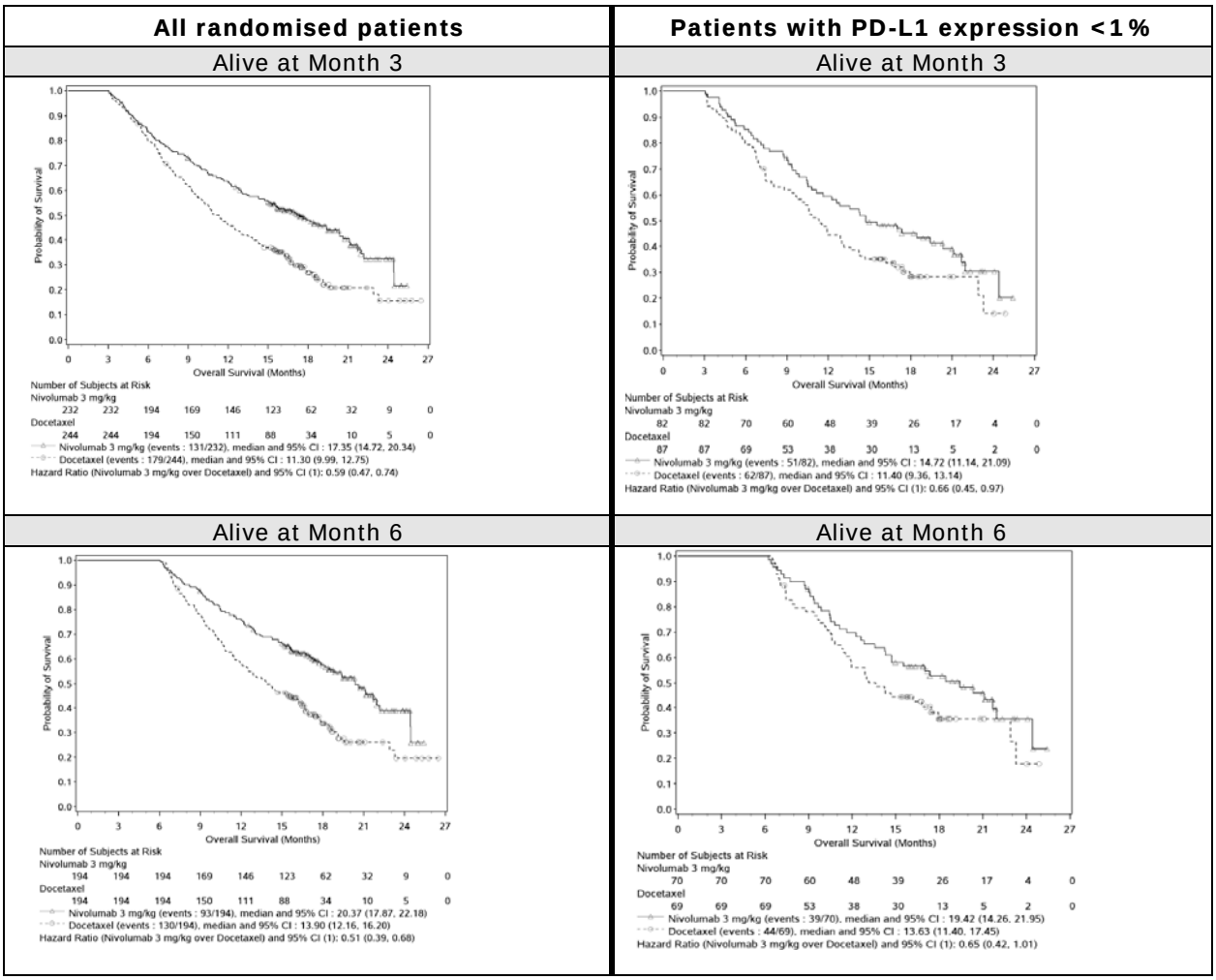


Figure 13: Kaplan Meier of OS by landmark endpoints for patients alive at 3 and 6 months for the overall population and patients with PDL1 expression < 1%. Patients alive at month 3 and at month 6 - CA209057

Additional analyses according to baseline PD-L1 expression were also provided for the comparison of the early death rate (OS < 3 months).

In the nivolumab group, baseline PD-L1 expression levels did not distinguish the early death subgroup. While 41/50 subjects with quantifiable PD-L1 expression in the early death subgroup had <10% PD-L1 expression, most subjects (104/145) with < 10% PD-L1 did not experience early death. This is consistent with the other PD-L1 expression levels (82/108 with < 1% expression and 98/136 with < 5% expression).

Table 20: Frequency of PD-L1 expression at baseline by early death status (3 months cut off all randomised nivolumab subjects - CA209057

Population PD-L1 Expression Category	Early Death (Yes) N = 59	Early Death (No) N = 233	Total N = 292
OVERALL	59	233	292
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	50 (84.7)	181 (77.7)	231 (79.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	24/ 50 (48.0)	99/181 (54.7)	123/231 (53.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	26/ 50 (52.0)	82/181 (45.3)	108/231 (46.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	12/ 50 (24.0)	83/181 (45.9)	95/231 (41.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	38/ 50 (76.0)	98/181 (54.1)	136/231 (58.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10%	9/ 50 (18.0)	77/181 (42.5)	86/231 (37.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10%	41/ 50 (82.0)	104/181 (57.5)	145/231 (62.8)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE (N(%))	9 (15.3)	52 (22.3)	61 (20.9)

In summary, there are differences in early death rates between these patient population (PD-L1 <10%) and the patient population defined by a PD-L1 expression >10%. At 3 months, the OS rate is 72% vs. 90% in favour of the patients with a high PD-L1 expression. Therefore, it is cannot be ruled out that the baseline PD-L1 expression percentage may affect the early death rate.

- Multivariate analyses.

The applicant performed various post hoc multivariate analyses to predict early death with different cut of values of baseline PD-L1 expression number, 1, 5, 10 and 50%.

The covariates selected in the model included treatment group, PD-L1 expression, and other relevant baseline prognostic factors such as ECOG PS (0 vs ≥1), time since last prior treatment (< 3 months vs. ≥ 3 months), and best response to most recent prior systemic therapy (progressive disease vs other). Interactions between the individual covariate and treatment were explored to determine whether any factors had a differential risk for subjects randomised to nivolumab vs. docetaxel.

Table 21: Multivariate logistic models: predictors for death prior to 3 months - CA209057

Covariate	Model 1: PD-L1 <1% vs ≥1%		Model 2: PD-L1 <5% vs ≥5%		Model 3: PD-L1 <10% vs ≥10%		Model 4: PD-L1 <50% vs ≥50%	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Interaction								
Treatment x PD-L1 (**X%**)		0.2535		0.0224		0.0064		0.0002
Treatment x ECOG		0.0179		0.0182		0.0186		0.0164
Nivolumabvs Docetaxel for:								
PD-L1 ≥X% & ECOG 0	0.40 (0.12, 1.35)		0.22 (0.06, 0.84)		0.17 (0.04, 0.66)		0.06 (0.01, 0.29)	
PD-L1 ≥X% & ECOG 1	1.72 (0.84, 3.52)		0.95 (0.39, 2.30)		0.72 (0.28, 1.85)		0.26 (0.07, 0.92)	
PD-L1 <X% & ECOG 0	0.69 (0.20, 2.45)		0.83 (0.25, 2.76)		0.88 (0.27, 2.89)		0.90 (0.28, 2.93)	
PD-L1 <X% & ECOG 1	3.01 (1.36, 6.66)		3.63 (1.82, 7.22)		3.80 (1.93, 7.49)		4.06 (2.15, 7.66)	
PD-L1 Non-Q & ECOG 0	0.25 (0.06, 1.01)		0.25 (0.06, 1.01)		0.25 (0.06, 1.01)		0.24 (0.06, 0.98)	
PD-L1 Non-Q & ECOG 1	1.08 (0.39, 3.02)		1.07 (0.38, 3.01)		1.08 (0.38, 3.02)		1.07 (0.38, 3.01)	
Time Since Last Treatment :								
<3 Months vs ≥3 Months	1.85 (1.10, 3.12)	0.0209	1.89 (1.12, 3.21)	0.0180	1.91 (1.13, 3.25)	0.0164	1.86 (1.09, 3.17)	0.0225
Best Response to Prior Treatment: PD vs Other	2.09 (1.31, 3.32)	0.0019	2.17 (1.36, 3.47)	0.0012	2.14 (1.34, 3.42)	0.0016	2.20 (1.37, 3.54)	0.0011

Abbreviations: ECOG: Eastern Cooperative Oncology Group, Non-Q: non-quantifiable, PD: disease progression, PD-L1: programmed death ligand-1

The additional post hoc analyses showed that there was an association with PD-L1 expression level (e.g. <1%, <5%, <10%, <50%) and ECOG score (e.g. ECOG PS 1). Other factors associated with early death were time since last treatment < 3 months and progressive disease as best response to last treatment. The increased odds of early death was associated with nivolumab treatment among subjects beginning at the <1% PD-L1 expression level when combined with ECOG PS 1.

A summary of the key outcome measures according to baseline PD-L1 expression is presented below.

Table 22: ORR and OS by tumour PD-L1 expression - CA209057

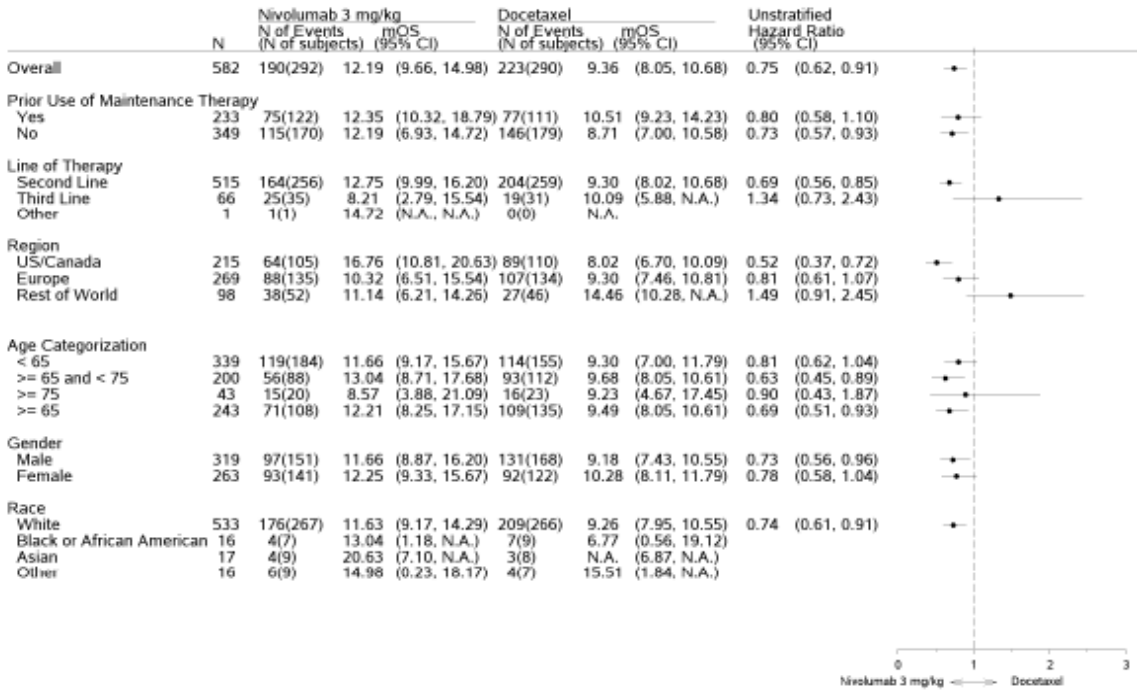
PD-L1 Expression	nivolumab	docetaxel	
	ORR by tumour PD-L1 expression		
			Odds Ratio (95% CI)
<1%	10/108 (9.3%)	15/101 (14.9%)	0.59 (0.22, 1.48)
	95% CI: 4.5, 16.4	95% CI: 8.6, 23.3	
≥1%	38/123 (30.9%)	15/123 (12.2%)	3.22 (1.60, 6.71)
	95% CI: 22.9, 39.9	95% CI: 7.0, 19.3	
≥1% to <10%[a]	6/37 (16.2%)	5/ 44 (11.4%)	1.51 (0.35, 6.85)
	95% CI: 6.2, 32.0	95% CI: 3.8, 24.6	
≥10% to <50%[a]	5/20 (25.0%)	7/33 (21.2%)	1.24 (0.26, 5.48)
	95% CI: 8.7, 49.1	95% CI: 9.0, 38.9	
≥50%[a]	27/66 (40.9%)	3/46 (6.5%)	9.92 (2.68, 54.09)
	95% CI: 29.0, 53.7	95% CI: 1.4, 17.9	
	OS by tumour PD-L1 expression		
	Number of events (number of patients)		**Unstratified Hazard Ratio (95% CI)**
<1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥1% to <10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥10% to <50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)

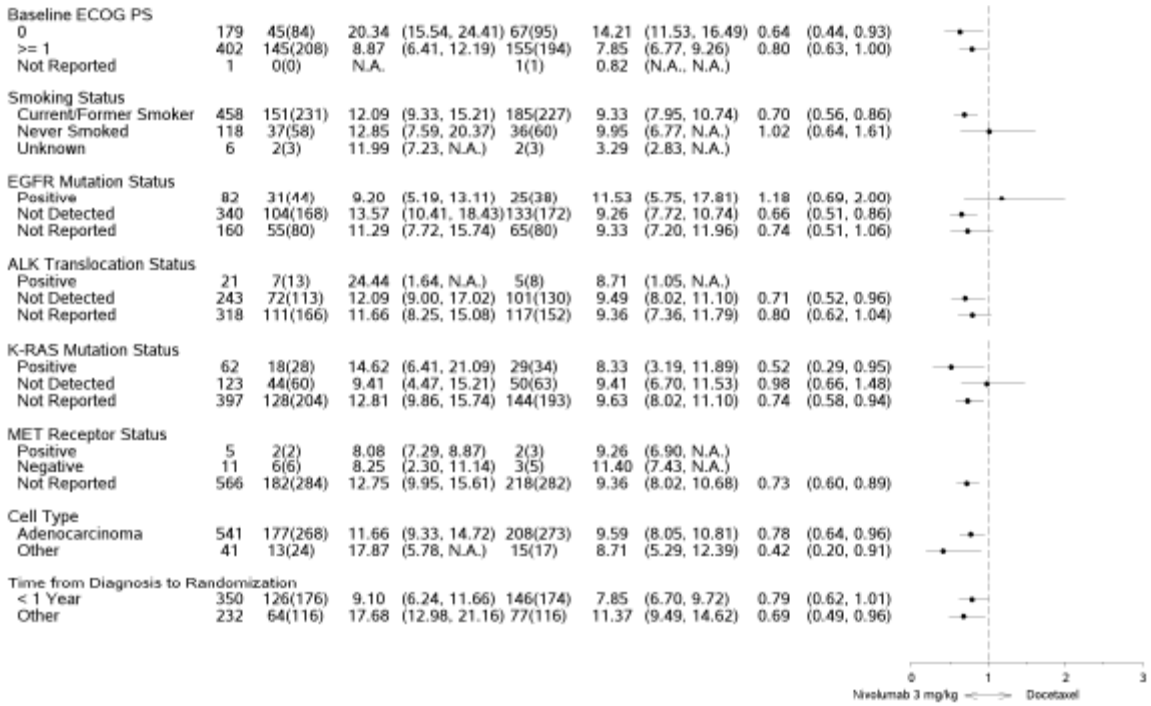
[a] Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels

Subgroup analyses

Various subgroup analyses were conducted by the applicant.

Table 23: Forest Plot of Treatment Effect on OS in Pre-defined Subsets - All Randomised Subjects





Despite the limitations of subgroup analysis methodology, the OS HR favoured nivolumab vs. docetaxel for the majority of pre-defined subsets with the exception of the subgroups of never smokers and patients with an EGFR mutation. The analysis of PD-L1 expression in these subgroups indicated that the distribution of PD-L1 expression appeared comparable to the overall population.

An overall numerical improvement in OS was observed in the nivolumab arm compared to docetaxel, except for the patients with a positive EGFR mutation. In the patient population with a positive EGFR mutation, docetaxel showed a numerically favourable ORR, PFS and OS compared to nivolumab.

