EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2015
EMA/CHMP/392114/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nivolumab BMS

International non-proprietary name: NIVOLUMAB

Procedure No. EMEA/H/C/003840/0000

Note

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

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List of abbreviations

1Q: First quarter

2L: Second-line

3L: Third-line

4L: Fourth-line

4Q: Fourth quarter

ADCC: Antibody-dependent cell-mediated cytotoxicity

AE: Adverse event

ALP: alkaline phosphatase

ALT: alanine aminotransferase

ARDS: acute respiratory distress syndrome

AST: aspartate aminotransferase

BEV: bevacizumab

BMS: Bristol-Myers Squibb

BOR: Best overall response

BSC: Best supportive care

CAR: carboplatin

CIS: cisplatin

CR: Complete response

CRC: Colorectal adenocarcinoma

CSR: clinical study report

CTLA-4: cytotoxic T lymphocyte antigen-4

DLT: dose limiting toxicity

DMC: data monitoring committee

DOR: Duration of response

DSD: Duration of stable disease

DTIC: dacarbazine

ECG: electrocardiogram

ECOG: Eastern Cooperative Oncology Group

EGFR-TKI: Epidermal growth factor receptor tyrosine kinase inhibitor

ERL: erlotinib

FDA: Food and Drug Administration

FPFV: First patient first visit

GEM: gemcitabine

GI: gastrointestinal

HED: Human equivalent dose

HuMAb: Human monoclonal antibody

IB: Investigator Brochure

IgG4: Immunoglobulin G4

Ipi: ipilimumab

IRC: independent review committee

ISEL: Iressa Survival Evaluation in Lung Cancer

IV: Intravenous

LCSS: Lung Symptom Cancer Scale

LLN: lower limit of normal

LSQ: lung squamous

mAb: monoclonal antibody

Max: Maximum

mCRPC: Metastatic castrate-resistant prostate cancer

MedDRA: Medical Dictionary for Regulatory Activities

Min: Minimum

MTD: Maximum tolerated dose

NA: Not available

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events

NR: Not reached

NSCLC: Non-small cell lung cancer

NSQ: non-squamous

OLSQ: ongoing lung squamous

OMM: ongoing melanoma monotherapy

OR: objective response

ORR: Objective response rate

OS: Overall survival

PD: Progressive disease

PD-1: Programmed death 1

PD-L1: Programmed death 1 ligand 1

PD-L2: Programmed death 1 ligand 2

PFS: Progression-free survival

PK: Pharmacokinetics

PR: Partial response

Q2W: Every 2 weeks

RCC: Renal cell carcinoma

RECIST: Response Evaluation Criteria in Solid Tumours

SAE: Serious adverse event

SCE: Summary of Clinical Efficacy

SCP: Summary of Clinical Pharmacology

SCS: Summary of Clinical Safety

SD: Stable disease

SQ: Squamous

TTR: Time to response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 3 September 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nivolumab BMS, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication Nivolumab BMS is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that nivolumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a multiple of Opdivo as both applications were submitted simultaneously.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0064/2014 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver CW/1/2011.

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

Not applicable.

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.

New active Substance status

The applicant requested the active substance nivolumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 January 2012, 19 July 2012 and 17 January 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Nivolumab has been given a Marketing Authorisation in in Japan on 4 July 2014 and in the USA on 22 December 2014.

1.2. Manufacturers

Manufacturers of the active substance

Lonza Biologics, Inc.
101 International Drive
Portsmouth, New Hampshire
03801
USA

Manufacturer responsible for batch release

Bristol-Myers Squibb S.r.l.
Loc. Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

1.3. Steps taken for the assessment of the product

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

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

CHMP Peer reviewer: Jan Mueller-Berghaus

The EMA Product Team Leader: Elias Pean

The Procedure Manager: Hector Boix Perales

- The application was received by the EMA on 3 September 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 December 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014.
- During the meeting on 9 January 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 22 January 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 March 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of

Questions to all CHMP members on 29 April 2015.

- During the meeting on 7 May 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 21 May 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nivolumab BMS.

2. Scientific discussion

2.1. Introduction

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) and squamous cell (epidermoid) carcinoma accounting for approximately 15% to 25% of all NSCLC (~230,000 to 380,000 cases)[1,2].

Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer, and is also the most frequently occurring in non-smokers as reported in United States (US) data (American Cancer Society 2013).

Non-small cell lung cancer is associated with high mortality rates as >70% of the patients are diagnosed with locally advanced or metastatic disease (Molina et al 2008) [stages III and IV according to the American joint committee on cancer staging (AJCC)].

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 non-SQ NSCLC occurs in patients with a never smoker history and a strong correlation with the presence of an activating epidermal growth factor receptor (EGFR) mutation or gene translocation. Squamous NSCLC almost universally occur in patients with a history of tobacco use and only rarely are tumours found, which contain an EGFR activating mutation[3].

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. Common morbidities include generalized weakness and fatigue, cough, and dyspnoea. Local spread of tumour can result in obstructive pneumonia, lobar collapse, haemoptysis, pain from chest wall and rib invasion, and pleural effusions, while distant spread to bone, brain, liver, and adrenals can lead to pain, neurologic sequelae, and laboratory abnormalities. Generalized effects of metastatic disease also include cachexia, thrombotic and embolic events, paraneoplastic conditions, and infections.

Historically, patients with locally advanced or metastatic NSCLC have been treated with standard chemotherapy and/or radiation, and while these treatments may provide modest survival benefits, they are rarely curative.

[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.

Refractory SQ NSCLC

Despite new treatments for NSCLC in the last 15 years, most of the available agents do not benefit patients with SQ NSCLC, because they are not efficacious for this subtype (bevacizumab [BEV], pemetrexed [PEM]) or since activity is limited to tumours with specific mutations and gene alterations that are rarely found in SQ NSCLC tumours (erlotinib, gefitinib, afatanib, crizotinib). Reports from multi-institution, retrospective studies demonstrate treatment with cytotoxic chemotherapy and EGFR inhibitors produce little clinical benefit in refractory SQ NSCLC patients. Massarelli et al[4] described results from 43 third-line or more patients that were treated in 2 large academic centers in France at the Institut Gustave Roussy (IGR) and in the US at the MD Anderson Cancer Center (MDACC). All patients had at least two chemotherapy regimens, including at least one course of a platinum-based therapy and one course of docetaxel, given concurrently or as separate treatment regimens and 26% had SQ histology. Patients were treated with a variety (>10) of different cytotoxic regimens mostly consisting of monotherapy or combinations of carboplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, and etoposide. The investigator-assessed objective response rate (ORR) in the last line treatment was 2.3% and for all patients, the median OS and 1 year OS were 4 months and 5.5%, respectively. Scartozzi et al reported on a series of 143 previously treated NSCLC patients treated in multiple centers across Italy. Only 52 of the 143 patients were able to receive third-line therapy. Of these, the majority had adenocarcinoma (58%) or SQ (11%) histology. A range of treatments were provided including a variety of cytotoxic therapies (58%) and EGFR inhibitors (42%). The investigator assessed ORR was 8% and the median OS was 4.8 months in the SQ subset.

A summary of United States (US) Medicare data indicates treatment in third-line is variable. Thirty-four distinct third-line regimens were utilized for SQ patients. This variation implies lack of a clear standard of care. Survival is poor for third-line SQ patients. The median OS is 5 months from initiation of third-line, with 1 year and 2-year survival rates of 18% and 3%, respectively[5].

This patient population therefore represents an area of high and urgent unmet medical need.

About the product

The co-inhibitory receptor programmed cell death – 1 (PD-1) is a key regulator of T cell activity that belongs to the same immunoglobulin superfamily which includes the co-stimulatory receptor CD28 and the co-inhibitory receptor CTLA-4. , Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the PD-1 receptor and blocks its interaction with PD-1 ligand (PD-L1) and PD-1 ligand 2 (PD-L2). The PD-1 receptor is a negative regulator of T cell activity that has been shown to be involved in the control of T cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

The applicant applied for an accelerated procedure for the following indication:

Treatment of locally advanced or metastatic NSCLC after prior chemotherapy.

The final approved indication was:

[4] Massarelli E, Andre F, Liu DD, et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer. Lung Cancer 2003;39:55-61.
[5] Interim Study Report for Study CA209060: Observational Study in Non-Small Cell Lung Cancer (NSCLC) Survival, Treatment Patterns, and Cost in a U.S. Medicare Population. Bristol-Myers Squibb Company; 2014. Document Control No. 930081546.

Treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. The infusion must be administered through a sterile, non- pyrogenic, low protein binding in- line filter with a pore size of 0.2 1.2 µm.

Nivolumab BMS must not be administered as an intravenous push or bolus injection.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 1 of the SmPC. Detailed guidelines for the management of immune related adverse reactions are described in section 4.4 of the SmPC.

The total dose of Nivolumab BMS required can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection.

2.2. Quality aspects

2.2.1. Introduction

Nivolumab is a human monoclonal immunoglobulin G4 (IgG4) antibody directed against the programmed death-1 (PD-1) receptor. It is an IgG4 consisting of four polypeptide chains; two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter-chain disulfide bonds.

Nivolumab active substance is produced from large-scale cell culture using a Chinese hamster ovary (CHO) cell line and is purified using standard chromatography and filtration steps using a manufacturing process designated as Process C. Commercial nivolumab is manufactured by Lonza Biologics, Inc., Portsmouth, New Hampshire, USA (Lonza-Portsmouth). Finished product from Process B active substance manufacturing process was used in pivotal clinical trials. Comparability of products manufactured from Process C to that manufactured from Process B was assessed by analytical comparability, product degradation profiles and in-process data comparability. Active substance is packaged in polyethylene bioprocess containers. Long-term stability studies support a 24-month shelf life for active substance when stored refrigerated (2°C to 8°C) and protected from light.

Nivolumab BMS injection is available as 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL) single-use presentations. Both presentations have the same protein concentration and are packaged in the same primary packaging which consists of a 10 mL, Type I flint glass tubing vial sealed with a 20mm grey butyl stopper and an aluminium flip-off seal. The only difference between the two presentations is the fill volume. Both presentations are packaged in a paperboard folded carton. Secondary packaging into paperboard cartons and final release will occur at the Bristol Myers Squibb facility in Anagni, Italy (BMS-Anagni). The long-term stability data support a 24-month finished product shelf life when stored refrigerated (2°C to 8°C) and protected from light.

2.2.2. Active Substance

Manufacture, characterisation and process controls

Manufacture

Active substance manufacturing takes place at Lonza Biologics in Portsmouth (USA). Nivolumab is manufactured in bioreactors. One production bioreactor leads to one bulk active substance lot. Bulk active substance lots are not combined at the active substance stage.

Nivolumab is produced from manufacturing-scale cell culture using a Chinese hamster ovary (CHO) cell line that was transfected with an expression vector containing coding sequences for the heavy and light chains of the nivolumab IgG. A conventional two-tiered cell banking system is employed, consisting of a Master Cell Bank from which a Working Cell Bank (WCB) is derived.

The upstream manufacturing process is a conventional fermentation process. Upstream processing starts with expansion of the WCB in a pre-culture step and a subsequent seed fermentation step. The expanded cells are transferred to a bioreactor and cultured under optimised conditions by means of a fed-batch process. Cell culture conditions and in-process controls (IPCs) have been sufficiently described.

The downstream process comprises chromatography and viral inactivation/clearance steps. The concentrated clarified bulk from the primary recovery step is processed across a series of chromatography, viral inactivation, filtration and ultrafiltration/diafiltration steps. The active substance is stored at 2ºC to 8ºC prior to shipping to the finished product manufacturing facility.

Control of materials

Raw materials used in the nivolumab commercial manufacturing process are controlled to ensure the quality and safety of the active substance and to maintain the consistency of the manufacturing process. Raw materials are purchased from qualified vendors. Raw material quality is assessed as defined in the testing specification for each raw material.

Nivolumab production cells are CHO cells transfected with an expression vector containing the coding sequences for both heavy and light chains of the nivolumab IgG, in which the variable region genes were isolated from mouse hybridoma cells. The hybridoma cells were generated by the fusion of mouse myeloma cells with spleen cells from a PD-1 receptor immunised Human Ig transgenic mouse (HuMAb-Mouse) of the HCo7+KCo5 lineage. A hybridoma clone, 5C4.B8, which produced an anti-PD-1 antibody was selected. The immunoglobulin genes coding for the variable regions from the anti-PD-1 expressing hybridoma were cloned into an expression vector, which was used to establish CHO cell line M48A expressing the nivolumab antibody. The M48A cell line is used in the nivolumab manufacturing process at the Lonza Biologics facility Portsmouth (USA).

The MCB is stored in the vapour phase of liquid nitrogen in a cryofreezer designated for long-term storage of released cell banks. The nivolumab MCB is re-evaluated at 5 year intervals.

The WCB was derived from a single vial of MCB. This WCB is stored in the vapour phase of liquid nitrogen in a cryofreezer designated for long term storage of released cell banks. WCBs are tested for safety and productivity in accordance with regulatory guidelines and standard operating procedures before their release for manufacturing use.

The limit of *in vitro* cell age for the nivolumab production cell line was determined through extended passages during the inoculum expansion and seed bioreactor steps for the nivolumab manufacturing process at manufacturing-scale during process performance qualification (PPQ). The results support the stability of the

nivolumab production cell line and have been suitably demonstrated, with respect to biosafety, growth characteristics of the inoculum expansion and seed bioreactor steps, biochemical product quality assessment and genetic stability.

Process validation

The process validation strategy for nivolumab active substance is based on a lifecycle management approach that includes the process design stage, process performance qualification (PPQ) stage, and ongoing (also referred to as continued) process verification stage.

The nivolumab PPQ campaign qualified the media and buffer preparation, the upstream process, and the downstream process at Lonza Biologics, Portsmouth (USA). The PPQ protocols included prospectively defined acceptance criteria consisting of numerical limits for release testing results, (Critical) Process Parameters ((C)PPs) and (Critical) Performance Attributes ((C)PAs) as defined in the IPC strategy presented. Acceptance criteria for the upstream manufacturing process and downstream manufacturing process were met. The acceptance criteria for PPQ described in the process validation section of the dossier reflect the IPC in place at the time the PPQ studies were conducted. After PPQ was completed, the IPC ranges and classifications were reviewed and compared to manufacturing-scale data and small-scale process characterisation data. Some ranges were amended and a number of (C)PPs and (C)PAs was reclassified.

Control of critical steps

An in-process control (IPC) strategy was defined for the nivolumab active substance manufacturing process. The IPC strategy is a planned set of controls derived from current product and process understanding that ensures consistent process performance and product quality. The controls include parameters and attributes related to active substance manufacturing to ensure the active substance meets the established specifications. The IPC strategy utilises a tiered set of in-process alert ranges, action ranges and critical ranges to ensure the consistent monitoring and control of the nivolumab active substance manufacturing process. The classification of IPC levels for each input and output is based upon an assessment of the potential impact of the parameter on the manufacturing process as well as the CQAs of the nivolumab active substance. Excursions from the established ranges are investigated for product quality impact.

Manufacturing process development

The development of the nivolumab manufacturing process in CHO cells started in 2006 and progressed during clinical development from manufacture of active substance by Process A, via Process B to Process C. Process C is currently the validated nivolumab manufacturing process at the Lonza Biologics facility, located in Portsmouth, New Hampshire and is intended for commercial manufacture. All pivotal clinical studies included in the submission have been performed using nivolumab from active substance Process B.

The early development of the manufacturing process in conjunction with initial manufacturing scale experience was used to provide basic process understanding. Using the basic process understanding, upstream process characterisation was conducted to refine process understanding. Each unit operation of the manufacturing process was assessed to identify process parameters (PPs) with a potential impact on critical quality attributes (CQAs). An upstream in-process control strategy was established to ensure that CQAs of the molecule were maintained within acceptable ranges.

The upstream manufacturing Process C is identical to Process B for majority of the steps. The development of the upstream manufacturing Process B is therefore directly applicable to Process C for these steps. The downstream manufacturing Process C was developed with a series of chromatographic steps. The downstream process also includes viral inactivation , viral filtration, and a UF/DF step which yields UFB. Polysorbate 80 is then

added to UFB yielding the formulated bulk, which is subsequently filtered through a membrane ending in the final active substance. Process development activities have established several in-process control parameter ranges through a series of one-factor and multi-factor experiments. Development of process conditions was completed for each process step. Early development of the manufacturing process in conjunction with initial manufacturing scale experience provided basic process understanding. Process characterisation was then conducted to refine process understanding and establish the downstream in-process control strategy. A scale-down model was completed for design of experiment (DoE) screening and statistically-designed response surface method (RSM) studies. The parameters that were demonstrated from development or screening studies to have a potential to impact product quality or process robustness were explored in RSM characterisation studies using the appropriate scale-down models.

Comparability between Processes A, B and C

Nivolumab manufacturing Process A was modified to accommodate scale-up and transfer to a new facility. The resulting process was designated Process B. Modifications to the upstream process were made to align with the manufacturing facility and to provide improved throughput while maintaining product quality. Comparability of active substance manufactured using Process A to that using Process B was established using biochemical comparability studies that included routine release and extended characterisation tests. The purification steps of Process B were modified to further increase process robustness and provide improved process control. The resulting process was designated as Process C.

A comparison of the active substance release data from representative lots of Process A, Process B, and Process C was performed to confirm comparability of Process C active substance to Processes A and B active substance. Raw data and statistical analysis are presented. A comparison of the differences in mean responses for quantitative assays was performed between the Process B and Process C lots. The difference in means is calculated as the mean for Process C results minus the mean from the Process B results prior to rounding of the mean results. All individual Process C results fall within the Tolerance Limits (TL) of Processes A and B, and the intervals defined by the average ± 3 SD of the Process C data also fall within the TLs determined for Process A and B.

Identification of Critical Quality Attributes and classification of process parameters

Potential CQAs were identified for product-related variants, process-related impurities and formulation related quality attributes. The available knowledge for each attribute, both specific to nivolumab and from relevant supporting class knowledge was compiled and then each attribute was assigned as critical or non-critical.

An IPC strategy was established for the nivolumab active substance manufacturing process based on an integrated control strategy, which includes process control establishment and process control elements of each unit operation for quality attributes. Information is provided on the development of the strategy; the justifications for process parameter (PP) and performance attribute (PA) designations and their numerical ranges. The establishment of the IPC strategy for the nivolumab manufacturing process was based on toxicological assessments, process development, manufacturing-scale impurity mapping, stability testing, pilot-scale experience and manufacturing-scale experience to identify process control points for each quality attribute. Process development studies were designed to assess the influence of PPs on the quality of the active substance and the performance of the nivolumab manufacturing process. The results of these studies in combination with manufacturing experience were used to classify the process variables and establish IPC ranges for the upstream and downstream process steps. The IPC strategy process control elements for quality attributes include input material testing, in-process testing, PPs and specifications. Process control elements also include procedural controls for each unit operation.

Characterisation

Physical and biochemical properties of nivolumab were characterised using a series of orthogonal techniques, using all PPQ lots of nivolumab active substance. The techniques included liquid chromatography mass spectrometry (LC-MS/MS) for the determination of primary structure; circular dichroism (CD) for determination of secondary structure; and other techniques for examination of higher order structure of nivolumab that included size exclusion chromatography (SEC), SEC-multi-angle light scattering (SEC-MALS), sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), capillary electrophoresis SDS (CE-SDS), and analytical ultracentrifugation (AUC) to characterize the size variants. Disulfide bonds were characterised by LC-MS. Protein conformation was examined by differential scanning calorimetry (DSC) and hydrogen-deuterium exchange mass spectrometry (HDX-MS).

The biological properties of nivolumab were characterised using a direct binding enzyme-linked immunosorbent assay (ELISA), binding competition ELISA (potency ELISA) and a cell-based bioassay. The binding kinetics of nivolumab to the PD-1 receptor was determined using surface plasmon resonance (SPR).

The interactions of the Fc region of the nivolumab molecule with human FcγRs (CD64, CD32 and CD16) and complement were assessed in both FcγR binding assays and in cellular cytotoxicity assays. The binding of nivolumab to the FcγRs was characterised by SPR. Nivolumab does not elicit measurable ADCC or CDC activity in vitro. Nivolumab has been shown to retain binding to neonatal Fc receptor (FcRn) in SPR binding studies.

Potential process related impurities in nivolumab have been identified and are controlled by in-process testing, release testing according to specifications and/or process performance qualification.

Potential product-related impurities have been studied through the characterisation process and have been identified as HMW and LMW species, which are controlled at release by SE-HPLC.

Specification

Nivolumab quality control testing for batch release includes appearance, quality, pH, purity, identity, potency, process-related impurities and endotoxins/bioburden. The specification set for nivolumab active substance are in accordance with the Ph.Eur. Monograph on Monoclonal Antibodies for Human Use.

The Applicant's approach for selection of the release and shelf life tests is based on a multistep process including definition of CQAs, consideration of clinical experience, patient safety limits, stability of the active substance and finished product and process and method variability.

The biological activity is tested in three assays, i.e., (1) binding activity ELISA, (2) potency ELISA, and (3) cell-based bioassay. Each of the three proposed assays measure a relevant biological effect of the product at different levels in its mechanism of action and are considered important for release. The three proposed biological activity release/shelf life tests are also stability indicating.

Batch Analysis

Batch (lot) information for nivolumab active substance including the process designation, site of manufacture, date of manufacture, batch size and designated use for each active substance batch is presented for all process A, B and C lots. All batch analysis data were in line with the acceptance criteria that applied at the time of testing.

Reference standards of materials

During development, a series of Research Reference Standards (RRSs) was used. The initial reference standard was established as the reference standard prior to PPQ, and will serve as the initial Working Reference Standard (WRS) for release and stability testing of commercial lots.

BMS plans to implement a two-tiered reference standard strategy, at which time the existing reference Standard will become the Primary Reference Standard (PRS) and will be used to qualify future Working Reference Standards. The existing reference standard was prepared using Process B active substance; finished product manufactured from this lot was used in pivotal clinical trials for lung cancer and melanoma and thus provides a direct link to clinical experience.

Container closure system

Active substance is filled into single-use, pre-sterilised multi-layered low density polyethylene (LDPE) bioprocess containers. Bioprocess containers are made from virgin plastics specifically manufactured from non-recycled material for use by pharmaceutical and biological manufacturers.

No semi-volatile organic compounds and non-volatile organic compounds were detected. Several metal ions were detected but all were below ppm levels and therefore not reported. Leachables studies were performed by storing the bags under two real-time and accelerated conditions. Leachables identified from nivolumab active substance or formulation buffer were evaluated in a toxicological review in which the estimated maximum daily exposure was compared to the permissible daily exposure (PDE) for each leachable. Results indicated that no leachable compounds are anticipated to pose a safety risk when nivolumab is administered as directed.

Stability

Stability studies have been conducted on batches of nivolumab active substance in accordance with ICH stability guidelines and demonstrate that the active substance is stable for up to 24 months when stored at 2°C to 8°C. Some of the batches were manufactured according to Process C and three according to Process B. Active substance manufactured according to Process C was shown to be comparable to active substance manufactured according to Process B. While in the first submission only the batches manufactured according to Process B had stability data for 24 months, in the Applicant's responses new data up to 24 months was also submitted for the batches manufactured according to Process C. Stability data were evaluated according to the specification as provided. The specification evolved during the execution of the stability studies.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Two commercial presentations, Nivolumab BMS injection, 100 mg/10 mL (10 mg/mL) and Nivolumab BMS injection, 40 mg/4 mL (10 mg/mL) have been developed. Both presentations have the same protein concentration and are packaged in the same primary packaging which consists of a 10 mL, Type I flint glass tubing vial and sealed with a 20 mm butyl stopper and an aluminium, flip-off seal. The only difference between the two presentations is the fill volume. Both presentations are packaged in a paperboard folded carton.

The formulation contains sodium citrate as buffering agent, sodium chloride and mannitol as tonicity modifier, pentetic acid as metal ion chelator, polysorbate 80 as surfactant, hydrochloric acid/sodium hydroxide for pH adjustment and water for injection as solvent. Choice and concentrations of the excipients and the pH of the formulation were adequately justified by formulation studies. In addition, the robustness of the formulation was studied for slight variations in pH, and concentrations of citrate buffer, sodium chloride, mannitol and pentetic acid with satisfactory results. An overfill is included in each vial to account for loss in the vial.

Nivolumab BMS injection is a clear to opalescent, colorless to pale yellow liquid which may contain light (few) particulates. The finished product is a sterile, non-pyrogenic, single-use, preservative-free, isotonic aqueous solution for intravenous (IV) administration. Nivolumab BMS injection may be administered undiluted at a

concentration of 10 mg/mL or further diluted with 0.9% sodium chloride injection (sodium chloride 9 mg/mL (0.9%) solution for injection) or 5% dextrose injection (50 mg/mL (5%) glucose solution for injection) to nivolumab concentrations as low as 1 mg/mL.

Manufacture of the product and process controls

The manufacturing process for the 100/10 ml and 40 mg/ml vials is straightforward and was described in sufficient detail. Briefly, buffer solution is prepared and the active substance is diluted with filtered buffer in two steps, followed by sterile filtration, filling and finishing. Appropriate in-process tests are performed with limits that ensure that the product will meet the corresponding finished product specifications (pH, osmolarity, protein concentration, endotoxin). Hold times were justified by validation studies performed during process development and were confirmed during process performance qualification.

During development no major changes were introduced in the formulation, manufacturing process or container closure system of the finished product. Only early clinical studies (phase 1) were performed with a formulation that containedlower amount of polysorbate 80 and a direct fill and finishing procedure. The change in active substance manufacturing process from Process B to C is discussed in the active substance section.

Product specification

Finished product release testing includes general quality tests composition, identity, purity, potency, total protein, and microbial test (sterility, bacterial endotoxin, container closure integrity test). Many test procedures and specifications are the same or similar to those for the active substance.

The finished product may contain low levels of visible particles. For administration of Nivolumab BMS, an infusion set with an in-line low protein binding filter will be used.

Satisfactory finished product batch analysis data of Process A batches, 8 Process B batches and 13 Process C batches have been provided. The data show, overall, that the process is running consistently.

Stability of the product

A shelf life of 24 months at 2°C to 8°C is proposed for both presentations. Stability studies were appropriately designed. For the 100 mg/10 ml long term stability data were provided for Process B and Process C batches. For the 40 mg/4 ml presentation long term stability data for three batches were provided. The information provided in the Applicant's responses contains data for at least 24 months in all the above 100 mg/10 ml batches and for 15 months in the 40 mg/4 ml batches.

Adventitious agents

No raw material of animal origin (primary source) was used in the manufacture and cryopreservation of the Research Cell bank, MCB and WCB for nivolumab. The nivolumab active substance manufacturing process does not use any material of animal or human origin.