Table 24: Treatment effect on ORR, PFS and OS in the overall population and the predefined subgroups of never smokers, EGFR –positive and ALK positive patients (made by assessor)

	Nivolumab			**Docetaxel**				
	events/N	**%**	**95% CI**	**events/N**	**%**	**95% CI**	**HR**	**95% CI**
Overall response rate								
Overall population	56 (292)	19.2%	14.8- 24,2	36 (290)	12.4%	8.8- 16.8		
never smokers	5 (58)	8.6 %	2.9-19.0	9 (60)	15 %	7.1- 26.6		
EGFR+	5 (44)	11.4%	3.8- 24,6	6 (38)	15.8 %	6.0 -31.3		
ALK pos	5(13)	38.5%	13.9- 68.4	0 (8)	0 %	0.-36.9		
PFS								
	Events/N	median months		Events/N	median months		HR	95% CI
Overall population	234 (292)	2.33	2.17- 3.32	245 (290)	4.21	3.45- 4.86	0.91	0.76- 1.09
never smokers	44 (58)	2.33	2.10-4.17	41 (60)	4.83	3.25-6.87	1.39	0.90-2.13
EGFR+	39 (44)	2.1	1.64- 3.25	29 (38)	4.83	2.10- 6.87	1.46	0.90-2.37)
ALK pos	11 (13)	5.88	1.18- 14.78	7 (8)	2.1	1.05- 3.25	NA	
Overall survival								
	Events/N	months (median)		Events/N	median months		HR	95% CI
overall population	190 (292)	12.19	9.66-14.98	223 (290)	9.36	8.05-10.68	0.75	0.62- 0.91

never smokers	37 (58)	12.85	7.59-20.37	36 (60)	9.95	6.77- NA	1.02	0.64- 1.61
EGFR+	31 (44)	9.2	5.19-13.11	25 (38)	11.53	5.75-17.81	1.18	0.69- 2.00
ALK pos	7 (13)	24.44	1.64- NA	5 (8)	8.71	1.05- NA	NA	

Summary of main study

The following table summarises 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 25: Summary of Efficacy for trial CA209057

Title: An Open-label Randomised Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Metastatic Non-Squamous Non-small Cell Lung Cancer (NSCLC)			
Study identifier	CA209057		
Design	This was a Phase 3, randomised, open-label study of nivolumab vs docetaxel in adult (≥18 years) subjects with advanced or metastatic non-squamous NSCLC after failure of prior platinum-based doublet chemotherapy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	02-Nov-2012 to 05-Feb-2015 (last patient last visit for analysis) not applicable on-going	
Hypothesis	Superiority		
Treatments groups	Nivolumab at 3 mg/kg	Nivolumab at 3 mg/kg was administered as an IV infusion over 60 minutes on Day 1 of each 2-week cycle.	
	Docetaxel 75 mg/m^2	Docetaxel 75 mg/m2 was administered every 3 weeks.	
Endpoints and definitions	Primary endpoint	OS	Defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS was censored on the last date the subject was known to be alive.
	Secondary endpoint	PFS (investigator-assessed)	Defined as the time from randomization to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause.
	Secondary endpoint	ORR (investigator-assessed)	Defined as the number of subjects whose best confirmed objective response (BOR) was either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomised subjects.
Database lock	18-Mach-2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	**Treatment group**	Nivolumab 3 mg/kg	Docetaxel 75 mg/m2
	Number of subject	292	290
	OS (months) median	12.19	9.36
	95% CI	9.66, 14.98	8.05, 10.68
	Investigator-assessed PFS (months) Median	2.33	4.21

	95% CI	2.17, 3.32	3.45, 4.86
	Investigator-assessed ORR n, (%)	56 (19.2)	36 (12.4)
	95% CI	14.8, 24.2	8.8, 16.8
Effect estimate per comparison	Primary endpoint OS	Comparison groups	nivolumab vs. docetaxel
		HR	0.73
		95% CI	0.59, 0.89
		P-value	0.0015
	Secondary endpoint: PFS	Comparison groups	nivolumab vs. docetaxel
		HR	0.92
		95% CI	0.77, 1.11
		P-value	0.3932
	Secondary endpoint: ORR	Comparison groups	nivolumab vs. docetaxel
		odds ratio	1.68
		95% CI	1.07, 2.64
		P-value	0.0246
Notes			

Clinical studies in special populations

Hepatic/renal impairment

Based on data form the pivotal study, OS results in subjects with hepatic impairment (median OS 9.00 months [95% CI 6.31, 18.4]) are smaller in magnitude than those reported for the overall population, but they are considered clinically meaningful.

In subjects with renal impairment, OS (median 18.4 months [95% CI 7.82, NA]) and safety results do not suggest a negative impact of renal impairment.

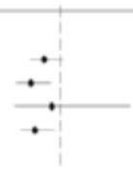
Elderly patients

In order to adequately characterise efficacy of nivolumab in this population, the Applicant was requested to provide main efficacy data (OS, PFS, ORR data) from the pivotal study using the following age subgroups: Age <65 years, 65 to 74 years old, 75 to 84 years old and >85 years old (see tables below).

Table 26: Forest plot treatment effect on overall survival and progression free survival in pre-defined subsets in CA209057 – All randomised subjects

Overall Survival:

	N	Nivolumab 3 mg/kg N of Events (N of subjects)	mOS (95% CI)	Docetaxel N of Events (N of subjects)	mOS (95% CI)	Unstratified Hazard Ratio (95% CI)
Age Categorization						
< 65	339	119(184)	11.66 (9.17, 15.67)	114(155)	9.30 (7.00, 11.79)	0.81 (0.62, 1.04)
>= 65 and < 75	200	56(88)	13.04 (8.71, 17.68)	93(112)	9.68 (8.05, 10.61)	0.63 (0.45, 0.89)
>= 75	43	15(20)	8.57 (3.88, 21.09)	16(23)	9.23 (4.67, 17.45)	0.90 (0.43, 1.87)
>= 65	243	71(108)	12.21 (8.25, 17.15)	109(135)	9.49 (8.05, 10.61)	0.69 (0.51, 0.93)



Source: refer to Figure S.5.7 (OS) of the CA209057 CSR

Progression-free Survival:

	N	Nivolumab 3 mg/kg N of Events (N of subjects)	mPFS (95% CI)	Docetaxel N of Events (N of subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Age Categorization						
< 65	339	143(184)	2.20 (2.14, 3.09)	131(155)	3.45 (2.17, 4.86)	0.89 (0.70, 1.13)
>= 65 and < 75	200	74(88)	3.84 (2.27, 4.99)	97(112)	4.53 (3.48, 5.06)	0.94 (0.69, 1.27)
>= 75	43	17(20)	2.25 (1.91, 7.72)	17(23)	4.86 (2.10, 6.24)	0.97 (0.49, 1.95)
>= 65	243	91(108)	3.52 (2.23, 4.86)	114(135)	4.67 (3.52, 5.39)	0.94 (0.71, 1.24)

Source: refer to Figure S.5.13 (PFS) of the CA209057 CSR

Table 27: Objective response ratye by age in CA209057 – All randomised subjects

		Objective Response Rate (%) (a) 95% CI	
		Nivolumab 3 mg/kg N = 292	Docetaxel N = 290
AGE CATEGORIZATION			
	< 65	32/184 (17.4%) (12.2, 23.7)	20/155 (12.9%) (8.1, 19.2)
	>= 65 AND < 75	22/88 (25.0%) (16.4, 35.4)	12/112 (10.7%) (5.7, 18.0)
	>= 75	2/20 (10.0%) (1.2, 31.7)	4/23 (17.4%) (5.0, 38.8)
	>= 65	24/108 (22.2%) (14.8, 31.2)	16/135 (11.9%) (6.9, 18.5)

(a) CR+PR as per RECIST 1.1 criteria confirmation of response required (Investigator Assessment), confidence interval based on the Clopper and Pearson method.
Source: refer to Table S.5.11 of the CA209057 CSR

Table 28: Overall survival multivariate analysis in CA209057 – All randomised subjects -

	HR(2) (95% CI)	P-value (2)
TREATMENT		
NIVOLUMAB 3 MG/KG VS DOCETAXEL (1)	0.71 (0.58, 0.87)	0.0008
TIME FROM DIAGNOSIS TO RANDOMIZATION		
OTHER VS < 1 YEAR	0.56 (0.45, 0.70)	<0.0001
AGE CATEGORY (YEARS)		
>= 65 VS < 65	**1.03 (0.84, 1.26)**	**0.7656**
GENDER		
MALE VS FEMALE	0.93 (0.76, 1.14)	0.4805
BASELINE ECOG PERFORMANCE STATUS		
>= 1 VS 0	1.82 (1.46, 2.28)	<0.0001
SMOKING STATUS		
NEVER/UNKNOWN VS CURRENT/FORMER	0.78 (0.60, 1.02)	0.0652
KNOWN MUTATION STATUS		
MUTATION POSITIVE VS OTHER (3)	1.14 (0.85, 1.53)	0.3964

(1) Effect of treatment adjusted for time from diagnosis to randomization, gender, baseline ECOG, smoking status, age categorization, ALK/EGFR mutation status and cell type.
(2) P-values and HRs from multivariate Cox Model stratified by prior maintenance therapy (yes vs no) and line of therapy (2L vs 3L) as entered into the IVRS.
(3) Mutation positive is defined as baseline EGFR mutation or ALK translocation vs. Other, defined as negative or unknown.

Source: refer to Table S.5.6 of the CA209057 CSR

Supportive study

Main evidence of the effect of nivolumab beyond second line in NSQ NSCLC derives from the Phase 1 study MDX1106-03, which included a cohort of 74 patients with NSQ NSCLC. This study was previously assessed in the original MAA for the SQ NSCLC indication.

A total of 43 NSQ patients (58.1%) from study MDX1106-03 had received ≥3 lines prior to study entry. Additional baseline disease characteristics indicate that this was an advanced and heavily pre-treated population subgroup.

Table 29: Summary of Efficacy - All Treated Subjects with Non-small Cell Lung Cancer - study MDX1106-03

Efficacy parameter	SQ NSCLC n = 54	NSQ NSCLC n = 74	TOTAL NSCLC N = 129
Best overall response[a], N (%)			
Complete response	0	0	0
Partial response	9 (16.7)	13 (17.6)	22 (17.1)
Stable disease	15 (27.8)	16 (21.6)	32 (24.8)
Disease progression	20 (37.0)	38 (51.4)	58 (45.0)
Unable to be determined	10 (18.5)	7 (9.5)	17 (13.2)
ORR[b], N (%)	9 (16.7)	13 (17.6)	22 (17.1)
95% CI	7.9, 29.3	9.7, 28.2	11.0, 24.7
Time to response (range, weeks)	7.4 - 15.4	7.6 - 31.4	7.4 - 31.4
Median DOR (weeks)	NR	63.9	74.0
95% CI	42.1, -	29, -	42.1, -
PFSR (95% CI)			
At 8 weeks	94 (87, 100)	90 (83, 97)	92 (87, 97)
At 24 weeks	42 (27, 57)	29 (18, 39)	33 (25, 42)

[a] BOR was derived centrally by the sponsor using RECIST 1.0 criteria on investigator assessed tumor measurements.
[b] Includes all subjects with a response of CR or PR
Abbreviations: CI: confidence interval, DOR: duration of response, NSCLC: non-small cell lung cancer; NR: not reached, NSQ: non-squamous; ORR: objective response rate, PFSR: progression-free survival rate;: squamous

The median OS in patients with NSQ NSCLC was 10.1 months [95% CI: 5.7, 13.7].

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of OPDIVO in the treatment of advanced non-squamous NSCLC is based on a single pivotal study (CA209057).This study was a Phase 3, randomised, open-label study of nivolumab vs. docetaxel in adults with metastatic or recurrent non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy. Its design largely resembles that of study CA209017, the phase 3 study which supported the SQ NSCLC indication.

Dose-selection for this application is based on study MDX1106-06, a phase 1, dose-escalating study that assessed tolerability of various nivolumab doses/regimen in several types of solid tumours. This study was already assessed during the original MAA. Specific dose-finding studies have not been submitted for this application which is considered acceptable.

In the pivotal study, docetaxel was used as the comparator, which could be considered the best option for a non-selected population in second-line.

Patients were stratified according to prior maintenance therapy (yes/no) and line of therapy (second or third line of therapy). Stratification by PD-L1 status was not applied because, at the time of study initiation, the value of the PD-L1 as a predictive biomarker was uncertain, and the IHC assay was not verified. Therefore,

this decision seemed appropriate, although nowadays the use of a validated biomarker is recommended to tailor therapy by identifying responders versus non-responders.

The primary endpoint was OS and the key secondary endpoints were PFS and ORR (both per investigator). OS and key secondary endpoints were also assessed based on PD-L1 status at baseline (secondary endpoint). From a methodological point of view, the results of the PD-L1 analyses must be regarded with caution, despite the underlying clear biological rationale. Response and progressive disease were both assessed using RECIST v 1.1. criteria.

A total of 24 % of the nivolumab treated patients crossed over to docetaxel. It is considered that docetaxel might still be effective in this patient population and may have contributed to the observed OS improvement in the nivolumab group. Almost, no patients crossed over from docetaxel to nivolumab or another immunotherapy.

Efficacy data and additional analyses

Demographic and baseline characteristics were mostly comparable for both treatment groups, with the exception of age (more elderly patients were randomised to the docetaxel arm). In the overall ITT population, races/ethnicities other than white was limited. In addition, the proportion of patient ≥75 years of age included in the pivotal trial is limited and no conclusion can be drawn on the efficacy of nivolumab in this patient population (see section 5.1 of the SmPC).

The study limited the inclusion of patients to those with a baseline ECOG performance status of 0 or 1. The lack of ECOG PS 2 patients can be considered a limitation, since patients with ECOG PS 2 might represent a proportion of the target population. This information has been reflected in the SmPC (see section 4.2 of the SmPC).

All patients had received prior platinum doublet-based therapy and the majority of patients (88.5%) in the overall population received nivolumab as second line treatment. A total of 11.2% of patients had received at least 2 prior lines of treatment and no patients had received ≥3 prior systemic cancer therapies.

The reported protocol deviations do not seem to impact study results.

At the date of the clinical database lock (18-Mar-2015), 43 nivolumab patients continued in the treatment period (none in the docetaxel group). The most frequent reason for discontinuing treatment was disease progression for both groups (194 patients (67.6%) in the nivolumab group, 179 patients (66.8%) in the docetaxel group), followed by drug toxicity in docetaxel patients (n=42, 15.7%) and unrelated AE in the nivolumab group (n=19, 6.6%).

A total of 413 deaths were included in the primary analysis of OS. The minimum follow-up was 13.2 months. The median OS was 12.2 months for the nivolumab group versus 9.36 months for the docetaxel group, with a hazard ratio (HR) of 0.73 (95% confidence interval [CI]: 0.60, 0.89), p 0.0015 (stratified log-rank test). This represents an approximate median gain of 2.8 months for nivolumab over docetaxel. However, the profile of the OS curve for nivolumab, with a crossing at approximately 7 months, jeopardises the achievement of reliable conclusions from this analysis. A higher frequency of death during the first 6 months of treatment due to malignant neoplasm progression for nivolumab in comparison to docetaxel treatment was observed. Additional analyses on the patients with an OS< 6 months (occurrence of death dichotomised ≤ 3 months and > 3 to ≤ 6 months) in terms of baseline and disease characteristics, as well as prior lines of therapy (both arms), suggest that nivolumab results in a meaningful gain in OS for those patients who live past the first 3 month interval even those who are labelled <1% PD-L1 expression. A multivariate post-hoc analysis provided by the Applicant suggests that poorer prognostic features and/or aggressive disease, in combination with no/low PD-L1 expression, characterize patients with potential for death within the first 3 months.

The analyses of OS in pre-defined subgroups were conducted. The OS HR favoured nivolumab vs. docetaxel for the majority of pre-defined subsets with the exception of the subgroups of never smokers, patients an EGFR mutation. However the subgroups are small and show a large overlap in confidence intervals, which precludes any definitive conclusion. Overall, the effect in these subgroups appears to be comparable to the overall population.

The higher frequency of death during the first 6 months of treatment due to malignant neoplasm progression for nivolumab in comparison to docetaxel treatment is still not fully understood. The Applicant provided additional analyses on the patients with an OS< 6 months (occurrence of death dichotomised ≤ 3 months and > 3 to ≤ 6 months) in terms of baseline and disease characteristics, as well as prior lines of therapy (both arms). From these data, it seems that nivolumab results in a meaningful gain in OS for those patients who live past the first 3 month interval even for those who are labelled as having tumour expression of <1% PD-L1 expression.

Although the MAH claimed that no single factor or group of factors can be identified as predictor of an early death (OS<3 months), it seems reasonable to assume that those patients with a poor prognosis and a more aggressive disease would benefit less because of the delayed effect of immunotherapy on OS. A multivariate analysis provided by the Applicant suggests that poorer prognostic features and/or aggressive disease, in combination with no/low PD-L1 expression, characterise patients with potential for early death within the first 3 months. It is therefore considered appropriate to make all relevant information available in the SmPC to the prescribers, including the baseline characteristics suggestive of a poorer disease that were associated with early death rates in the nivolumab patients group. Furthermore, several factors could be contributing to these early deaths, therefore, restricting the indication based on PD-L1 expression does not seem appropriate since even in patients with a low PD-L1 expression have shown durable responses even though the response rate was considerably lower than for those labelled with a high PD-L1 expression. A similar effect was not identified for the squamous histology subset of NSCLC, which are deemed rapidly progressing patients

The additional analyses provided by the MAH showed that the biological behaviour of the tumour with baseline PD-L1 expression between 1-10% is more comparable to the tumour behaviour of tumours showing no PD-L1 expression (PD-L1 <1%) than with the tumour showing a high PD-L1 expression value (PD-L1 ≥ 10%). Regarding OS benefit and other key efficacy results according to baseline PD-L1 status, it is noted that results in PD-L1 negative/non-quantifiable patients are similar to those seen in the docetaxel patients, with practically no differences between this subset of patients and those in the docetaxel group, with numerically more deaths in nivolumab patients than docetaxel during the first 6 months of treatment. However, PD-L1 positive patients (defined by a cut of valued ⩾ 1%, ⩾ 5% or ⩾ 10%) showed a significant improvement over docetaxel for the ORR, PFS and OS. Additional post-hoc analyses with higher cut-off values (e.g. <50%, ⩾ 50%) suggest the same trend. However, considering the post-hoc nature of these analyses and the limited size of some of the subgroups, these results need to be taken with caution.

Based on the Kaplan Meier curves for PFS, more than half of the patients in both treatment arms already showed progressive disease before 3 months of treatment. There was no benefit in terms of PFS as no statistically significant difference between treatment groups could be demonstrated (median PFS estimate of 2.3 months for nivolumab vs. 4.2 months for docetaxel). A late separation of the K-M curves (after 7 months) is also observed, with 1-year PFS rates favouring nivolumab (18.5% for nivolumab vs. 8.1% for docetaxel). Given the PFS curve for nivolumab, median PFS might not be the best measure to assess treatment benefit in terms of PFS. HR and/ or 6 months and 12 months survival rate are considered more informative.

Overall, these findings point out to a delayed effect of nivolumab treatment, which has been previously described for immunotherapy agents such as ipilimumab.

Subgroup analyses were largely consistent with those from the overall population. In some of the subgroups (e.g. EGFR activating mutations, never smokers of patients with CNS metastases) nivolumab did not show a benefit, however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

The number of patients with renal or hepatic impairment included in the pivotal trial is limited. Although efficacy results seem to be clinically meaningful in these patient subgroups, they need to be taken cautiously due to the small sample size.

The MAH provided specific efficacy data according to the following age subgroups: ≥65 <75, ≥75 <85, and ≥85 years of age. OS results in each subgroup favoured nivolumab, with median OS ranging from 8.57 (≥75) to 13.04 (≥65 and <75) months. With the exception of the ≥75 subgroup, results are in line or slightly better than those for the overall study population.

PFS results were in line with those from the overall population. In addition, ORRs were consistently higher for nivolumab across most of the age subgroups (except ≥75 subgroup), indicating that nivolumab has antitumour activity, regardless of age. In general, the difference in terms of efficacy could be partially explained by the small size of the ≥75 subgroup (n=43).

The main efficacy data in patients with NSQ NSCLC from the supportive study MDX1106-03 (58.1% received ⩾3 lines of treatment) seem to indicate a somewhat smaller effect size than those seen in the pivotal study (median OS 10.1[5.7, 13.7] and 12.19 [9.66, 14.98], for MDX1106-03 and CA209057, respectively). However, these findings are not totally unexpected in a later disease setting. Furthermore, a deleterious effect is not shown in the more advanced non-SQ population, which is reassuring. Other additional efficacy results available also point to a favourable effect in this population.

Additional expert consultation

A SAG-O meeting was convened, which took place on 14 January 2016. The following issues were discussed:

1. Validity of PD-L1 testing

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

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

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

on multivariate analysis of PD-L1 expression and other factors associated with clinical benefit to guide patient selection.

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

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

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

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

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

2. Nivolumab showed an overall clinically relevant improvement in overall survival compared to docetaxel for the whole population. However, concerns exist as the overall survival and PFS data show that this effect might be limited to certain subgroups, in particular the population with a high PD-L1 expression (PD-L1 ≥5%). The experts are invited to discuss

- To what extent the PDL-1 status should be used to indicate the benefit of nivolumab (also considering the discussion under 1).
- Whether other patient characteristics can be identified that influence the effect on OS.

In the non-SQ NSCLC indication, PD-L1 expression ≥10% was associated with higher increase survival for nivolumab v. docetaxel, compared to lower PD-L1 expression. However, considerable uncertainty remains about the existence of an optimal cut-off in terms of PD-L1 expression in view of the limitations described above.

There are some concerns that the effect on survival associated with nivolumab might be slightly worse during the first few months (based on visual exploration of the survival curves), particularly in patients with the poorest prognosis, as claimed by the applicant. This may be due to a delay in the onset of the therapeutic effect of immunotherapy compared to chemotherapy, although this remains an assumption and a detrimental interaction in terms of disease progression cannot be excluded. Based on the current data, in patients with rapidly progressing disease, chemotherapy might be the preferred option. In patients with poor prognostic factors, chemotherapy might not always be the optimal choice. The decision should be taken on a case by case basis.

Concerning PD-L1 expression for patient selection, the limitations described in the answer to question No. 1 apply, including inadequate exploration of optimal cut-off values. Thus, clear restrictions based on the currently explored cut-offs do not seem appropriate. However, while awaiting the results of further and more

comprehensive analyses (see answer to question No. 1), the available information (including subgroup analyses, e.g., non-smokers and EGFR mutation) is considered useful to guide treatment decisions and should be described in the product information.

2.4.4. Conclusions on the clinical efficacy

Nivolumab in the treatment of non-SQ NSCLC results in a meaningful OS gain for patients that live past the first 3 months interval and are labeled as <10%, <5% and <1% PD-L1 expression. Patients with PD-L1 expression ≥50% (assessed by a post hoc exploratory analysis), although small in size, seem to reach OS>3 months more frequently.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see sections 4.4 and 5.1 of the SmPC).

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

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

  - Melanoma: studies CA209038 and CA209066

  - NSCLC: studies CA209017, CA209057 and CA209026

- To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in studies CA209066 and CA209057.

2.5. Clinical safety

Introduction

A total of 582 patients were randomized in study CA209057 (287 patient have been treated in the nivolumab group and 268 in the docetaxel group).

The safety data from CA209057 were pooled with supportive data from treated subjects in the Phase 3 study CA209017 (N=260), and the Phase 2 study CA209063 (n=117), which used the same nivolumab dosing regimen of 3 mg/kg nivolumab Q2W.

For the purpose of the assessment of this variation, the population from study CA209057 is considered the main safety dataset.

Patient exposure

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

Table 30: End of Treatment Subject Status - All Enrolled, All Randomised, and All Treated Subjects in CA209057

	Nivolumab 3 mg/kg	Docetaxel	Total
SUBJECTS ENROLLED			792
SUBJECTS RANDOMIZED	292	290	582
SUBJECTS NOT TREATED (%)	5 (1.7)	22 (7.6)	27 (4.6)
REASON FOR NOT BEING TREATED (%)			
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.3)	0	1 (0.2)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	4 (1.4)	4 (0.7)
SUBJECT WITHDREW CONSENT	0	12 (4.1)	12 (2.1)
LOST TO FOLLOW-UP	0	1 (0.3)	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	4 (1.4)	5 (1.7)	9 (1.5)
SUBJECTS TREATED (%)	287 (98.3)	268 (92.4)	555 (95.4)
	N = 287	**N = 268**	**N = 555**
SUBJECTS CONTINUING IN THE TRT PERIOD (%)	43 (15.0)	0	43 (7.7)
SUBJECTS NOT CONTINUING IN THE TRT PERIOD (%)	244 (85.0)	268 (100.0)	512 (92.3)
REASON FOR NOT CONTINUING IN THE TRT PERIOD (%)			
DISEASE PROGRESSION	194 (67.6)	179 (66.8)	373 (67.2)
STUDY DRUG TOXICITY	17 (5.9)	42 (15.7)	59 (10.6)
DEATH	1 (0.3)	1 (0.4)	2 (0.4)
ADVERSE EVENT UNRELATED TO STUDY DRUG	19 (6.6)	11 (4.1)	30 (5.4)
SUBJECT REQUEST TO DISCONTINUE STUDY TRT	5 (1.7)	16 (6.0)	21 (3.8)
SUBJECT WITHDREW CONSENT	4 (1.4)	6 (2.2)	10 (1.8)
MAXIMUM CLINICAL BENEFIT	0	10 (3.7)	10 (1.8)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (0.7)	0	2 (0.4)
OTHER	2 (0.7)	3 (1.1)	5 (0.9)

Source: Refer to Table 5.1-1 of CA209057 Final CSR

Twenty-four (24) subjects with disease progression reported as the reason for discontinuation also had unrelated AEs leading to discontinuation reported (Nivolumab group (n = 17), docetaxel group (n = 7)).

Reasons for withdrawal of consent, when given, were: no desire for further treatment, no desire to continue in the study, refusal to visit the clinical site, no desire to continue in the study due to the subject not receiving the experimental drug, and no desire to continue with anti-neoplastic treatment.

“Other” reasons for discontinuing the study therapy were: required steroid therapy; health status had not improved, was being treated with steroids, will receive radiotherapy, subject was confused; required prolonged hospitalization; symptomatic deterioration; fatigue/investigator decided to stop treatment.

In CA209057, the minimum follow-up was approximately 13.2 months

The median duration of study therapy was 2.6 months (95% CI: 1.91, 3.25) for nivolumab treatment and 2.3 months (95% CI: 2.10, 2.83) for docetaxel treatment. As evidenced by the separation in the K-M estimates of therapy duration, a substantially higher proportion of subjects in the nivolumab group had duration of therapy lasting > 6 months as compared to the docetaxel group, and this trend persisted for duration of therapy> 12 months. Accordingly, a greater number of subjects were continuing nivolumab at the time of the analysis (43/287), as compared to no subjects who were continuing docetaxel.

Table 31: Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects in CA209057

	Nivolumab 3 mg/kg N = 287	Docetaxel N = 268
NUMBER OF DOSES RECEIVED		
MEAN (SD)	12.6 (13.49)	5.5 (4.17)
MEDIAN (MIN - MAX)	6.0 (1 - 52)	4.0 (1 - 23)
CUMULATIVE DOSE (1)		
MEAN (SD)	37.76 (40.433)	394.41 (330.671)
MEDIAN (MIN - MAX)	18.02 (3.0 - 156.0)	301.69 (70.4 - 3505.7)
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	1 (0.4)
90% TO < 110%	237 (82.6)	176 (65.7)
70% TO < 90%	42 (14.6)	70 (26.1)
50% TO < 70%	7 (2.4)	14 (5.2)
< 50%	1 (0.3)	0
MISSING	0	7 (2.6)

(1) Dose units are mg/m² for docetaxel and mg/kg for nivolumab.
Source: Table S.4.1

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

Most subjects received all doses of study medication without an infusion interruption, rate reduction, or delay. Most of the subjects in the docetaxel group did not require a dose reduction; dose reductions were not permitted with nivolumab treatment.

Infusion interruptions:

The most common reason for infusion interruption in the nivolumab group was “other” further described as: infusion running faster than expected, to give IV diluted, bradycardia, discussion with physician, infusion nurse error, went to bathroom mid-infusion/upon return had swelling on IV site, felt anxious, AE bronchitis, paraesthesia in upper limbs and feet, and non-compliant

The most common reason for infusion interruption in the docetaxel group was hypersensitivity reaction.

Dose delays

The majority of delays in the both treatment groups were reported as due to an “other” reason and more specifically to personal or administrative reasons.

Dose reductions:

Dose reductions were not allowed for nivolumab-treated patients. Those patients experiencing any grade 4 toxicity were to discontinue nivolumab permanently. In the docetaxel group, 25.7% of subjects required a dose reduction, most of which were due to AEs (89.6%).

Table 32: Infusion Interruption, Infusion Rate Reduction, and Dose Delays of Study Therapy - All Treated Subjects in CA209057

	Nivolumab 3 mg/kg N = 287	Docetaxel N = 268
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	**17 (5.9)**	**22 (8.2)**
NUMBER OF INFUSION INTERRUPTED PER SUBJECT (%)		
0	270 (94.1)	246 (91.8)
1	15 (5.2)	17 (6.3)
2	2 (0.7)	4 (1.5)
3	0	1 (0.4)
>= 4	0	0
TOTAL NUMBER INFUSION INTERRUPTED/TOTAL NUMBER INFUSION RECEIVED	19/3611 (0.5)	28/1482 (1.9)
REASON FOR INFUSION INTERRUPTION (A)		
HYPERSENSITIVITY REACTION	5 (26.3)	20 (71.4)
INFUSION ADMIN ISSUES	4 (21.1)	2 (7.1)
OTHER	10 (52.6)	6 (21.4)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	**4 (1.4)**	**19 (7.1)**
NUMBER OF INFUSION WITH IV RATE REDUCED PER SUBJECT (%)		
0	283 (98.6)	249 (92.9)
1	1 (0.3)	13 (4.9)
2	0	3 (1.1)
3	2 (0.7)	1 (0.4)
>= 4	1 (0.3)	2 (0.7)
TOTAL NUMBER IV RATE REDUCED/TOTAL NUMBER DOSE RECEIVED	12/3611 (0.3)	38/1482 (2.6)
REASON FOR IV RATE REDUCTION (B)		
HYPERSENSITIVITY REACTION	1 (8.3)	20 (52.6)
INFUSION ADMIN ISSUES	0	2 (5.3)
OTHER	11 (91.7)	16 (42.1)
SUBJECTS WITH AT LEAST ONE CYCLE DELAYED (%) (C)	**112 (39.0)**	**99 (36.9)**
NUMBER OF CYCLE DELAY PER SUBJECT		
0	175 (61.0)	169 (63.1)
1	59 (20.6)	66 (24.6)
2	31 (10.8)	25 (9.3)
3	9 (3.1)	3 (1.1)
>=4	13 (4.5)	5 (1.9)
TOTAL NUMBER CYCLE DELAYED/TOTAL NUMBER CYCLE RECEIVED (D)	219/3324 (6.6)	147/1214 (12.1)
REASON FOR CYCLE DELAY (E)		
ADVERSE EVENT	99 (45.2)	67 (45.6)
OTHER	115 (52.5)	77 (52.4)
NOT REPORTED	5 (2.3)	3 (2.0)
LENGTH OF DELAY (E)		
4 - 7 DAYS	117 (53.4)	99 (67.3)
8 - 14 DAYS	53 (24.2)	34 (23.1)
15 - 42 DAYS	40 (18.3)	14 (9.5)
> 42 DAYS	9 (4.1)	0

(A) Percentages are computed out of the total number of dose interrupted by treatment group.
(B) Percentages are computed out of the total number of infusions with IV rate reduction by treatment group.
(C) A dose was considered as actually delayed if the delay exceeded 3 days.
(D) Total number cycles received excluded the first cycle.
(E) Percentages were computed out of the total number of cycles delayed.
Sources: Table S.4.2 (dose delay), Table S.4.3 (infusion interruption), Table S.4.4 (infusion rate reduction)

Adverse events

In CA209057, all-causality AEs of any grade were reported at similar frequencies between the treatment groups, whereas Grade 3-4 events were reported less frequently in the nivolumab vs. docetaxel group (46.0% vs 67.2%).

Table 33: Summary of AEs (All Causality) reported within 30 Days of last dose in ≥5% of All Treated Subjects -CA209057

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	280 (97.6)	132 (46.0)	23 (8.0)	265 (98.9)	180 (67.2)	14 (5.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	196 (68.3)	35 (12.2)	3 (1.0)	202 (75.4)	46 (17.2)	3 (1.1)
FATIGUE	91 (31.7)	9 (3.1)	0	102 (38.1)	18 (6.7)	0
ASTHENIA	59 (20.6)	10 (3.5)	0	62 (23.1)	11 (4.1)	0
PYREXIA	35 (12.2)	1 (0.3)	0	42 (15.7)	0	0
OEDEMA PERIPHERAL	31 (10.8)	2 (0.7)	0	45 (16.8)	2 (0.7)	0
PAIN	23 (8.0)	6 (2.1)	0	21 (7.8)	5 (1.9)	0
NON-CARDIAC CHEST PAIN	16 (5.6)	2 (0.7)	0	15 (5.6)	3 (1.1)	0
MUCOSAL INFLAMMATION	6 (2.1)	1 (0.3)	0	21 (7.8)	5 (1.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	165 (57.5)	41 (14.3)	4 (1.4)	151 (56.3)	29 (10.8)	2 (0.7)
COUGH	76 (26.5)	1 (0.3)	0	62 (23.1)	0	0
DYSPNOEA	65 (22.6)	14 (4.9)	1 (0.3)	63 (23.5)	10 (3.7)	0
HAEMOPTYSIS	16 (5.6)	0	0	16 (6.0)	2 (0.7)	0
PLEURAL EFFUSION	16 (5.6)	7 (2.4)	0	7 (2.6)	2 (0.7)	0
PRODUCTIVE COUGH	15 (5.2)	0	0	10 (3.7)	0	0
OROPHARYNGEAL PAIN	11 (3.8)	0	0	15 (5.6)	0	0
DYSPNOEA EXERTIONAL	8 (2.8)	0	0	16 (6.0)	3 (1.1)	0
GASTROINTESTINAL DISORDERS	161 (56.1)	17 (5.9)	0	161 (60.1)	17 (6.3)	0
CONSTIPATION	66 (23.0)	2 (0.7)	0	45 (16.8)	2 (0.7)	0
NAUSEA	63 (22.0)	5 (1.7)	0	80 (29.9)	2 (0.7)	0
DIARRHOEA	45 (15.7)	3 (1.0)	0	73 (27.2)	3 (1.1)	0
VOMITING	36 (12.5)	1 (0.3)	0	30 (11.2)	0	0
ABDOMINAL PAIN	15 (5.2)	0	0	17 (6.3)	3 (1.1)	0
STOMATITIS	6 (2.1)	1 (0.3)	0	24 (9.0)	2 (0.7)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	131 (45.6)	20 (7.0)	0	117 (43.7)	13 (4.9)	0
ARTHRALGIA	46 (16.0)	2 (0.7)	0	32 (11.9)	2 (0.7)	0
MUSCULOSKELETAL PAIN	39 (13.6)	1 (0.3)	0	12 (4.5)	0	0
BACK PAIN	36 (12.5)	5 (1.7)	0	17 (6.3)	2 (0.7)	0
PAIN IN EXTREMITY	27 (9.4)	2 (0.7)	0	27 (10.1)	3 (1.1)	0
MYALGIA	18 (6.3)	1 (0.3)	0	35 (13.1)	0	0
MUSCULOSKELETAL CHEST PAIN	15 (5.2)	3 (1.0)	0	12 (4.5)	1 (0.4)	0
METABOLISM AND NUTRITION DISORDERS	123 (42.9)	25 (8.7)	0	91 (34.0)	22 (8.2)	0
DECREASED APPETITE	83 (28.9)	5 (1.7)	0	58 (21.6)	4 (1.5)	0
HYPERGLYCAEMIA	13 (4.5)	7 (2.4)	0	15 (5.6)	5 (1.9)	0
NERVOUS SYSTEM DISORDERS	100 (34.8)	9 (3.1)	0	124 (46.3)	7 (2.6)	0
HEADACHE	29 (10.1)	2 (0.7)	0	32 (11.9)	0	0
DIZZINESS	25 (8.7)	1 (0.3)	0	24 (9.0)	1 (0.4)	0
PARAESTHESIA	12 (4.2)	0	0	23 (8.6)	0	0
NEUROPATHY PERIPHERAL	9 (3.1)	0	0	25 (9.3)	3 (1.1)	0
DYSGEUSIA	7 (2.4)	0	0	27 (10.1)	0	0
INFECTIONS AND INFESTATIONS	98 (34.1)	26 (9.1)	1 (0.3)	112 (41.8)	30 (11.2)	2 (0.7)
PNEUMONIA	17 (5.9)	10 (3.5)	1 (0.3)	23 (8.6)	14 (5.2)	1 (0.4)
UPPER RESPIRATORY TRACT INFECTION	17 (5.9)	0	0	12 (4.5)	1 (0.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	97 (33.8)	3 (1.0)	0	117 (43.7)	2 (0.7)	0
RASH	36 (12.5)	1 (0.3)	0	13 (4.9)	0	0
PRURITUS	33 (11.5)	0	0	5 (1.9)	0	0
DRY SKIN	20 (7.0)	0	0	8 (3.0)	0	0
ERYTHEMA	6 (2.1)	0	0	18 (6.7)	1 (0.4)	0
ALOPECIA	4 (1.4)	0	0	70 (26.1)	0	0
INVESTIGATIONS	88 (30.7)	15 (5.2)	0	78 (29.1)	29 (10.8)	0
WEIGHT DECREASED	22 (7.7)	0	0	16 (6.0)	0	0
ALANINE AMINOTRANSFERASE INCREASED	16 (5.6)	1 (0.3)	0	5 (1.9)	1 (0.4)	0
NEUTROPHIL COUNT DECREASED	1 (0.3)	1 (0.3)	0	19 (7.1)	16 (6.0)	0
WHITE BLOOD CELL COUNT DECREASED	0	0	0	22 (8.2)	12 (4.5)	0
PSYCHIATRIC DISORDERS	56 (19.5)	5 (1.7)	0	42 (15.7)	5 (1.9)	0
INSOMNIA	20 (7.0)	2 (0.7)	0	22 (8.2)	0	0
ANXIETY	16 (5.6)	0	0	5 (1.9)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	47 (16.4)	24 (8.4)	13 (4.5)	15 (5.6)	5 (1.9)	7 (2.6)
MALIGNANT NEOPLASM PROGRESSION	25 (8.7)	14 (4.9)	11 (3.8)	8 (3.0)	1 (0.4)	6 (2.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	44 (15.3)	7 (2.4)	0	157 (58.6)	110 (41.0)	1 (0.4)
ANAEMIA	34 (11.8)	5 (1.7)	0	68 (25.4)	12 (4.5)	1 (0.4)
NEUTROPENIA	2 (0.7)	1 (0.3)	0	87 (32.5)	75 (28.0)	0
FEBRILE NEUTROPENIA	0	0	0	30 (11.2)	29 (10.8)	0
LEUKOPENIA	0	0	0	29 (10.8)	23 (8.6)	0
EYE DISORDERS	33 (11.5)	0	0	38 (14.2)	0	0
LACRIMATION INCREASED	3 (1.0)	0	0	22 (8.2)	0	0
ENDOCRINE DISORDERS	25 (8.7)	1 (0.3)	0	1 (0.4)	0	0
HYPOTHYROIDISM	19 (6.6)	0	0	0	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.5.1-1 of CA209057 Final CSR

When incidence rates were exposure-adjusted, overall the rate of AEs was lower in the nivolumab group compared to the docetaxel group (1745.1 vs. 2862.4 incidence rate per person-years of exposure).