Viral clearance is achieved through viral inactivation, physical removal of virus by nanofiltration and three orthogonal chromatographic steps. Low-pH viral inactivation and virus removal filtration are the dedicated viral clearance steps.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The overall standard of the Module 3 Quality dossier presented in support of this application is high, with the description of the manufacture and control of the active substance and finished product in general containing sufficient detail to permit an in-depth assessment of the marketing authorisation application.

Active substance

Manufacture

The nivolumab active substance manufacturing process was described in sufficient detail. The virus filtration (VF) and final filtration and fill steps may be reprocessed when, for example, the viral filter post-use integrity test fails or if processing is not performed as intended. The reprocessing steps were sufficiently described and were properly validated.

Information provided on control and compositions of media, buffers, solvents, reagents and auxiliary substances used in the manufacturing process of nivolumab was considered acceptable. Control of materials mainly relies on suppliers' certificates of analysis. Specifications were set and provided for the raw materials used in the fermentation process, harvesting and purification steps, as well as for the column materials. The information on materials from biological origin was sufficiently detailed. Certificates of analysis and, where available, EDQM CEPs were provided. The data provided did not give rise to safety concerns as regards viral and/or TSE issues. The nivolumab active substance manufacturing process starting from WCB does not use any material of animal or human origin. A number of other concerns were identified regarding the raw materials and the control of the cell banks and were appropriately addressed by the Applicant.

The establishment and genealogy of the CHO cell line and the construction of the nivolumab expression vector used in the nivolumab manufacturing process at the Lonza Biologics facility were described in sufficient detail. According to the information provided in the initial submission, it was concluded that the cell banks were fully characterised, including at the limit of *in vitro* age, to evaluate their ability to consistently produce nivolumab active substance. A cell bank stability program was in place for ongoing monitoring.

Taken into consideration all information provided, it was considered that the quality of the active substance is consistently maintained at the Lonza facility. Manufacturing process changes were made during development from Process A through Process B to Process C. An extensive comparability program was performed to demonstrate comparable product quality. The lot numbers mentioned and the results from the analytical comparability testing suggest that a limited number of batches from Process A and from Process B were tested to establish comparability of these processes, which is generally not deemed sufficient to draw a sound conclusion on comparability of Process A and Process B. However, the level of comparability between Process A and Process B manufactured active substance is deemed of minor importance in demonstrating comparability of Process B (i.e. process used for pivotal clinical trial material) and Process C (i.e. intended commercial process) manufactured active substance. Therefore, requesting more information was considered of limited value.

An extensive data package was provided to demonstrate comparability of the active substance manufactured by Process B and Process C. Only minor differences were detected between active substance lots from Process B versus Process C lots. These differences were sufficiently discussed and are not expected to have a negative impact on the quality of the product. In summary, based on the comparison of the release testing data provided and further supported by a data set on extended characterisation and forced degradation, it could be concluded that active substance manufactured using Process C (commercial process) is comparable to active substance manufactured using Process B used in pivotal clinical trials.

Process validation

Process verification was based on the manufacture of multiple PPQ lots . At each step, all (Critical) Process Parameters ((C)PPs) and (Critical) Performance Attributes ((C)PAs) that were identified during upstream and downstream process parameter designation were monitored c.q. analysed. Sufficient actual numerical data were given for process controls, results of in-process testing and yields of the different steps. All PPQ lots passed release testing and met the acceptance criteria in place at the time of the PPQ.

Intentional reprocessing was performed to demonstrate that reprocessing of nivolumab through the VF and final filtration and fill steps does not impact the quality of the in-process material or the resulting active substance at release. Both the post-VF pool and the filtrated and filled nivolumab active substance met the acceptance criteria after reprocessing.

Several deviations against the PPQ protocol acceptance criteria occurred. The way these deviations were investigated and handled was sufficiently described. The impact of each deviation on the production process/product quality was discussed. All deviations appeared to be related to operational or technical errors (equipment) and did not influence CPPs or CPAs and thus did not affect any critical quality attribute (CQA). Deviations during process verification were sufficiently addressed.

Overall, the results of the validation lots were very consistent and confirmed that the final manufacturing process performs effectively and is able to produce nivolumab intermediates and active substance meeting their predetermined acceptance criteria, on an appropriate number of consecutive batches on commercial scale when operating within the Proven Acceptable Ranges.

The impact of the hold times and conditions on the product quality were appropriately evaluated. The maximum hold time for each process intermediate was justified based on analysis of an appropriate set of stability indicating assays and parameters, including a number of relevant performance attributes (High Molecular Weight (HMW), degradation, bioburden, endotoxins, binding ELISA). The maximum hold times are considered adequate.

After PPQ was completed, the in-process control (IPC) ranges and classifications were reviewed and compared to manufacturing-scale data and small-scale process characterisation data. An overview of all adjusted IPC ranges was presented and each adjustment was justified. Furthermore, a number of process variables were upgraded to CPP.

The completed studies defined in the PPQ protocols demonstrated the effective and consistent production of nivolumab active substance. The upstream and downstream steps of the manufacturing process used to produce nivolumab active substance are considered qualified.

Control of critical steps / Control strategy

The manufacturing process development is based on an enhanced approach using several QbD elements, such as the use of available knowledge for each quality attribute, risk assessments to assign the criticality of quality attributes, Design of Experiments (DoE) studies to assign the criticality of process parameters and finally to define an integrated control strategy. It is noted that no Design Space is claimed.

Overall, the approach was deemed appropriate, and as requested the Applicant defined potency as an active substance CQA in line with the approach taken for the finished product. Extensive information was provided in support of the assigned process parameters and performance attributes based on an in-depth evaluation of each operation unit in terms of process parameter variability and impact on quality attributes. Process parameters

and performance attributes and respective alert/actions limits were sufficiently supported by process characterisation studies.

Excursions from established alert, action or critical ranges were investigated to evaluate the possible root cause and possible impact on product quality. The Applicant justified that the investigation of these excursions entails sufficient rigour to ensure that the quality of the product is unaffected.

Multiple levels of control were established throughout the nivolumab manufacturing process to minimise the risk of contamination of the finished product with adventitious viruses. Cell banks were extensively tested for adventitious as well as endogenous agents. Cell culture is performed under serum free conditions using media that contain no components of animal or human origin. Pre-harvest samples from each nivolumab production batch are tested for bioburden, endotoxin, mycoplasma, *in vitro* adventitious agents and minute virus of mice.

Five process steps were investigated in virus validation studies to determine the manufacturing process capacity for virus inactivation/removal. In general, the strategy for virus validation was considered acceptable.

Characterisation

Overall, the analytical methods applied for characterisation of nivolumab were considered adequate and provide a complete characterisation of the molecule. The analytical methods applied were described in sufficient detail.

Control of active substance

The Applicant's approach for selection of the release and shelf life tests is based on a multistep process including definition of CQAs, consideration of clinical experience, patient safety limits, stability of the active substance and finished product and process and method variability. The approach is adequately documented in the application and is generally acceptable.

Specifications for the biological assays were also tightened, as requested during the procedure.

Discontinuation of the tests for impurities was based on consistent low results at the level of unformulated bulk active substance, often at or below the quantitation limit, in-process testing during process qualification, spiking studies at small scale and safety assessment. The results of the analysis of these studies indeed warrant discontinuation of these tests.

The test for residual host-cell protein will be continued at the level of the unformulated active substance, which is endorsed. The Applicant agreed to develop and implement a process-specific HCP method, which should be available by the end of March 2016.

Analytical methods applied for batch release and stability testing were described in sufficient detail. Appropriate controls and relevant parameters ensuring the validity of the test were included. Methods were adequately validated and are suitable for their purpose.

Satisfactory active substance batch analysis data have been provided. The data show, overall, that the process is running consistently.

Reference standards of materials

Adequate information was provided for reference standards. The current reference standard was prepared using Process B active substance; finished product manufactured from this lot was used in pivotal clinical trials for lung cancer and melanoma and thus provides a direct link to clinical experience. The Applicant plans to implement a two-tiered reference standard strategy, at which time the current Reference Standard will become the Primary Reference Standard (PRS) and will be used to qualify future Working Reference Standards.

Active substance stability

Since the active substance manufactured by Process C was shown to be comparable to active substance processed by Process B, the stability data available for Process B batches were regarded representative and could be considered supportive for the proposed active substance storage time of 24 months. In any case, updated finished product stability data was provided during the proceduresupporting the acceptability of the proposed finished product shelf life of 24 months when stored at 2-8ºC and protected from light. A number of concerns raised about the analytical methods and the proposed active substance (release and) end-of-shelf-life specifications were satisfactorily addressed in the Applicant's responses, in some cases including commitments.

Finished product

The manufacture of the finished product is a straightforward aseptic filling process for a liquid formulation. Satisfactory information with regard to manufacturing process development was provided.

Whilst the control strategy (i.e. the type and number of controls) was generally considered acceptable, a number of concerns was identified. The process to assign a criticality status to process parameters and controls was not sufficiently described for a number of parameters and some relevant parameters were lacking. These issues were considered resolved following the submission of the Applicant's responses.

The Applicant's approach for selection of the release and shelf life tests is based on a multi-step process including definition of critical quality attributes (CQAs), consideration of clinical experience, patient safety limits, stability of the active substance and finished product and process and method variability. The approach was adequately documented in the application and was generally acceptable.

The compatibility of the finished product with the container closure system was sufficiently studied. Compatibility was established for the recommended final infusion concentration range, diluents, containers, IV administration sets, in-line filters (0.2 and 1.2 µm polyethersulfone membranes) and infusion flow rates. An appropriate matrix design was used. The leachables studies did not give rise to any concerns. Given the relatively high concentration of citrate in the finished product, glass delamination was investigated with three compatibility studies and no risk of delamination was found.

Updated finished product stability data were provided during the procedure supporting the acceptability of the proposed finished product shelf life of 24 months at 2-8 °C and protected from light for both presentations.

Adventitious agents

The risk of TSE is considered very low in the nivolumab manufacturing process.

Viral elimination/inactivation studies were validated, but only a summary of the results was presented. The Applicant was asked to provide the full reports plus some other minor clarifications. All information was submitted with the Applicant's responses and was considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Nivolumab BMS is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The

manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall Quality of Nivolumab BMS is considered acceptable. Several Recommendations on Quality aspects, agreed by the Applicant, are listed in Section 2.2.6.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacology of PD-1 blockade was evaluated *in vitro* using primarily human and murine cells and *in vivo* in mice using a murine homolog product. Safety of nivolumab was evaluated exclusively in nonhuman primates, the only relevant and pharmacologically responsive model.

The pivotal toxicology studies supporting the safety of nivolumab were conducted in compliance with Good Laboratory Practice (GLP) regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Affinity study by surface plasmon resonance (MDX-1106-025-R930046580 and amendments)

Nivolumab binding to PD-1 on T cells and its affinity to human and cynomolgus PD-1 was assessed using surface plasmon resonance (SPR). Recombinant PD-1-Ig fusion protein was coated on a substrate chip and several concentrations of the antibody were flowed over the chip to obtain binding and dissociation kinetics. The results are shown in Table 1.

Table 1: Affinities of nivolumab by surface plasmon resonance

Antibody	antigen	K_D x 10^{-9} (M)	ka x 10^4 (1/Ms)	kd x10^{-4} (1/s)
nivolumab	human PD-1	3.06	25.00	7.68
nivolumab	cynomolgus PD-1	3.92	11.8	4.65

PD-1 epitope sequence (BDX-1106-321 930072902)

Physical binding experiments were performed by immunoprecipitation with either intact PD-1 or PD-1 peptides generated from various enzymatic digests. As shown in the figure below, three peptides were identified, 1a (62-69), 1b (70-86) and 2 (118-136). Peptides 1a and 1b are adjacent to one another in the linear sequence of

PD-1. Peptide 1a was found to have the strongest affinity to nivolumab. The binding of nivolumab to antigen was found to be dependent upon glycosylation of PD-1.

^{1}MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNA^{50}
^{51}TFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQL^{100}
^{101}PNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAE^{150}

Figure 1: Amino acids 1-150 of human PD-1, peptide sequences precipitated by nivolumab are underlined

The cynomolgus amino acid sequence is highly homologous to human PD-1 and within the peptides 1a, 1b and 2, all but one amino acid are identical.

Binding of nivolumab to recombinant human PD-1 and related proteins (MDX-1106-025-R 930046580 and amendments)

The ability of nivolumab to bind recombinant human PD-1-Ig fusion protein was demonstrated by ELISA. The results show an EC50 = 0.39 nM while demonstrating no binding to select other members of the related immunoglobulin supergene family i.e. CD28, ICOS, CTLA-4 and BTLA.

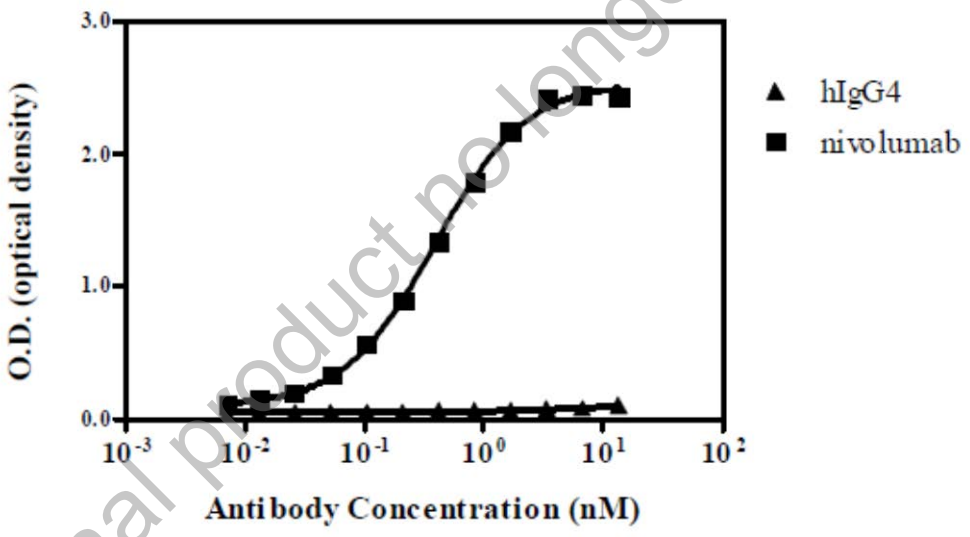


Figure 2: Binding of nivolumab to PD-1-Fc by enzyme-linked immunosorbent assay

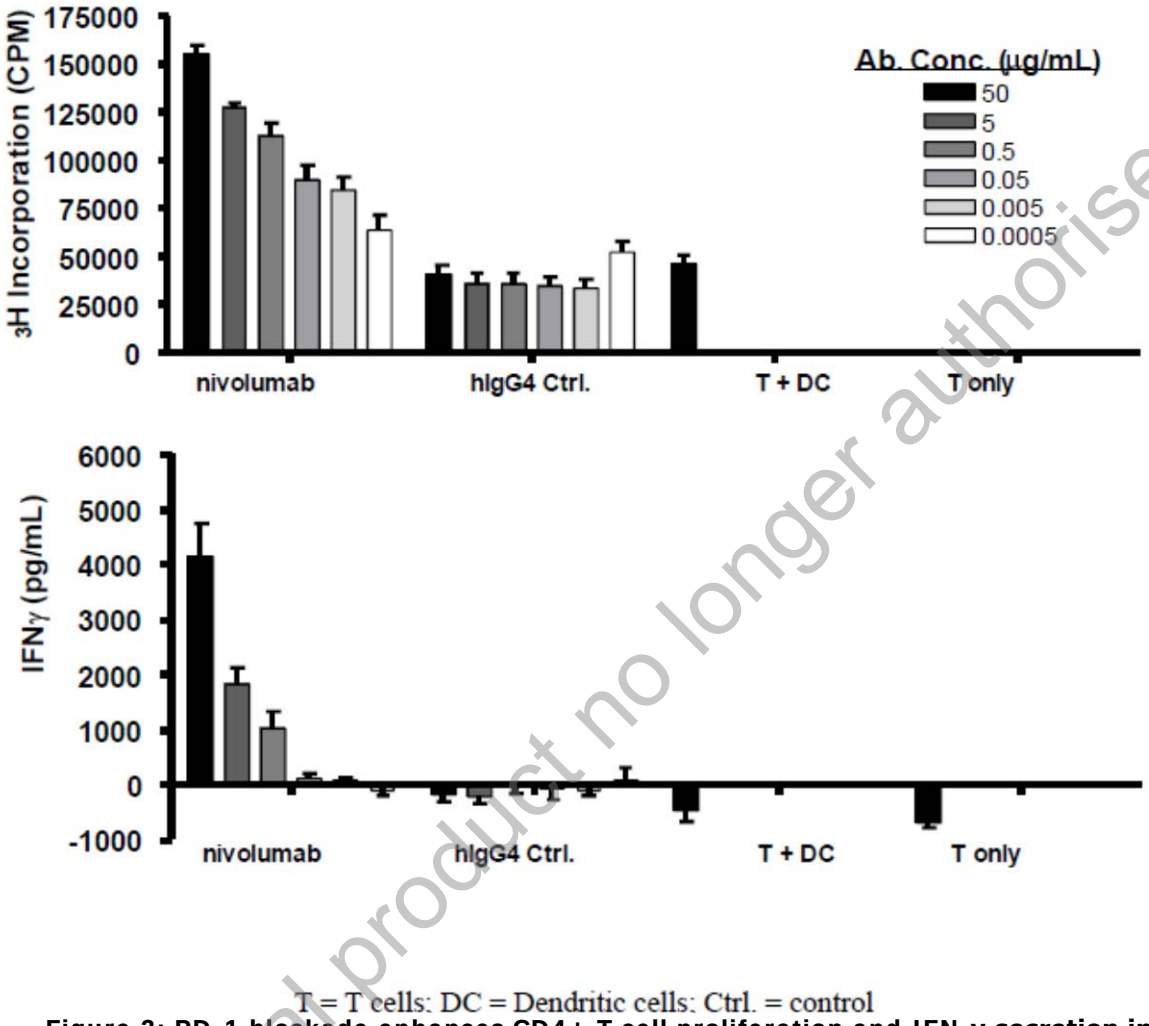
Binding of nivolumab to activated human peripheral T cells (MDX-1106-025-R 930046580 and amendments)

To confirm binding of nivolumab to native PD-1, activated human peripheral T cells which upregulate PD-1 on the cell surface were used to test binding of nivolumab by flow cytometry. Nivolumab binds to native PD-1 molecules expressed on activated T cells with an EC50 of 0.64 nM. No binding of the isotype control IgG4 antibody was observed. Notably, no binding of nivolumab was detected to activated rat or rabbit T cells.

Functional activity of nivolumab in vitro

Studies were undertaken to establish that nivolumab can inhibit binding between PD-1 and ligands PD-L1 and PD-L2. In vitro assays were performed for MLR, tumour antigen-specific CD8+ T cell restimulations and viral antigen-specific responses to evaluate the functional effect of nivolumab.

- *Activity of nivolumab in the mixed lymphocyte reaction (MDX-1106-026R 930046581):* The effect of PD-1 blockade by nivolumab on the immune response was studied using the MLR in which CD4+ T cells recognize allogeneic monocyte-derived dendritic cells and results in T cell proliferation and cytokine secretion. Results are shown in Figure 3.



T = T cells; DC = Dendritic cells; Ctrl. = control

Figure 3: PD-1 blockade enhances CD4+ T cell proliferation and IFN-γ secretion in a dendritic cell-T cell MLR

- *Nivolumab enhances an antigen-specific recall response in vitro (MDX-1106-042R 930046579 and amendments):* The effect of nivolumab on an antigen-specific CD4+ T cell recall response was investigated using the response of human PBMC to a cytomegalovirus (CMV)-restimulation as assessed by secretion of IFN-γ. Nivolumab augmented IFN-γ secretion in response to stimulation by CMV antigen in a dose-dependent manner EC50 = 0.001 to 0.018 µg/mL (0.0067-0.12 nM). Maximum IFN-γ secretion was 2.5 to 5.3-fold more than CMV lysate stimulation alone.

- *PD-1 blockade and activation of HCV-specific T cells (MDX-1106-228R 930049318):* The effect of PD-1 blockade on the ability of HCV-specific CD8+ T cells to produce the cytokines IFN-γ and TNF-α was measured using an intracellular cytokine stain (ICS). HCV-seropositive donor PBMCs were cultured in vitro with HCV-specific peptide (4H) and nivolumab or hIgG4 isotype antibody for 6 days. The PBMCs were harvested and restimulated with HCV-specific peptide and assayed for cytokines in the CD8+ T cell subset using flow cytometry. The results shown in Figure 4

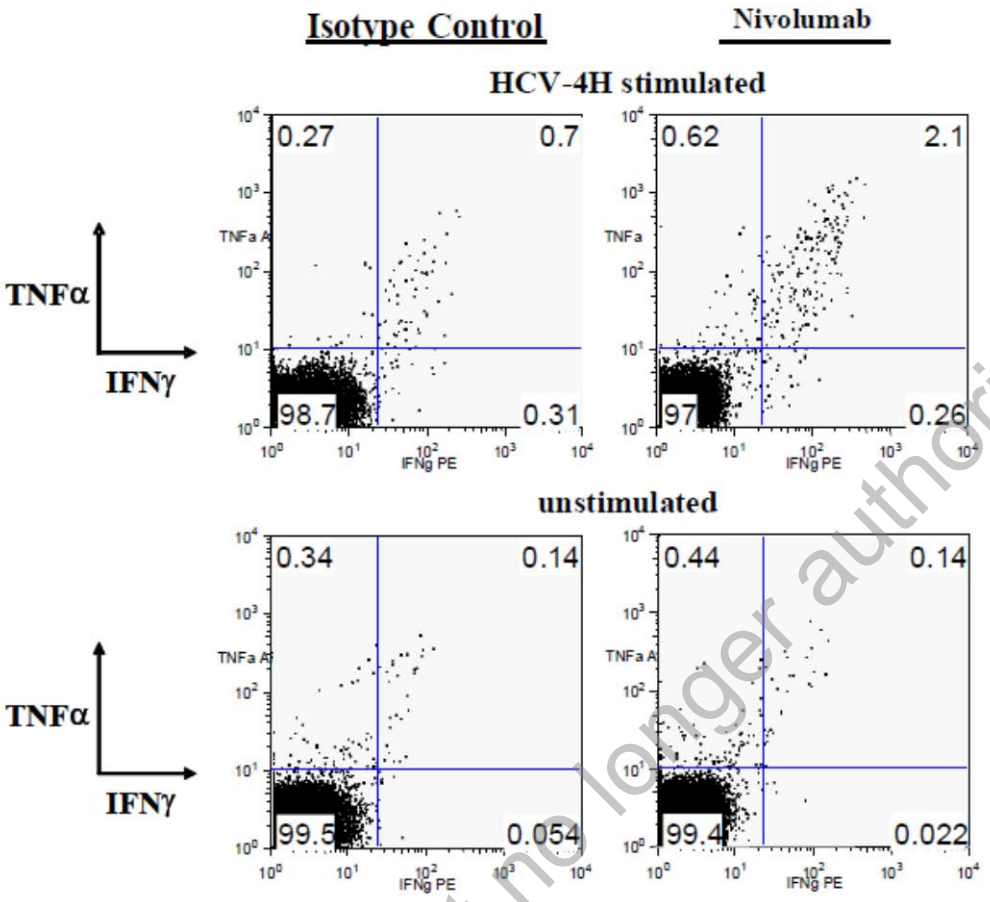


Figure 4: PD-1 blockade with nivolumab enhances IFN-γ and TNF-α production by HCV-specific CD8+ T cells in an ICS assay.

PD-1 blockade increases the frequency and absolute numbers of melanoma antigen-specific cytotoxic T lymphocytes

The applicant provided literature data to show that blocking PD-1 would result in an increase in antigen-specific cytotoxic T cells.[6]

In vitro activity of nivolumab in assays of antibody effector function

Antibody-dependent cell-mediated cytotoxicity (BDX-1106-320 930073399)

An antibody-dependent cell-mediated cytotoxicity (ADCC) assay using IL-2 activated PBMC was conducted to evaluate whether nivolumab could induce ADCC of target cells. Among four donors, nivolumab did not mediate ADCC of activated human PD-1+ CD4+ T cells at most concentrations with only minor lytic activity at high concentrations. The mean values of percentage of cell lysis for nivolumab were 3.6 and 1.2% at 12.5 and 50 µg/mL, whereas for the positive control anti-HLA-1 antibody (HLA1 IgG1) the cell lysis were 33.8 and 26.1% at the same concentrations.

[6] Wong RM; Scotland RR, Lau RL, et al. Programmed death 1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs. Int Immunol 2007;19:1223-34.

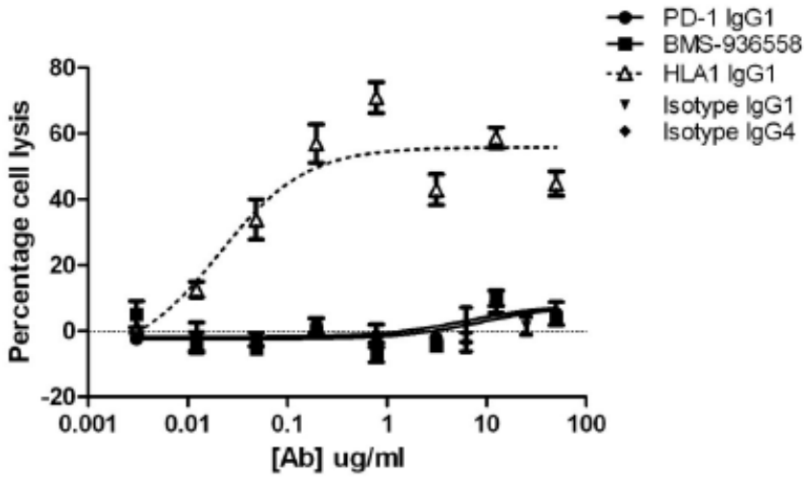


Figure 5: ADCC of Nivolumab on activated human CD4+ T cells

Complement-dependent cytotoxicity (MDX-1106-025R 930046580 and amendments)

Complement-dependent cytotoxicity (CDC) of nivolumab was examined using activated human PD-1+ CD4+ T cells. CDC studies demonstrated that, at concentrations up to 50 µg/mL, nivolumab did not elicit cytotoxicity of PD-1-expressing activated human CD4+ T.cells.