The overall frequency of drug-related AEs (including Grade 3-4) was lower in the nivolumab group than the docetaxel group.

Table 34: Drug-Related AEs Reported Within 30 Days of Last Dose in ≥2% of All Treated Subjects - CA209057

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	199 (69.3)	30 (10.5)	0	236 (88.1)	144 (53.7)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	90 (31.4)	4 (1.4)	0	149 (55.6)	23 (8.6)	0
FATIGUE	46 (16.0)	3 (1.0)	0	78 (29.1)	13 (4.9)	0
ASTHENIA	29 (10.1)	1 (0.3)	0	47 (17.5)	6 (2.2)	0
CHILLS	11 (3.8)	0	0	4 (1.5)	0	0
OEDEMA PERIPHERAL	8 (2.8)	0	0	28 (10.4)	1 (0.4)	0
PYREXIA	8 (2.8)	0	0	17 (6.3)	0	0
PAIN	4 (1.4)	0	0	14 (5.2)	0	0
MUCOSAL INFLAMMATION	2 (0.7)	0	0	20 (7.5)	5 (1.9)	0
GASTROINTESTINAL DISORDERS	74 (25.8)	4 (1.4)	0	129 (48.1)	11 (4.1)	0
NAUSEA	34 (11.8)	2 (0.7)	0	70 (26.1)	2 (0.7)	0
DIARRHOEA	22 (7.7)	2 (0.7)	0	62 (23.1)	3 (1.1)	0
VOMITING	15 (5.2)	0	0	20 (7.5)	0	0
CONSTIPATION	13 (4.5)	0	0	21 (7.8)	2 (0.7)	0
ABDOMINAL PAIN UPPER	3 (1.0)	0	0	9 (3.4)	0	0
STOMATITIS	3 (1.0)	0	0	23 (8.6)	2 (0.7)	0
DYSPEPSIA	2 (0.7)	0	0	7 (2.6)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	60 (20.9)	3 (1.0)	0	100 (37.3)	1 (0.4)	0
RASH	27 (9.4)	1 (0.3)	0	8 (3.0)	0	0
PRURITUS	24 (8.4)	0	0	4 (1.5)	0	0
DRY SKIN	11 (3.8)	0	0	5 (1.9)	0	0
ERYTHEMA	4 (1.4)	0	0	11 (4.1)	0	0
ALOPECIA	1 (0.3)	0	0	67 (25.0)	0	0
NAIL DISCOLOURATION	0	0	0	8 (3.0)	0	0
ONYCHOMADESIS	0	0	0	6 (2.2)	0	0
METABOLISM AND NUTRITION DISORDERS	43 (15.0)	2 (0.7)	0	55 (20.5)	7 (2.6)	0
DECREASED APPETITE	30 (10.5)	0	0	42 (15.7)	3 (1.1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	36 (12.5)	3 (1.0)	0	66 (24.6)	1 (0.4)	0
ARTHRALGIA	16 (5.6)	0	0	16 (6.0)	0	0
MUSCULOSKELETAL PAIN	9 (3.1)	0	0	7 (2.6)	0	0
MYALGIA	7 (2.4)	1 (0.3)	0	30 (11.2)	0	0
PAIN IN EXTREMITY	2 (0.7)	0	0	8 (3.0)	0	0
INVESTIGATIONS	35 (12.2)	4 (1.4)	0	47 (17.5)	28 (10.4)	0
ALANINE AMINOTRANSFERASE INCREASED	9 (3.1)	0	0	4 (1.5)	1 (0.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	9 (3.1)	1 (0.3)	0	2 (0.7)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	6 (2.1)	0	0	0	0	0
NEUTROPHIL COUNT DECREASED	1 (0.3)	1 (0.3)	0	19 (7.1)	16 (6.0)	0
WHITE BLOOD CELL COUNT DECREASED	0	0	0	22 (8.2)	12 (4.5)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	29 (10.1)	7 (2.4)	0	33 (12.3)	4 (1.5)	0
COUGH	9 (3.1)	0	0	2 (0.7)	0	0
PNEUMONITIS	8 (2.8)	3 (1.0)	0	1 (0.4)	1 (0.4)	0
DYSPNOEA	7 (2.4)	2 (0.7)	0	8 (3.0)	1 (0.4)	0
NERVOUS SYSTEM DISORDERS	26 (9.1)	2 (0.7)	0	82 (30.6)	4 (1.5)	0
DYSGEUSIA	5 (1.7)	0	0	25 (9.3)	0	0
PARAESTHESIA	5 (1.7)	0	0	20 (7.5)	0	0
DIZZINESS	3 (1.0)	0	0	7 (2.6)	0	0
NEUROPATHY PERIPHERAL	3 (1.0)	0	0	25 (9.3)	3 (1.1)	0
HEADACHE	2 (0.7)	0	0	6 (2.2)	0	0
PERIPHERAL SENSORY NEUROPATHY	1 (0.3)	0	0	13 (4.9)	0	0
ENDOCRINE DISORDERS	24 (8.4)	0	0	0	0	0
HYPOTHYROIDISM	19 (6.6)	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11 (3.8)	1 (0.3)	0	142 (53.0)	99 (36.9)	0
ANAEMIA	6 (2.1)	1 (0.3)	0	53 (19.8)	7 (2.6)	0
NEUTROPENIA	1 (0.3)	0	0	83 (31.0)	73 (27.2)	0
FEBRILE NEUTROPENIA	0	0	0	27 (10.1)	26 (9.7)	0
LEUKOPENIA	0	0	0	27 (10.1)	22 (8.2)	0
EYE DISORDERS	9 (3.1)	0	0	20 (7.5)	0	0
LACRIMATION INCREASED	1 (0.3)	0	0	14 (5.2)	0	0
INFECTIONS AND INFESTATIONS	9 (3.1)	2 (0.7)	0	35 (13.1)	12 (4.5)	0
PNEUMONIA	1 (0.3)	1 (0.3)	0	8 (3.0)	5 (1.9)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9 (3.1)	0	0	10 (3.7)	1 (0.4)	0
INFUSION RELATED REACTION	8 (2.8)	0	0	8 (3.0)	1 (0.4)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.5 of CA209057 Final CSR

Selected AEs

In order to characterise AEs of special clinical interest that are potentially associated with the use of nivolumab, the applicant identified AEs based on the following 4 guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity

- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

Endocrine Events

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

In the nivolumab group the median time to onset for any grade drug-related endocrine select AE was 12.1 weeks. Twelve of the 27 subjects (44.4%) with endocrine AEs had resolution of their events. Most AEs belonging to the endocrine select AE category had not yet resolved (median time to resolution not reached) since some events, though well-controlled with hormone replacement therapy, were not considered resolved due to the continuing for replacement therapy.

Table 35: Summary of endocrine select AEs reported up to 30 Days after last dose in All Treated Subjects - CA209057

Sub Category (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	31 (10.8)	2 (0.7)	0	3 (1.1)	0	0
THYROID DISORDER	29 (10.1)	0	0	1 (0.4)	0	0
HYPOTHYROIDISM	19 (6.6)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	6 (2.1)	0	0	0	0	0
HYPERTHYROIDISM	4 (1.4)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	3 (1.0)	0	0	1 (0.4)	0	0
THYROIDITIS	1 (0.3)	0	0	0	0	0
ADRENAL DISORDER	1 (0.3)	1 (0.3)	0	1 (0.4)	0	0
ADRENAL INSUFFICIENCY	1 (0.3)	1 (0.3)	0	1 (0.4)	0	0
DIABETES	1 (0.3)	1 (0.3)	0	1 (0.4)	0	0
DIABETES MELLITUS	1 (0.3)	1 (0.3)	0	1 (0.4)	0	0
DRUG RELATED						
TOTAL SUBJECTS WITH AN EVENT	27 (9.4)	0	0	1 (0.4)	0	0
THYROID DISORDER	27 (9.4)	0	0	0	0	0
HYPOTHYROIDISM	19 (6.6)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	6 (2.1)	0	0	0	0	0
HYPERTHYROIDISM	4 (1.4)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	1 (0.3)	0	0	0	0	0
THYROIDITIS	1 (0.3)	0	0	0	0	0
DIABETES	0	0	0	1 (0.4)	0	0
DIABETES MELLITUS	0	0	0	1 (0.4)	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.14 (all-causality) and Table S.6.16 (drug-related) of the CA209057 Final CSR

In the pooled data of patients treated with nivolumab monotherapy (including completed melanoma and NSCLC studies), the incidence of thyroid disorders was 8.7% (115/1322). Grade 2 and Grade 3 thyroid disorders were reported in 5.1% (67/1322) and <0.1% (1/1322) of patients, respectively. Grade 2 and Grade 3 hypophysitis occurred in <0.1% (1/1322) and 0.2% (2/1322) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency each occurred in 0.2% (2/1322). Diabetes mellitus (Grade 2), and diabetic ketoacidosis (Grade 3) were each reported in<0.1% (1/1322) of patients. No Grade 4 or 5 endocrinopathies were reported. Median time to onset of these endocrinopathies was 2.8 months (range: 0.4-13.4). One patient (<0.1%) with Grade 3 adrenal insufficiency required discontinuation of nivolumab. Eight patients received high dose corticosteroids (at least 40 mg prednisone equivalents) at median initial dose of 0.9 mg/kg (range: 0.5-1.3) for a median duration of 2.4 weeks (range: 0.6-4.9). Resolution occurred in 60 patients (48.4%) with a median time to resolution of 26.1 weeks (range: 0.4-94.1).

Gastrointestinal Events

The GI select AE category included the following terms: colitis, colitis ulcerative, diarrhoea, enteritis, enterocolitis, frequent bowel movements, and GI perforation.

In the nivolumab group, the median time to onset for any grade drug-related GI select AE was 4.7 weeks. The median time to onset of the Grade 3 drug-related events (in 2 subjects) was 11.7 weeks. The median time to resolution for any grade drug-related GI select AEs was 1.5 weeks.

Table 36: Summary of gastrointestinal select AEs reported up to 30 days after last dose in All Treated Subjects - CA209057

	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	45 (15.7)	3 (1.0)	0	73 (27.2)	3 (1.1)	0
DIARRHOEA	45 (15.7)	3 (1.0)	0	73 (27.2)	3 (1.1)	0
COLITIS	2 (0.7)	1 (0.3)	0	0	0	0
DRUG RELATED						
TOTAL SUBJECTS WITH AN EVENT	22 (7.7)	2 (0.7)	0	62 (23.1)	3 (1.1)	0
DIARRHOEA	22 (7.7)	2 (0.7)	0	62 (23.1)	3 (1.1)	0
COLITIS	2 (0.7)	1 (0.3)	0	0	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.10 (all-causality) and Table S.6.12 (drug-related) of CA209057 Final CSR

In the pooled safety data, the incidence of diarrhoea or colitis was 13.9% (184/1322). Grade 2 and Grade 3 cases were reported in 2.9% (38/1322) and 1.4% (19/1322) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.8 months (range: 0.0-20.9). Eleven patients (0.8%) required permanent discontinuation of nivolumab. Twenty-four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.4-4.7) for a median duration of 3.4 weeks (range: 0.4-40.3). Resolution occurred in 163 patients (90.1%) with a median time to resolution of 1.6 weeks (range: 0.1-86.4).

Hepatic Events

The hepatic select AE category included the following terms: acute hepatic failure, ALT increased, AST increased, autoimmune hepatitis, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, drug-induced liver injury, GGT increased, hepatic enzyme increased, hepatic failure, hepatitis, hepatitis acute, hepatotoxicity, hyperbilirubinemia, liver disorder, liver function test abnormal, liver injury, and transaminases increased.

In the nivolumab group, the median time to onset of any grade drug-related hepatic AE was 5.1 weeks. The median time to onset of the Grade 3-4 drug-related events was 1.9 weeks. The median time to resolution for any grade drug-related hepatic select AE was 2.1 weeks.

Table 37: Summary of hepatic select AEs reported up to 30 days after last dose in All Treated Subjects - CA209057

	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	29 (10.1)	8 (2.8)	0	7 (2.6)	2 (0.7)	0
ALANINE AMINOTRANSFERASE INCREASED	16 (5.6)	1 (0.3)	0	5 (1.9)	1 (0.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	11 (3.8)	2 (0.7)	0	2 (0.7)	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	6 (2.1)	2 (0.7)	0	5 (1.9)	1 (0.4)	0
LIVER FUNCTION TEST ABNORMAL	4 (1.4)	3 (1.0)	0	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	3 (1.0)	2 (0.7)	0	0	0	0
BLOOD BILIRUBIN INCREASED	2 (0.7)	1 (0.3)	0	0	0	0
TRANSAMINASES INCREASED	2 (0.7)	1 (0.3)	0	0	0	0
HEPATOTOXICITY	1 (0.3)	0	0	0	0	0
HYPERBILIRUBINAEMIA	1 (0.3)	0	0	1 (0.4)	0	0
DRUG RELATED						
TOTAL SUBJECTS WITH AN EVENT	15 (5.2)	3 (1.0)	0	5 (1.9)	2 (0.7)	0
ALANINE AMINOTRANSFERASE INCREASED	9 (3.1)	0	0	4 (1.5)	1 (0.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	9 (3.1)	1 (0.3)	0	2 (0.7)	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	2 (0.7)	0	0	4 (1.5)	1 (0.4)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	2 (0.7)	2 (0.7)	0	0	0	0
TRANSAMINASES INCREASED	2 (0.7)	1 (0.3)	0	0	0	0
BLOOD BILIRUBIN INCREASED	1 (0.3)	0	0	0	0	0
HEPATOTOXICITY	1 (0.3)	0	0	0	0	0
HYPERBILIRUBINAEMIA	1 (0.3)	0	0	1 (0.4)	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.10 (all-causality) and Table S.6.12 (drug-related) of CA209057 Final CSR

In the pooled safety data, the incidence of liver function test abnormalities was 5.7% (75/1322). Grade 2, Grade 3, and Grade 4 cases were reported in 0.9% (12/1322), 1.1% (14/1322), and 0.5 % (6/1322) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.1 months (range: 0.0-14.3). Fourteen patients (1.1%) required permanent discontinuation of nivolumab. Fourteen patients

received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.4-4.7) for a median duration of 4.0 weeks (range: 1.0-8.9). Resolution occurred in 58 patients (77.3%) with a median time to resolution of 4.0 weeks (range: 0.1-68.6).

Pulmonary Events

The pulmonary select AE category included the following terms: acute respiratory distress syndrome, acute respiratory failure, interstitial lung disease, lung infiltration, and pneumonitis.

In the nivolumab group, the median time to onset of any-grade drug-related pulmonary select AE was 31.1 weeks. The median time to onset of the Grade 3 drug-related events (in 4 subjects) was 27.5 weeks.

The median time to resolution for any grade drug-related pulmonary select AE was 5.7 weeks.

Table 38: Summary of pulmonary select AEs reported up to 30 days after last dose in All Treated Subjects - CA209057

	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	11 (3.8)	4 (1.4)	0	3 (1.1)	3 (1.1)	0
PNEUMONITIS	8 (2.8)	3 (1.0)	0	2 (0.7)	2 (0.7)	0
INTERSTITIAL LUNG DISEASE	2 (0.7)	1 (0.3)	0	0	0	0
LUNG INFILTRATION	1 (0.3)	0	0	0	0	0
ACUTE RESPIRATORY FAILURE	0	0	0	1 (0.4)	1 (0.4)	0
DRUG RELATED						
TOTAL SUBJECTS WITH AN EVENT	10 (3.5)	4 (1.4)	0	1 (0.4)	1 (0.4)	0
PNEUMONITIS	8 (2.8)	3 (1.0)	0	1 (0.4)	1 (0.4)	0
INTERSTITIAL LUNG DISEASE	2 (0.7)	1 (0.3)	0	0	0	0

MedDRA Version: 17.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.10 (all-causality) and Table S.6.12 (drug-related) of CA209057 Final CSR

In the pooled safety data, the incidence of pneumonitis, including interstitial lung disease, was 2.9% (38/1322). Grade 2 and Grade 3 cases were reported in 1.5% (20/1322) and 0.7% (9/1322) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 3.0 months (range: 0.6-19.6). Thirteen patients (1.0%) required permanent discontinuation of nivolumab. Twenty-nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.1 mg/kg (range: 0.5-17.6) for a median duration of 3.4 weeks (range: 0.1-13.1). Resolution occurred in 32 patients (84.2%) with a median time to resolution of 4.6 weeks (range: 0.6-32.3).