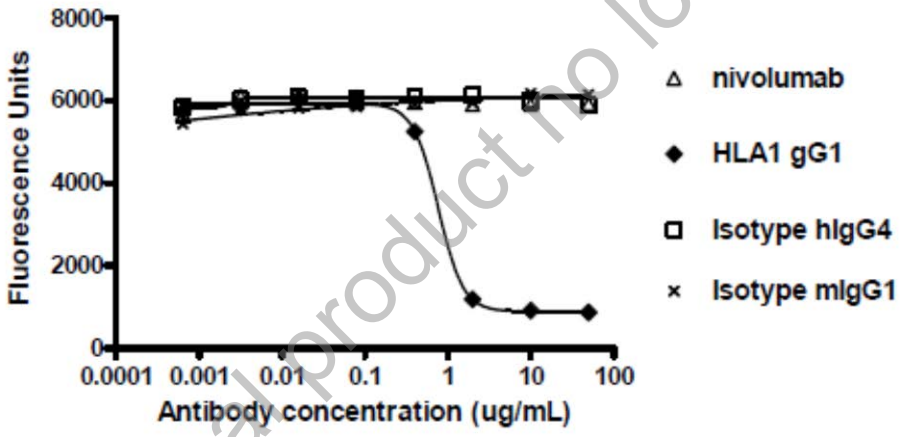


Figure 6: CDC of Nivolumab on Activated Human CD4+T cells

Effects of PD-1 blockade in tumour models (MDX-1106-028R 930046578)

The efficacy of PD-1 blockade on the growth of transplantable tumours in mice was tested. As nivolumab does not recognize mouse PD-1, a surrogate anti-mouse PD-1 antibody (clone 4H2; mouse IgG1 isotype) was derived and shown to bind to cells expressing murine PD-1 (EC50 = 2.9 nM) and block binding of mouse PD-L1 and PD-L2 to mouse PD-1, with an EC50 for blocking of 3.6 and 4.9 nM, respectively. The effects of 4H2 anti-PD-1 antibody blockade were tested in the following murine syngeneic tumor models: MC38 colon carcinoma, SA1/N fibrosarcoma, J558 melanoma, Renca kidney model, B16F10 melanoma, 4T1breast carcinoma, and CT26 colon carcinoma. The results are summarised in Table 2.

Table 2: Summary of key findings in in vivo studies with different tumour models

In Vitro Type of Study	Test System			Noteworthy Findings	Testing Facility	Report No.
Renca cells implanted into BALB/c mice using anti-PD-1 antibody; staged tumor study	Days 11, 14, 17, and 21	10 mg/kg of 4H2	Females 8 mice per group	No effect	Bristol-Myers Squibb	MDX-1106-036-R/ 930046562
4T1 cells implanted into BALB/c mice using anti-PD-1 antibody ; staged tumor study	Days 8, 11, 14 and 18 Saline 28 day study	10 mg/kg of 4H2	Females 9 mice per group	No effect	Bristol-Myers Squibb	MDX-1106-035-R/ 930046543
CT26 cells implanted into BALB/c mice using anti-PD-1 antibody; Staged	Days 10, 14, 17, and 21 Saline24 day study	10 mg/kg of 4H2	Females 10 mice per group	No effect	Bristol-Myers Squibb	MDX-1106-021-R/ 930046575 Amendment 01
B16F10 cells implanted into C57BL/6 mice using anti-PD-1 antibody; Staged	Days 8, 11, 14, and 17 Saline 28 day study	10 mg/kg of 4H2	Females 8 mice per group	No effect	Bristol-Myers Squibb	MDX-1106-020-R/ 930046576 Amendment 01
Sa1N cells implanted in A/J mice using anti-PD-1 antibody; staged tumor study	Days 7,10,13 and 16. Saline 41 day study	3 and 10 mg/kg of 4H2	Females 8 mice per group	Mean TGI on Day 20 was 31% for mice administered 10 mg/kg 4H2. Median TGI on Day 23 was 50% for mice administered 3 mg/kg 4H2 at and 16% for mice administered 10 mg/kg.4H2	Bristol-Myers Squibb	MDX-1106-013-R/ 930046563
Staged J558 cells implanted in BALB/c mice using anti-PD-1 antibody	Days 10, 13, and 17 Saline 38day study	10 mg/kg of 4H2	Females 8 mice per group	25% of the mice were tumor-free at the end of the study. Mean TGI on day 14 was 11% and median TGI on day 17 was 31%.	Bristol-Myers Squibb	MDX-1106-034-R/ 930046561 Amendment 01

The administration of anti-mouse PD-1 antibody 4H2 resulted in delayed tumor progression in the MC38, Sa1N, and J558 models, with complete tumor regressions observed in some individual mice in these studies. In these models, PD-1 blockade delivered at the time of tumor implantation (prophylactic or unstaged) or after tumors were established (therapeutic or staged) delayed or prevented the outgrowth of tumors. Four other syngeneic tumor models (Renca, 4T1, CT26, and B16F10) were refractory to anti-PD-1 treatment. In the Renca and 4T1 models, the prophylactic administration of an anti-PD-1 mAb did not impact tumor growth, and growth rates were nearly identical between the 4H2-treated and control groups. In the therapeutic B16F10 and CT26 models, the tumors grew very aggressively and 4H2 failed to significantly reduce the growth rate of established tumors.

MC38 model in C57BL/6 mice (MDX-1106-023R 930046542, MDX-1106-032R 930046566)

MC38 cells are colon adenocarcinoma cells derived from C57BL/6 mice that express PD-L1 *in vivo*, although *in vitro* expression of PD-L1 is very low. Two *in vivo* studies with MC38 tumours were conducted in mice. In both

studies mice were transplanted with an unstaged MC38 tumour (subcutaneous implantation of 2 million cells) and treated with control IgG or anti-PD-1 antibody 4H2 (nivolumab murine surrogate) at 10 mg/kg IP. In the first study each animal received the first antibody or control dose the same day of the tumour implantation, and additional doses on days 3 and 6 post-implantation. At day 21, 83% tumour growth inhibition was observed, with 30% of mice tumour-free at the study endpoint. In the other study, treatment with control IgG or anti-PD-1 antibody 4H2 was conducted on days 7 post-tumour implantation and again on days 10 and 13, resulting in a mean tumour growth inhibition of 62% at day 13 and a median growth inhibition of 76% by day 20.

Dose titration of anti-PD-1 antibody in the MC38 model (MDX-1106-200R 930046571)

A dose titration was performed with anti-PD-1 antibody to determine whether there is a relationship between dose and efficacy in a staged MC38 tumour model. With dosing on days 6, 10 and 13 post-implantation, antitumor responses were most potent at 30 mg/kg and little difference was observed between animals treated with 3 and 10 mg/kg/dose. Results are shown in table 3.

Table 3: Median tumour volume over time in a staged MC38 model (dose titration)

	Day 6	Day 13		Day 20		Day 59
Treatment	Mean Tumor Volume (mm^3)	Mean Tumor Volume (mm^3)	Mean % TGI	Median Tumor Volume (mm^3)	Median % TGI	% Mice Tumor-Free
m-IgG1-10 mg/kg + r-IgG1-10 mg/kg	93.56	580.6	N/A	1566.0	N/A	0
4H2-10 mg/kg + r-IgG1-10 mg/kg	96.67	204.4	65	190.3	88	0
4H2-3 mg/kg	85.13	205.0	65	632.0	60	20
4H2-10 mg/kg	84.22	229.7	60	505.0	68	10
4H2-30 mg/kg	83.64	150.3	74	70.0	96	10

Secondary pharmacodynamic studies

The applicant did not submit secondary pharmacodynamic studies (see non-clinical discussion).

Safety pharmacology programme

In the single-dose cardiovascular safety study, groups of 6 telemetered Cynomolgus monkeys (3 per sex) were administered 0 (vehicle control), 10, or 50 mg/kg nivolumab intravenously. Both were well tolerated and there were no nivolumab-related effects on clinical signs, body weights, cardiovascular parameters, or body temperature. In repeat-dose toxicity studies, weekly (QW) or 2QW IV doses of nivolumab were administered for 1 or 3 months, respectively, at dose levels up to 50 mg/kg. No nivolumab-related clinical signs of toxicity or effects on body weight, food consumption, blood pressure, heart rate, respiration rate, or ophthalmic or electrocardiographic parameters were observed.

Pharmacodynamic drug interactions

The pharmacodynamics activity of nivolumab in cynomolgus monkeys was evaluated in combination with anti-CTLA (ipilimumab) and anti-LAG-3 (BMS-986016) monoclonal antibodies.

Combination study of nivolumab and ipilimumab (SUV00106 930036346)

The pharmacodynamic activity of nivolumab when administered in combination with ipilimumab was studied in a 1-month combination study in cynomolgus monkeys which included an assessment of the Immune function was evaluated by measurement of antibody response to keyhole limpet haemocyanin (KLH) (study SUV00106). Immunophenotypic analyses of peripheral blood were conducted at different intervals to identify changes in the composition of immune cells. This study included 5 animals/sex/group treated at 3 mg/kg ipilimumab and 10 mg/kg nivolumab or 10 mg/kg ipilimumab and 50 mg/kg nivolumab infused IV once weekly for 4 consecutive weeks.

The high dose combination showed variable but significant increases in the number and frequency of peripheral blood CD3+CD4+ T cells and CD3+CD8+ T cells on day 7, whereas no changes were observed in the number or frequency of monocytes or natural killer cells. Similar changes were observed in the 3-month toxicity study with nivolumab alone (study WIL-552003). In addition, an increased incidence of immune-mediated adverse effects (GI toxicity/colitis) was also observed in this combination study, which was consistent with the observed potentially enhanced T cell numbers and activity.

Combination study of nivolumab and BMS-986016 (DN12123 930070016)

In a 1-month combination study, nivolumab (50 mg/kg) or BMS-986016 alone (30 and 100 mg/kg) and in combination (50 mg/kg nivolumab and 100 mg/kg BMS-986016) were administered to monkeys (5/group/sex) for a total of 5 weekly doses. Serum nivolumab exposures when administered in combination with BMS-986016 were comparable to exposures observed when nivolumab was administered alone. There were no nivolumab-related changes in T-cell dependent antibody responses to KLH and hepatitis B surface antigen (HBsAg), ex vivo recall responses to KLH in CD8+CD4- T cells or HBsAg in CD4+CD8+ or CD8+CD4- T cells. However, nivolumab alone and in combination with BMS-986016 caused increases in immune cell parameters, consistent with pharmacological mechanisms of action of nivolumab and BMS-986016. In both cases, cytokine production was greater in the combination group than in the monotherapy groups.

2.3.3. Pharmacokinetics

The cynomolgus monkey was determined to be a relevant animal species because nivolumab binds to cynomolgus monkey PD-1 receptor. Therefore, all pharmacokinetic studies were conducted in cynomolgus monkeys. Since the intended route of administration in patients is intravenous, nivolumab was administered IV in all nonclinical studies as a solution in 20 nM sodium citrate, 50 nM sodium chloride, 20 µM diethylenetriamine pentacetic acid (DTPA), 3% mannitol, 0.01% polysorbate 80 (pH 6). This was similar to the clinical formulation.

Table 4: Pharmacokinetic data of nivolumab

Study ID	Species	N	Dose (mg/kg)	Route	Cmax (µg/mL)	Tmax (h)	AUC∞ (µg·h/mL)	T½ el (h)
SUV00027	monkey	3/sex	1	IV	♂34.3±2.2	0.25-0.5	4470±423	124±20.3
					♀30.6 ±1.71	0.25	4050±616	139±12.7
		3 males	10		343±21.6	0.25-0.5	64200±27400	261±226
SUV00025	monkey	5/sex/group	1	IV	♂22.0±4.34[a]	NC	1740±411[b]	148±34.5
					♀23.1±3.37[a]	NC	2040±370[b]	146±25.5
			10		♂288±40.1[a]	NC	23800±1650[b]	267±104
					♀255±40.3[a]	NC	21600±2950[b]	223±37.5
			50		♂1120±133[a]	NC	91700±9070[b]	238±94.5
					♀1200±131[a]	NC	109000±14200[b]	260±133

a: concentration at 0.25 hours after dosing
b: AUC (0-168h). AUC∞ not reported because data was only collected for a period equivalent to approximately a single t½.

In study SUV00027, consistent with the long t½, total serum clearance (CLT) was low (0.172-0.250 mL/h/kg), with slightly more rapid clearance after 1 mg/kg doses than after the 10 mg/kg doses in males. The volume of distribution at steady state (Vss) was low, with values of 0.046-0.06 L/kg at all doses. For study SUV00025, consistent with the long t½, CTLs were 0.266-0.323 mL/h/kg at 1 mg/kg and 0.161-0.222 mL/h/kg at higher doses.

The applicant did not submit distribution, metabolism and excretion studies (see non-clinical discussion).

2.3.4. Toxicology

The nonclinical toxicity studies of nivolumab were performed in a battery of nonGLP studies, and GLP- and ICH-compliant *in vitro* tissue binding studies in multiple species and *in vivo* toxicology studies in cynomolgus monkeys.

Single dose toxicity

A single-dose IV of nivolumab at dose levels of 1 or 10 mg/kg was administered in cynomolgus monkeys.

Table 5: Single dose toxicity studies with nivolumab in Cynomolgus monkeys

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
SUV00027/GLP	Cynomolgus monkey	1-10, 3/s/g low 3M high	NA/10	None

All animals survived the study, and no effect of nivolumab was observed on clinical observations, body-weight measurements, food consumption, or clinical pathology parameters.

Repeat dose toxicity

A 1- and 3-month IV repeat-dose toxicity studies of nivolumab were conducted in cynomolgus monkeys.

Table 6: Overview of repeat dose toxicity studies in Cynomolgus monkey including major study findings

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL	Major findings
SUV00025/ GLP	Cynomolgus monkey, 5/s/g	0-1-10-50/ IV QW	30d	50 mg/kg	No major findings
WIL-552003/GLP	Cynomolgus monkey, 6/s/g	0-10-50/ IV /2QW	3 months	50 mg/kg	**Clinical observation** ≥10F:Slight increase in occurrence of soft feces, **Microscopy** ≥10M/F: Slight increase in incidence of mononuclear infiltrate in Heart, Kidney and Liver from minimal up to (on occasion) moderate severity, Slight increase in chronic inflammation of lungs minimal to mild ≥10M: Heart mononuclear infintrate minimal 50% both groups **Serum chemistry** =50M:↓Phos slight, =50F: ↓T3 **Cytometry** **=50:** ↑CD8 effector memory, ↑CD4+ effector memory, ↑CD8+ central memory **Other** Almost all male animals have immature epididymis, prostate, testes

In the 1-month toxicity study in cynomolgus monkeys, 5 weekly IV doses of nivolumab were administered at dose levels of 0 (vehicle control), 1, 10, or 50 mg/kg. There were no nivolumab-related clinical signs or changes in body weight; food consumption; blood pressure; heart and respiration rates; ophthalmic or electrocardiographic parameters; clinical pathology parameters (serum chemistry, hematology, coagulation, thyroid hormone, urinalysis, or urine chemistry); or gross or microscopic pathology findings. In addition, there were no nivolumab-related changes in immune cell parameters.

In the 3-month toxicity study in cynomolgus monkeys, IV doses of nivolumab were administered 2QW (for a total of 27 doses) at dose levels of 0 (vehicle control), 10, or 50 mg/kg. There were no nivolumab related effects on body weight, cardiovascular, neurologic, respiratory, ophthalmic, urinalysis, hematologic, or organ weight parameters, and no gross or microscopic pathology findings.

Genotoxicity

The applicant did not submit genotoxicity studies (see non-clinical discussion).

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction Toxicity

In the ePPND study, nivolumab was administered 2QW at 10 or 50 mg/kg to pregnant monkeys from GD 20 to 22 until parturition. Nivolumab was well tolerated at both doses and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints, or clinical/anatomic pathology parameters in these females throughout the study. However, in the offspring, maternal nivolumab administration at both doses was associated with fetal/neonatal mortality characterized by: 1) dose-dependent increases in third trimester fetal losses (12.5% and 33.3% at 10 and 50 mg/kg, respectively, relative to 7.1% in controls), which occurred predominately after GD 120; and 2) increased neonatal mortality at 10 mg/kg, which was noted in 3 infants with extreme prematurity during the first 2 postnatal weeks. The cause(s) of these fetal losses and infant prematurity could not be determined. The remaining offspring of nivolumab-treated females survived to scheduled termination and there were no nivolumab-related effects on any of the parameters evaluated throughout the 6-month postnatal period.

Table 7: Overview of reproductive toxicity studies conducted with nivolumab in nonhuman primates

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings
ePPND/DN12001	Cynomolgus; 16F/g	0-10-50 2QW	GD20-parturition	**Clinical observations** ≥10F: ↑Stillbirths on/after GD140 =50F: ↑Abortions before GD140 **Hematology** =10F: ↑RBC slight =50F: ↑LUC (NS high variance) **Serum chemistry** =50 pooled infants: ↑Phos d84 slight but not d182, ↑AST d182 slight, ↑Ca d182 minimal, **Cytometry** =50F: ↓cytotoxic activated lymphocytes NS high variance, ≥10 pooled infants: ↑T-lymphocytes NS high variance BD84, @50 elevated at BD182 NS, =50 pooled infants:↑T-helper regulatory cells at BD182, ↑Cytotoxic t-regulaotr lymphocytes and trend at 10mg/kg **Gross pathology** =50 male infants: ↑prostate **Mortalities** =10 infant M: 3xUnscheduled necropsy d1-13 (premature)

Table 8: Summary of pregnancy and infant losses

Nivolumab Dose	Nivolumab Dose (mg/kg)			Historical Controls[a]	
	0 (Control)	10	50	Overall Incidence (%)	Incidence Range (%)
First trimester (GD 20-50) loss	2/16 (12.5%) GD 33, 47	0	3/16 (18.8%)[b] GD 31, 32, 33	7.7	0-16.7
Second trimester (GD 51-100) loss	0	0	0	1.5	0-11.1
Third trimester (> GD 100) loss	1/14 (7.1%) GD 121	2/16 (12.5%) GD 124, 158	4/12 (33.3%) GD 113, 127, 161, 167	15.7	0-31.3
Infant loss	2/13 (15.4%) GD 138/BD 16 GD 153/BD 32	3/14 (21.4%)[c] GD 131/BD 1 GD 135/BD 1 GD 143/BD 13	0	11.2	0-20.0
Surviving infants	11	10	8	NA	NA

Abbreviation: NA = Not applicable.
For pregnancy loss, GD xx = Gestation day when pregnancy loss was first noted.
For infant loss, GD xx/BD xx = Gestation length/day of infant loss after birth.
a The first trimester results were based on control data from 6 embryo-fetal development studies (2006 to 2012) and 12 ePPND (2008 to present) studies conducted at the Testing Facility; results for all other periods/parameters were based on control data from12 ePPND studies.
b Excluded 1 embryonic loss caused by umbilical thrombus and was unrelated to nivolumab treatment.
c Excluded 1 infant loss, that occurred under ketamine sedation for blood sampling and was unrelated to nivolumab treatment.

Studies in juvenile animals

The potential developmental effects of nivolumab were examined in the ePPND study that included assessments in infant monkeys up to 6 month old. In addition, pivotal toxicity studies up to 3 months in duration included cynomolgus monkeys as young as 2 years of age, which is approximately equivalent to a 6-year-old human. No developmental effects were observed in the pivotal intermittent-dose toxicity studies, and no developmental effects were observed in the surviving infants in the ePPND study.

Toxicokinetic data

Table 9: TK data in nivolumab 1-month repeat dose study (SUV00025)

Parameter	Day	Nivolumab Dose					
		1 mg/kg		10 mg/kg		50 mg/kg	
		Males	Females	Males	Females	Males	Females
C(0.25h) (µg/mL)	1	22.0[a]	23.1[a]	288[a]	255[a]	1,120[a]	1,200[a]
	22	27.9/33.5[b]	21.4/27.8[b]	411/496[b]	496[a]	1,930/2,150[b]	2,230[a]
AUC(0-168h) (µg•h/mL)	1	1,740[a,c]	2,040[a,c]	23,800[a,c]	21,600[a,c]	91,700[a,c]	109,000[a,c]
	22	3,060[d]/ 3,820[b,c]	2,120[e,f]/ 2,850[b,e]	36,700[g]/ 45,700[b,h]	51,200[a,c]	196,000[h] 242,000[b,c]	224,000[a,c]

a No anti-nivolumab antibodies were detected.
b Means were calculated with the inclusion/exclusion of data from animals with detectable anti-nivolumab antibodies.
c Mean systemic exposures were averaged from individual AUC(0-168h) values.
d Mean systemic exposures were averaged from individual AUC(0-2h) and AUC(0-168h) values.
e Mean systemic exposures were averaged from individual AUC(0-24h) and AUC(0-168h) values.
f N = 4 because all of individual concentrations in Animal No. 2504 were less than the detection limit (1 µg/mL).
g Mean systemic exposures were averaged from individual AUC(0-24h), AUC(0-72h), and AUC(0-168h) values.
h Mean systemic exposures were averaged from individual AUC(0-72h) and AUC(0-168h) values.

Table 10: TK data in nivolumab 3-month repeat dose study (WIL-552003)

Parameter	Week	Nivolumab	
		10 mg/kg 2QW	50 mg/kg 2QW
Cmax[a] (µg/mL)	13	801	3,610
AUC(0-168h) (µg•h/mL)	13	117,000	531,000

a Cmax values were estimates of time 0 (i.e., initiation of dosing).

Local Tolerance

The local tolerance of nivolumab was assessed in single- and repeat-dose IV studies (QW, 2QW, and monthly) in monkeys. Nivolumab was administered at up to 50 mg/kg/dose. No irritation or local tolerance issues were observed.

Other toxicity studies

Immunogenicity

Nivolumab was immunogenic in study SUV00027, with 5 of 6 animals at 1 mg/kg and 2 of 3 animals at 10 mg/kg tested positive for anti-drug antibodies 27 days after dosing. There was no apparent effect of these antibodies on the PK of nivolumab.

Nivolumab binds cynomolgus monkey PD-1 and human PD-1 with similar affinities (KD of 3.06 nM to human PD-1 and 3.92 nM to cynomolgus monkey PD-1), and exhibits pharmacologic activity in humans and monkeys, but nivolumab does not bind homologous PD-1 in other traditional toxicology species (eg, rat, rabbit).

2.3.5. 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.

2.3.6. Discussion on non-clinical aspects

The similarities in tissue binding profiles between cynomolgus monkeys and humans indicate that the cynomolgus monkey was an appropriate animal model for preclinical toxicity testing of nivolumab. In contrast, cross-reactivity studies conducted with rat and rabbit PD-1 showed no binding.

The applicant did not submit studies on distribution, metabolism and excretion. This is acceptable as in accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6), no tissues distribution studies, metabolism studies, mass balance are considered necessary. The single-dose PK of nivolumab in cynomolgus monkeys were characterized by a long t½, a low CLTs and a low distribution volume at the Vss which are characteristics for a mAb. The metabolism and clearance of nivolumab *in vivo* is expected to follow the degradation route of Abs in general, via biochemical pathways that are independent of metabolising enzymes. Formal distribution studies with nivolumab were not conducted. The low volume of distribution ranging between 0.046-0.071 L/kg at steady state suggests that most of the monoclonal antibody remains in the bloodstream. While there was no accumulation of the mAb at 10mg/kg/month, accumulation was apparent at 1 to 50 mg/kg given weekly or bi-weekly in animals not positive for ADA. When ADA are not predominant, kinetics are typical for IgG/FcRn mediated elimination with long half-lives of 5.2-11.1 days and slow clearance 0.16-0.32mL/h/kg.

The apparent elimination half-life of nivolumab in cynomolgus monkeys following a single IV dose of 1 mg/kg was 124 to 148 hours and was longer with higher doses. Consistent with the long half-life, the total serum clearance after a single dose of nivolumab was low (0.16-0.32 mL/h/kg). The steady state volume of distribution was similar to the reported plasma volume of monkeys (0.046-0.071 L/kg), suggesting that nivolumab remains mainly in the vascular system.

Since nivolumab is a monoclonal antibody and does not belong to a class of medicinal products expected to cause cardiovascular effects, specific safety pharmacology studies were limited to a single-dose cardiovascular safety study in Cynomolgus monkeys. This limited safety pharmacology evaluation of nivolumab is supported by ICH guidelines S6(R1), S7A, and S9, which do not require specific safety pharmacology studies for biotechnology-derived products, such as monoclonal antibodies, or for anticancer pharmaceuticals. It is considered that for this type of product, the lack of studies for secondary pharmacodynamics are acceptable.

In the repeat toxicity studies, serum chemistry changes were limited to a 28% decrease in mean plasma triiodothyronine (T3) levels at 50 mg/kg in female monkeys at the end of the 3-month dosing phase of the study with complete recovery after a 4-week dose-free period. The relevance of the lower T3 levels in females, in the absence of any correlative changes in other hormones or in the thyroid or pituitary gland, is unknown but does not cause any particular concern.

The applicant did not submit studies for genotoxicity, carcinogenicity as well as fertility and early embryonic development. According to ICH guideline S6(R1) "Preclinical safety evaluation of biotechnology-derived pharmaceuticals" (EMA/CHMP/ICH/731268/1998), these studies are not required and are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH guideline S9 "Nonclinical evaluation for anticancer pharmaceuticals" EMEA/CHMP/ICH/646107/2008), the lack of studies is acceptable.

In repeat-dose toxicity studies, no nivolumab-related gross or microscopic pathology changes were observed. Pivotal 1- and 3-month IV repeat-dose toxicity studies of nivolumab alone were conducted in cynomolgus monkeys. The product was well tolerated, with no adverse effects at doses ≤50 mg/kg administered up to one month once a week or 3 months twice a week. In the 1-month study, while PD-1 receptor occupancy was demonstrated throughout the dosing phase, no changes in peripheral blood immune cell subpopulations were observed. In the 3-month study, changes in immune cell parameters were observed, demonstrating that nivolumab elicited pharmacological responses in healthy monkeys.

Regarding reproductive toxicity, the ePPND study was conducted following the recommendations included in the PIP P/0064/2014 agreed with the EMA on March 2014 with the non-clinical working group of the PDCO. Nivolumab was administered 2QW at 10 or 50 mg/kg to pregnant monkeys from GD 20 to 22 until parturition. Nivolumab was well tolerated and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints or clinical/anatomic pathology parameters in dams throughout the study. However, in the offspring, maternal nivolumab administration was associated with foetal/neonatal mortality, with dose-dependent increases in third trimester foetal loses and increased neonatal mortality at 10 mg/kg during the first 2 postnatal weeks. The cause of these foetal losses and infant prematurity could not be determined. However, a relationship between pregnancy failure and a break in tolerance by the abrogation of PD-1 signalling by nivolumab cannot be ruled out. This information is stated in section 5.3 and the potential risk to pregnant women is adequately addressed in section 4.6 of the SmPC. The risk of embryofoetal toxicity has been included in the RMP as an important potential risk.

No juvenile toxicity studies were conducted by the Applicant. In the ePPND study infant monkeys were assessed up to 6 month old, whereas in the pivotal toxicity studies some monkeys were 2 years old, approximately equivalent to a 6-year old human. No developmental effects were observed in any of these studies.

Considering the lack of irritation or local tolerance issues found in the repeat-dose toxicity studies in cynomolgus monkeys, no additional local tolerance studies are considered necessary.