Renal Events

The renal select AE category included the following terms: blood creatinine increased, blood urea increased, creatinine renal clearance decreased, hypercreatinemia, nephritis, nephritis allergic, nephritis autoimmune, renal failure, acute renal failure, renal tubular necrosis, tubulointerstitial nephritis, and urine output decreased.

In the nivolumab group, the median time to onset of any grade drug-related renal AE in the nivolumab group was 6.7 weeks. The median time to resolution for any grade drug-related renal select AE was 10.1 weeks.

Table 39: Summary of renal select AEs reported up to 30 days after last dose in All Treated Subjects - CA209057

	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	16 (5.6)	0	0	3 (1.1)	0	0
BLOOD CREATININE INCREASED	11 (3.8)	0	0	3 (1.1)	0	0
RENAL FAILURE	3 (1.0)	0	0	0	0	0
RENAL FAILURE ACUTE	2 (0.7)	0	0	0	0	0
DRUG-RELATED						
TOTAL SUBJECTS WITH AN EVENT	7 (2.4)	0	0	1 (0.4)	0	0
BLOOD CREATININE INCREASED	5 (1.7)	0	0	1 (0.4)	0	0
RENAL FAILURE	1 (0.3)	0	0	0	0	0
RENAL FAILURE ACUTE	1 (0.3)	0	0	0	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.10 (select AEs) and Table S.6.12 (drug-related select AE) of CA209057 Final CSR

In the pooled safety data, the incidence of nephritis and renal dysfunction was 2.0% (27/1322). Grade 2 and Grade 3 cases were reported in 0.5% (7/1322) and 0.4% (5/1322) of patients, respectively. No Grade 4 or 5 nephritis and renal dysfunction was reported. Median time to onset was 2.3 months (range: 0.0-11.7). One patient (<0.1%) with Grade 2 acute renal failure required permanent discontinuation of nivolumab. Eight patients received high dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.7 mg/kg (range: 0.5-2.1) for a median duration of 2.0 weeks (range: 0.1-9.7). Resolution occurred in 17 patients (65.4%) with a median time to resolution of 6.1 weeks (range: 0.1-65.3).

Skin Events

The skin select AE category included the following terms: blister, dermatitis, dermatitis exfoliative, drug eruption, eczema, erythema, erythema multiform, exfoliative rash, palmarplantar erythrodysesthesia syndrome, photosensitivity reaction, pruritus, pruritus allergic, pruritus generalized, psoriasis, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, skin exfoliation, skin hypopigmentation, skin irritation, Stevens-Johnson Syndrome, toxic epidermal necrolysis, urticaria, and vitiligo

In the nivolumab group, the median time to onset of any grade drug-related skin AE was 5.1 weeks. The median time to resolution of any grade drug-related skin select AE was 12.1 weeks.

Table 40: Summary of skin select AEs reported up to 30 Days after last dose in All Treated Subjects -CA209057

	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	76 (26.5)	2 (0.7)	0	49 (18.3)	1 (0.4)	0
RASH	36 (12.5)	1 (0.3)	0	13 (4.9)	0	0
PRURITUS	33 (11.5)	0	0	5 (1.9)	0	0
RASH MACULO-PAPULAR	7 (2.4)	0	0	1 (0.4)	0	0
ERYTHEMA	6 (2.1)	0	0	18 (6.7)	1 (0.4)	0
DERMATITIS	4 (1.4)	1 (0.3)	0	1 (0.4)	0	0
ECZEMA	4 (1.4)	0	0	0	0	0
RASH MACULAR	4 (1.4)	0	0	2 (0.7)	0	0
URTICARIA	4 (1.4)	0	0	3 (1.1)	0	0
BLISTER	3 (1.0)	0	0	0	0	0
RASH ERYTHEMATOUS	3 (1.0)	0	0	3 (1.1)	0	0
RASH PRURITIC	3 (1.0)	0	0	2 (0.7)	0	0
SKIN EXFOLIATION	3 (1.0)	0	0	2 (0.7)	0	0
DRUG ERUPTION	2 (0.7)	0	0	0	0	0
PHOTOSENSITIVITY REACTION	1 (0.3)	0	0	1 (0.4)	0	0
PRURITUS GENERALISED	1 (0.3)	0	0	1 (0.4)	0	0
RASH GENERALISED	1 (0.3)	0	0	1 (0.4)	0	0
SKIN IRRITATION	1 (0.3)	0	0	0	0	0
DERMATITIS EXFOLIATIVE	0	0	0	1 (0.4)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	0	0	0	3 (1.1)	0	0
RASH PAPULAR	0	0	0	1 (0.4)	0	0
DRUG-RELATED						
TOTAL SUBJECTS WITH AN EVENT	51 (17.8)	2 (0.7)	0	35 (13.1)	0	0
RASH	27 (9.4)	1 (0.3)	0	8 (3.0)	0	0
PRURITUS	24 (8.4)	0	0	4 (1.5)	0	0
RASH MACULO-PAPULAR	5 (1.7)	0	0	1 (0.4)	0	0
ERYTHEMA	4 (1.4)	0	0	11 (4.1)	0	0
ECZEMA	3 (1.0)	0	0	0	0	0
RASH PRURITIC	3 (1.0)	0	0	1 (0.4)	0	0
URTICARIA	3 (1.0)	0	0	2 (0.7)	0	0
RASH ERYTHEMATOUS	2 (0.7)	0	0	1 (0.4)	0	0
RASH MACULAR	2 (0.7)	0	0	2 (0.7)	0	0
SKIN EXFOLIATION	2 (0.7)	0	0	2 (0.7)	0	0
DERMATITIS	1 (0.3)	1 (0.3)	0	0	0	0
DRUG ERUPTION	1 (0.3)	0	0	0	0	0
RASH GENERALISED	1 (0.3)	0	0	1 (0.4)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	0	0	0	3 (1.1)	0	0
PHOTOSENSITIVITY REACTION	0	0	0	1 (0.4)	0	0
PRURITUS GENERALISED	0	0	0	1 (0.4)	0	0
RASH PAPULAR	0	0	0	1 (0.4)	0	0

MedDRA Version: 17.1; CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.10 (select AEs) and Table S.6.12 (drug-related select AE) of CA209057 Final CSR.

In the pooled safety data, the incidence of rash was 29.0% (383/1322). Grade 2 and Grade 3 cases were reported in 5.1% (68/1322) and 1.0% (13/1322) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.4 months (range: 0.0-15.3). Four patients (0.3%) required permanent discontinuation of nivolumab. Sixteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.9 mg/kg (range: 0.4-2.7) for a median duration of 2.1 weeks (range: 0.1-38.7). Resolution occurred in 220 patients (58%) with a median time to resolution of 18.0 weeks (range: 0.1-97.3).

Hypersensitivity/Infusion Reactions

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

In the nivolumab group, the median time to onset of any grade drug-related hypersensitivity/infusion reaction was 0.93 weeks. The median time to resolution of any grade drug-related hypersensitivity/infusion reaction was 0.14 weeks.

Table 41: Summary of hypersensitivity/infusion reaction AEs reported up to 30 days after last dose in All Treated Subjects - CA209057

	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY						
TOTAL SUBJECTS WITH AN EVENT	10 (3.5)	0	0	14 (5.2)	1 (0.4)	0
INFUSION RELATED REACTION	8 (2.8)	0	0	9 (3.4)	1 (0.4)	0
BRONCHOSPASM	3 (1.0)	0	0	3 (1.1)	0	0
HYPERSENSITIVITY	1 (0.3)	0	0	4 (1.5)	0	0
DRUG-RELATED						
TOTAL SUBJECTS WITH AN EVENT	8 (2.8)	0	0	12 (4.5)	1 (0.4)	0
INFUSION RELATED REACTION	8 (2.8)	0	0	8 (3.0)	1 (0.4)	0
HYPERSENSITIVITY	1 (0.3)	0	0	4 (1.5)	0	0
BRONCHOSPASM	0	0	0	2 (0.7)	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.10 (select AEs) and Table S.6.12 (drug-related select AE) of CA209057 Final CSR

In the pooled safety data, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, was 3.8% (50/1322). Grade 2, Grade 3, and Grade 4 cases were reported in 1.5% (20/1322), 0.2% (3/1322), and <0.1% (1/1322) of patients, respectively. No Grade 5 cases were reported.

Adverse drug reactions

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

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

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

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

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

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

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

Table 43: Adverse drug reactions as reported in the pooled safety data (melanoma and NSCLC)

		ADR frequency %
Infections and infestations		
Uncommon	Upper respiratory tract infection	0.9
Uncommon	Pneumonia	0.3
Uncommon	Bronchitis	0.2
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Rare	Histocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	<0.1
Blood and lymphatic system disorders		
Uncommon	Eosinophilia	0.2
Immune system disorders		
Common	Infusion related reaction	2.2
Common	Anaphylactic reaction	<0.1
Common	Hypersensitivity	1.7
Endocrine disorders		
Common	Hypothyroidism	6.2
Common	Hyperthyroidism	2.2
Uncommon	Adrenal insufficiency	0.3
Uncommon	Hypopituitarism	0.3
Uncommon	Hypophysitis	0.2
Uncommon	Thyroiditis	0.5
Uncommon	Hyperglycaemia	0.7
Rare	Diabetic ketoacidosis	<0.1
Rare	Diabetes mellitus	<0.1
Metabolism and nutrition disorders		
Common	Decreased appetite	9.8

Uncommon	Dehydration	0.6
Nervous system disorders		
Common	Peripheral neuropathy	2.1
Common	Headache	3.9
Common	Dizziness	2.3
Uncommon	Autoimmune neuropthy (including facial and abducens nerve paresis)	0.2
Rare	Guillain-Barré syndrome,	<0.1
Rare	Demyelination	<0.1
Rare	Myasthenic syndrome	<0.1
Rare	Polyneuropathy	<0.1
Eye disorders		
Common	Vision blurred	1.0
Uncommon	Uveitis	0.5
Cardiac disorders		
Uncommon	Tachycardia	0.5
Rare	Arrhythmia (including ventricular arrhythmia)[c]	<0.1
Rare	Atrial fibrillation	<0.1
Vascular disorders		
Common	Hypertension	1.0
Uncommon	Vasculitis	0.2
Respiratory, thoracic and mediastinal disorders		
Common	Pneumonitis	2.8
Common	Dyspnoea	4.2
Common	Cough	4.0
Uncommon	Pleural effusion	0.2
Rare	Lung infiltration	<0.1
Gastrointestinal disorders		
Very common	Diarrhoea	13.5
Very common	Nausea	13.0
Common	Stomatitis	2.3
Common	Vomiting	5.4
Common	Abdominal pain	4.0
Common	Constipation	5.5
Common	Dry mouth	2.9
Uncommon	Colitis	0.9
Uncommon	Pancreatitis	0.3
Rare	Gastritis	<0.1
Rare	Duodenal ulcer	<0.1
Hepatobiliary disorders		
Uncommon	Hepatitis	0.2
Skin and subcutaneous tissue disorders		
Very common	Rash	18.5
Very common	Pruritus	13.5
Common	Vitiligo	5.2
Common	Dry skin	3.9
Common	Erythema	1.9
Common	Alopecia	1.2
Uncommon	Psoriasis	0.2
Uncommon	Rosacea	0.2

Uncommon	Urticaria	0.3
Rare	Erythema multiforme	<0.1
Musculoskeletal and connective tissue disorders		
Common	Musculoskeletal pain	7.7
Common	Arthralgia	6.0
Uncommon	Polymyalgia rheumatica	0.2
Uncommon	Arthritis	0.7
Rare	Myopathy	<0.1
Renal and urinary disorders		
Uncommon	Tubulointerstitial nephritis	0.2
Uncommon	Renal failure	0.8
General disorders and administration site conditions		
Very common	Fatigue	32.9
Common	Pyrexia	4.9
Common	Oedema (including peripheral oedema)	3.1
Uncommon	Pain	0.7
Uncommon	Chest pain	0.5
Investigations		
Very common	Increased AST	26.1
Very common	Increased ALT	21.1
Very common	Increased alkaline phosphatase	23.5
Very common	Increased lipase	27.1
Very common	Increased amylase	16.1
Very common	Increased creatinine	16.7
Very common	Lymphopaenia (*lymphocyte absolute)*	43.3
Very common	Leukopaenia *(leukocyte absolute)*	13.1
Very common	thrombocytopaenia *(platelet count)*	11.2
Very common	Anaemia (*haemoglobin (B))*	36.6
Very common	Hypocalcaemia	17.1
Very common	Hyperkalaemia	17.6
Very common	Hypokalaemia	11.9
Very common	Hypomagnesaemia	14.9
Very common	Hyponatraemia	26.9
Common	Hypercalcaemia	9.3
Common	Increased total bilirubin	8.3
Common	Neutropaenia (*absolute neutrophil count)*	9.7
Common	Hypermagnesaemia	5.1
Common	Hypernatraemia	5.7
Common	Weight decreased	2.0

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

Serious adverse event / deaths / other significant events

Serious adverse events

In CA209057, the overall frequency of all-causality SAEs (any grade and Grade 3-4) was similar between the treatment groups.

Table 44: Summary of SAEs (All Causality) reported within 30 Days of last dose in >1% of All Treated Subjects - CA209057

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	134 (46.7)	95 (33.1)	23 (8.0)	111 (41.4)	91 (34.0)	14 (5.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	41 (14.3)	28 (9.8)	4 (1.4)	22 (8.2)	18 (6.7)	2 (0.7)
PULMONARY EMBOLISM	11 (3.8)	8 (2.8)	2 (0.7)	3 (1.1)	3 (1.1)	0
DYSPNOEA	9 (3.1)	5 (1.7)	1 (0.3)	5 (1.9)	4 (1.5)	0
PLEURAL EFFUSION	8 (2.8)	4 (1.4)	0	3 (1.1)	2 (0.7)	0
RESPIRATORY FAILURE	6 (2.1)	5 (1.7)	1 (0.3)	4 (1.5)	2 (0.7)	2 (0.7)
PNEUMONITIS	4 (1.4)	3 (1.0)	0	0	0	0
HAEMOPTYSIS	2 (0.7)	0	0	3 (1.1)	2 (0.7)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	38 (13.2)	20 (7.0)	13 (4.5)	11 (4.1)	4 (1.5)	7 (2.6)
MALIGNANT NEOPLASM PROGRESSION	23 (8.0)	12 (4.2)	11 (3.8)	7 (2.6)	1 (0.4)	6 (2.2)
METASTASES TO CENTRAL NERVOUS SYSTEM	3 (1.0)	1 (0.3)	0	1 (0.4)	1 (0.4)	0
INFECTIONS AND INFESTATIONS	24 (8.4)	19 (6.6)	1 (0.3)	28 (10.4)	24 (9.0)	2 (0.7)
PNEUMONIA	12 (4.2)	9 (3.1)	1 (0.3)	13 (4.9)	11 (4.1)	1 (0.4)
BRONCHITIS	3 (1.0)	2 (0.7)	0	3 (1.1)	2 (0.7)	1 (0.4)
RESPIRATORY TRACT INFECTION	1 (0.3)	1 (0.3)	0	3 (1.1)	3 (1.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	23 (8.0)	14 (4.9)	3 (1.0)	16 (6.0)	9 (3.4)	3 (1.1)
PAIN	5 (1.7)	4 (1.4)	0	3 (1.1)	3 (1.1)	0
GENERAL PHYSICAL HEALTH DETERIORATION	4 (1.4)	3 (1.0)	1 (0.3)	3 (1.1)	3 (1.1)	0
PYREXIA	4 (1.4)	1 (0.3)	0	4 (1.5)	0	0
ASTHENIA	3 (1.0)	1 (0.3)	0	3 (1.1)	2 (0.7)	0
GASTROINTESTINAL DISORDERS	18 (6.3)	13 (4.5)	0	11 (4.1)	8 (3.0)	0
NAUSEA	4 (1.4)	3 (1.0)	0	2 (0.7)	1 (0.4)	0
DIARRHOEA	3 (1.0)	2 (0.7)	0	1 (0.4)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	11 (3.8)	11 (3.8)	0	5 (1.9)	4 (1.5)	0
BACK PAIN	2 (0.7)	2 (0.7)	0	3 (1.1)	2 (0.7)	0
NERVOUS SYSTEM DISORDERS	10 (3.5)	8 (2.8)	0	2 (0.7)	2 (0.7)	0
HEADACHE	4 (1.4)	2 (0.7)	0	0	0	0
CARDIAC DISORDERS	9 (3.1)	8 (2.8)	1 (0.3)	6 (2.2)	5 (1.9)	0
PERICARDIAL EFFUSION	2 (0.7)	2 (0.7)	0	3 (1.1)	3 (1.1)	0
PSYCHIATRIC DISORDERS	4 (1.4)	2 (0.7)	0	5 (1.9)	5 (1.9)	0
MENTAL STATUS CHANGES	0	0	0	3 (1.1)	3 (1.1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.7)	1 (0.3)	0	37 (13.8)	35 (13.1)	1 (0.4)
ANAEMIA	2 (0.7)	1 (0.3)	0	4 (1.5)	2 (0.7)	1 (0.4)
FEBRILE NEUTROPENIA	0	0	0	24 (9.0)	24 (9.0)	0
NEUTROPENIA	0	0	0	8 (3.0)	8 (3.0)	0
METABOLISM AND NUTRITION DISORDERS	2 (0.7)	2 (0.7)	0	5 (1.9)	4 (1.5)	0
DEHYDRATION	0	0	0	4 (1.5)	4 (1.5)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.3.1-1 of CA209057 Final CSR

The overall frequency of drug-related SAEs (any grade and Grade 3-4) was lower in the nivolumab group than in the docetaxel group.

Table 45: Summary of drug-related SAEs reported within 30 days of last dose in All Treated Subjects -CA209057

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	21 (7.3)	15 (5.2)	0	53 (19.8)	48 (17.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (2.8)	6 (2.1)	0	1 (0.4)	1 (0.4)	0
PNEUMONITIS	4 (1.4)	3 (1.0)	0	0	0	0
INTERSTITIAL LUNG DISEASE	2 (0.7)	1 (0.3)	0	0	0	0
DYSPNOEA	1 (0.3)	1 (0.3)	0	0	0	0
HYPOXIA	1 (0.3)	1 (0.3)	0	0	0	0
PULMONARY EMBOLISM	1 (0.3)	1 (0.3)	0	0	0	0
HYDROTHORAX	0	0	0	1 (0.4)	1 (0.4)	0
GASTROINTESTINAL DISORDERS	5 (1.7)	3 (1.0)	0	5 (1.9)	4 (1.5)	0
COLITIS	2 (0.7)	1 (0.3)	0	0	0	0
NAUSEA	2 (0.7)	1 (0.3)	0	1 (0.4)	1 (0.4)	0
DIARRHOEA	1 (0.3)	1 (0.3)	0	1 (0.4)	0	0
ABDOMINAL PAIN	0	0	0	1 (0.4)	1 (0.4)	0
LARGE INTESTINE PERFORATION	0	0	0	1 (0.4)	1 (0.4)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	0	0	0	1 (0.4)	1 (0.4)	0
CARDIAC DISORDERS	2 (0.7)	2 (0.7)	0	0	0	0
CARDIAC TAMPONADE	1 (0.3)	1 (0.3)	0	0	0	0
PERICARDIAL EFFUSION	1 (0.3)	1 (0.3)	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.7)	0	0	0	0	0
INFUSION RELATED REACTION	2 (0.7)	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.7)	2 (0.7)	0	0	0	0
OSTEONECROSIS	1 (0.3)	1 (0.3)	0	0	0	0
POLYMYALGIA RHEUMATICA	1 (0.3)	1 (0.3)	0	0	0	0
HEPATOBILIARY DISORDERS	1 (0.3)	0	0	0	0	0
HEPATOTOXICITY	1 (0.3)	0	0	0	0	0
INFECTIONS AND INFESTATIONS	1 (0.3)	1 (0.3)	0	13 (4.9)	12 (4.5)	0
ENCEPHALITIS	1 (0.3)	1 (0.3)	0	0	0	0
BRONCHITIS	0	0	0	2 (0.7)	2 (0.7)	0
LOBAR PNEUMONIA	0	0	0	1 (0.4)	0	0
LUNG INFECTION	0	0	0	1 (0.4)	1 (0.4)	0
NAIL INFECTION	0	0	0	1 (0.4)	1 (0.4)	0
PNEUMONIA	0	0	0	5 (1.9)	5 (1.9)	0
PNEUMONIA MYCOPLASMAL	0	0	0	1 (0.4)	1 (0.4)	0
POST PROCEDURAL PNEUMONIA	0	0	0	1 (0.4)	1 (0.4)	0
RESPIRATORY TRACT INFECTION	0	0	0	2 (0.7)	2 (0.7)	0
SEPTIC SHOCK	0	0	0	1 (0.4)	1 (0.4)	0
INVESTIGATIONS	1 (0.3)	1 (0.3)	0	1 (0.4)	1 (0.4)	0
BLOOD CREATININE INCREASED	1 (0.3)	0	0	0	0	0
TRANSAMINASES INCREASED	1 (0.3)	1 (0.3)	0	0	0	0
NEUTROPHIL COUNT DECREASED	0	0	0	1 (0.4)	1 (0.4)	0
NERVOUS SYSTEM DISORDERS	1 (0.3)	1 (0.3)	0	0	0	0
CEREBROVASCULAR ACCIDENT	1 (0.3)	1 (0.3)	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	34 (12.7)	33 (12.3)	0
ANAEMIA	0	0	0	3 (1.1)	2 (0.7)	0
FEBRILE NEUTROPENIA	0	0	0	22 (8.2)	22 (8.2)	0
HAEMATOTOXICITY	0	0	0	1 (0.4)	1 (0.4)	0
LEUKOPENIA	0	0	0	1 (0.4)	1 (0.4)	0
NEUTROPENIA	0	0	0	8 (3.0)	8 (3.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	9 (3.4)	4 (1.5)	0
ASTHENIA	0	0	0	3 (1.1)	2 (0.7)	0
FATIGUE	0	0	0	2 (0.7)	2 (0.7)	0
MALAISE	0	0	0	1 (0.4)	0	0
MUCOSAL INFLAMMATION	0	0	0	1 (0.4)	1 (0.4)	0
PYREXIA	0	0	0	3 (1.1)	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	3 (1.1)	3 (1.1)	0
DEHYDRATION	0	0	0	3 (1.1)	3 (1.1)	0
HYPOKALAEMIA	0	0	0	1 (0.4)	1 (0.4)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.68 of CA209057 Final CSR

Death

In CA209057, a total of 185 subjects (64.5%) in the nivolumab group and 204 (76.1%) subjects in the docetaxel group died prior to the CA209057 database lock; the majority of deaths reported were due to disease progression (54.7% and 66.8%, respectively).

Table 46: Summary of Deaths - All Treated Subjects - CA209057

	Nivolumab 3 mg/kg N = 287	Docetaxel N = 268
NUMBER OF SUBJECTS WHO DIED (%)	185 (64.5)	204 (76.1)
PRIMARY REASON FOR DEATH (%)		
DISEASE	157 (54.7)	179 (66.8)
STUDY DRUG TOXICITY [a]	0	1 (0.4)
UNKNOWN	7 (2.4)	13 (4.9)
OTHER	21 (7.3)	11 (4.1)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 days OF LAST DOSE (%)	36 (12.5)	21 (7.8)
PRIMARY REASON FOR DEATH (%)		
DISEASE	27 (9.4)	15 (5.6)
STUDY DRUG TOXICITY	0	1 (0.4)
UNKNOWN	1 (0.3)	1 (0.4)
OTHER	8 (2.8)	4 (1.5)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 days OF LAST DOSE (%)	93 (32.4)	76 (28.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE	72 (25.1)	63 (23.5)
STUDY DRUG TOXICITY [a]	0	1 (0.4)
UNKNOWN	4 (1.4)	4 (1.5)
OTHER	17 (5.9)	8 (3.0)

a 1 death was attributed to nivolumab (encephalitis); association to nivolumab was changed after database lock

Source: Refer to Table 8.2-1 of CA209057 Final CSR

Grade 5 events were more frequent in the nivolumab group mainly due to more grade 5 SAEs of malignant progression (3.8% vs 2.2% respectively).

One death in the nivolumab group (encephalitis) and two deaths in the docetaxel group (1 due febrile neutropenia, 1 due to interstitial lung disease) were assessed as related to study drug. The death in the nivolumab group, although reported prior to database lock, had its association with nivolumab changed after database lock.

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last treatment dose were primarily Grade 1-2 in the nivolumab group. The only Grade 3-4 hematologic abnormality reported in ≥5% of subjects in the nivolumab group was absolute lymphocyte decrease (12.2% Grade 3, 1.0% Grade 4). In the docetaxel group, the majority of hematologic abnormalities in haemoglobin, platelet count, and absolute lymphocyte count were Grade 1-2, while the majority of abnormalities in leukocytes and absolute neutrophil count were Grade 3-4. Grade 3 and 4 hematologic abnormalities were reported in ≥5% of subjects in the docetaxel group in all the hematologic tests monitored except Grade 4 absolute lymphocyte count and Grade 3-4 platelet count.

A higher number of subjects in the docetaxel group experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality.

Serum Chemistry

Hepatic parameters

In the nivolumab group, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2, with Grade 3-4 abnormalities reported in ≥2% of subjects limited to AST (2.8%) and ALT (2.4%). In the docetaxel group, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2, and no Grade 3-4 hepatic parameter abnormalities were reported in ≥2% of subjects in the docetaxel group.

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

Renal parameters

In the nivolumab group, any reported abnormalities in creatinine (increases) were primarily Grade 1 or 2. There were no Grade 3-4 abnormalities in creatinine in the nivolumab group. In the docetaxel group, abnormalities in creatinine were also primarily Grade 1-2, with the exception of 1 Grade 3 abnormality. There were no Grade 4 creatinine abnormalities reported in either treatment group.

Thyroid function tests

The proportion of subjects with elevated TSH > ULN who had TSH ≤ULN at baseline was greater in the nivolumab group compared to the docetaxel group (16.7% and 5.3%, respectively). The proportion of subjects with at least 1 TSH > ULN and at least 1 FT3/FT4 value < LLN was greater in the nivolumab group (12.0%) compared to the docetaxel group (2.4%). No meaningful differences were noted between treatment groups for subjects with on-treatment TSH < LLN who had TSH ≥ LLN at baseline.

Electrolytes

Abnormalities in electrolytes were primarily Grade 1 to 2 in severity.

- In the nivolumab group, Grade 3-4 abnormalities in electrolyte levels were reported for hyponatremia (21 subjects, 7.3%), hyperkalaemia (5 subjects, 1.7%), hypokalaemia (4 subjects, 1.4%), hypomagnesemia (4 subjects, 1.4%), hypercalcemia (2 subjects, 0.7%), and hypermagnesaemia (2 subjects, 0.7%); no Grade 3-4 abnormalities were reported forhypocalcaemia or hypernatremia.
- In the docetaxel group, Grade 3-4 abnormalities were reported for hyponatremia (9 subjects, 3.4%), hypokalaemia (7 subjects, 2.7%), hypermagnesaemia (2 subjects, 0.8%), hypomagnesemia (2 subjects, 0.8%), and hyperkalaemia (2 subjects, 0.8%); no Grade 3-4 abnormalities were reported for hypercalcemia, hypocalcaemia, and hypernatremia.

Vital signs

In CA209057, vital signs were monitored and recorded at the site during each treatment infusion. Review of vital signs identified no safety concerns.

Pooled safety data

In patients treated with nivolumab monotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.2% for anaemia (all Grade 3), 0.4% for thrombocytopenia, 8.1% for lymphopenia, 0.7% for neutropenia, 1.6% for increased alkaline phosphatase, 2.7% for increased AST, 2.1% for increased ALT, 1.2% for increased total bilirubin, 0.4% for increased creatinine, 1.9% for increased amylase, 8.3% for increased lipase, 6% for hyponatremia, 1.7% for hyperkalaemia, 1.5% for hypokalaemia, 0.8% for hypercalcemia, 0.7% for hypermagnesemia, 0.6% for hypomagnesemia, 0.6% for hypocalcaemia, 0.6% for leukopenia, and <0.1% for hypernatremia.

Safety in special populations

In CA209057, 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.

Age

Summaries of on-treatment adverse events by age subgroups (≥65 to <75, ≥75 to <85, and ≥85 years of age) are provided for the non-squamous non-small cell lung cancer (NSQ NSCLC) population (CA209057) in the table below. There is no safety data presented for the ≥85 years age group as there were no subjects in that age group treated with nivolumab in the CA209057 study.

Table 47: Summary of on-treatment AEs by age group - All Nivolumab-Treated Subjects in CA209057

MedDRA Terms (%)	Age Group (Years) < 65 (N= 182)	65-74 (N= 85)	75-84 (N= 20)	Total (N= 287)
TOTAL SUBJECTS WITH AN EVENT	180 (98.9)	81 (95.3)	19 (95.0)	280 (97.6)
SERIOUS AE - TOTAL	86 (47.3)	38 (44.7)	10 (50.0)	134 (46.7)
FATAL	34 (18.7)	9 (10.6)	3 (15.0)	46 (16.0)
HOSPITALIZATION/PROLONGATION	76 (41.8)	38 (44.7)	9 (45.0)	123 (42.9)
LIFE THREATENING	8 (4.4)	0	0	8 (2.8)
CANCER	4 (2.2)	1 (1.2)	0	5 (1.7)
DISABILITY/INCAPACITY	0	1 (1.2)	0	1 (0.3)
IMPORTANT MEDICAL EVENT	8 (4.4)	1 (1.2)	1 (5.0)	10 (3.5)
AE LEADING TO DISCONTINUATION	30 (16.5)	15 (17.6)	3 (15.0)	48 (16.7)
PSYCHIATRIC DISORDERS	32 (17.6)	19 (22.4)	5 (25.0)	56 (19.5)
NERVOUS SYSTEM DISORDERS	64 (35.2)	30 (35.3)	6 (30.0)	100 (34.8)
ACCIDENT AND INJURIES	13 (7.1)	5 (5.9)	3 (15.0)	21 (7.3)
CARDIAC DISORDERS	21 (11.5)	7 (8.2)	3 (15.0)	31 (10.8)
VASCULAR DISORDERS	25 (13.7)	14 (16.5)	3 (15.0)	42 (14.6)
CEREBROVASCULAR DISORDERS	4 (2.2)	4 (4.7)	1 (5.0)	9 (3.1)
INFECTIONS AND INFESTATIONS	64 (35.2)	25 (29.4)	9 (45.0)	98 (34.1)
ANTICHOLINERGIC SYNDROME	63 (34.6)	28 (32.9)	6 (30.0)	97 (33.8)
QUALITY OF LIFE DECREASED	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	27 (14.8)	13 (15.3)	2 (10.0)	42 (14.6)

MedDRA Version: 17.1; CTC Version: 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
There were no subjects >=85 years old treated with nivolumab.
Program Source: /dbs/prod/clin/programs/ca/209/057/csrfa01/rpt/adhoc/20151002/rt-ae-susum-v01.sas

Renal/Hepatic impairment

Summary of drug-related AEs in subjects with baseline hepatic impairment are shown in the table below.

Table 48: Summary of safety by worst CTC grade (any grade, grade 3-4, Grade 5) – All Treated subjects with abnormal hepatic function at baseline - CA209057

AE Type (%)	Nivolumab 3 mg/kg N=47 Any Grade	Grade 3-4	Grade 5	Docetaxel N=34 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN AE	46 (97.9)	23 (48.9)	3 (6.4)	32 (94.1)	21 (61.8)	3 (8.8)
DRUG-RELATED AE	32 (68.1)	4 (8.5)	0	24 (70.6)	17 (50.0)	0
SERIOUS AE	22 (46.8)	15 (31.9)	3 (6.4)	15 (44.1)	12 (35.3)	3 (8.8)
DRUG-RELATED SERIOUS AE	2 (4.3)	2 (4.3)	0	7 (20.6)	7 (20.6)	0
AE LEADING TO DISCONTINUATION	9 (19.1)	7 (14.9)	1 (2.1)	5 (14.7)	2 (5.9)	0
DRUG-RELATED AE LEADING TO DISCONTINUATION	2 (4.3)	2 (4.3)	0	4 (11.8)	1 (2.9)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy
Subjects with abnormal hepatic function at baseline includes subjects with baseline CTC grade greater than or equal to 1 for any of the following tests: AST, ALT or Total Bilirubin

Subjects with abnormal renal function at baseline includes subjects with baseline CTC grade greater than or equal to 1 for creatinine

All select AEs reported were low grade except for one event of diarrhea and one event of dermatitis in nivolumab-treated subjects with baseline hepatic impairment.

Table 49: Summary of any select AEs by worst CTC grade (any grade, grade 3-4, Grade 5) – All Treated subjects with abnormal hepatic function at baseline - CA209057

Sub Category (%) Preferred Term (%)	Nivolumab 3 mg/kg (N=47)			Docetaxel (N=34)		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ENDOCRINE ADVERSE EVENTS						
TOTAL SUBJECTS WITH AN EVENT	2 (4.3)	0	0	1 (2.9)	0	0
THYROID DISORDER	2 (4.3)	0	0	0	0	0
HYPOTHYROIDISM	2 (4.3)	0	0	0	0	0
THYROIDITIS	1 (2.1)	0	0	0	0	0
ADRENAL DISORDER	0	0	0	1 (2.9)	0	0
ADRENAL INSUFFICIENCY	0	0	0	1 (2.9)	0	0
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	9 (19.1)	1 (2.1)	0	10 (29.4)	0	0
DIARRHOEA	9 (19.1)	1 (2.1)	0	10 (29.4)	0	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	6 (12.8)	0	0	2 (5.9)	1 (2.9)	0
ALANINE AMINOTRANSFERASE INCREASED	5 (10.6)	0	0	1 (2.9)	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	3 (6.4)	0	0	1 (2.9)	0	0
TRANSAMINASES INCREASED	1 (2.1)	0	0	0	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	0	0	0	1 (2.9)	1 (2.9)	0
HYPERBILIRUBINAEMIA	0	0	0	1 (2.9)	0	0
PULMONARY ADVERSE EVENT						
THERE ARE NO SUBJECTS IN THIS CATEGORY.						
RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	1 (2.1)	0	0	0	0	0
BLOOD CREATININE INCREASED	1 (2.1)	0	0	0	0	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	10 (21.3)	1 (2.1)	0	7 (20.6)	0	0
PRURITUS	4 (8.5)	0	0	1 (2.9)	0	0
RASH	3 (6.4)	0	0	1 (2.9)	0	0
RASH MACULO-PAPULAR	2 (4.3)	0	0	0	0	0
DERMATITIS	1 (2.1)	1 (2.1)	0	1 (2.9)	0	0
ERYTHEMA	1 (2.1)	0	0	5 (14.7)	0	0
SKIN EXFOLIATION	1 (2.1)	0	0	1 (2.9)	0	0
HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	1 (2.1)	0	0	1 (2.9)	0	0
INFUSION RELATED REACTION	1 (2.1)	0	0	1 (2.9)	0	0
BRONCHOSPASM	0	0	0	1 (2.9)	0	0
HYPERSENSITIVITY	0	0	0	1 (2.9)	0	0

MedDRA Version: 17.1
CTC Version: 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Subjects with abnormal hepatic function at baseline includes subjects with baseline CTC grade greater than or equal to 1 for any of the following tests: AST, ALT or Total Bilirubin

Summary of drug-related AEs in subjects with baseline hepatic impairment are shown in the table below.

Table 50: Summary of safety by worst CTC grade (any grade, grade 3-4, Grade 5) – All Treated subjects with abnormal renal function at baseline - CA209057

AE Type (%)	Nivolumab 3 mg/kg N=31			Docetaxel N=29		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN AE	31 (100.0)	15 (48.4)	1 (3.2)	28 (96.6)	21 (72.4)	2 (6.9)
DRUG-RELATED AE	25 (80.6)	2 (6.5)	0	25 (86.2)	16 (55.2)	0
SERIOUS AE	14 (45.2)	12 (38.7)	1 (3.2)	14 (48.3)	12 (41.4)	2 (6.9)
DRUG-RELATED SERIOUS AE	2 (6.5)	1 (3.2)	0	7 (24.1)	6 (20.7)	0
AE LEADING TO DISCONTINUATION	5 (16.1)	3 (9.7)	0	8 (27.6)	7 (24.1)	0
DRUG-RELATED AE LEADING TO DISCONTINUATION	2 (6.5)	0	0	4 (13.8)	3 (10.3)	0

All select AEs reported were low grade in nivolumab-treated subjects with baseline renal impairment.