As a selective immunomodulator, nivolumab is expected to elicit pharmacologically mediated effects on the immune system. Repeated administration of nivolumab alone for 3 months at ≥ 10 mg/kg produced pharmacologic effects on specific immune cell sub-populations, but no general nonspecific immunostimulatory or autoimmune-related toxicities were observed.

ADAs were detected in 4% of monkeys receiving 2QW doses of nivolumab, 20% to 53% of monkeys receiving weekly doses of nivolumab, and 67% of monkeys receiving monthly doses of nivolumab. Nivolumab concentrations were lower in animals with anti-nivolumab antibodies. ADA incidence was predominantly increased in the low dose groups, which may be a result of assay interference.

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.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for nivolumab, were considered adequate and acceptable for the assessment of non-clinical aspects. The lack of carcinogenicity, mutagenicity, fertility and early embryonic development were well justified. Based on cynomolgus monkey studies, there is a potential risk for foetal loss in the third semester in humans. In addition, the cynomolgus monkey model showed development of ADAs after repeat administration. These risks are adequately addressed in the SmPC and RMP.

2.4. Clinical aspects

2.4.1. 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

Table 11: Summary of Nivolumab Clinical Development Program in Previously Treated NSCLC

	Phase 2/3 Studies			Phase 1 Studies
NSCLC Histology	**SQ**		**NSQ**	**SQ + NSQ**
Study Number	**CA209063**	**CA209017**	**CA209057**	**MDX1106-03/ CA209003**
Study Population/Number Randomized or Treated	At least 1 platinum doublet-based chemotherapy and 1 additional systemic therapy	1 prior platinum doublet-based chemotherapy	1 prior platinum doublet-based chemotherapy	At least 1 prior systemic therapy
Number Randomized or Treated	N = 117 treated	N = 272 randomized; 259 treated	N = 582 randomized; 555 treated	N=129 treated (NSCLC cohort)
Study Design	Phase 2, single-arm	Phase 3, nivolumab vs. docetaxel	Phase 3, nivolumab vs. docetaxel	Phase 1b (expansion)
Nivolumab Regimen	3 mg/kg Q2W	3 mg/kg Q2W	3 mg/kg Q2W	1, 3, and 10 mg/kg Q2W
Primary Efficacy Endpoint	ORR (IRC-assessed)	OS	OS	ORR and DOR (sponsor-assessed)
Additional Efficacy Endpoints	ORR (investigator-assessed), DOR, TTR, PFS, OS, efficacy by PD-L1 expression	ORR (investigator-assessed), DOR, TTR, PFS, efficacy by PD-L1 expression	ORR (investigator-assessed), DOR, TTR, PFS, efficacy by PD-L1 expression	TTR, PFS, OS
Study Status	Completed analysis of primary endpoint; OS follow up ongoing	Enrollment completed Nov-2013; interim OS data availability event-driven (expected between 4Q 2014 and 1Q 2015)	Enrollment completed Nov-2013; interim OS data availability event-driven (expected between 4Q 2014 and 1Q 2015)	Completed analysis of primary endpoints; OS follow up ongoing

Abbreviations: 1Q, first quarter; 4Q, fourth quarter; DOR, duration of response; IRC, independent review committee; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death 1 ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; SQ, squamous; NSQ, non-squamous; TTR, time to response

Table 12: Summary of clinical studies contributing to pharmacology profiling of nivolumab

Study number	Treatment	Number of treated subjects	Pharmacology component
MDX1106-01 (CA209001) Phase 1	0.3, 1, 3, 10 mg/kg	39	Single dose PK popPK
MDX1106-03 (CA209003) Phase 1	0.1, 0.3, 1, 3, 10 mg/kg Q2W	306 NSCLC=129 Melanoma=107 RCC=34 CRC=19 mCPRC=17	Multiple dose PK Dose selection popPK Receptor binding T cell distribution ALC PD-L1 tumour tissue Exposure response immunogenicity
CA209009 *study ongoing*	0.3, 2, 10 mg/kg Q3W	91 RCC	PBMC Cytokine concentrations
CA209010 Phase 2	0.3, 2, 10 mg/kg Q3W	167 RCC	Sparse PK – popPK QTc prolongation
CA209063 **Phase 2** **(pivotal)**	**3 mg/kg Q2W**	**117 NSCLC**	Sparse PK – popPK immunogenicity
CA209037 **Phase 3** **(pivotal)**	**3 mg/kg Q2W**	**268 melanoma**	Sparse PK – popPK Exposure response immunogenicity
ONO-4538-01 Phase 1 Japanese	1, 3, 10, 20 mg/kg Q2W	17	Single dose PK and sparse PK for multiple dose - popPK
ONO-4538-02 Japanese	2 mg/kg Q3W	35 melanoma	Sparse PK - popPK

2.4.2. Pharmacokinetics

Absorption

Nivolumab is dosed via the IV route and therefore is completely bioavailable.

Distribution

Single Dose Pharmacokinetics: Study MDX1106-01

The single-dose PK of nivolumab was described by non-compartmental analysis (NCA) of data from 39 subjects in MDX1106-01 (also known as CA209001), which was a Phase 1 study in patients with selected refractory or

relapsed malignancies. The single-dose PK of nivolumab was determined from serum concentrations collected up to 85 days following single doses of 0.3, 1, 3 and 10 mg/kg, given as 1-hour IV infusion in MDX1106-01.

Following a single-dose IV administration of nivolumab ranging from 0.3 mg/kg to 10 mg/kg mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. Mean clearance and mean elimination half-life ranged from 0.13 to 0.19 ml/h/kg and between 17 and 25 days, across the range of 0.3 to 10 mg/kg dose.

Table 13: Summary of nivolumab single-dose pharmacokinetic parameters – Study MDX1106-01

Dose (mg/kg)	Cmax (µg/mL) Geo. Mean [N] (%CV)	Tmax (h) Median [N] (Min-Max)	AUC(0-T) (µg*h/mL) Geo. Mean [N] (%CV)	AUC(INF) (µg*h/mL) Geo. Mean [N] (%CV)	T-HALF (day) Mean [N] (SD)	CLT (mL/h/kg) Geo. Mean [N] (%CV)	Vz (mL/kg) Mean [N] (SD)
0.3	6.7 [6]	3.0[6]	970 [6]	2343 [3]	18.9 [3]	0.13 [3]	82.8 [3]
	(21.6)	(1.0-6.8)	(47)	(16)	(7.05)	(16.93)	(27.19)
1	16.0 [6]	1.9 [6]	3244 [6]	6014 [4]	17.0 [4]	0.17 [4]	99.6 [4]
	(32.1)	(1.0-7.0)	(62)	(30)	(2.36)	(29.80)	(23.04)
3	60.0 [5]	3.1 [5]	13909 [5]	15813 [5]	17.0 [5]	0.19 [5]	112.7 [5]
	(27.6)	(1.0-5.0)	(44)	(44)	(4.70)	(42.66)	(39.50)
10	196.3 [21]	1.6 [21]	55324 [21]	76541 [19]	24.8 [19]	0.13 [19]	109.4 [19]
	(19.5)	(0.9-7.0)	(39)	(27)	(7.22)	(28.42)	(26.70)

Abbreviations: Geo mean=geometric mean; CV=coefficient of variation; SD=standard deviation
Volume of distribution as estimated by popPK analysis was 8.00 L (35.3%).

Multiple-dose Administration: Study MDX1106-03

The multiple-dose PK of nivolumab given Q2W was assessed by NCA in MDX1106-03. Intensive PK serum concentration samples were collected from all subjects enrolled in 0.1, 0.3, and 1 mg/kg melanoma cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts over 336 hours (15 days) after first dose (Cycle 1) and ninth dose (Cycle 3). Limited PK samples were collected from all other pre-amendment 4 subjects and from all subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC in this study. Single samples were collected to evaluate serum concentrations of nivolumab at all follow-up visits.

The results from study MDX1106-03 is shown in Table 14.

Table 14: Summary of nivolumab multiple dose pharmacokinetic parameters – Study MDX1106-03

Nivolumab Dose	Dose Number	Cmax (μg/mL) GEO.MEAN[N] (%CV)	Tmax (h) MEDIAN[N] (MIN-MAX)	AUC(TAU) (μg*h/mL) GEO.MEAN[N] (%CV)	AI_Cmax GEO.MEAN[N] (%CV)	AI_AUC GEO.MEAN[N] (%CV)	CLT (mL/h) GEO.MEAN[N] (%CV)	Effective T-HALF (h) Mean [N] (SD)
0.1 mg/kg	First	1.9[15] (23.6)	1.1[15] (0.3-51.0)	279.4[13] (32.5)				
	Ninth	3.7[5] (42.2)	8.0[5] (0.6-24.0)	1104.4[4] (26.6)	2.3[4] (13.0)	3.1[4] (31.0)	8.3[4] (40.0)	622 [4] (235)
0.3 mg/kg	First	7.0[17] (32.3)	1.2[17] (0.9-24.3)	954.7[15] (26.9)				
	Ninth	17.8[2] (26.6)	24.7[2] (1.3-48.0)	3406.1[2] (12.8)	2.0[2] (26.7)	2.9[2] (6.1)	6.9[2] (17.8)	555 [2] (42)
1 mg/kg	First	19.6[17] (29.5)	1.2[17] (0.9-48.0)	3589.6[10] (23.8)				
	Ninth	46.9[10] (26.1)	1.0[10] (0.9-24.1)	10190.4[9] (25.8)	2.4[9] (21.4)	3.1[9] (34.7)	8.0[9] (31.1)	636 [9] (267)
3 mg/kg	First	61.3[13] (26.4)	2.1[13] (0.8-8.0)	8785.8[13] (22.7)				
	Ninth	132.0[7] (19.8)	4.0[7] (1.0-8.0)	30640.3[5] (17.5)	2.4[5] (13.6)	3.3[5] (25.5)	10.3[5] (18.1)	661 [5] (202)
10 mg/kg	First	191.2[14] (40.0)	3.9[14] (1.0-48.2)	31095.1[12] (25.4)				
	Ninth	475.0[5] (24.6)	22.3[5] (1.0-24.5)	99621.7[3] (26.0)	2.4[3] (12.6)	3.1[3] (11.0)	8.5[3] (6.4)	595 [3] (80)

The population PK analysis showed a 2-compartment PK model with first order elimination. Both the clearance and the volume in the central compartment on nivolumab increase with body weight (ranged from 34 to 162 kg with a mean weight of 81 kg). This fact has been addressed by means of weight normalized dosing.

Elimination

The mean terminal elimination half-life of nivolumab ranged between 17 and 27.5 days following single dose (study MDX1106-01) and Q2W administration (MDX1106-03) across the range of 0.1 to 10 mg/kg dose.

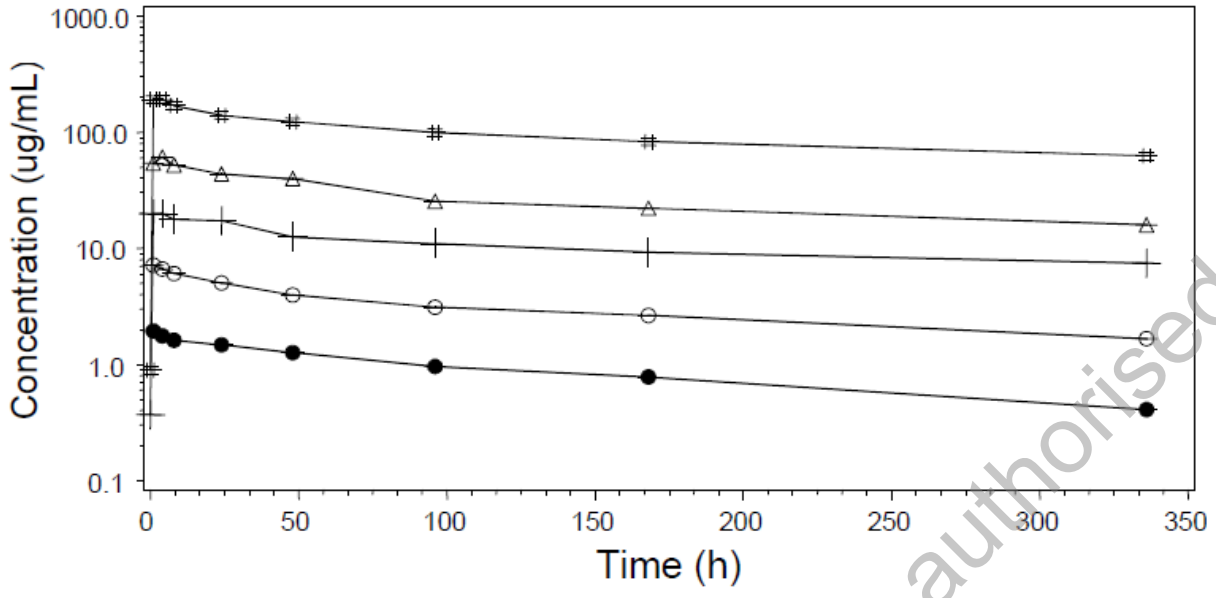
The geometric mean (%CV) of PopPK model-based estimates of individual nivolumab CL, volume of distribution at steady state (VSS), and terminal half-life were 9.5 mL/h (49.7%), 8.0 L (30.4%), and 26.7 days (101.0%), respectively. The typical clearance was 8.7 mL/h.

Metabolism

No formal studies were conducted as nivolumab is a human monoclonal immunoglobulin and not metabolized by cytochrome P450 enzymes, it is degraded to small peptides and individual amino acids.

Dose proportionality and time dependencies

The proportionality of the pharmacokinetics of nivolumab over the dose range 0.1 mg/kg-10 mg/kg was investigated in study MDX1106-03 and is presented in Figure 9. Following a one hour IV infusion, maximum concentrations of nivolumab were reached at median Tmax of 1.1 to 3.9h after Cycle 1/Day 1 dose.



0.1 mg/kg nivolumab (●); 0.3 mg/kg nivolumab (o); 1 mg/kg nivolumab (+); 3 mg/kg nivolumab (Δ); 10 mg/kg nivolumab (#)

Figure 7: Plot of Mean Nivolumab Serum Concentration Profile versus Time After First Nivolumab Dose - Study MDX1106-03

- **Time dependency**

Following Q2W administration, accumulation of nivolumab Cmin from first to ninth dose was in the range of 3.1 to 4.8, whereas accumulation of Ceoinf was in the range of 1.5 to 2.2.

Table 15: Summary of trough and end of infusion concentration values of nivolumab administered every two weeks – Study MDX1106-03

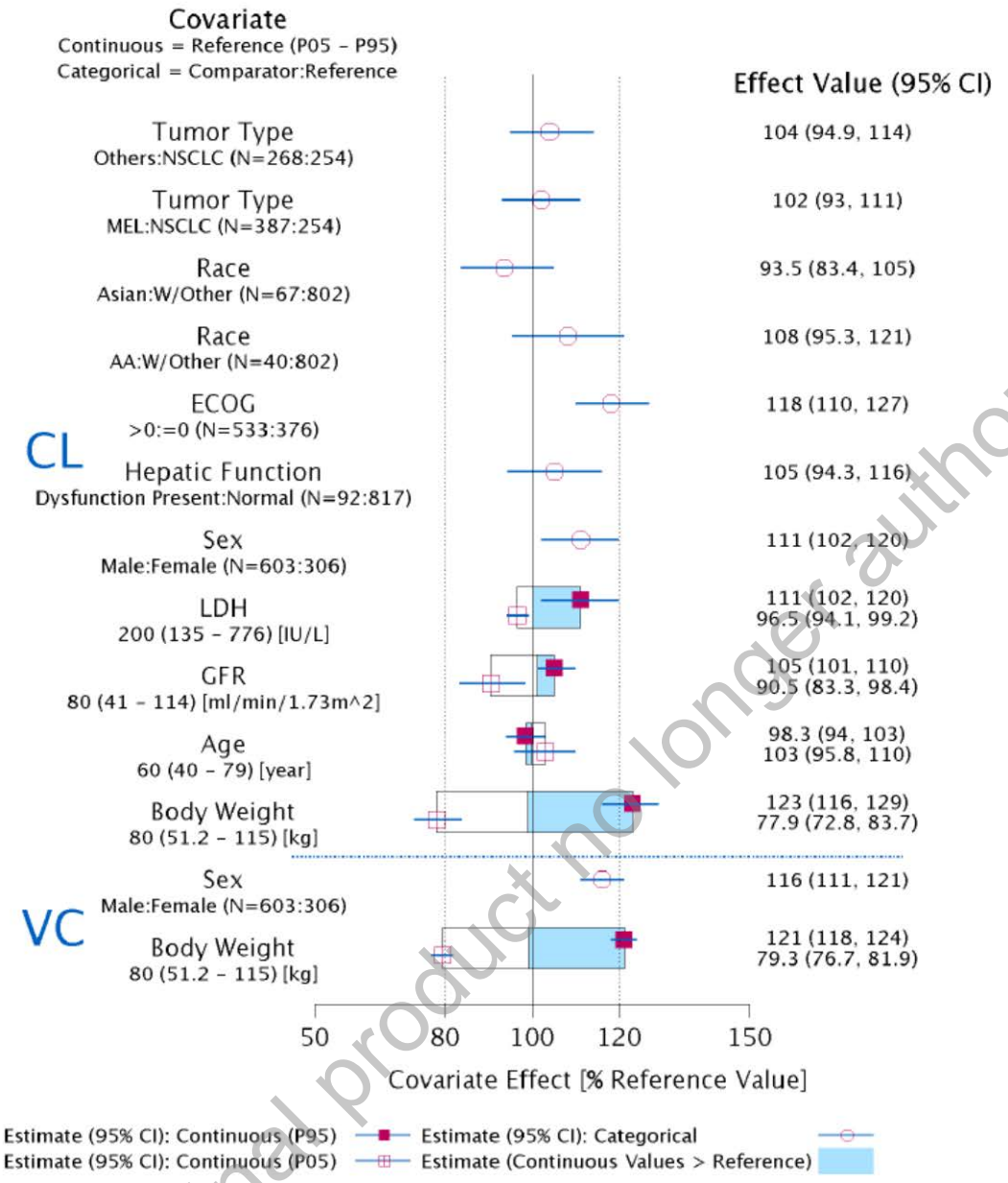
Nivolumab Dose	Dose Number	Cmin (µg/mL) GEO.MEAN[N] (%CV)	Ceoinf (µg/mL) GEO.MEAN[N] (%CV)	AI_Cmin GEO.MEAN[N] (%CV)	AI_Ceoinf GEO.MEAN[N] (%CV)
0.1 mg/kg	First	0.3[16] (56.9)	1.9[16] (27.7)		
	Ninth	2.5[7 (27.7)	2.8[4] (53.1)	4.8[7] (26.2)	1.5[4] (58.9)
0.3 mg/kg	First	1.4[15] (47.6)	6.9[18] (32.8)		
	Ninth	6.4[5] (47.1)	17.2[2] (31.3)	4.7[5] (102.3)	1.9[2] (31.5)
1 mg/kg	First	5.5[72] (42.8)	19.7[82] (31.3)		
	Ninth	19[35] (38.8)	39.7[38] (30.1)	3.1[35] (34.5)	1.9[36] (32.6)
3 mg/kg	First	16.6[46] (34.4)	58.6[50] (28.3)		
	Ninth	57[21] (35.9)	121.5[23] (20.7)	3.2[20] (25.3)	2.2[23] (49.4)
10 mg/kg	First	56.5[116] (30.6)	179.6[120] (26.3)		
	Ninth	188.8[44] (36.9)	331.4[43] (33.6)	3.2[44] (34.6)	1.8[42] (39.4)

Cmin and Ceoinf data shown are based on Day 1 samples, except for the Cycle1 Cmin which is based on Day 15 samples

Special populations

PopPK analyses

Population PK (popPK) analysis was based on intensive and sparse PK sampling mainly between Day 1 (Cycle 1) and Day 99 (Cycle 8) from 909 patients with solid tumours who received 3 mg/kg or 10 mg/kg Q2W during the dosing period (MDX1106-01, ONO-4538-01, ONO- 4538-02, MDX1106-03, CA209010, CA209063 and CA209037). The PopPK model parameters were estimated with precision, and the model evaluation demonstrated that there was good agreement between model predictions and observations (Figure 8).



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 CA/others female age=60 yr, ECOG=0, LDH=200 IU/L, GFR=80 ml/min/1.73m^2 and body weight=80kg, subject with normal hepatic function. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Figure 8: Covariate effect on PK model parameters (full PPK model)

Impaired renal function

Specific PK studies in patients with renal impairment were not conducted. Lack of effect of renal function (normal, mild or moderate) on the PK of nivolumab was obtained from the PopPK analysis. The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 m^2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m^2; n = 342) in population PK analyses. Limited data (n=2) were available for severe renal impairment assessment.

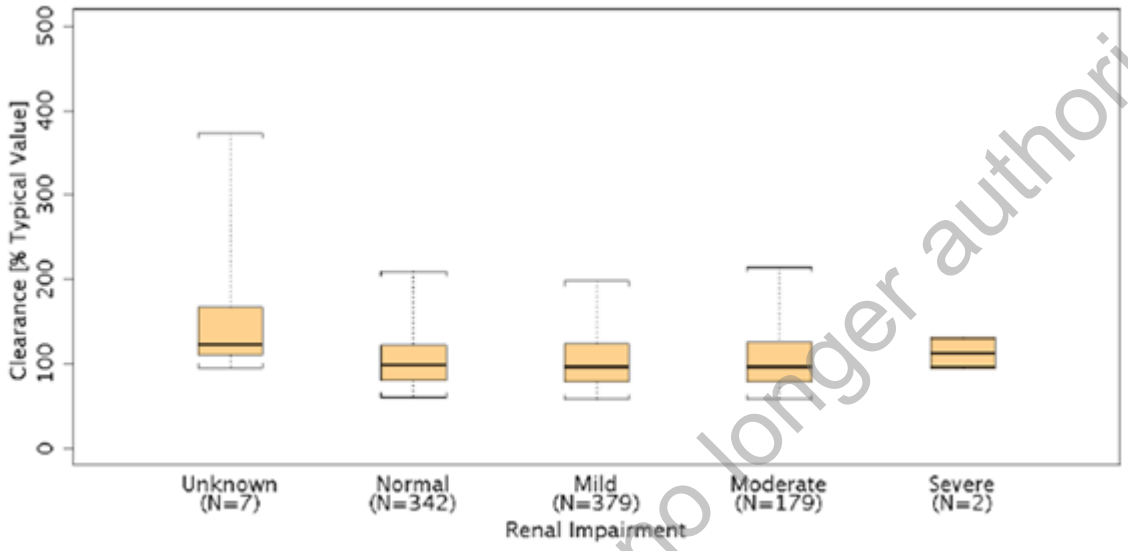


Figure 9: Boxplots showing the lack of relationship between renal function status and nivolumab exposure (dose normalised Cavgss) at Q2W dose regimen

Impaired hepatic function

The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see sections 4.2 and 5.2 of the SmPC).

- **Body Weight**

PopPK analysis with CDA209037 showed that both clearance (CL) and volume of central compartment (VC) increase with body weight. However, nivolumab exposures (dose normalized Cminss and Cavgss) are comparable across the range of body weight (34-162 kg) when administered based on mg/kg.

- **Elderly**

The number of subjects in different age groups by study is summarised in the table below.

Table 16: Summary of subjects in different age groups by study

	Total number of subjects	Number (%) of Subjects Age 65-74	Number (%) of Subjects Age 75-84	Number (%) of Subjects Age 85+	Total number of subjects age ≥ 65 (%)
CA209063	115	43 (37.39)	15 (13.04)	1 (0.87)	59 (51.30)
CA209037	232	48 (20.69)	28 (12.07)	3 (1.29)	79 (34.05)
CA209010	167	44 (26.35)	11 (6.59)	0 (0)	55 (32.93)
CA209003	304	87 (28.62)	47 (15.46)	3 (0.99)	137 (45.07)
CA209001	39	13 (33.33)	3 (7.69)	1 (2.56)	17 (43.59)
ONO-01	17	6 (35.29)	0 (0)	0 (0)	6 (35.29)
ONO-02	35	11 (31.43)	5 (14.29)	0 (0)	16 (45.71)
Total	909	252 (27.72)	109 (11.99)	8 (0.88)	369 (40.59)

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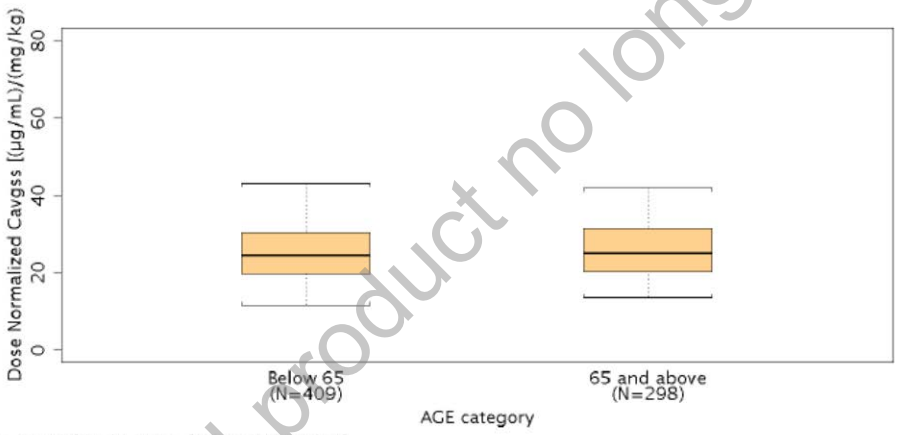
Program Source: Analysis-Directory/sp/scripts/sum-age.ssc
Source: Analysis-Directory/sp/export/ca209-mel-age-sum.xls

PopPK analysis including study CDA209037 showed that age was not a significant covariate on nivolumab CL. Nivolumab exposure (dose normalized Cavgss) was similar across the age ranging from 29 to 87 years.