Table 51: Summary of any select AEs by worst CTC grade (any grade, grade 3-4, Grade 5) – All Treated subjects with abnormal renal function at baseline - CA209057

	Nivolumab (N=31)			Docetaxel (N=29)		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Endocrine Adverse Events						
TOTAL SUBJECTS WITH AN EVENT	6 (19.4)	0	0	0	0	0
THYROID DISORDER	6 (19.4)	0	0	0	0	0
HYPOTHYROIDISM	4 (12.9)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	1 (3.2)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	1 (3.2)	0	0	0	0	0
HYPERTHYROIDISM	1 (3.2)	0	0	0	0	0
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	4 (12.9)	0	0	6 (20.7)	0	0
DIARRHOEA	4 (12.9)	0	0	6 (20.7)	0	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	3 (9.7)	0	0	1 (3.4)	1 (3.4)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (3.2)	0	0	1 (3.4)	1 (3.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (3.2)	0	0	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (3.2)	0	0	0	0	0
LIVER FUNCTION TEST ABNORMAL	1 (3.2)	0	0	0	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	0	0	0	1 (3.4)	0	0
PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	1 (3.2)	0	0	1 (3.4)	1 (3.4)	0
INTERSTITIAL LUNG DISEASE	1 (3.2)	0	0	0	0	0
PNEUMONITIS	0	0	0	1 (3.4)	1 (3.4)	0
RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	9 (29.0)	0	0	1 (3.4)	0	0
BLOOD CREATININE INCREASED	5 (16.1)	0	0	1 (3.4)	0	0
RENAL FAILURE	3 (9.7)	0	0	0	0	0
RENAL FAILURE ACUTE	1 (3.2)	0	0	0	0	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	9 (29.0)	0	0	2 (6.9)	0	0
PRURITUS	3 (9.7)	0	0	0	0	0
RASH	3 (9.7)	0	0	0	0	0
RASH MACULO-PAPULAR	3 (9.7)	0	0	0	0	0
DERMATITIS	1 (3.2)	0	0	0	0	0
ECZEMA	1 (3.2)	0	0	0	0	0
RASH MACULAR	1 (3.2)	0	0	1 (3.4)	0	0
ERYTHEMA	0	0	0	1 (3.4)	0	0
HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	1 (3.2)	0	0	0	0	0
BRONCHOSPASM	1 (3.2)	0	0	0	0	0

MedDRA Version: 17.1
CTC Version: 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Subjects with abnormal renal function at baseline includes subjects with baseline CTC grade greater than or equal to 1 for creatinine

Baseline PD-L1 Expression Status

Exploratory safety analyses by PD-L1 expression status were conducted using a ≥1% and <1% PD-L1 pre-study (baseline) expression level. Among 287 nivolumab-treated subjects, safety analyses were performed on 227 subjects with quantifiable PD-L1 expression.

Table 52: Summary of Safety by PD-L1 Pre-study (Baseline) Expression Level (by 1% Expression Level) – All Treated Subjects in CA209057

	Number (%) Subjects											
	< 1% PD-L1 Expression						≥ 1% PD-L1 Expression					
	Nivolumab N = 106			Docetaxel N = 92			Nivolumab N = 121			Docetaxel N = 115		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
All AEs (Regardless of Causality)	103 (97.2)	44 (41.5)	8 (7.5)	90 (97.8)	62 (67.4)	5 (5.4)	118 (97.5)	52 (43.0)	13 (10.7)	114 (99.1)	80 (69.6))	5 (4.3)
Drug-related AEs	65 (61.3)	8 (7.5)	0	78 (84.8)	53 (57.6)	0	90 (74.4)	16 (13.2)	0	104 (90.4)	61 (53.0)	0
All SAEs	47 (44.3)	34 (32.1)	8 (7.5)	36 (39.1)	30 (32.6)	5 (5.4)	59 (48.8)	38 (31.4)	13 (10.7)	50 (43.5)	40 (34.8)	5 (4.3)
Drug-related SAEs	7 (6.6)	3 (2.8)	0	17 (18.5)	16 (17.4)	0	8 (6.6)	6 (5.0)	0	25 (21.7)	22 (19.1)	0
All AEs Leading to DC	17 (16.0)	13 (12.3)	0	17 (18.5)	9 (9.8)	1 (1.1)	21 (17.4)	18 (14.9)	2 (1.7)	29 (25.2)	17 (14.8)	1 (0.9)
Drug-related AEs Leading to DC	3 (2.8)	2 (1.9)	0	14 (15.2)	7 (7.6)	0	6 (5.0)	5 (4.1)	0	20 (17.4)	9 (7.8)	0

Source: Table AD.42 (AEs), Table AD.43 (drug-related AEs), Table AD.44 (SAEs), Table AD.45 (drug-related SAEs), Table AD.46 (AEs leading to discontinuation), Table AD.47 (drug-related AEs leading to discontinuation), Table S.10.16 (select AEs)

Discontinuation due to adverse events

In CA209057, the overall frequency of all-causality, any grade AEs leading to discontinuation was lower in the nivolumab group than the docetaxel group; Grade 3-4 AEs leading to discontinuation were similar between treatment groups.

Table 53: Summary of AEs leading to discontinuation (All Causality) reported within 30 days of last dose in ≥1% of All Treated Subjects - CA209057

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	48 (16.7)	38 (13.2)	3 (1.0)	58 (21.6)	34 (12.7)	2 (0.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	15 (5.2)	12 (4.2)	1 (0.3)	4 (1.5)	3 (1.1)	1 (0.4)
MALIGNANT NEOPLASM PROGRESSION	9 (3.1)	8 (2.8)	1 (0.3)	2 (0.7)	1 (0.4)	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	15 (5.2)	11 (3.8)	2 (0.7)	7 (2.6)	6 (2.2)	0
RESPIRATORY FAILURE	4 (1.4)	3 (1.0)	0	1 (0.4)	1 (0.4)	0
DYSPNOEA	3 (1.0)	3 (1.0)	0	2 (0.7)	2 (0.7)	0
PNEUMONITIS	3 (1.0)	3 (1.0)	0	1 (0.4)	1 (0.4)	0
PULMONARY EMBOLISM	3 (1.0)	1 (0.3)	2 (0.7)	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (2.1)	3 (1.0)	0	25 (9.3)	11 (4.1)	0
ASTHENIA	1 (0.3)	1 (0.3)	0	5 (1.9)	3 (1.1)	0
FATIGUE	1 (0.3)	0	0	9 (3.4)	5 (1.9)	0
GENERAL PHYSICAL HEALTH DETERIORATION	1 (0.3)	1 (0.3)	0	3 (1.1)	3 (1.1)	0
OEDEMA PERIPHERAL	0	0	0	5 (1.9)	0	0
INFECTIONS AND INFESTATIONS	4 (1.4)	4 (1.4)	0	7 (2.6)	6 (2.2)	1 (0.4)
PNEUMONIA	1 (0.3)	1 (0.3)	0	5 (1.9)	5 (1.9)	0
NERVOUS SYSTEM DISORDERS	4 (1.4)	2 (0.7)	0	10 (3.7)	1 (0.4)	0
NEUROPATHY PERIPHERAL	0	0	0	5 (1.9)	1 (0.4)	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.4.1-1 of CA209057 Final CSR

The overall frequency of drug-related AEs leading to discontinuation (any grade and Grade 3-4) was lower in the nivolumab group than the docetaxel group.

Table 54: Summary of drug-related AEs leading to discontinuation reported within 30 days of last dose in All Treated Subjects - CA209057

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	14 (4.9)	11 (3.8)	0	40 (14.9)	18 (6.7)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (2.4)	6 (2.1)	0	4 (1.5)	3 (1.1)	0
PNEUMONITIS	3 (1.0)	3 (1.0)	0	1 (0.4)	1 (0.4)	0
INTERSTITIAL LUNG DISEASE	2 (0.7)	1 (0.3)	0	0	0	0
COUGH	1 (0.3)	0	0	0	0	0
DYSPNOEA	1 (0.3)	1 (0.3)	0	1 (0.4)	1 (0.4)	0
HYPOXIA	1 (0.3)	1 (0.3)	0	0	0	0
PULMONARY EMBOLISM	1 (0.3)	1 (0.3)	0	0	0	0
BRONCHOSPASM	0	0	0	1 (0.4)	0	0
HYDROTHORAX	0	0	0	1 (0.4)	1 (0.4)	0
PLEURAL EFFUSION	0	0	0	1 (0.4)	0	0
CARDIAC DISORDERS	2 (0.7)	2 (0.7)	0	1 (0.4)	1 (0.4)	0
CARDIAC TAMPONADE	1 (0.3)	1 (0.3)	0	0	0	0
PERICARDIAL EFFUSION	1 (0.3)	1 (0.3)	0	0	0	0
TACHYCARDIA	0	0	0	1 (0.4)	1 (0.4)	0
GASTROINTESTINAL DISORDERS	2 (0.7)	1 (0.3)	0	3 (1.1)	2 (0.7)	0
COLITIS	1 (0.3)	1 (0.3)	0	0	0	0
NAUSEA	1 (0.3)	0	0	0	0	0
ABDOMINAL PAIN	0	0	0	1 (0.4)	1 (0.4)	0
DIARRHOEA	0	0	0	2 (0.7)	1 (0.4)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.7)	0	0	21 (7.8)	7 (2.6)	0
FATIGUE	1 (0.3)	0	0	9 (3.4)	5 (1.9)	0
PYREXIA	1 (0.3)	0	0	1 (0.4)	0	0
ASTHENIA	0	0	0	4 (1.5)	2 (0.7)	0
GENERALISED OEDEMA	0	0	0	1 (0.4)	0	0
MALAISE	0	0	0	2 (0.7)	0	0
OEDEMA PERIPHERAL	0	0	0	5 (1.9)	0	0
HEPATOBILIARY DISORDERS	1 (0.3)	0	0	0	0	0
HEPATOTOXICITY	1 (0.3)	0	0	0	0	0
INFECTIONS AND INFESTATIONS	1 (0.3)	1 (0.3)	0	2 (0.7)	2 (0.7)	0
ENCEPHALITIS	1 (0.3)	1 (0.3)	0	0	0	0
PNEUMONIA	0	0	0	1 (0.4)	1 (0.4)	0
SEPTIC SHOCK	0	0	0	1 (0.4)	1 (0.4)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.3)	1 (0.3)	0	1 (0.4)	0	0
OSTEONECROSIS	1 (0.3)	1 (0.3)	0	0	0	0
PAIN IN EXTREMITY	0	0	0	1 (0.4)	0	0
NERVOUS SYSTEM DISORDERS	1 (0.3)	1 (0.3)	0	10 (3.7)	1 (0.4)	0
CEREBROVASCULAR ACCIDENT	1 (0.3)	1 (0.3)	0	0	0	0
DYSAESTHESIA	0	0	0	1 (0.4)	0	0
DYSGEUSIA	0	0	0	1 (0.4)	0	0
NEUROPATHY PERIPHERAL	0	0	0	5 (1.9)	1 (0.4)	0
PARAESTHESIA	0	0	0	1 (0.4)	0	0
PERIPHERAL SENSORY NEUROPATHY	0	0	0	1 (0.4)	0	0
POLYNEUROPATHY	0	0	0	1 (0.4)	0	0
RENAL AND URINARY DISORDERS	1 (0.3)	0	0	0	0	0
RENAL FAILURE ACUTE	1 (0.3)	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	3 (1.1)	3 (1.1)	0
FEBRILE NEUTROPENIA	0	0	0	2 (0.7)	2 (0.7)	0
HAEMATOTOXICITY	0	0	0	1 (0.4)	1 (0.4)	0
NEUTROPENIA	0	0	0	1 (0.4)	1 (0.4)	0
IMMUNE SYSTEM DISORDERS	0	0	0	1 (0.4)	1 (0.4)	0
DRUG HYPERSENSITIVITY	0	0	0	1 (0.4)	1 (0.4)	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	2 (0.7)	1 (0.4)	0
DECREASED APPETITE	0	0	0	1 (0.4)	0	0
DEHYDRATION	0	0	0	1 (0.4)	1 (0.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	5 (1.9)	0	0
DERMATITIS ACNEIFORM	0	0	0	1 (0.4)	0	0
ERYTHEMA	0	0	0	1 (0.4)	0	0
NAIL DYSTROPHY	0	0	0	1 (0.4)	0	0
ONYCHOMADESIS	0	0	0	1 (0.4)	0	0
PAIN OF SKIN	0	0	0	1 (0.4)	0	0
RASH	0	0	0	1 (0.4)	0	0
SKIN FISSURES	0	0	0	1 (0.4)	0	0

MedDRA Version: 17.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.119 of CA209057 Final CSR

Immunogenicity

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

Table 55: Summary of Anti-Drug Antibody Assessments, based on 16-week definition for persistent positive - All Nivolumab treated subjects with baseline and at least one post-baseline assessment - CA209057

	Number of Subjects (%)
	Nivolumab 3 mg/kg N = 251
BASELINE ADA POSITIVE	18 (7.2)
ADA POSITIVE	43 (17.1)
PERSISTENT POSITIVE	0
ONLY AT LAST SAMPLE POSITIVE	12 (4.8)
OTHER POSITIVE	31 (12.4)
NEUTRALIZING ADA POSITIVE[a]	3 (1.2)
ADA NEGATIVE	208 (82.9)

Of the 3 subjects with neutralizing ADA samples, only 1 subject had drug-related AEs reported (Grade 1 goiter and thyroiditis, Grade 2 hypothyroidism and adenoviral conjunctivitis), which occurred after the neutralizing ADA sample (Day 98 vs. Day 29), and no SAEs were reported. A total of 8 nivolumab subjects experienced hypersensitivity/infusion site reactions in this study, and the ADA status of 6 of those subjects was negative.

Of the 1037 patients who were treated with nivolumab 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 128 patients (12.3%) tested positive for treatment-emergent anti-product-antibodies by an electrochemiluminescent (ECL) assay. Nine patients (0.9%) had neutralising antibodies. There was no evidence of altered pharmacokinetic profile, or toxicity profile associated with anti-product-antibody development based on the pharmacokinetic and exposure-response analyses. Neutralizing antibodies were not associated with loss of efficacy (see section 4.8 of the SmPC).

Integrated analyses of the overall safety profile in the NSCLC population

Pooling of the safety data across NSCLC studies (NSQ and SQ) was conducted to provide a larger sample size.

Table 56: Safety presentation for NSCLC pooled populations

Study	CA209057+CA209017		CA209057+CA209017+CA209063
Treatment	Docetaxel	Nivolumab	Nivolumab
Treated	N=397	N=418	N=535

The pooled safety data for NSCLC populations indicated a safety profile that was consistent with previous findings and did not significantly alter the frequencies, types, and severity of AEs, SAEs, AEs leading to discontinuation, and select AEs for both all causality and drug-related events.

The NSQ-NSCLC population and the SQ-NSCLC population showed a comparable incidence of adverse events (97.6% vs. 96.9%), serious adverse events (46.7% vs. 46.6%). However, the NSQ-NSCLC showed a higher incidence of AEs leading to discontinuation of the study (16.7% vs. 10.7%) and the overall incidence of select AEs (75% vs.54.4%).

Both populations reported the same most frequently AE's: fatigue, decreased appetite, and cough. The most reported drug related AE's were fatigue, nausea and decreased appetite.

The NSQ-NSCLC population reported a higher incidence of pulmonary embolism (4.2 % vs. 1.5 %); grade 3-4 AEs (3.1% vs. 1.5%), SAE pulmonary embolism (3.8 % vs. 1.5%). The NSQ-NSCLC reported 2 deaths possibly related to pulmonary embolism within 10 days of drug administration, with no such deaths reported in the nivolumab SQ-NSCLC population. Although the association between thromboembolism and lung

cancer adenocarcinoma is higher than squamous cell carcinoma, the concern is raised that nivolumab might be associated with a more severe risk of embolism in the NSQ-NSCLC. This observation is supported by the lower incidence of reported pulmonary embolism in the comparable docetaxel NSQ-NSCLC population.

The overall incidence of select drug related adverse events is for the NSQ-NSCLC population higher than for the SQ-NSCLC population 48.8% vs 31.5%, including a higher incidence of grade 3-4 AEs: 3.8% vs. 2.4%. No grade 5 select adverse events were reported.

The NSQ-NSCLC population showed a higher incidence of drug-related endocrine-related adverse events (9.4%), hepatic events (5.2 %), skin related events (17.8%) and hypersensitivity events (2.8%). The reported incidence in the SQ population was 3.8%, 1.5%, 4.6%. 9.2% and 0.8% respectively. Noticeable differences were observed for the select endocrine AE hypothyroidism (9.4% vs. 3.8%) and rash (9.4% vs. 3.8%).
The incidence (of gastrointestinal (7.7% vs. 8.4%) and renal AE 2.4% vs. 3.1%) was comparable, the pulmonary drug related AE lower (3.5% vs. 4.6 %).
The NSQ-NSCLC population showed a higher incidence than the SQ-NSCLC population for the grade 3-4 AE for the hepatic (1.0% vs. 0%), pulmonary (1.4% vs. 0%), and skin related (0.7 vs. 0) select AEs. Both populations did not report grade 3-5 drug related endocrine or hypersensitivity AE's.

2.5.1. Discussion on clinical safety

For the purpose this variation, the population from study CA209057 is considered the main safety dataset.

The pivotal study had an open label design, which might be vulnerable to allocation bias of treatment related adverse events. Therefore, more weight is given to the comparison of the all-causality adverse events.

The main reason for discontinuation in both groups was (clinical/radiological) disease progression. The proportion of patients discontinuing due to AEs was in general low in both treatment groups, with a higher percentage of patients discontinuing in the docetaxel group (5.9% vs. 15.7% in the nivolumab and docetaxel groups, respectively).

The mean duration of study therapy was slightly higher for the nivolumab group than the docetaxel group (2.6 months vs. 2.3 months, respectively), with a relative dose intensity of 82.6% and 65.7%, respectively.