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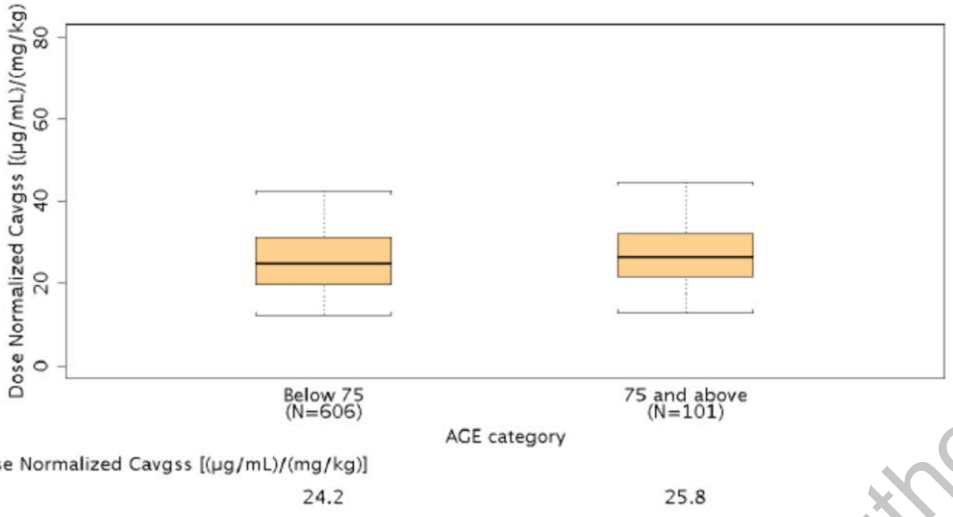
Program Source: Analysis-Directory/sp/scripts/age-category.ssc
Source: Analysis-Directory/sp/export/cavgss-vs-AGEC65.png

Figure 10: Comparison of model predicted Q2W dose normalised Cavgss between subjects <65 years old and ≥ 65 years old



Analysis-Directory: /global/pkms/data/CA/209/C07/prd/ppk_eud120/final/
Program Source: Analysis-Directory/sp/scripts/age-category.ssc
Source: Analysis-Directory/sp/export/cavgss-vs-AGEC75.png

Figure 11: Comparison of model predicted Q2W dose normalised Cavgss between subjects <75 years old and ≥ 75 years old

Pharmacokinetic interaction studies

The applicant did not submit drug-drug interaction studies (see pharmacology discussion).

Pharmacokinetics using human biomaterials

The applicant did not submit PK using biomaterials studies (see pharmacology discussion).

2.4.3. Pharmacodynamics

The PD effects of nivolumab were studied by assessing receptor occupancy (RO), peripheral immune cell population modulation, systemic cytokine modulation, and change in absolute lymphocyte count (ALC) in studies MDX1106-03 and/or CA209009.

Mechanism of action

PD-1 Receptor Occupancy by Nivolumab

PD-1 receptor occupancy by nivolumab was investigated in studies MDX1106-03 and CA209009. In study MDX1106-03, RO was determined in using frozen peripheral CD3+ T-cells from 65 melanoma subjects treated with one cycle (4 doses Q2W) of nivolumab at doses of 0.1 to 10.0 mg/kg. The median PD-1-receptor occupancy by nivolumab was 64 to 70% across all dose levels (Table 17).

Table 17: Receptor occupancy prior to fifth dose administration (all treated subjects with receptor occupancy) - Study MDX1106-03

Nivolumab Dose (mg/kg)	N	MEAN	SD	MEDIAN	MIN	MAX
0.1	11	61.12	11.761	64.1	29.8	73.8
0.3	11	63.81	8.338	63.9	52.0	80.6
1.0	21	66.00	8.919	65.0	48.9	85.0
3.0	12	67.39	10.792	67.8	51.1	84.6
10.0	10	69.52	9.045	70.1	57.1	81.9

In the nivolumab metastatic RCC study CA209009, receptor occupancy was assessed using fresh whole blood specimens. RO of >90% was achieved at one hour post nivolumab treatment at all dose levels, and remained near this level through Dose 8 Day 1.

Lymphocyte phenotype, absolute lymphocyte count, cytokine and chemokine modulation by nivolumab

Peripheral immune cell populations as measured by flow cytometry and change in ALC from baseline was evaluated in study MDX1106-03. The effect of nivolumab on cytokine modulation was assessed in CA209009 by measuring cytokine levels during the course of nivolumab treatment. The activated CD8+ T-cell mean changes by nivolumab dose were on average 3.8%, 0.4%, 2.3%, 5.8%, and 0.1% for 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. No meaningful rise over baseline was observed in mean ALC.

The effect of nivolumab on cytokine modulation was assessed in CA209009 by measuring cytokine levels during the course of nivolumab treatment. Nivolumab was administered at 0.3, 2 and 10 mg/kg dose levels every three weeks. Cytokine levels were measured at Dose 1 (0, 3, 7, 24 hr), Dose 2 (0, 168 hr), Dose 4 (0 hr), Dose 7 (0,168 hr) and Dose 8 (0 hr). The study showed that IL-1A, IL-1B, INF-γ, TNF-α, IL-12P and IL-23M were found to be below the lower limit of quantification. The levels of IL-6, IL-10 and IL-2 soluble receptor α showed transient changes but these were not consistent between individuals. The levels of CXCL-9 and CXCL-10 increased from baseline across any treatment dose group.

Primary and Secondary pharmacology

PD-1 Receptor Occupancy by Nivolumab

PD-1 RO by nivolumab was investigated in studies MDX1106-03 and CA209009. In study MDX1106-03, RO was determined in using frozen peripheral CD3+ T-cells from 65 melanoma subjects treated with one cycle (4 doses Q2W) of nivolumab at doses of 0.1 to 10.0 mg/kg. The median PD-1-receptor occupancy by nivolumab was 64 to 70% across all dose levels (Table 18). These results demonstrate that the majority of PD-1 receptors are bound by nivolumab at the lowest dose tested (0.1 mg/kg). Increasing doses up to 10.0 mg/kg did not substantially increase PD-1 receptor occupancy at the time point tested.

Table 18: Receptor Occupancy Prior to Fifth Dose Administration - All Treated Subjects with Receptor Occupancy - Study MDX1106-03

Nivolumab Dose (mg/kg)	N	MEAN	SD	MEDIAN	MIN	MAX
0.1	11	61.12	11.761	64.1	29.8	73.8
0.3	11	63.81	8.338	63.9	52.0	80.6
1.0	21	66.00	8.919	65.0	48.9	85.0
3.0	12	67.39	10.792	67.8	51.1	84.6
10.0	10	69.52	9.045	70.1	57.1	81.9

In the nivolumab metastatic RCC study CA209009, RO was assessed using fresh whole blood specimens. RO of peripheral CD3+ T cells (and CD4+ or CD8+ subsets) was measured at baseline and at six timepoints following initiation of nivolumab treatment (Dose 1-1H, Dose 2-0H, Dose 4-0H, Dose 7-0H, Dose 7-1H, Dose 8-0H). Kinetics of RO were similar across all dose cohorts (0.3 mg/kg, 2 mg/kg, 10 mg/kg, 10 mg/kg-treatment naive) (Figure 12) Receptor occupancy of >d90% was achieved at one hour post nivolumab treatment at all dose levels, and remained near this level through Dose 8 Day 1.

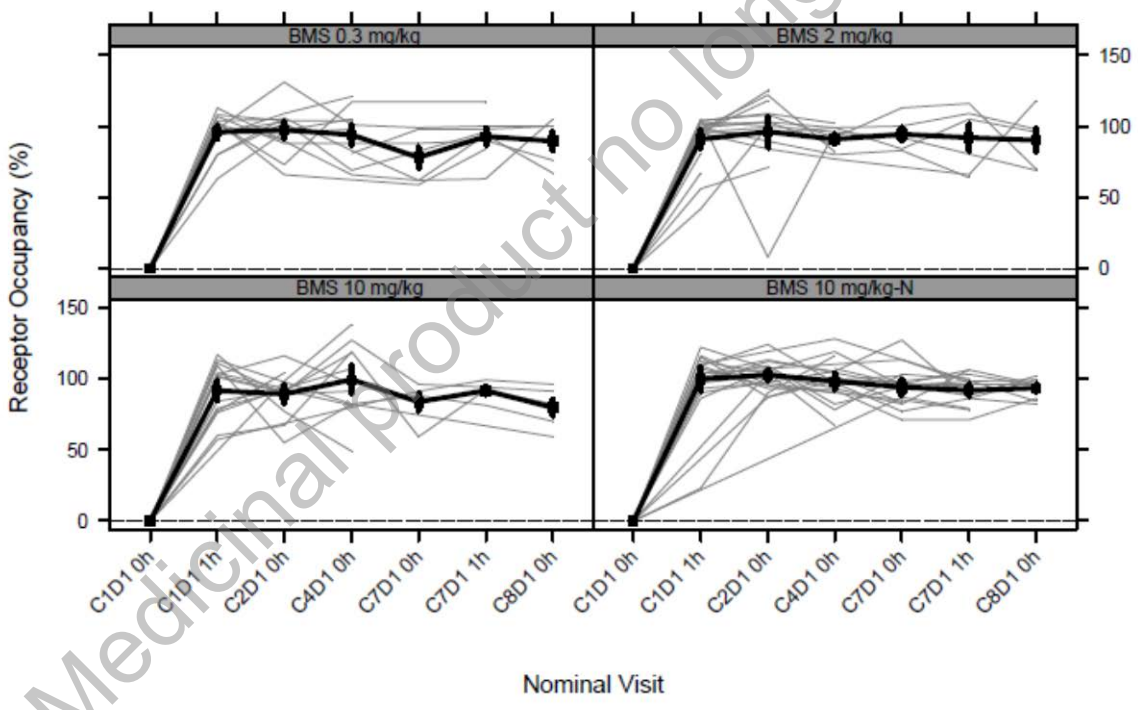


Figure 12: Time course of PD-1 occupancy by nivolumab by dose level – Study CA209009

PD-L1 Expression as a Potential Biomarker

In study MDX1106-03, evaluable archival tumour tissue was available from 36% (38/107) of melanoma and 49% (63/129) of NSCLC subjects indicating a low ascertainment rate. For PD-L1 expression data analysis, 1% and 5% thresholds were utilized to assess PD-L1 positivity. The proportion of PD-L1 positive tumour samples were determined in both melanoma and NSCLC tumours (Table 19).

PD-L1 expression in one or more immune cells was analysed. Using either tumour cell PD-L1 positivity (1% and 5%) or any immune cell PD-L1 expression as an indicator of a positive sample, the proportion of PD-L1 positive subjects was around 90% in both melanoma and NSCLC.

Table 19: PD-L1 expression in melanoma and NSCLC tissue samples – Study MDX1106-03

	n (%)	
PD-L1 Expression	**Melanoma N = 107**	**NSCLC N = 129**
No. of evaluable subjects	38	63
1% - tumor only	25 (66)	35 (56)
5% - tumor only	17 (45)	31 (49)
5% - tumor + immune cells[a]	35 (92)	56 (89)

A Includes 5% PD-L1 expression on tumour cells or immune cells

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology profile of nivolumab has been characterized based on data from 8 Phase 1/2/3 clinical studies conducted in the clinical program. Pharmacokinetics has mainly been documented in patients with different type of solid tumours (NSCLC, Melanoma, RCC, CRC, CRPC, others) and not in healthy volunteers.

The dose proposed for nivolumab montherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.

Study MDX1106-01 pharmacokinetics of nivolumab was analysed by non-compartmental analysis (NCA) of data from 39 subjects dose ranging between 0.3 and 10 mg/kg. The single-dose PK of nivolumab was dose proportional in the range of 0.3 to 10 mg/kg: there was no correlation between dose and clearance, volume of distribution or elimination half-life. The mean volume of distribution after a single dose administration was small (between 83 to 113 mL/kg) and consistent with localization in the extracellular fluid, as observed for other IgG mAbs with large molecular weight. Pharmacokinetics of nivolumab seemed dose proportional over the dose range 0.1 mg/kg-10 mg/kg. No signs of time dependent PK parameters were observed over the period studied. According to popPK analysis nivolumab accumulation index of approximately 3-fold was consistent with the estimated half-life of 26.7 days for 3 mg/kg dosing every 2 weeks. Steady state was achieved approximately at the 6th dose (12 weeks).

The geometric mean (%CV) of PopPK model-based estimates of individual nivolumab CL, volume of distribution at steady state (Vss), terminal half-life and average exposure at steady state at 3 mg/kg every 2 weeks were 9.5 mL/h (49.7%), 8.0 L (30.4%), 26.7 days (101.0%) and 75.3 μg/mL, respectively. The typical clearance was 8.7 mL/h. Nivolumab is expected to be cleared through receptor mediated endocytosis or non-specific endocytosis followed by proteolytic degradation mainly in hepatic or reticuloendothelial cells. Therefore, no renal elimination is expected given the large molecular weight of monoclonal antibodies. As nivolumab is not subject of metabolism by CYP450 enzymes no classical studies regarding metabolism or elimination were deemed necessary. The estimated terminal half-life ranged between 17 and 25 days and was consistent with a fully human mAb. The proposed dosing interval of 2 weeks is shorter than the observed terminal half-life. The

metabolic pathway of nivolumab has not been characterised. Nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

No formal studies have been conducted in special populations, such as renal and hepatic impaired patients. PopPk analysis has shown no clinically important differences in the CL of nivolumab between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see sections 4.2 and 5.2 of the SmPC). No dose adjustment is needed for subject with mild and moderate renal impairment. Subjects with mild hepatic impairment had similar CL and exposures relative to normal subjects, suggesting that no dose adjustment is needed for subjects with mild hepatic impairment. PopPK analysis did not have any subject with moderate and severe hepatic impairment, thus the assessment of effect of moderate and severe hepatic was not available. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. The popPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumour type, tumour size, and hepatic impairment. PopPK analysis indicated a higher clearance of nivolumab with increasing body weight. With dosing of nivolumab on an mg/kg basis, no additional dose adjustment is needed for body weight. Body weight normalised dosing produced approximately uniform steady state trough concentration over a wide range of body weights (34 162 kg). This range is reflected in the SmPC in section 4.2. The PopPK model seems to provide an adequate description of nivolumab concentration-time data in solid tumours. The values of the PopPK analysis are consistent with the corresponding values estimated by non-compartmental analysis and they can be considered in line with data from other fully human IgG antibodies.

No formal drug-drug interaction studies have been conducted to support the use of nivolumab as monotherapy. As nivolumab is not expected to be metabolized by liver cytochrome P450 or other drug metabolizing enzymes, it is unlikely to have an effect on CYPs or other drug metabolizing enzymes in terms of inhibition or induction. However, recent literature reports suggest that therapeutic proteins that modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009. This dose range covers the exposure of nivolumab at proposed dosing regimen of 3 mg/kg Q2W. There was no meaningful change in cytokines across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab (see section 4.5 of the SmPC).

An impact of nivolumab on the response was not observed for systemic or inhaled corticosteroid use.

No thorough QT/QTc study with nivolumab was submitted, which is considered acceptable. The nivolumab exposure obtained with the 10 mg/kg Q3W in the QT study was considered sufficient for obtaining a relevant outcome as 10 mg/kg Q3W provides higher Cmin and AUC compared to proposed 3 mg/kg Q2W dosing regimen. Nivolumab, within the range of doses studied up to 10 mg/kg Q3W did not meaningfully affect the QTc interval. There was no discernible relationship between nivolumab serum concentration and change in QTcF.

Peripheral RO of PD-1 was saturated at doses ≥ 0.3 mg/kg dose levels, which was lower than the proposed dose of 3 mg/kg. In peripheral blood, neither clinically relevant changes in the count of activated T cells nor changes in the absolute lymphocyte counts during treatment with nivolumab were observed. Demonstration of peripheral immunomodulatory activity of nivolumab was limited to chemokines CXCL9 and CXCL10. Relation between baseline absolute lymphocyte count and response to treatment could not be established. PD-L1 expression on the tumour did not appear to be related to efficacy response in study MXD1106-03. The value of PD-L1 and PD-L2 as biomarker to predict the efficacy of nivolumab should be further investigated (see clinical discussion).

2.4.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of nivolumab has been mainly characterized by means of a PopPK model which is considered acceptable. The dose is considered to be appropriately investigated and well defined. The CHMP is of the opinion that the relevance of PD-L1 and PD-L2 expression as biomarkers, in the tumour microenvironment as well as in the peripheral compartment, should be further explored (see clinical conclusions).

2.5. Clinical efficacy

2.5.1. Dose response study

Dose rationale

In study MDX1106-03, increasing doses of nivolumab were tested in order to evaluate efficacy response in patients with different type of tumours. There was a greater percent of objective responses observed in NSCLC subjects treated with 3 mg/kg (24.3%) and 10 mg/kg (20.3%) nivolumab than with 1 mg/kg (3%) nivolumab. There was no apparent relationship between nivolumab dose and ORR in melanoma and RCC (Table 20).

Table 20: Overview of objective response rates of nivolumab across tumour types and dose levels – Study MDX1106-03

Nivolumab Dose(mg/kg)	% Objective Response Rate (95% Confidence Interval)					
	0.1	0.3	1	3	10	Total
All NSCLC	NA	NA	3.0 (0.1, 15.8) N=33	24.3 (11.8, 41.2) N=37	20.3 (11.0, 32.8) N=59	17.1 (11.0, 24.7) N=129
Melanoma	35.3 (14.2, 61.7) N=17	27.8 (9.7, 53.5) N=18	31.4 (16.9, 49.3) N=35	41.2 (18.4, 67.1) N=17	20.0 (5.7, 43.7) N= 20	30.8 (22.3, 40.5) N=107
RCC	NA	NA	27.8 (9.7, 53.5) N=18	NA	31.3 (11.0, 58.7) N=16	29.4 (15.1, 47.5) N=34

In study MDX1106-03, increasing doses of nivolumab were tested in order to evaluate efficacy response in patients with different type of tumours. The nature, frequency, and severity of adverse events (AEs) were similar across the dose range 0.1 to 10 mg/kg and across tumour types (Table 21).

Table 21: Frequency of Drug-related Adverse Events across Dose Groups – Study MDX1106-03

Total Number (%) subjects with AE	Dose (mg/kg Q2W)					
	0.1 (N=17)	0.3 (N=18)	1 (N=86)	3 (N=54)	10 (N=131)	Total (N=306)
Any Grade DR-AE	13 (77)	14 (78)	70 (81)	40 (74)	93 (71)	230 (75)
Gr 3-4 DR-AE	5 (29)	3 (17)	12 (14)	11 (20)	21(16)	52 (17)
Gr 3-4 DR-SAE	1 (6)	0	4 (5)	5 (9)	14 (11)	24 (8)
DR-AE leading to DC	3 (18)	0	9 (11)	4 (7)	16 (12)	32 (11)
DR-AE deaths	0	0	1 (1)	0	1 (1)	2 (1)

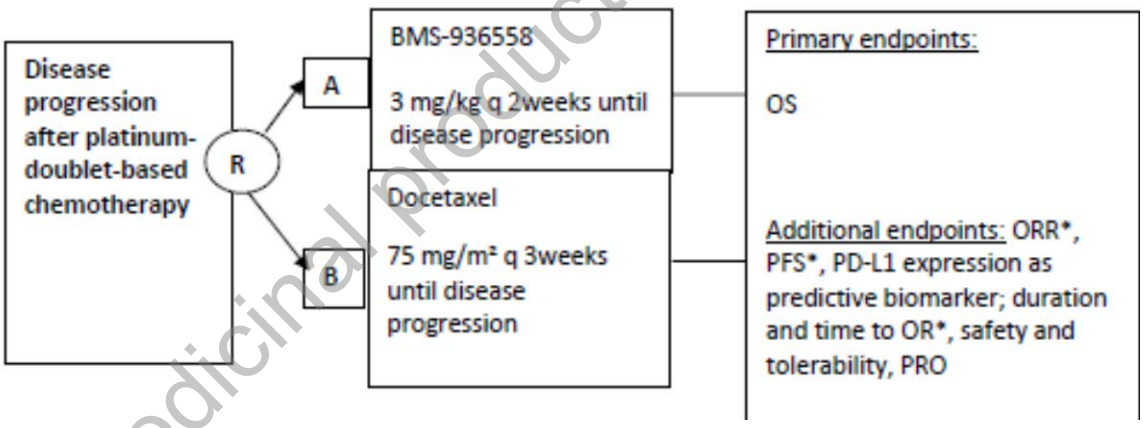
Based on above data and analyses across tumour types, 3 mg/kg IV Q2W was selected as the nivolumab monotherapy dose and schedule for all indications (see discussion on clinical efficacy).

2.5.2. Main study(ies)

Study CA209017: An Open-Label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer (NSCLC)

Table 22: Study Design Schematic – Study CA209017

Methods



* Objective Response and progression (by RECIST 1.1) as determined by investigator

Study Participants

Main inclusion criteria:

- men & women ≥ 18 years of age

- Patients with histologically or cytological-documented squamous cell NSCLC who present with Stage IIIB/IV disease or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo radiation therapy for locally advanced disease.)

- Disease recurrence or progression during/after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease

- Measurable disease by CT/MRI per RECIST 1.1 criteria

- ECOG performance status ≤ 1

- A formalin fixed, paraffin-embedded (FFPE) tumour tissue block or unstained slides of tumour sample (archival or recent) must be available for biomarker evaluation. Biopsy should be excisional, incisional or core needle.

Main exclusion criteria:

- Patients with untreated CNS metastases.

- Patients with carcinomatous meningitis.

- Patients with active, known or suspected autoimmune disease.

- Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of randomization.

- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

- Prior treatment with docetaxel

- Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have been resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

- Treatment with any investigational agent within 14 days of first administration of study treatment.

Treatments

- Nivolumab 3 mg/kg solution intravenously every two weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or study end
- Docetaxel 75 mg/m2 solution intravenously every three weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends

Docetaxel is approved for use upon progression from first line therapy in NSCLC based upon improvements in PFS and OS when compared to best supportive care (BSC) or active chemotherapies. Pemetrexed has not been approved for use in squamous cell NSCLC due to its relative lack of efficacy. Erlotinib is another agent that has been studied in second-line squamous and non-squamous NSCLC; however, its uptake has not been universal in the squamous population. Docetaxel was, therefore, chosen as the comparator for this study.

No premedications were recommended for initiation of dosing of nivolumab. Premedication with corticosteroids were to be given to subjects randomized to the docetaxel treatment group.

Objectives

Main objective of the trial is to compare overall survival of nivolumab with Docetaxel in patients with squamous cell lung cancer (NSCLC), after failure of prior platinum-based chemotherapy. The OS is defined as the time from randomization to the date of death.

The secondary objectives included the comparison of objective response rate (ORR), progression free survival (PFS), the evaluation of PD-L1 as predictive biomarker for OS, ORR or PFS, the evaluation of the proportion of subjects exhibiting disease-related symptom improvement by 12 weeks, as measured by Lung Symptom Cancer Scale (LCSS), in nivolumab and docetaxel groups.

Other exploratory objectives were assessment of safety, PK, health status (using EQ-5D index) characterisation of immunogenicity.

Outcomes / endpoints

The primary endpoint was overall survival (OS) in all randomised subjects.

The secondary endpoints were ORR (including investigator-assessed ORR, duration of response and time to tumour response), investigator-assessed PFS per RECIST v1.1 criteria, and OS, ORR or PFS based on PD-L1 expression level. Improvement of disease-related symptoms by week 12 as measured by Lung Symptom Cancer Scale (LCSS) was also evaluated.

Exploratory endpoints were safety, health status (using EQ-5D index) and characterisation of immunogenicity.

OS was 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.

ORR is defined as the number of subjects whose best confirmed objective response (BOR) is either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomized subjects. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions), whichever occurs first.

Duration of objective response (DOR) is defined as the time between the date of first confirmed response to the date of the first documented tumour progression (per RECIST 1.1), or death due to any cause, whichever occurs first.

Time to Objective Response (TTR) is defined as the time from randomization to the date of the first confirmed response. TTR will be evaluated for responders only.

PFS was 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. Subjects who started any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumour assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

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 validated Dako PD-L1 IHC assay.

Disease-related symptom improvement is defined as the proportion of randomized subjects who had 10 points or more decrease from baseline in average symptom burden index score at any time between randomization and week 12. The subject portion of the LCSS scale consisted of six symptom-specific questions that address cough, dyspnoea, fatigue, pain, haemoptysis, and anorexia, plus three summary items on symptom distress, interference with activity level, and global health-related quality of life.

Sample size

The sample size was calculated in order to compare OS between subjects randomized to receive nivolumab versus docetaxel. The final analysis of OS was planned to take place after 231 deaths were observed among 272 randomized subjects. One interim analysis of OS was planned after at least 196 deaths (85% of total deaths required for final analysis) had been observed. 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 immuno-oncology drug ipilimumab in recent phase 3 studies.

Piecewise mixture model assumptions were as follows: a 4-months delayed separation of curves between docetaxel and nivolumab treatment groups, an exponential distribution for docetaxel (7 months median OS), a 18% 'cure' rate (long term survival) in the nivolumab treatment group, and a 7.9 months median OS for 'non-cured' nivolumab subjects. The piecewise mixture distribution for nivolumab had an overall 8.9 months median OS for all randomized nivolumab subjects. Hazard ratio between nivolumab and docetaxel group followed the following pattern: Months 0-4: HR=1; Month 6: HR=0.62; Month 12: HR= 0.51; Month 24: HR=0.28; Month 36: HR=0.13. Simulations were performed using Power Analysis & Sample Size Software®7 to assess power and timing of interim and final OS analyses.

Duration of the study from start of randomization to final analysis was approximately 38 months (14 months of accrual + 24 months of follow-up). The expected duration until interim analysis was approximately 26 months after start of randomization. The average overall HR at interim and final OS analysis was estimated to be 0.74 and 0.66 respectively. Power at interim and final OS analysis was 55% and 90% respectively. The stopping boundaries at interim and final analyses were derived based on the number of deaths using O'Brien and Fleming alpha spending function.

Randomisation

Patients who met all eligibility criteria were randomized by IVRS in a 1:1 ratio to the nivolumab group or the docetaxel group, with stratification by prior paclitaxel vs other prior treatment, and region (US/Canada vs. Europe vs. Rest of World).

Blinding (masking)

N/A

Statistical methods

For the primary efficacy analysis, a stratified log-rank test was performed to test the comparison between time to event distributions. Stratification factors were prior use of paclitaxel vs. other prior treatment, and region (US/Canada vs. Europe vs. Rest of World) as entered into the IVRS.

The stratified hazard ratio between 2 treatment groups along with CI was obtained by fitting a stratified Cox model with the treatment group variable as unique covariate.