The majority of patients (>90%) in both groups did not require an infusion interruption or infusion rate decreased. Cycle delays were reported by 39.0% of nivolumab patients and 36.9% of docetaxel patients. In terms of dose delays, cycles delayed ≥4 days were more frequently reported for docetaxel than nivolumab (53.4% vs. 67.3%).The most common reason for the delay was "other reasons" (approximately 52% in both groups), followed by AE (approximately 45% in both groups). The category "other reasons" includes a heterogeneous group of administrative/personal reasons (which account for approximately half of them), along with other clinical or disease-related reasons.

The most common treatment-related AEs for the nivolumab-treated patients were: fatigue (16%), nausea (11%), decreased appetite (10.5%), asthenia (10.1%) and rash (9.4%). Most of them were mild-moderate in severity. In the docetaxel-treated patients, the most common treatment-related AEs were consistent with that already known for docetaxel. In both treatment groups, frequencies of all causality AEs followed similar trends to those observed for treatment-related AEs.

In nivolumab subjects, selected AEs were more frequently reported in the skin and GI SOCs, and most of them were mild-moderate in severity. In general, the observed profile of selected AEs does not differ from that observed in the SQ NSCLC indication.

In the pulmonary drug-related selected AEs, more nivolumab patients experienced pneumonitis and interstitial lung disease (n=10), compared to docetaxel (n=2). This imbalance was previously observed in the SQ-NSCLC and a warning is currently included in section 4.4 of the SmPC. Four out of the 10 cases were

grade 3-4, and 8 of the cases (including all grade 3-4 events) required corrective treatment with immune-modulating drugs. At the time of the data cut-off, 8 out of the 10 cases had reported the event as solved.

The MAH also compared the exposure adjusted rate of pulmonary embolism between nivolumab and docetaxel (7.7 vs. 6.3 per 100 patient-years). In addition, the background incidence of pulmonary embolism in lung cancer is 16.5-18/100 patient-years, which is higher than observed in the study. Pulmonary embolism will be monitored as a routine pharmacovigilance.

Skin selected AEs were reported in 26.5% of patients (n=76). Most of them were mild-moderate in severity and no grade 4-5 events were reported in this category. Regarding toxic epidermal necrolysis (TEN) cases, the MAH stated that 3 cases of fatal TEN were reported during on-going routine pharmacovigilance. This type of events has been evaluated in a safety variation (EMEA/H/C/003985/II/0004 adopted on 17 December 2015) and sections 4.4 and 4.8 of the SmPC had been updated.

Most drug related select adverse events were grade 1-2 and most events resolved. At the time of database lock, both populations showed a comparable incidence of unresolved drug related select adverse events (NQ-NSCLC population 13%, SQ-NSCLC population 15%).

The frequency of SAEs (all causalities) was slightly higher for nivolumab than docetaxel, with a similar percentage of G3-4 events. In the nivolumab group, respiratory disorders were the most frequently reported SAEs, which can be expected due to the location of the primary tumour. The second most frequently reported SOC was neoplasms including 8% of patients reporting a disease progression SAE (compared to 2.6% in the docetaxel group). Patients treated in the docetaxel group experienced more frequent SAEs in the blood/lymphatic disorders and infections/infestations SOCs (mostly grade 3-4 events).

The most common primary reason for death was “disease progression” in both treatment groups (54.7% vs. 66.8%, for nivolumab and docetaxel, respectively. Deaths due to drug toxicity were infrequent in both groups (1 [<1%] in each group), which is at least reassuring. The risk of nivolumab related toxic death therefore appears to be low.

AEs leading to discontinuation (all causality) were more frequently reported in docetaxel than nivolumab patients with a slightly higher % of grade 3-4 AEs in the nivolumab group. The most frequent AE leading to discontinuation in docetaxel patients was fatigue, while in nivolumab patients the most frequent was malignant neoplasm progression.

In terms of drug-related AEs leading to discontinuation, similar trends can be observed for the docetaxel group. In the nivolumab group, the most frequently reported drug-related AE leading to discontinuation was pneumonitis (in 3 patients). The low numbers reported in some of the SOC hamper reaching a conclusion.

In general the safety profile of patients <65 and those 65-74 years old seems comparable, with few minor differences. Information provided for the patients over the age of 74 does not show any alarming data, but the reduced number of patients does not allow reaching a conclusion (see section 4.8 of the SmPC).

Patients with pre-established renal/hepatic failure were not explicitly excluded from the pivotal study. Safety results do not suggest a negative impact due to renal impairment. The safety profile of nivolumab seems less favourable in patients with hepatic impairment (in comparison with the overall population) however these results need to be taken cautiously due to the small sample size. This has been reflected in section 4.8 of the SmPC.

In general, no large differences can be observed in terms of AEs, SAEs and AEs leading to discontinuation according to PD-L1 status. The main difference observed is a higher number of grade 5 events in the ≥1% PD-L1 expression group (none of them were considered drug-related). The significance of this finding is unknown.

Criteria for endocrinopathy treatment modification were amended in the SmPC to provide clear guidance to

physicians including more conservative discontinuation criteria for adrenal insufficiency. Each of Grade 4 endocrinopathy events has been added for completeness as a criterion for permanent discontinuation (see sections 4.2 and 4.4 of the SmPC).

As with all therapeutic proteins, there is a potential for an immune response to nivolumab. In an integrated analysis of nivolumab immunogenicity assessments, the overall rate of ADA development in the assessed population is low given the low percentage of ADA positive subjects, low titers in positive subjects, very low number of subjects categorized as persistent positive and very low number of subjects positive for neutralizing antibodies. Moreover, no association was established between the presence of neutralizing antibodies and loss of efficacy.

Based on a cross comparison with the SQ-NSCLC dossier, the safety profile of nivolumab might be more favourable in the SQ-NSCLC population compared with the NSQ-NSCLC population. The current NSQ-NSCSL showed a higher incidence of AEs leading to discontinuation of the study (16.7% vs. 10.7%) and the overall incidence of select AEs (75% vs. 54.4%).

The NSQ-NSCLC population reported a higher incidence of select adverse events including a higher frequency of Grade 3-4 pneumonitis than the SQ-NSCLC population. The potential contribution of nivolumab to more severe pulmonary embolism in the NSQ-NSCLC population was discussed during the assessment. The exposure-adjusted data and the risk for pulmonary embolism did not seem to be increased. However, these observations need to be taken cautiously due to the small numbers.

2.5.2. Conclusions on clinical safety

The safety profile of nivolumab in patients with non-SQ NSCLC seems to be largely consistent with that previously observed in SQ-NSCLC patients. No new safety signals have been identified.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

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

The PRAC agreed by consensus decision that the RMP version 3.0 (dated 03 November 2015) is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the above decision with minor changes.

The CHMP endorsed the RMP version 4.2 (dated 23 February 2016) with the following content:

Safety concerns

Table 57 - Summary of Safety Concerns

Important identified risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis or renal dysfunction
	Immune-related endocrinopathies
	Immune-related rash
	Other immune-related ARs

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

Pharmacovigilance plan

Table 58 - Ongoing and Planned Additional PV Studies/Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status**	**Estimated Date for Submission of Interim or Final Reports**
CA209234: Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice. Category 3	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Post-marketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, and myasthenic syndrome), and infusion reactions	Planned	Final CSR submission: 4Q2024

Risk minimisation measures

Table 59 – Summary table of Risk Minimization Measures

Safety Concern	***Routine Risk Minimization Measures***	***Additional Risk Minimization Measures***
<u>Important Identified Risks</u>		
Immune-related pneumonitis *Immune-related colitis* *Immune-related hepatitis* *Immune-related nephritis or*	*Wording in section 4.2, 4.4 and 4.8 of the SmPC*	*To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan.* *The Plan comprising 2 tools to be distributed to potential prescribers at launch by BMS:*

Safety Concern	***Routine Risk Minimization Measures***	***Additional Risk Minimization Measures***
renal dysfunction *Immune-related endocrinopathies* *Immune related rash* *Other immune-related ARs*		*- Adverse Reaction Management Guide* *- Patient Alert Card*
Severe infusion reactions	*Wording in section 4.4 and 4.8. of the SmPC*	*None*
Important Potential Risks		
Embryofetal Toxicity	*Wording in section 4.6 and 5.3 of the SmPC*	*None*
Immunogenicity	*Wording in section 4.8 of the SmPC*	*None*
Cardiac arrhythmias (previously treated melanoma indication, only)	*Wording in section 4.8 of the SmPC*	*None*
Missing Information		
Pediatric patients	*Wording in section 4.2 of the SmPC*	*None*
Severe hepatic and/or renal impairment	*Wording in section 4.2 and 5.2 of the SmPC*	*None*
Patients with autoimmune disease	*Wording in section 4.4 of the SmPC*	*None*
Patients already receiving systemic immunosuppressants before starting nivolumab	*Wording in section 4.4 and 4.5 of the SmPC*	*None*

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

The PRAC also considered that routine pharmacovigilance remains sufficient to monitor the effecti

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to the higher number of deaths within 3 months observed with nivolumab compared to docetaxel in non-squamous NSCLC has been added to the product information. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to align the annexes with the latest QRD template version 9.1 and to implement minor editorial changes.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the changes introduced are not considered to substantially impact the readability of the package leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of Opdivo in the treatment of advanced non-squamous NSCLC after prior chemotherapy in adults is based on a single pivotal study (CA209057). At the time of the analysis, the minimum follow-up time was 13.2 months.

Results from the study revealed a median overall survival of 12.19 months (95%CI: 9.66, 14.98) for the nivolumab group and 9.36 months for the docetaxel group (95%CI: 8.05, 10.68). The OS rate at 12 months was 50.5% (95% CI: 44.6, 56.1) for nivolumab, in comparison to 39.0% (95% CI: 33.3, 44.6) for docetaxel.

This effect was further supported by the results of the key secondary efficacy endpoint: ORR 19.2 % (95% CI: 14.8, 24.2) for nivolumab and 12.4% (95% CI: 8.8, 16.8) for docetaxel (odds ratio estimate 1.68 (95% CI: 1.07, 2.64, p 0.0246). Results obtained for other secondary efficacy endpoints (TTR and DOR) were also supportive. The majority of pre-specified subgroup analyses also showed statistically significant results.

Uncertainty in the knowledge about the beneficial effects

The survival curve for nivolumab is lower than that for docetaxel in the first 6 months, indicating a higher frequency of deaths in the nivolumab group. A multivariate analysis suggests an association between early death and low PD-L1 expression, ECOG score 1, time since last therapy < 3 months and “progressive disease” as best response to prior therapy. These analyses indicate that poorer prognostic features and/or aggressive disease, in combination with no/low PD-L1 expression, characterise patients treated with nivolumab with higher potential for death within the first 3 months, compared to docetaxel.

There seems to be a negative association between nivolumab benefit and level of PD-L1 expression. Accordingly, the OS difference compared to docetaxel seems to decrease or disappear with lower PD-L1 expression. This is different to the previous melanoma and SQ-NSCLC indications, in which a benefit of nivolumab was seen for both patients with PD-L1 positive and negative tumours. Also, analyses were not consistent across different efficacy endpoints. However, these findings need confirmation and estimation of a cut-off point for PD-L1 expression in tumours cannot be established with the analyses presented. A number of biomarker investigations will be conducted by the MAH to address this issue (see Annex II condition).

Risks

Unfavourable effects

The most common treatment-related AEs for the nivolumab-treated patients in the pivotal study were: fatigue (16%), nausea (11%), decreased appetite (10.5%), asthenia (10.1%) and rash (9.4%). Most of them were mild-moderate in severity. In nivolumab subjects, immune-related AEs were more frequently reported in the skin (26.5% patients) and GI (15.7% patients) SOCs, and most of them were mild-moderate severity.

The frequency of SAEs (all causalities) was slightly higher for nivolumab than docetaxel (46.7% vs. 41.4%, respectively), with a similar percentage of G3-4 events (33.1% vs. 34.0%, respectively).

At the time of the data cut- off, 64.5% and 76.1% of patients in the nivolumab and docetaxel groups, respectively, had died. The most common primary reason for death was “disease progression” in both treatment groups (54.7% vs. 66.8%, for nivolumab and docetaxel, respectively). Grade 5 (All causality) AEs were more frequent in the nivolumab group (n=23, 8.0%) than docetaxel (n=14, 5.2%), but deaths due to drug toxicity were infrequent in both groups (1 [<1%] in each group).

In general, the observed profile of selected AEs does not differ largely from that observed in the SQ NSCLC indication.

Uncertainty in the knowledge about the unfavourable effects

An unexpected higher frequency of malignant neoplasm progression as SAE has been reported for nivolumab treated patients in the CA209057 study (8% vs. 2.6%, for nivolumab vs. docetaxel, respectively).

Nivolumab also noted more cases of other malignant neoplasms (n=5) compared to docetaxel (n=0).

Nivolumab showed a higher incidence of pulmonary embolism, (4.2%) compared with docetaxel (2.1%) with more serious events (3.8% vs. 1.1%) and reported deaths (n=4) than the docetaxel group (n=1). However, the numbers were too low to be conclusive and these events will be monitored via routine pharmacovigilance.

The inclusion of elderly (>75 years) patients was limited to 43 (7%) patients, with no patients over the age of 84 receiving treatment with nivolumab. Although no new safety signals has been identified in elderly patients, the data in patients >75 years is considered too limited to draw any conclusion.

Safety data in patients with renal/hepatic impairment is limited (see sections 4.2 and 4.8 of the SmPC).

Effects Table

Table 60: Effects Table for nivolumab in the treatment of advanced pre-treated non-SQ NSCLC (data cut-off: 18-March-2015)

Effect	Short Description	Unit	Nivolumab 3mg/kg	Docetaxel 75 mg/m^2
Favourable Effects				
OS	Primary endpoint	Median (months) 95%CI	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
PFS*	Secondary endpoint	Median (months) 95%CI	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
ORR	2ndary endpoint (CR + PR)	Number (%) 95%CI	56 (19.2) 14.8, 24.2	36 (12.4) 8.8, 16.8
Unfavourable Effects				
Fatigue		% %	AE 31.7% G3/4 3.1% SAE <1%	AE 38.1% G3/4 6.7% SAE <1%
Cough			AE 26.5%	AE 23.1%

Effect	Short Description	Unit	Nivolumab 3mg/kg	Docetaxel 75 mg/m^2
			G3/4 0.3% SAE <1%	G3/4 0% SAE <1%
Constipation		%	AE 23.0% G3/4 0.7% SAE <1%	AE 16.8% G3/4 0.7% SAE <1%
Dyspnoea		%	AE 22.6% G3/4 4.9% SAE 3.1%	AE 23.5% G3/4 3.7% SAE 1.9%
Nausea		%	AE 22.0% G3/4 1.7% SAE 1.4%	AE 29.9% G3/4 0.7% SAE 0.7%
Tolerability			AE 97.6% ⩾ 1 dose delay: 61.0% ⩾ 1 infusion interruption: 5.9% AE leading to discontinuations 16.7% SAE 46.7%	AE 98.9% ⩾ 1 dose delay: 63% ⩾ 1 infusion interruption: 8.2% AE leading to discontinuation 21.6% SAE 41.4%

*Not statistically significant

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The data on nivolumab in the pivotal study showed an overall clinically relevant improvement with difference in median OS of 2.8 months in the overall survival compared to docetaxel as second line treatment in an overall population of NSQ-NSCLC showing progressive disease. The safety profiles of nivolumab and docetaxel are different but comparable in terms of tolerability. The overall incidences of adverse events, serious adverse events and events leading to discontinuation were relatively similar. However, a higher rate of pneumonitis and pulmonary embolism was reported. Nivolumab showed a low number of toxic deaths (n=5, including four possible associated cased of pulmonary embolism). Nivolumab's toxicity appears to be manageable. The safety profile is not associated with the well-known toxic effects of chemotherapy and this might be of specific benefit for patients showing sequelae after first line chemotherapy.

Benefit-risk balance

Nivolumab showed a clinically relevant improvement in overall survival compared to docetaxel for the whole population, which is considered clinically relevant.

From a safety point of view, treatment appears well tolerated and the different AEs profile appears to be manageable in a clinical practice setting. No new safety findings were identified in the data submitted.

The benefit risk balance is therefore considered positive.

Discussion on the Benefit-Risk Balance

The beneficial results seemed to be related to the level of expression of the baseline PD-L1 receptor. Nivolumab showed a higher ORR and higher improvement in OS in patients with a high baseline PD-L1 expression value.

In patients with low PD-L1 expression level, the overall survival was comparable to docetaxel. Nivolumab could therefore represent an alternative treatment option because of its different safety profile.

Multivariate analysis suggested an association between early death (within the first 3 months) and poorer prognostic features and/or aggressive disease, no/low PD-L1 expression, ECOG score 1, time since last therapy < 3 months and "progressive disease" as best response to prior therapy. It is reasonable to assume that patients with a poor prognosis and a more aggressive disease would benefit less taking into account the delayed effect of immunotherapy on OS.

Several uncertainties regarding PD-L1 assay validity and availability in "real-life" setting remain and should be addressed by the MAH (see Annex II condition). A number of investigations to clarify the role of this biomarker are ongoing.

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, IIIA and IIIB

Extension of Indication to include treatment as monotherapy of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults based on study CA209057. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, SmPC section 4.8 has been revised with updated combined clinical trial exposure numbers to reflect inclusion of studies in non-squamous NSCLC and in advanced melanoma. In addition, the MAH took the opportunity to align the annexes with the latest QRD template version 9.1, to update the agreed post-authorisation measures in Annex II and to implement minor editorial changes. A revised RMP version 4.2 was agreed during the procedure.

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

This CHMP recommendation is subject to the following amended conditions:

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

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

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

Description	**Due date**
4. The value of biomarkers to predict the efficacy of nivolumab should be further explored, specifically:	
• To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy. These analyses will be conducted in studies CA209037 and CA209066 in patients with advanced melanoma.	30th September 2015
• To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, etc.) as predictive of nivolumab efficacy. This will be provided for all the approved indications:	
- Melanoma: studies CA209038 and CA209066	30th September 2017
- NSCLC: studies CA209017, CA209057 and CA209026	31st March 2018
- RCC: studies CA209025 and CA209009	31st March 2018
• To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies (CA209009, CA209038 and CA209064).	31st March 2017
• To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in studies CA209066, CA209057 and CA209025.	30th June 2018
• To further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in studies CA209009, CA209038 and CA209064.	30th September 2017