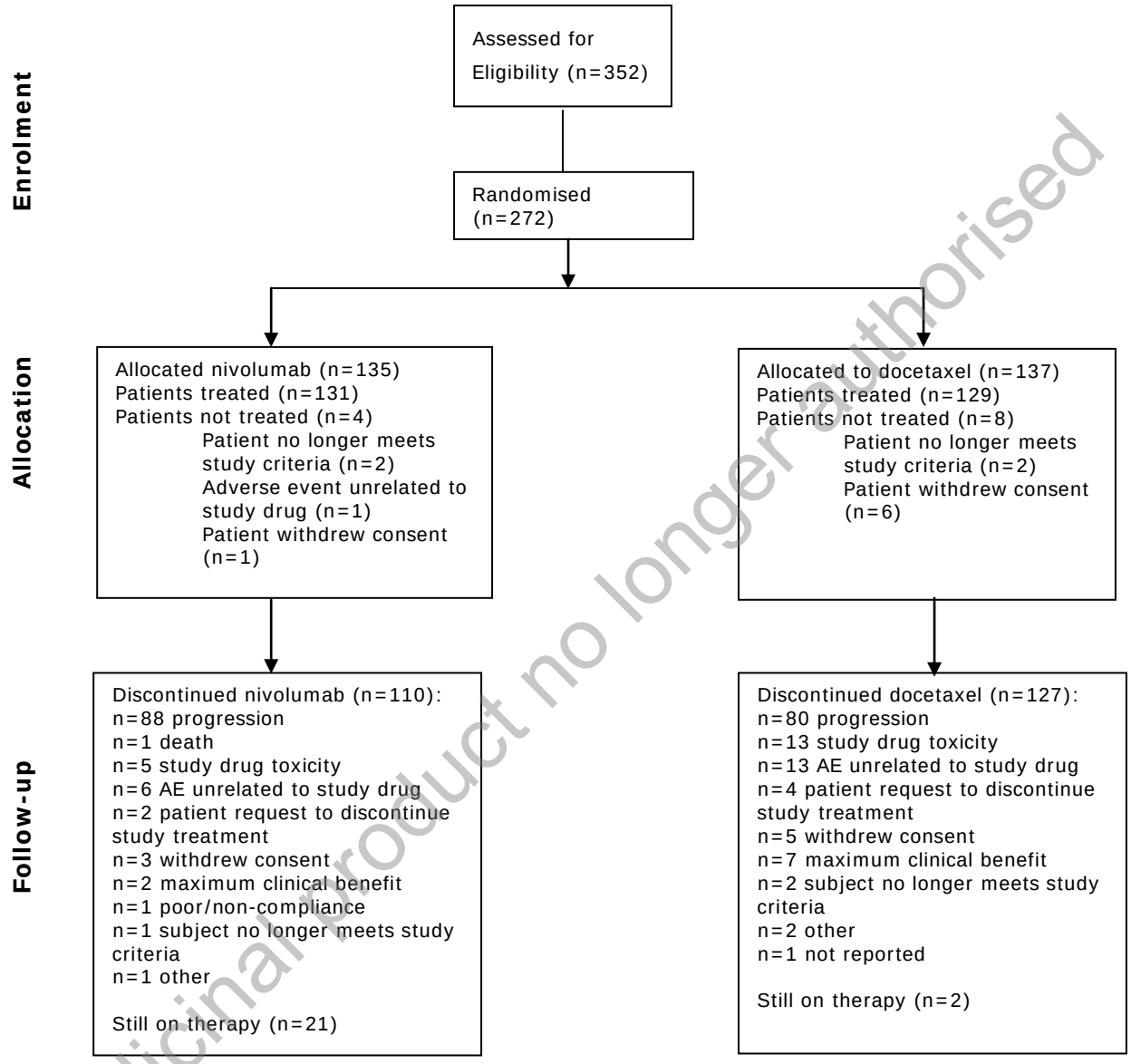
The difference in rates between the two treatment groups along with their two-sided 95% CI was estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the stratification factors. In order to preserve an experimental-wise type I error rate of 5%, a hierarchical testing approach was applied to key secondary endpoints following analysis of the primary endpoint of OS. The hierarchical ordering of key secondary endpoints was as follows:

1) Objective Response Rate

2) Progression-free Survival

Results

Participant flow



Recruitment

Patients were enrolled from October 2012 until November 2013. This study was conducted at 92 sites in 21 countries (Argentina, Australia, Austria, Canada, Chile, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Netherlands, Norway, Peru, Poland, Romania, Russian Federation, Spain, United Kingdom, and United States).

Conduct of the study

An independent Data Monitoring Committee (DMC) was established to provide general oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio for this study and provided advice to the sponsor regarding actions the committee deemed necessary for the continuing protection of subjects. Following review

of the reported safety and efficacy data, the DMC recommends continuation, modification, or discontinuation of the study. The DMC had 3 formal interim safety meetings on 12-Sep-2013, 7-Mar-2014, and 28-Jul-2014, and at each meeting recommended continuation of the study without modification.

The DMC met on 10-Jan-2015 for the formal interim analysis of OS (based on a 15-Dec-2014 database lock). The DMC confirmed that the pre-specified boundary was crossed and noted that there were no concerning safety signals. The data were consistent across all parameters. The DMC was unanimous in declaring superiority for OS as defined in the DMC charter, and the applicant decided to stop the comparative portion of the trial..

Changes to the study protocol was based on 10 amendments, the most relevant are included in the table below.

Table 23: Protocol amendments – Study CA209017

Document	Site(s)	Date of Issue
Amendment No. 01	Site specific: all sites permitting pharmacogenetic studies • Permitted the collection and storage of blood samples for use in future exploratory pharmacogenetic research	12-Jun-2012
Amendment No. 06	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 to include changes to the guidance on contraception.	08-Mar-2013
Amendment No. 07	Site specific: all sites • Modified the trial to require confirmation of objective response per RECIST 1.1 criteria. This modification is in response to a request of the US FDA. 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 • Modification of the tumor assessment schedule for non-progressing subjects who initiate a subsequent anticancer therapy • Inclusion of additional safety information on Nivolumab for opportunistic infections related to immunosuppression • The inclusion of "nivolumab" throughout the protocol, as the approved generic name for BMS-936558 • Minor, additional clarifications and typographical revisions throughout the protocol.	29-May-2013

Amendment No. 09	Site specific: all sites • Modified the overall survival (OS) analysis for CA209017, relative to the number of required events and timing of interim and final OS analyses. These changes were made to address the potential for long-term survival and delayed onset of benefit observed in prior studies with immuno-oncology drugs such as ipilimumab. • Modified to move objective response rate from a co-primary endpoint to a secondary endpoint (OS remains as the sole primary endpoint). This modification was based on mature ORR results from an expanded cohort of NSCLC subjects treated in the Phase 1b study MDX1106-03. ORR according to the investigator was to be the first secondary endpoint to be tested in the statistical hierarchy if OS is positive, at either the interim or final OS analysis.	25-Apr-2014

Baseline data

Most randomised subjects were from the EU (n=131, 48.2%), followed by North America (n=86, 31.6%), South America (n=18, 6.6%) and Central America (n=8, 2.9%).

Table 24: Baseline Demographic Characteristics - All Randomized Subjects

	Nivolumab 3 mg/kg N = 135	Docetaxel N = 137	Total N = 272
AGE (YEARS)			
N	135	137	272
MEAN	62.2	64.4	63.3
MEDIAN	62.0	64.0	63.0
MIN , MAX	39 , 85	42 , 84	39 , 85
STANDARD DEVIATION	8.33	8.28	8.36
AGE CATEGORIZATION (%)			
< 65	79 (58.5)	73 (53.3)	152 (55.9)
>= 65 AND < 75	45 (33.3)	46 (33.6)	91 (33.5)
>= 75 AND < 85	10 (7.4)	18 (13.1)	28 (10.3)
>= 85	1 (0.7)	0	1 (0.4)
>= 75	11 (8.1)	18 (13.1)	29 (10.7)
>= 65	56 (41.5)	64 (46.7)	120 (44.1)
GENDER (%)			
MALE	111 (82.2)	97 (70.8)	208 (76.5)
FEMALE	24 (17.8)	40 (29.2)	64 (23.5)
RACE (%)			
WHITE	122 (90.4)	130 (94.9)	252 (92.6)
BLACK OR AFRICAN AMERICAN	6 (4.4)	2 (1.5)	8 (2.9)
ASIAN	4 (3.0)	2 (1.5)	6 (2.2)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
OTHER	1 (0.7)	2 (1.5)	3 (1.1)
NOT REPORTED	2 (1.5)	1 (0.7)	3 (1.1)
ETHNICITY (%)			
HISPANIC OR LATINO	7 (5.2)	5 (3.6)	12 (4.4)
NOT HISPANIC OR LATINO	61 (45.2)	60 (43.8)	121 (44.5)
NOT REPORTED	67 (49.6)	72 (52.6)	139 (51.1)

Table 25: Baseline Disease Characteristics and Tumor Assessments - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab 3 mg/kg N = 135	Docetaxel N = 137	Total N = 272
DISEASE STAGE			
STAGE IIIB	29 (21.5)	24 (17.5)	53 (19.5)
STAGE IV	105 (77.8)	112 (81.8)	217 (79.8)
NOT REPORTED	1 (0.7)	1 (0.7)	2 (0.7)
TIME FROM INITIAL DIAGNOSIS (YEARS)			
N	135	137	272
MEDIAN (MIN - MAX)	0.74 (0.1 - 10.0)	0.73 (0.1 - 4.6)	0.74 (0.1 - 10.0)
TIME FROM INITIAL DIAGNOSIS (%)			
< 1 YEAR	94 (69.6)	99 (72.3)	193 (71.0)
1- < 2 YEARS	26 (19.3)	25 (18.2)	51 (18.8)
2- < 3 YEARS	7 (5.2)	7 (5.1)	14 (5.1)
3- < 4 YEARS	3 (2.2)	2 (1.5)	5 (1.8)
4- < 5 YEARS	0	4 (2.9)	4 (1.5)
>= 5 YEARS	5 (3.7)	0	5 (1.8)
CELL TYPE			
SQUAMOUS	133 (98.5)	137 (100.0)	270 (99.3)
OTHER	2 (1.5)	0	2 (0.7)
SUBJECTS WITH AT LEAST ONE LESION (B) (%)	134 (99.3)	137 (100.0)	271 (99.6)
SITE OF LESION (A) (B) (%)			
ADRENAL GLAND	14 (10.4)	11 (8.0)	25 (9.2)
ASCITES	1 (0.7)	0	1 (0.4)
BONE	22 (16.3)	15 (10.9)	37 (13.6)
BONE MARROW	1 (0.7)	0	1 (0.4)
BREAST	2 (1.5)	0	2 (0.7)
CENTRAL NERVOUS SYSTEM	9 (6.7)	8 (5.8)	17 (6.3)
CHEST WALL	4 (3.0)	0	4 (1.5)
EFFUSION	20 (14.8)	17 (12.4)	37 (13.6)
ESOPHAGUS	1 (0.7)	1 (0.7)	2 (0.7)
KIDNEY	8 (5.9)	7 (5.1)	15 (5.5)
LIVER	27 (20.0)	34 (24.8)	61 (22.4)
LUNG	115 (85.2)	121 (88.3)	236 (86.8)
LYMPH NODE	68 (50.4)	80 (58.4)	148 (54.4)
MEDIASTINUM	14 (10.4)	19 (13.9)	33 (12.1)
OTHER	21 (15.6)	18 (13.1)	39 (14.3)
PANCREAS	1 (0.7)	1 (0.7)	2 (0.7)
PELVIS	2 (1.5)	2 (1.5)	4 (1.5)
PERICARDIUM	3 (2.2)	5 (3.6)	8 (2.9)
PERITONEUM	1 (0.7)	1 (0.7)	2 (0.7)
PLEURA	16 (11.9)	11 (8.0)	27 (9.9)
SKIN/SOFT TISSUE	10 (7.4)	5 (3.6)	15 (5.5)
SPLEEN	2 (1.5)	0	2 (0.7)
VISCERAL, OTHER	6 (4.4)	0	6 (2.2)
NUMBER OF SITES WITH AT LEAST ONE LESION (B) (%)			
1	19 (14.1)	22 (16.1)	41 (15.1)
2	42 (31.1)	49 (35.8)	91 (33.5)
3	40 (29.6)	43 (31.4)	83 (30.5)
4	23 (17.0)	15 (10.9)	38 (14.0)
>=5	10 (7.4)	8 (5.8)	18 (6.6)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	134 (99.3)	137 (100.0)	271 (99.6)
SITE OF TARGET LESION (A) (%)			
ADRENAL GLAND	11 (8.1)	11 (8.0)	22 (8.1)
BONE	2 (1.5)	2 (1.5)	4 (1.5)
BREAST	2 (1.5)	0	2 (0.7)
CHEST WALL	4 (3.0)	0	4 (1.5)
KIDNEY	5 (3.7)	6 (4.4)	11 (4.0)
LIVER	22 (16.3)	28 (20.4)	50 (18.4)
LUNG	110 (81.5)	113 (82.5)	223 (82.0)
LYMPH NODE	51 (37.8)	52 (38.0)	103 (37.9)
MEDIASTINUM	6 (4.4)	6 (4.4)	12 (4.4)
OTHER	13 (9.6)	10 (7.3)	23 (8.5)
PANCREAS	0	1 (0.7)	1 (0.4)
PELVIS	1 (0.7)	1 (0.7)	2 (0.7)
PERICARDIUM	2 (1.5)	0	2 (0.7)
PERITONEUM	1 (0.7)	0	1 (0.4)
PLEURA	4 (3.0)	4 (2.9)	8 (2.9)
SKIN/SOFT TISSUE	8 (5.9)	5 (3.6)	13 (4.8)
SPLEEN	2 (1.5)	0	2 (0.7)
VISCERAL, OTHER	4 (3.0)	0	4 (1.5)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)			
N	134	137	271
MEDIAN (MIN - MAX)	87.5 (12 - 250)	74.0 (10 - 259)	81.0 (10 - 259)

CNS METASTASIS			
YES	9 (6.7)	8 (5.8)	17 (6.3)
NO	126 (93.3)	129 (94.2)	255 (93.8)
SMOKING STATUS			
CURRENT/FORMER	121 (89.6)	129 (94.2)	250 (91.9)
NEVER SMOKED	10 (7.4)	7 (5.1)	17 (6.3)
UNKNOWN	4 (3.0)	1 (0.7)	5 (1.8)
PERFORMANCE STATUS (ECOG) [%]			
0	27 (20.0)	37 (27.0)	64 (23.5)
1	106 (78.5)	100 (73.0)	206 (75.7)
NOT REPORTED	2 (1.5)	0	2 (0.7)

(A) Subjects may have lesions at more than one site.
(B) Includes both target and non-target lesions.
Source: Table S.3.2 (ECOG), Table S.3.3 (baseline disease characteristics), Table S.3.4 (time from diagnosis to randomization), and Table S.3.6 (pretreatment tumor assessments).

Numbers analysed

Table 26: Analysis Population –

Population	Nivolumab Group N	Docetaxel Group N	Total N
All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.	NA	NA	352
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.	135	137	272
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.	131	129	260
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).	117	96	213
PD-L1 Quantifiable Subjects: All randomized subjects with quantifiable PD-L1 expression at baseline	117	108	225
Immunogenicity Subjects: All nivolumab-treated subjects with baseline and at least one post-baseline assessment for ADA	109	NA	NA

Source: Table S.2.2 (enrolled), Table S.2.6 (randomized), Table S.4.1 (treated), Figure S.5.16 (response-evaluable), Table S.10.6 (PD-L1 tested, quantifiable PD-L1 expression at baseline), Table S.7.10A (ADA)

Outcomes and estimation

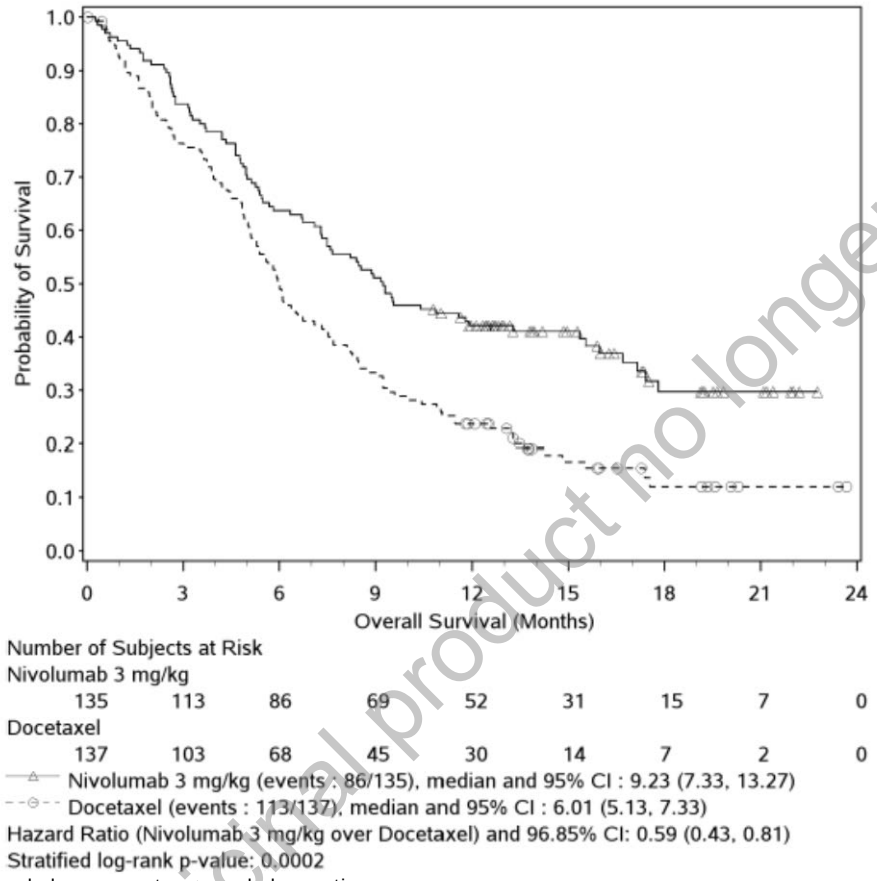
The following table summarizes the main efficacy results for study CA209017 after the planned interim analyses of 196 deaths (85% of deaths).

Table 27: Summary of Efficacy - CA209017 (All Randomized Subjects)

Efficacy parameter	Nivolumab 3 mg/kg (N = 135)	Docetaxel 75mg/m² (Reference group) (N = 137)
Overall Survival		
Events, n (%) subjects who died	86 (63.7)	113 (82.5)
Stratified log-rank test p-value [a]	0.0002	
Hazard ratio [b]	0.59	
96.85% CI [c]	(0.43, 0.81)	
95% CI	(0.44, 0.79)	
Median (95% CI), months [d]	9.23 (7.33, 13.27)	6.01 (5.13, 7.33)
Rate at 12 months (95% CI), %	42.1 (33.7, 50.3)	23.7 (16.9, 31.1)
Progression-free Survival		
Events, n (%) subjects with disease progression/death	105 (77.8)	122 (89.1)
Stratified log-rank test p-value [a]	0.0004	
Hazard ratio (95% CI) [b]	0.62 (0.47, 0.81)	
Median (95% CI), months [d]	3.48 (2.14, 4.86)	2.83 (2.10, 3.52)
Rate at 12 months (95% CI)	20.8 (14.0, 28.4)	6.4 (2.9, 11.8)
Objective Response Rate [e]		
n (%)	27 (20.0)	12 (8.8)
(95% CI)	(13.6, 27.7)	(4.6, 14.8)
Odds ratio estimate (95% CI) [f]	2.64 (1.27, 5.49)	
p-value [g]	0.0083	
Best Overall Response		
Complete Response (CR)	1 (0.7)	0
Partial Response (PR)	26 (19.3)	12 (8.8)
Stable Disease (SD)[h]	39 (28.9)	47 (34.3)
Time to Response		
Number of responders	27	12
Median (range), months	2.2 (1.6, 11.8)	2.1 (1.8, 9.5)
Duration of Response		
Ongoing responders, n/N (%)	17/27 (63.0)	4/12 (33.3)
Median (range), months [d,i]	NR (2.9, 20.5+)	8.4 (1.4+, 15.2+)
Overall survival by PD-L1 Expression Status (≥ 5% tumour cell membrane expression cutoff)		
PD-L1 positive subjects, n (%)	42 (31.1)	39 (28.5)
Unstratified Hazard ratio (95% CI)	0.53 (0.31, 0.89)	
Median (95% CI), months	10.0 (5.8, 17.1)	6.4 (4.5, 9.0)
PD-L1 negative subjects, n (%)	75 (55.6)	69 (50.4)
Unstratified Hazard ratio (95% CI)	0.70 (0.47, 1.02)	
Median (95% CI), months	8.5 (5.5, 13.3)	6.1 (5.1, 8.3)
PD-L1 non-quantifiable subjects, n (%)	18 (13.3)	29 (21.2)
Unstratified Hazard ratio (95% CI)	0.39 (0.19, 0.82)	
Median (95% CI) (Months)	9.4 (7.1, NR)	5.1 (3.0, 6.1)

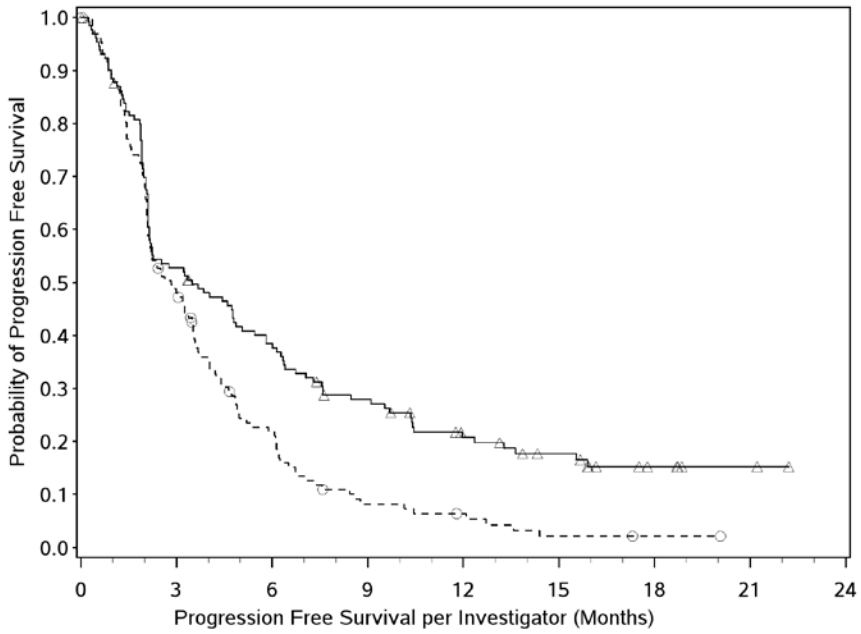
a Log-rank Test stratified by region (US/Canada, Rest of World, Europe) and prior treatment regimen (paclitaxel, another agent) as entered into the IVRS.
b Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over docetaxel.
c The boundary for statistical significance requires the p-value to be less than 0.0315..
d Median computed using Kaplan-Meier method.
e CR+PR per RECIST v 1.1, confidence interval based on the Clopper and Pearson method, as assessed by the Investigator.
f stratified by region (US/Canada vs Europe vs Rest of World) and prior treatment regimen (paclitaxel vs another agent) as entered into the IVRS. Strata adjusted odds ratio (nivolumab over docetaxel) using Mantel-Haenszel method.
g Two-sided p-value from stratified CMH Test.
h Median duration of SD was 6.3 months (95% CI: 4.8, 7.6) in the nivolumab group vs 4.4 months (95% CI: 3.6, 4.9) in the docetaxel group.
i Symbol + indicates a censored value.
Clinical database lock dates were 15-Dec-2014 for the CA209017 Final CSR.

The overall survival effect is further illustrated in the Kaplan-Meier curve in the figure below.



Symbols represent censored observations.
The boundary for statistical significance requires the p-value to be less than 0.0315.
Source: Refer to Figure S.5.1 of the CA209017 CSR

Figure 13: Kaplan-Meier of Overall Survival - All Randomized Subjects in CA209017



Number of Subjects at Risk

Nivolumab 3 mg/kg	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

Nivolumab 3 mg/kg (events : 105/135), median and 95% CI : 3.48 (2.14, 4.86)
Docetaxel (events : 122/137), median and 95% CI : 2.83 (2.10, 3.52)
Hazard Ratio (Nivolumab 3 mg/kg over Docetaxel) and 95% CI: 0.62 (0.47, 0.81)
Stratified log-rank p-value: 0.0004

Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.
Source: Refer to Figure S.5.9 of the CA209017 Final CSR.

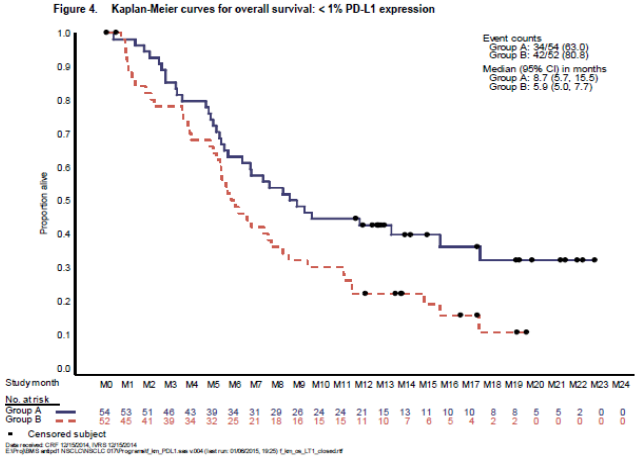
Figure 14: Kaplan-Meier of Progression-free Survival per investigator - All Randomized Subjects in CA209017

Ancillary analyses

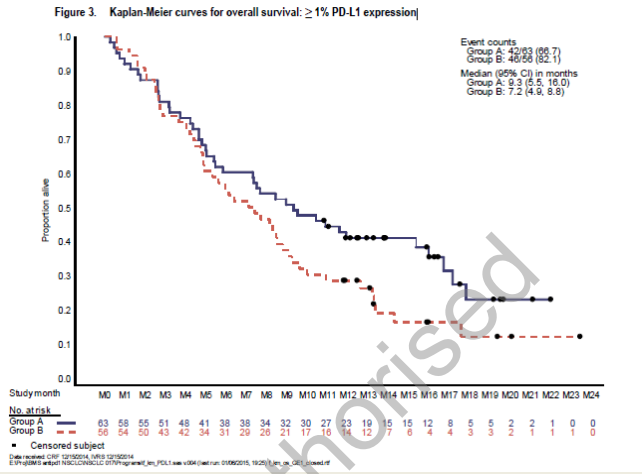
- Efficacy by PD-L1 expression

The special subset of patients according to PD-L1 expression and the value of PD-L1 as predictive biomarkers was discussed by the applicant and the efficacy results by PD-L1 expression status are summarized in the figure and table below.

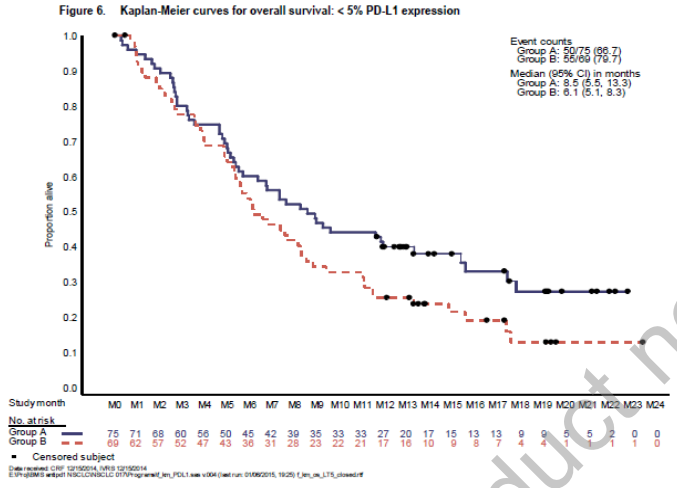
PDL status <1%



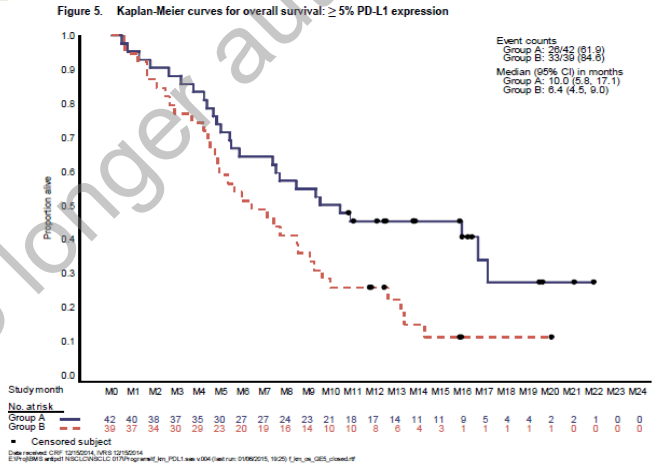
PDL status ≥1%



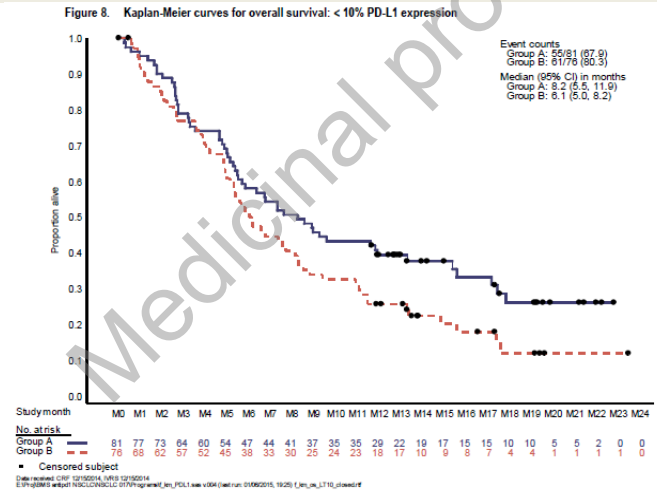
PDL status <5%



PDL status ≥5%



PDL status <10%



PDL status ≥10

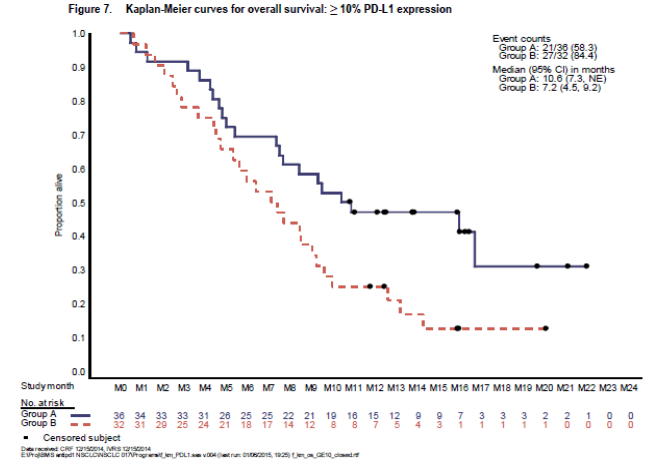


Figure 15: Overall survival by PDL1 expression (group A is nivolumab, group B is docetaxel)

Table 28: Investigator-assessed Objective Response Rate by Pre-treatment PD-L1 Expression Status – CA209017

	PD-L1 Expression Cutoff						
	1%		5%		10%		
	Positive (≥ 1%)	Negative (< 1%)	Positive (≥ 5%)	Negative (< 5%)	Positive (≥ 10%)	Negative (< 10%)	Not Quantifiable
CA209017							
Docetaxel							
ORR, % (n/N)	10.7 (6/56)	9.6 (5/52)	7.7 (3/39)	11.6 (8/69)	9.1 (3/33)	10.7 (8/75)	3.4 (1/29)
95% CI	4.0, 21.9	3.2, 21.0	1.6, 20.9	5.1, 21.6	1.9, 24.3	4.7, 19.9	< 0.1, 17.8
Nivolumab							
ORR, % (n/N)	17.5 (11/63)	16.7 (9/54)	21.4 (9/42)	14.7 (11/75)	19.4 (7/36)	16.0 (13/81)	38.9 (7/18)
95% CI	9.1, 29.1	7.9, 29.3	10.3, 36.8	7.6, 24.7	8.2, 36.0	8.8, 25.9	17.3, 64.3

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

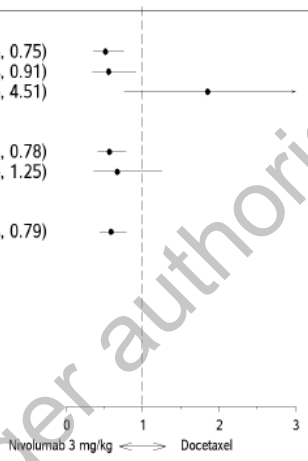
During the procedure, the applicant was requested to provide efficacy data by age subgroup.

- Efficacy in pre-defined subsets

Table 29: Forest Plot of Treatment Effect on OS and PFS in Pre-Defined Subsets in CA209017- All Randomized Subjects

Overall Survival:

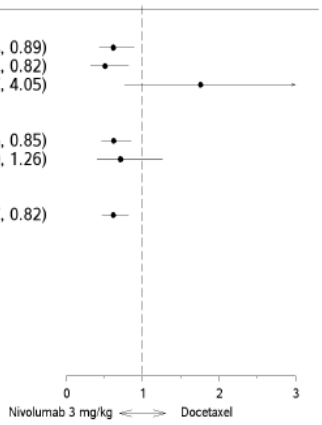
	N	Nivolumab 3 mg/kg N of Events (N of subjects)	mOS (95% CI)	Docetaxel N of Events (N of subjects)	mOS (95% CI)	Unstratified Hazard Ratio (95% CI)
Age Categorization III						
< 65	152	48(79)	9.53 (7.59, 17.15)	61(73)	6.08 (5.06, 7.69)	0.52 (0.35, 0.75)
>= 65 and < 75	91	28(45)	10.41 (5.13, 15.97)	39(46)	5.73 (4.50, 7.69)	0.56 (0.34, 0.91)
>= 75	29	10(11)	6.34 (2.60, 7.66)	13(18)	6.37 (3.65, 15.54)	1.85 (0.76, 4.51)
Gender						
Male	208	71(111)	9.30 (7.49, 15.34)	82(97)	5.73 (4.96, 6.57)	0.57 (0.41, 0.78)
Female	64	15(24)	7.31 (4.96, N.A.)	31(40)	7.52 (3.78, 9.23)	0.67 (0.36, 1.25)
Race						
White	252	79(122)	9.20 (7.29, 13.27)	109(130)	6.01 (5.06, 7.39)	0.59 (0.44, 0.79)
Black or African American	8	3(6)	N.A. (1.64, N.A.)	2(2)	5.57 (5.55, 5.59)	
Asian	6	2(4)	N.A. (7.29, N.A.)	0(2)	N.A.	
Other	3	1(1)	5.45 (N.A., N.A.)	1(2)	3.65 (N.A., N.A.)	
Not Reported	3	1(2)	N.A. (8.87, N.A.)	1(1)	6.08 (N.A., N.A.)	



Source: refer to Figure S.5.7 (OS) of the CA209017 CSR

Progression-free Survival:

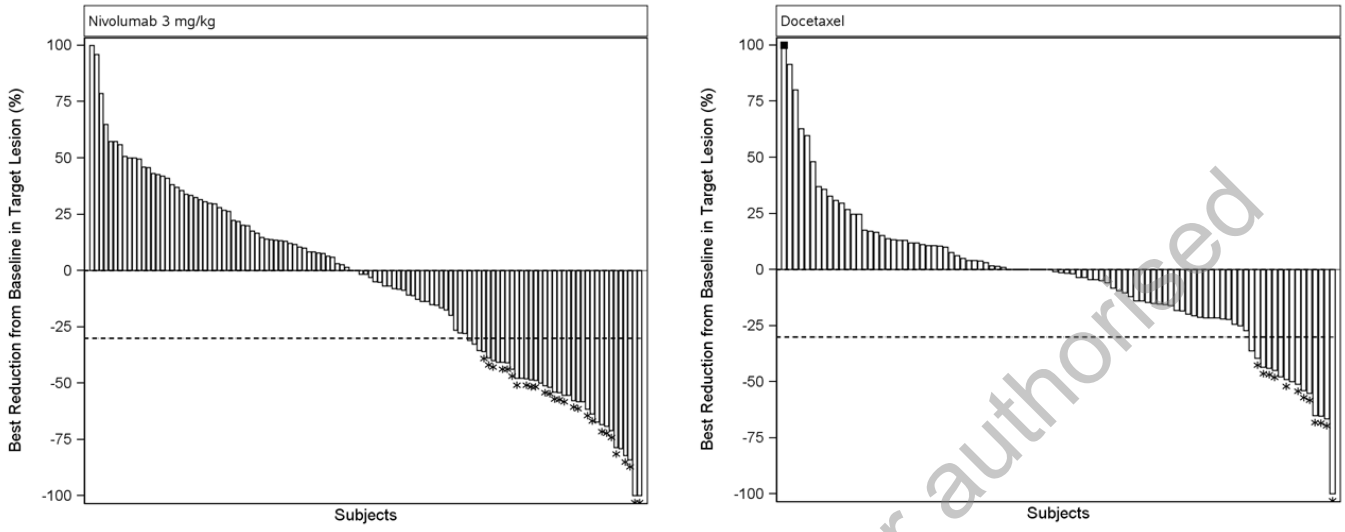
	N	Nivolumab 3 mg/kg N of Events (N of subjects)	mPFS (95% CI)	Docetaxel N of Events (N of subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Age Categorization III						
< 65	152	61(79)	3.68 (2.20, 5.45)	64(73)	2.92 (2.07, 3.55)	0.62 (0.44, 0.89)
>= 65 and < 75	91	34(45)	4.60 (2.10, 7.59)	43(46)	2.40 (1.94, 3.71)	0.51 (0.32, 0.82)
>= 75	29	10(11)	1.97 (0.85, 4.76)	15(18)	3.52 (2.07, 4.63)	1.76 (0.77, 4.05)
Gender						
Male	208	86(111)	3.48 (2.14, 5.82)	88(97)	2.96 (2.10, 3.52)	0.63 (0.46, 0.85)
Female	64	19(24)	3.04 (1.94, 7.06)	34(40)	2.63 (1.94, 3.71)	0.71 (0.40, 1.26)
Race						
White	252	94(122)	3.48 (2.14, 5.06)	117(130)	2.63 (2.10, 3.48)	0.62 (0.47, 0.82)
Black or African American	8	5(6)	1.84 (0.62, N.A.)	2(2)	2.56 (1.45, 3.68)	
Asian	6	3(4)	4.78 (0.23, N.A.)	1(2)	10.45 (N.A., N.A.)	
Other	3	1(1)	5.45 (N.A., N.A.)	1(2)	3.52 (N.A., N.A.)	
Not Reported	3	2(2)	4.81 (4.76, 4.86)	1(1)	2.23 (N.A., N.A.)	



Source: refer to Figure 5.13 (PFS) of the CA209017 CSR

- Reduction in sum of diameters of target lesions

Reductions in target lesion tumour burden are described in the figures below:



Subjects with target lesion at baseline and at least one evaluable target lesion assessment on-study= 117
Negative/positive value means maximum tumor reduction/minimum tumor increase.
Best reduction is 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 v1.1 response.
*: Responder per RECIST v1.1 criteria, confirmation of response required.

Figure 16: Waterfall Plot of Best Reduction from Baseline in Sum of Diameters of Target Lesions per Investigator - All Response Evaluable Subjects - CA209017

- Health-related quality of life (HRQoL)

The disease-related symptom improvement rate by Week 12 was defined as the proportion of randomized subjects who had 10 mm or more decrease from baseline in the average symptom burden index at anytime between randomization and Week 12. The disease related symptom improvement as measured by LCSS was similar between the two groups.

Table 30: Disease Related Symptom Improvement Rate by Week 12, LCSS Questionnaire - All Randomized Subjects

	Nivolumab 3 mg/kg N = 135	Docetaxel N = 137
#SUBJECTS WITH DISEASE RELATED SYMPTOM IMPROVEMENT BY WEEK 12/#RANDOMIZED SUBJECTS (1)	25/135	29/137
DISEASE RELATED SYMPTOM IMPROVEMENT RATE	18.5	21.2
(95% CI) (2)	(12.4,26.1)	(14.7,29.0)

(1) Disease-Related Symptom Improvement by Week 12 is defined as a 10 points or more decrease from baseline in average symptom burden index score at anytime between randomization and week 12.
(2) 95% exact CI computed using Clopper-Pearson Method.

However, The LCSS average symptom score in the nivolumab group generally decreased (improved) over time and the change from baseline exceeded the clinically meaningful threshold at about 10 months; in the docetaxel group, the average symptom index was stable over the period for which there were enough patients to interpret the data (about 6 months).

Table 31: Average Symptom Burden Index Score Summary - All Randomized Subjects

Period / Visit	Treatment Group	N#	Mean	SD	Median	Q25, Q75	Change From Baseline: Mean	SD	Median	Q25, Q75
BASELINE	NIVOLUMAB 3 MG/KG	90	29.99	16.594	30.08	15.00,39.67				
	DOCETAXEL	97	31.92	16.453	33.67	19.17,43.00				
ON-TRT	NIVOLUMAB 3 MG/KG	NA								
WEEK 3	DOCETAXEL	86	28.10	16.338	27.92	15.83,39.17	-2.50	14.671	-3.50	-10.67, 5.83
ON-TRT	NIVOLUMAB 3 MG/KG	94	31.67	16.007	29.08	20.83,43.33	1.92	14.553	2.17	-8.17, 9.17
WEEK 4	DOCETAXEL	NA								
ON-TRT	NIVOLUMAB 3 MG/KG	NA								
WEEK 6	DOCETAXEL	70	29.20	14.916	32.75	16.33,38.17	-0.78	12.435	-2.50	-9.42, 4.50
ON-TRT	NIVOLUMAB 3 MG/KG	67	27.81	19.065	20.17	12.00,40.83	-0.10	16.855	-1.50	-10.17, 9.17
WEEK 8	DOCETAXEL	NA								
ON-TRT	NIVOLUMAB 3 MG/KG	NA								
WEEK 9	DOCETAXEL	41	28.15	19.243	29.50	10.00,38.67	-0.25	13.830	-3.33	-6.83, 4.67
ON-TRT	NIVOLUMAB 3 MG/KG	52	22.25	18.065	16.42	5.92,35.17	-3.98	14.938	-4.00	-10.67, 0.33
WEEK 12	DOCETAXEL	32	24.70	15.341	22.50	9.50,36.67	-1.15	14.925	-4.67	-10.17, 7.17
ON-TRT	NIVOLUMAB 3 MG/KG	NA								
WEEK 15	DOCETAXEL	23	22.01	13.500	18.50	12.17,32.00	-0.13	11.598	-1.83	-6.67, 6.50
ON-TRT	NIVOLUMAB 3 MG/KG	45	20.60	16.406	15.00	7.00,32.83	-6.51	12.487	-5.82	-15.33, 0.33
WEEK 16	DOCETAXEL	NA								
ON-TRT	NIVOLUMAB 3 MG/KG	NA								
WEEK 18	DOCETAXEL	12	22.74	17.499	23.92	5.00,29.50	-1.13	15.262	-1.50	-15.42, 7.75
ON-TRT	NIVOLUMAB 3 MG/KG	38	19.82	15.844	17.67	6.17,30.50	-6.97	14.966	-5.17	-18.58, 2.50
WEEK 20	DOCETAXEL	NA								
ON-TRT	NIVOLUMAB 3 MG/KG	NA								
WEEK 21	DOCETAXEL	10	18.48	17.379	13.25	1.50,31.33	-3.46	10.324	-6.42	-8.83, 3.33
ON-TRT	NIVOLUMAB 3 MG/KG	31	19.68	17.300	12.83	5.50,37.50	-8.76	12.427	-10.50	-16.33, 0.33
WEEK 24	DOCETAXEL	11	23.48	17.525	27.00	5.83,39.33	-0.09	16.423	-0.17	-6.50, 6.67
ON-TRT	NIVOLUMAB 3 MG/KG	30	18.53	16.102	14.00	5.50,25.17	-8.27	14.362	-9.17	-19.42, 3.42
WEEK 30	DOCETAXEL	7	23.69	25.545	20.83	1.17,52.00	9.07	24.531	21.33	-6.33, 23.67
ON-TRT	NIVOLUMAB 3 MG/KG	24	12.92	14.083	7.58	3.75,14.58	-9.48	13.854	-9.83	-18.33, -2.83
WEEK 36	DOCETAXEL	7	24.76	22.907	22.67	3.83,45.50	10.10	22.978	21.00	-2.33, 26.33
ON-TRT	NIVOLUMAB 3 MG/KG	18	8.94	8.505	5.33	2.33,15.50	-14.24	14.530	-13.00	-24.17, -5.67
WEEK 42	DOCETAXEL	6	18.17	18.544	11.58	3.33,33.00	7.04	19.334	7.25	-9.00, 23.08
ON-TRT	NIVOLUMAB 3 MG/KG	13	10.54	12.957	4.33	2.33,13.50	-14.53	13.862	-14.33	-25.00, -4.83
WEEK 48	DOCETAXEL	5	19.60	14.192	15.33	12.67,18.33	1.21	23.682	5.83	-13.25, 15.67
ON-TRT	NIVOLUMAB 3 MG/KG	13	14.96	15.221	11.83	3.67,17.00	-14.15	14.377	-9.00	-21.50, -3.67
WEEK 54	DOCETAXEL	3	28.61	24.751	34.33	1.50,50.00	9.08	30.759	9.08	-12.67, 30.83
ON-TRT	NIVOLUMAB 3 MG/KG	9	14.48	15.356	5.00	4.00,31.00	-14.40	16.753	-14.00	-27.33, -6.00
WEEK 60	DOCETAXEL	2	15.50	17.442	15.50	3.17,27.83	-19.17		-19.17	-19.17,-19.17
ON-TRT	NIVOLUMAB 3 MG/KG	11	10.91	12.638	5.33	1.83,19.50	-14.80	11.217	-13.83	-19.67, -5.83
WEEK 66	DOCETAXEL	1	7.00		7.00	7.00, 7.00				
ON-TRT	NIVOLUMAB 3 MG/KG	7	9.02	8.602	9.17	1.17,13.67	-10.75	9.638	-13.58	-14.50, -1.67
WEEK 72	DOCETAXEL	1	30.50		30.50	30.50,30.50				
ON-TRT	NIVOLUMAB 3 MG/KG	6	11.83	12.198	10.00	0.67,19.67	-12.03	14.441	-14.50	-15.00,-13.50
WEEK 78	DOCETAXEL	1	6.67		6.67	6.67, 6.67				
ON-TRT	NIVOLUMAB 3 MG/KG	6	6.42	7.347	3.00	2.33,10.00	-16.97	9.302	-13.33	-15.17,-12.50
WEEK 84	DOCETAXEL	1	5.33		5.33	5.33, 5.33				
ON-TRT	NIVOLUMAB 3 MG/KG	1	0.17		0.17	0.17, 0.17	-33.50		-33.50	-33.50,-33.50
WEEK 96	DOCETAXEL	0								
FOLLOW-UP	NIVOLUMAB 3 MG/KG	39	35.76	16.755	37.67	27.50,49.00	6.01	17.053	5.42	-5.33, 13.33
FOLLOW-UP 1	DOCETAXEL	45	37.49	16.374	36.17	25.83,50.17	8.50	14.848	11.92	0.75, 19.75
FOLLOW-UP	NIVOLUMAB 3 MG/KG	21	33.79	18.850	39.67	18.17,47.33	7.48	23.574	8.67	-11.00, 19.50
FOLLOW-UP 2	DOCETAXEL	33	33.63	17.464	33.17	21.67,47.50	7.30	19.278	7.42	-6.50, 17.83

NA: Not Assessed.
Number of subjects who filled the questionnaire at study assessment and with baseline value.

For the EQ-VAS baseline health status scores were similar in the two groups and were similar to scores reported elsewhere for advanced lung cancer subjects. The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for subjects remaining on treatment.

Table 32: Overall Self-Rated Health Status EQ-VAS Summary All Randomized Subjects

	Nivolumab 3 mg/kg N = 135					Docetaxel N = 137				
Period Visit	N	Mean	SD	Median	Q25-Q75	N	Mean	SD	Median	Q25-Q75
BASELINE	93	63.0	18.19	60.0	50.0- 76.0	97	64.4	21.92	67.0	50.0- 80.0
TREATMENT WEEK 3	NA					90	65.6	21.41	63.0	50.0- 86.0
TREATMENT WEEK 4	98	61.8	19.65	60.0	50.0- 79.0	NA				
TREATMENT WEEK 6	NA					71	68.0	17.67	69.0	52.0- 80.0
TREATMENT WEEK 8	71	68.8	18.81	70.0	51.0- 82.0	NA				
TREATMENT WEEK 9	NA					42	66.9	21.00	68.0	50.0- 87.0
TREATMENT WEEK 12	54	72.9	21.25	79.0	50.0- 90.0	34	69.6	17.93	72.0	54.0- 84.0
TREATMENT WEEK 15	NA					24	69.2	22.20	72.0	60.0- 88.5
TREATMENT WEEK 16	47	72.1	18.56	78.0	61.0- 87.0	NA				
TREATMENT WEEK 18	NA					12	71.1	19.47	73.0	55.0- 89.0
TREATMENT WEEK 20	41	71.6	21.60	74.0	59.0- 89.0	NA				
TREATMENT WEEK 21	NA					10	80.6	15.25	84.5	69.0- 93.0
TREATMENT WEEK 24	34	73.4	23.03	80.0	60.0- 90.0	11	75.8	19.32	80.0	59.0- 91.0
TREATMENT WEEK 30	33	74.0	23.32	80.0	65.0- 95.0	7	79.4	17.42	90.0	63.0- 96.0
TREATMENT WEEK 36	25	78.0	22.05	80.0	70.0- 96.0	7	74.1	23.93	88.0	54.0- 91.0
TREATMENT WEEK 42	19	77.4	25.90	85.0	68.0- 95.0	6	77.5	21.96	87.5	62.0- 92.0
TREATMENT WEEK 48	14	84.3	16.74	90.5	81.0- 97.0	5	77.8	17.24	81.0	79.0- 85.0
TREATMENT WEEK 54	14	75.6	26.26	82.0	70.0- 92.0	3	81.7	13.58	89.0	66.0- 90.0
TREATMENT WEEK 60	9	86.0	12.77	87.0	80.0- 98.0	2	87.5	3.54	87.5	85.0- 90.0
TREATMENT WEEK 66	12	83.9	17.31	89.5	78.0- 97.0	1	95.0		95.0	95.0- 95.0
TREATMENT WEEK 72	7	85.7	10.09	85.0	79.0- 97.0	1	86.0		86.0	86.0- 86.0
TREATMENT WEEK 78	6	82.2	19.60	87.5	70.0- 98.0	1	98.0		98.0	98.0- 98.0
TREATMENT WEEK 84	6	89.0	11.78	92.0	84.0- 98.0	1	80.0		80.0	80.0- 80.0
TREATMENT WEEK 96	1	99.0		99.0	99.0- 99.0	0				
FOLLOW-UP FOLLOW-UP 1	39	58.2	23.11	59.0	40.0- 79.0	44	58.3	20.51	60.0	47.5- 75.5
FOLLOW-UP FOLLOW-UP 2	21	60.9	24.43	69.0	39.0- 77.0	33	69.3	15.97	70.0	60.0- 80.0

EQ-VAS ranges from 0 to 100, with 0 representing the worst health, 100 the best health.
NA: Not Assessed.

Summary of main study

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

Table 33: Summary of Efficacy for study CA209017

Title: An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC).			
Study identifier	CA209017		
Design	Phase 3, randomized, open-label study of nivolumab vs docetaxel in adult (☐ 18 years) subjects with advanced or metastatic squamous cell NSCLC after failure of prior platinum-doublet chemotherapy. Subjects were randomized 1:1 and stratified according to the following factors: prior treatment with paclitaxel-based doublet vs. other doublet, and region (US/Canada vs. Europe vs. Rest of World).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		FPFV: 16-Oct-2012; LPLV for primary endpoint: 17-Nov-2014 Not applicable On-going
Hypothesis	Superiority of nivolumab vs. docetaxel in terms of OS.		
Treatments groups	Nivolumab 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. Treatment was continued until disease progression (or discontinuation of nivolumab therapy in subjects receiving treatment beyond initial Response Evaluation Criteria in Solid Tumours [RECIST] v1.1-defined progression), discontinuation due to toxicity, or other protocol-defined reasons.
	Docetaxel 75 mg/m2		Docetaxel 75 mg/m2 was administered every 3 weeks. Treatment was continued until disease progression, discontinuation due to toxicity, or other protocol-defined reasons.
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	Investigator-assessed PFS	Defined as the time from randomization to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause.
	Secondary endpoint	Investigator-assessed ORR	Defined as the number of subjects whose best confirmed objective response (BOR) is either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomized subjects. BOR was defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions), whichever occurs first.
	Secondary endpoint	DOR and TTR	Duration of objective response (**DOR**) was defined as the time between the date of first confirmed response to the date of the first documented tumour progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Time to Objective Response (**TTR**) was defined as the time from randomization to the date of the first confirmed response (evaluated for responders only).

	Secondary endpoint	OS, ORR, or PFS based on pre-study PD-L1 expression level	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 validated Dako PD-L1 IHC assay.
Database lock	15-Dec-2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Treated Subjects		
Descriptive statistics and estimate variability	**Treatment group**	Nivolumab 3 mg/kg	Docetaxel 75 mg/m2
	Number of subject	n=135	n=137
	OS (months) Median 95% CI	9.23 (7.33, 13.27)	6.01 (5.13, 7.33)
	HR[a] 95% CI	0.59 (0.44, 0.79) P=0.0002	- -
	Investigator-assessed PFS (months) Median 95% CI	3.48 (2.14, 4.86)	2.83 (2.10, 3.52)
	HR (95% CI)[a]	0.62 (0.47, 0.81) P=0.0004	-
	Investigator-assessed ORR (n, %) 95% CI	27 (20.0) (13.6, 27.7)	12 (8.8) (4.6, 14.8)
	Odds ratio estimate (95% CI)[b]	2.64 (1.27, 5.49) P 0.0083[c]	- -
	DOR Median (range), months and TTR Median (range), months	NR (2.9, 20.5+) 2.2 (1.6, 11.8)	8.4 (1.4+, 15.2+) 2.1 (1.8, 9.5)

	OS, based on pre-study PD-L1 expression level	*PD-L1 positive subjects** 10.0 (5.8, 17.1) *PD-L1 negative subjects* 8.5 (5.5, 13.3)	*PD-L1 positive subjects* 6.4 (4.5, 9.0) *PD-L1 negative subjects* 6.1 (5.1, 8.3)

NE: not estimable.
a Stratified Cox proportional hazard model. Hazard ratio is nivolumab over docetaxel.
b For CA209017, stratified by region (US/Canada vs Europe vs Rest of World) and prior treatment regimen (paclitaxel vs another agent) as entered into the IVRS. Strata adjusted odds ratio (nivolumab over docetaxel) using Mantel-Haenszel method.
c Two-sided p-value from stratified CMH Test.
*PD-L1 positive subjects are pateints with a PD-L1 status ≥ 5% tumour membrane expression cut off

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

Clinical studies in special populations

No dedicated studies have been conducted in special populations.

The potential impact of hepatic and renal impairment in the PK of nivolumab has been evaluated by the means of PKPD modelling (see section 2.4.2 Clinical Pharmacology). Data on patients with varying degrees of hepatic/renal impairment from the clinical studies is very limited.

Data on the PK and efficacy in elderly patients in different age subgroups has been provided (see sections 2.4.2 clinical pharmacology and ancillary analyses).

Supportive study

Study CA209063

Study CA209063 was a phase 2 study designed to evaluate the antitumour activity of nivolumab monotherapy (3 mg/kg Q2W) in subjects with histologically or cytologically documented advanced or metastatic SQ NSCLC whose disease had progressed during or after both a platinum doublet-based chemotherapy regimen and at least 1 additional systemic therapy (refractory population).

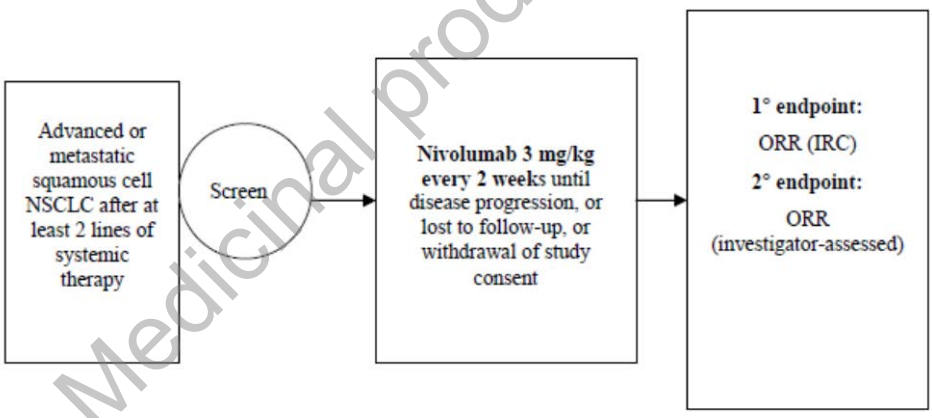


Figure17: Study Design

The primary efficacy endpoint was confirmed ORR (by IRC), defined as subjects with a BOR of confirmed PR or CR, using RECIST v1.1 criteria. ORR-related endpoints were also included: DOR, TTR, duration of SD. The secondary endpoint was ORR (by investigator). Main exploratory endpoints were PFS, OS and safety.

A total of 140 subjects were enrolled at 28 sites in 4 countries (US, France, Germany, and Italy). Of them, 117 (83.6%) subjects were treated with nivolumab 3 mg/kg Q2W, and 23 (16.4%) subjects were not treated because they no longer met study criteria at the time of planned first treatment (screen failures). The majority of subjects were male (72.6%) and white (84.6%), and the median age was 65.0 years. At study entry, the majority of treated subjects (82.9%) had stage IV disease. The proportion of subjects with a baseline ECOG performance status of 0 was 22.2% and the proportion of subjects with a baseline ECOG performance status of 1 was 77.8%. The majority (92.3%) of treated subjects were current or former smokers.

All patients received two or more prior systemic treatments: 35% received two, 44% received three, and 21% received four or more. The majority of patients (76%) received nivolumab within 3 months of completing their most recent prior regimen.

The following table summarizes the main efficacy results for the study CA209063 based on a minimum follow up of approximately 11 months.

Table 34: Efficacy Summary with Nivolumab Monotherapy in study CA209063

	CA209063 Final CSR Addendum 1
Efficacy parameter	**Nivolumab 3 mg/kg N = 117**
Overall Survival	
Events, n (%) subjects who died	72 (61.5)
Median (95% CI), months [a]	8.21 (6.05, 10.91)
Rate at 12 months (95% CI), %	40.8 (31.6, 49.7)
Progression-free Survival	
Events, n (%) subjects with disease progression/death	85 (72.6)
Median (95% CI), months [a]	1.87 (1.77, 3.15)
Rate at 12 months (95% CI)	20.0 (12.7, 28.5)
Objective Response Rate [b]	
n (%)	17 (14.5)
(95% CI)	(8.7, 22.2)
Best Overall Response	
Complete Response (CR)	0
Partial Response (PR)	17 (14.5)
Stable Disease (SD)[c]	30 (25.6)
Time to Response	
Number of responders	17
Median (range), months	3.3 (1.7, 8.8)
Duration of Response	
Ongoing responders, n/N (%)	13/17 (76.5)
Median (range), months [a,d]	NR (1.9+, 11.5+)
Overall survival by PD-L1 Expression Status (≥5% tumour cell membrane expression cutoff)	
PD-L1 positive subjects, n (%)	25 (21.4)
Unstratified Hazard ratio (95% CI)	-
Median (95% CI), months	15.7 (8.1, NR)
PD-L1 negative subjects, n (%)	51 (43.6)
Unstratified Hazard ratio (95% CI)	-
Median (95% CI), months	8.2 (5.0, 13.6)
PD-L1 non-quantifiable subjects, n (%)	10 (8.5)[e]
Unstratified Hazard ratio (95% CI)	-
Median (95% CI) (Months)	12.7 (1.1, 13.3)

a Median computed using Kaplan-Meier method.
b CR+PR per RECIST v 1.1, confidence interval based on the Clopper and Pearson method. As assessed by the IRC for CA209063.
c Median duration of SD was 6.0 months (95% CI: 4.7, 10.9) in CA209063 Addendum 1.
d Symbol + indicates a censored value.
e PD-L1 status indeterminate/not evaluable (n = 10). An additional 31 subjects in CA209063 did not have a sample tested.
Clinical database lock dates was 23-Jul-2014 for Addendum 1 to the CA209063 Final CSR.

2.5.3. Discussion on clinical efficacy

The efficacy of nivolumab in the treatment of previously treated SQ NSCLC was initially based on the results from two uncontrolled studies: one phase II, (Study CA209063), and 1 phase I, open label, dose-escalation study (MDX1106-03). Considering that both of these studies were uncontrolled, open label studies, and that the number of patients provided as part of the initial submission was limited, any conclusion on efficacy was challenging and insufficient to allow the assessment of the BR balance of nivolumab in the initially proposed indication. During the procedure, the applicant provided the primary analysis for the confirmatory phase III study (vs. docetaxel), study CA 20917.

Design and conduct of clinical studies

The pivotal Study CA209017 was a randomized, open-label, parallel phase 3 trial of nivolumab monotherapy (3 mg/kg, Q2W) versus docetaxel (75 mg/m2 q3w) in patients with advanced or metastatic squamous cell NSCLC whose disease had progressed during or after one prior platinum doublet-based chemotherapy regimen. The treatment could be provided until disease progression or if no longer tolerated. Subjects were randomized 1:1 and stratified according to prior treatment, and region. The primary objective was to show superiority in OS for nivolumab compared to docetaxel. The open label design of the study is accepted because of the different dosing frequencies.

In study CA209017, the patients were stratified according to region because of regional differences. Patients were also stratified according to previous paclitaxel use (both paclitaxel and docetaxel being taxanes). However, previous studies failed to show a reduced activity of docetaxel after paclitaxel [Fosella, Hanna,Shephard 2005, Spirodonidi 2001, Kosmas 2001]. Therefore, patients who received prior paclitaxel were to be stratified across the two treatment groups to ensure that the control arm will be unaffected by cross-resistance.

Stratification based on PD-L1 status was not performed as the applicant considered the PD-L1 status variable within the tumour and the value of the use of the PD-L1 as a predictive biomarker was uncertain, since at study initiation the results were still immature and an IHC assay method was not verified.

Docetaxel (75 mg/m^2) Q3W used as comparator is an acceptable standard second line treatment in locally advanced or metastatic NSCLC. The head to head comparison with a currently approved treatment facilitates the positioning of nivolumab in the current treatment armamentarium of SQ-NSCLC. However, the study limited the inclusion to patients with an ECOG 0-1 while chemotherapy will also be applied to patients with an ECOG 2[7].

The primary endpoint was OS, in accordance with the EU guideline. Secondary endpoints were the investigator's PFS and ORR by RECIST criteria more likely to show drug activity against the tumour, and OS, ORR, or PFS based on pre-study PD-L1 expression status. These endpoints are acceptable and in accordance with the EU Guideline on anticancer medicinal products. The use of the RECIST instead of iRECIST to measure PFS and ORR is accepted, since the comparator arm included a chemotherapy treatment. The PFS and overall response rate were measured by the investigator and not confirmed by an independent review committee. As the primary endpoint is the overall survival, this can be accepted.

Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of NSCLC. In the absence of data, nivolumab should be used with caution

[7] M. Reck1,2, S. Popat3,4, N. Reinmuth1,2, D. De Ruysscher5, K. M. Kerr6, S. Peters7 & on behalf of the ESMO Guidelines Working Group* Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 00: 1–13, 2014

in these populations after careful consideration of the potential risk-benefit on an individual basis (see sections 4.4, 4.5 and 5.1 of the SmPC).

A planned interim analysis was conducted when 199 deaths were reached. One interim analysis of OS was planned after 196 deaths (85% of deaths required for final analysis) have been observed. This formal comparison of OS allowed for early stopping for superiority.

The primary endpoint in study CA209017 was changed late in the study (25 April 2014, database lock 15 August 2014) from OS and ORR (co-primary with alpha split as 0.04 for OS and 0.01 for ORR) to OS as only primary endpoint (with alpha=0.05). Although the sponsor had access to safety data, the applicant clarified that they remained blinded for the efficacy review and that these analyses did not influence the decision to change the primary endpoint.

Efficacy data and additional analyses

The dose to be used in the clinical studies was selected from preclinical, pharmacokinetic and phase I clinical studies. The receptor occupancy tests failed to show larger receptor occupancy at higher doses. However, in the clinical study, the NSCLC cohort showed numerically better ORR with the 3 mg/kg and 10 mg/kg dose than with the 1 mg/kg dose. At the 10 mg/kg dose, however, the incidence of SAE was higher than with the lower 3 mg/kg dose for patients with NSCLC. Therefore, the applicant decided to proceed with the 3 mg/kg dose which is considered reasonable.

Study CA209017

A total of 135 patients were randomized to nivolumab 3 mg/kg Q2W and 137 patients to docetaxel. The median age was 62 years and 41.5% of subjects were ≥ 65 years old (8.1% over 75 and only one subject 85 or older). The median age is lower than for the general NSCLC population (71 years) however this can be observed in clinical studies conducted in NSCLC.

The study included a large number of former /current smokers (89.6%), a well-known risk factor for NSCLC. Most subjects were male but no difference in efficacy was observed based on gender. Most patients were white and although no racial differences are expected in terms of efficacy, the number is too limited to be conclusive. At the time of inclusion, most patients (77.8%) had stage IV disease with less than 1 year from initial diagnosis (69.6%, median time 0.74 years) and ECOG 1 status (78.5%) or less (20%). No patients with a worse ECOG PS ≥2 were included, although chemotherapy can also be offered to patients with ECOG 2. Therefore, the efficacy and safety of nivolumab in comparison with chemotherapy in patients with ECOG 2 is not known. ECOG is one of the multiple factors considered by prescribers and this limitation will be reflected in the SmPC (see sections 4.4 and 5.1).

Overall the included patient population is regarded representative for metastatic lung NSCLC.

The docetaxel group included more female patients (17.8 % vs.29.2%), ECOG PS 0 (21.5% vs. 27%), stage IV disease (78% vs. 82%) stable disease as best response after prior therapy (24% vs. 34%), patients ≥ 65 years (41.4% vs 46.1%), patients aged ≥ 75 years (8.1 % vs 13.1%) carboplatin use (60% vs. 74%). Favourable prognostic parameters are female, ECOG PS 0, stable disease. Less favourable factors are stage IV disease and older age.

Despite small differences, the baseline characteristics between the two groups were comparable.

This study was stopped early, during a pre-defined interim analysis. Superiority in terms of OS was demonstrated, with an absolute clinically relevant difference in OS between treatment arms of approximately 3 months and 42% vs 24% of patients alive at 12 months, nivolumab vs. docetaxel respectively. Treatment

differences in terms of PFS were more modest, with a 0.65 month gain for nivolumab over docetaxel. However, given the profile of the curves, the HR [0.62 (0.47, 0.81)] for PFS is considered much more informative.

The poor correlation observed between OS and PFS results is not totally unexpected, since PFS findings can be difficult to interpret for immunotherapy agents. Other efficacy endpoints (ORR, BOR, and DOR) and an early separation in the Kaplan-Meier OS estimates also seem to favour nivolumab treatment.

OS results in the subgroups analysed (prior paclitaxel use, gender, race, ECOG score, prior platinum regiment, time from completion of the most recent regimen to randomisation) support the robustness of the outcome in the whole population, with the only exception of patients >75 years. In the patients aged ≥ 75 years, the magnitude of the effect seems lower, although it should be interpreted with caution due to the small sample size (nivolumab n=11, docetaxel n=18) and the observed unbalance for ECOG PS between the two groups. The subgroup of patients age ≥65 years showed a response in favour of nivolumab (nivolumab n= 56, median OS 7.57 months [95 %CI CI 5.26-15. 34]; docetaxel n= median OS 5.8 months [95%CI 4.83-7.69] HR 0.70 (95 % CI 5.26-1.06). Data from patients 75 years of age or older are too limited to draw conclusions on this population (see sections 4.2 and 5.1 of the SmPC).

In order to further define the long-term efficacy of nivolumab, the CHMP requested the applicant to submit updated descriptive analysis of OS (see Annex II condition).

In terms of subsequent therapy, 36.3% of nivolumab subjects and 29.9% of docetaxel subjects received subsequent systemic anti-cancer therapy. In both groups, the most frequent type was chemotherapy (35.6% and 24.1%, for nivolumab and docetaxel, respectively). Sensitivity analyses taking this fact into consideration showed a consistent effect in favour of nivolumab (OS HR=0.50 (95% CI: 0.35, 0.71)). Although the inherent limitations to this analysis are acknowledged, these results can be considered supportive of the main results.

In addition, the benefit of nivolumab was observed regardless of the PD-L1 status. Patients who were PDL-positive showed the best (numerical) improvements, but the observed improvements in ORR, PFS and OS were comparable or even better than those obtained with docetaxel in PD-L1 negative patients.

Therefore, a restriction to the PD-L1 positive population is not justified. The variability within the tumour, changes within the tumour immune microenvironment with nivolumab treatment, differences in testing on tumour cells versus testing for PD-L1 positivity and PD-L2 status in immune cells, T cell infiltration, the use of archival tissue etc could explain this finding. The role of PD-L1 expression has not been fully elucidated.

The expression of PD-L1 and PD-L2 in the tumour microenvironment and the relationship with tumour responses therefore needs to be further investigated. The CHMP has imposed a condition to the marketing authorization in Annex II to perform further analyses to ascertain the potential role of the PD-L2 biomarker, to further explore the relationship between PD-L1 and PD-L2 expression on the efficacy of nivolumab, to continue the exploration of the optimal cut-off for PD-L1 positivity and to further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression.

Study CA209063

A total of 117 patients received at least one dose of nivolumab in this study. All patients had received at least 2 prior regimens (per inclusion criteria), with 44.4% having received 3 regimens and 20.5% having received ≥4 prior regimens. This indicates that the population included was heavily pre-treated.

In the initial submission, a response was obtained in 12% (14 out of 117) of the patients, indicating anti-tumour activity. BOR was PR in all 14 IRC-assessed confirmed responders, while the median time to response was 3.0 months (ranged from 1.7 to 4.8 months). ORR by investigator was consistent with the primary endpoint.

Median PFS (per IRC) was 1.9 months, median follow-up time for survival was 6.1 months (range 0.0 to 11.7 months), but median OS had not been reached at the time of the data lock point.

During the procedure, the applicant provided updated efficacy (and safety) data with a minimum follow-up for ORR of approximately 11 months (from the initial 5.5 months). The updated efficacy results for this study are in line with those provided in the initial submission.

The magnitude of the effect seen in study CA209063 seems smaller than in study CA209017; however it is probably due to a more advanced and heavily pre-treated population included in the phase 2 study.

In general these results are considered supportive of the efficacy of nivolumab in patients with SQ NSCLC who failed prior chemotherapy, a population with a high unmet medical need as the treatment options are limited.

A broad indication, including SQ and non-SQ NSCLC patients, was initially sought by the Applicant. During the procedure, the applicant proposed a restricted indication to SQ NSCLC patients.

2.5.4. Conclusions on the clinical efficacy

The efficacy of nivolumab in patients with advanced SQ NSCLC after failure of prior chemotherapy is currently based on one phase 3 study vs. docetaxel monotherapy, and two supportive phase I/II open label, uncontrolled studies conducted in patients with ECOG 0-1. The observed results can be considered clinically meaningful, and the B/R balance is considered positive in the 2nd and later lines setting.

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

- Post-authorisation efficacy study (PAES): The Applicant should submit the updated descriptive OS results for study CA209017
- 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 analysis will be conducted in Studies CA 209037 and CA209066 in patients with advanced melanoma.
    - To further investigate the value 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. These additional biomarker analyses are occurring in the context of Study CA209-038 and Study CA209-066.
    - To further investigate at post-approval the relation between PDL-1 and PDL-2 expression in Phase 1 studies (CA209009, CA209038 and CA209064).
    - To further investigate the associative analyses between PDL-1 and PDL-2 expression conducted in Study CA209-066.
    - To further investigate at post-approval the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in Studies CA209-009, CA209-038 and CA209-064.

2.6. Clinical safety

Patient exposure

The estimated total number of subjects treated with nivolumab 3 mg/kg monotherapy Q2W across multiple studies and indications is approximately 1800 as of the cut-off dates for the submission. The cumulative dose and dose intensities are shown in Table .

Table 35: Estimated Number of Subjects Treated with Nivolumab 3 mg/kg Monotherapy Every 2 Weeks in BMS-Sponsored Studies

Study Number	Phase	Study Design	No. of Nivolumab-treated Subjects at 3 mg/kg Q2W (No. of Total Treated Subjects)	Status at Time of SCS	SCS Database Lock Date
Melanoma					
CA209037	3	Randomized, open-label vs. investigator's choice	268 (370)	Ongoing[a]	30-Apr-2014
CA209038	1	Exploratory study of nivolumab	85 (85)	Ongoing	01-Apr-2014
CA209066	3	Randomized, double-blind vs. dacarbazine	206 (411)	Ongoing[c]	23-May-2014
CA209067	3	Randomized, double-blind, nivolumab monotherapy or combined with ipilimumab vs. ipilimumab monotherapy	302 (906)	Ongoing	27-Mar-2014
Refractory and advanced malignancies, including melanoma					
MDX1106-03 (NSCLC, melanoma, RCC, CRC, mCRPC)	1	Open-label, multicenter, multidose, dose escalation (0.1, 0.3, 1, 3, 10 mg/kg nivolumab)	54 (306)	Completed	04-Feb-2013
NSCLC					
CA209063	2	Single arm with nivolumab	117 (117)	Completed	06-Mar-2014
CA209017	3	Randomized, open-label vs. docetaxel	130 (259)	Ongoing	03-Feb-2014
CA209057	3	Randomized, open-label vs. docetaxel	278 (555)	Ongoing	30-Jan-2014
RCC[b]					
CA209025	3	Randomized, open-label vs. everolimus	395 (790)	Ongoing	11-Mar-2014
TOTAL			**1835 (3799)**		

[a] An interim CSR is available for this study. CA209037 is not considered completed because analyses of both primary endpoints are not yet available. OS data will be reported in a subsequent final CSR, estimated to be available in 4Q 2014/1Q 2015.
[b] Completed Study CA209010 in RCC is not included in this table because the 3 mg/kg dose of nivolumab was not assessed in CA209010.
[c] A Data Monitoring Committee (DMC) report is available for CA209066. A CSR is estimated to be available in 4Q 2014.
Abbreviations: CRC:= colorectal cancer; mCRPC = metastatic castrate-resistant prostate cancer; No. = number; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCS = summary of clinical safety.

Adverse events

The pooled analyses of study CA 20917 and CA 209063 show an incidence of adverse events of 98.4%, with an incidence of 14.5% of grade 3-4 AE's and 12% of grade 5 AE.

The most frequently adverse events are fatigue (39.5%), dyspnoea (37.1%), cough (31.5%) decreased appetite (29.4%) and nausea (21.8)

The most frequents grade 3-4 AEs are dyspnoea, (6.9%), fatigue (4.4%), nausea (2.0%), cough (1.6%) and decreased appetite (1.6%).

The following table described a summary of AEs for which the causal relationship to study therapy was assessed by the investigator as definite, probable, possible, or missing ("adverse reactions") in the pooled safety population.

Table 36: Drug-related adverse events by worse CTC grade - Pooled CA209017 and CA209063 studies

System Organ Class (%) Preferred Term (%)	CA209017 DOCETAXEL N = 129 Any Grade	CA209017 DOCETAXEL N = 129 Grade 3-4	CA209017 DOCETAXEL N = 129 Grade 5	CA209017 NIVOLUMAB 3 mg/kg N = 131 Any Grade	CA209017 NIVOLUMAB 3 mg/kg N = 131 Grade 3-4	CA209017 NIVOLUMAB 3 mg/kg N = 131 Grade 5	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Any Grade	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Grade 3-4	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Grade 5
TOTAL SUBJECTS WITH AN EVENT	111 (86.0)	71 (55.0)	3 (2.3)	76 (58.0)	9 (6.9)	0	163 (65.7)	29 (11.7)	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	67 (51.9)	14 (10.9)	0	41 (31.3)	1 (0.8)	0	95 (38.3)	6 (2.4)	0
FATIGUE	57 (44.2)	13 (10.1)	0	34 (26.0)	1 (0.8)	0	83 (33.5)	6 (2.4)	0
PYREXIA	10 (7.8)	1 (0.8)	0	6 (4.6)	0	0	10 (4.0)	0	0
CHILLS	1 (0.8)	0	0	4 (3.1)	0	0	6 (2.4)	0	0
OEDEMA	8 (6.2)	0	0	2 (1.5)	0	0	6 (2.4)	0	0
MALAISE	2 (1.6)	0	0	0	0	0	4 (1.6)	0	0
CHEST PAIN	1 (0.8)	0	0	0	0	0	2 (0.8)	0	0
INFLUENZA LIKE ILLNESS	1 (0.8)	0	0	1 (0.8)	0	0	2 (0.8)	0	0
GAIT DISTURBANCE	1 (0.8)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
CATHETER SITE RASH	1 (0.8)	0	0	0	0	0	0	0	0
INFUSION SITE ERYTHEMA	1 (0.8)	0	0	0	0	0	0	0	0
INJECTION SITE REACTION	1 (0.8)	0	0	0	0	0	0	0	0
PAIN	4 (3.1)	0	0	0	0	0	0	0	0
PERFORMANCE STATUS DECREASED	1 (0.8)	0	0	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	66 (51.2)	7 (5.4)	0	24 (18.3)	1 (0.8)	0	65 (26.2)	4 (1.6)	0
NAUSEA	30 (23.3)	2 (1.6)	0	12 (9.2)	0	0	30 (12.1)	0	0
DIARRHOEA	26 (20.2)	3 (2.3)	0	10 (7.6)	0	0	22 (8.9)	3 (1.2)	0
STOMATITIS	14 (10.9)	0	0	6 (4.6)	0	0	12 (4.8)	0	0
VOMITING	14 (10.9)	1 (0.8)	0	4 (3.1)	0	0	11 (4.4)	0	0
DRY MOUTH	1 (0.8)	0	0	2 (1.5)	0	0	9 (3.6)	0	0
CONSTIPATION	8 (6.2)	0	0	2 (1.5)	0	0	8 (3.2)	0	0
ABDOMINAL PAIN	7 (5.4)	1 (0.8)	0	2 (1.5)	0	0	7 (2.8)	0	0
CHEILITIS	1 (0.8)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
COLITIS	0	0	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
DUODENAL ULCER	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
DYSPEPSIA	2 (1.6)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
ABDOMINAL DISTENSION	1 (0.8)	0	0	0	0	0	0	0	0
ANAL PRURITUS	1 (0.8)	0	0	0	0	0	0	0	0
DYSPHAGIA	1 (0.8)	0	0	0	0	0	0	0	0
FLATULENCE	1 (0.8)	0	0	0	0	0	0	0	0
GASTRITIS	1 (0.8)	0	0	0	0	0	0	0	0
GLOSSITIS	1 (0.8)	0	0	0	0	0	0	0	0
INTESTINAL PERFORATION	1 (0.8)	1 (0.8)	0	0	0	0	0	0	0
ORAL DYSAESTHESIA	1 (0.8)	0	0	0	0	0	0	0	0
ORAL PAIN	3 (2.3)	0	0	0	0	0	0	0	0

System Organ Class (%) Preferred Term (%)	CA209017 DOCETAXEL N = 129 Any Grade	CA209017 DOCETAXEL N = 129 Grade 3-4	CA209017 DOCETAXEL N = 129 Grade 5	CA209017 NIVOLUMAB 3 mg/kg N = 131 Any Grade	CA209017 NIVOLUMAB 3 mg/kg N = 131 Grade 3-4	CA209017 NIVOLUMAB 3 mg/kg N = 131 Grade 5	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Any Grade	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Grade 3-4	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Grade 5
METABOLISM AND NUTRITION DISORDERS	37 (28.7)	5 (3.9)	0	20 (15.3)	1 (0.8)	0	50 (20.2)	3 (1.2)	0
DECREASED APPETITE	25 (19.4)	1 (0.8)	0	14 (10.7)	1 (0.8)	0	36 (14.5)	1 (0.4)	0
HYPOMAGNESAEMIA	3 (2.3)	0	0	2 (1.5)	0	0	6 (2.4)	0	0
HYPONATRAEMIA	2 (1.6)	2 (1.6)	0	1 (0.8)	0	0	3 (1.2)	2 (0.8)	0
HYPOPHOSPHATAEMIA	0	0	0	0	0	0	3 (1.2)	0	0
DEHYDRATION	5 (3.9)	2 (1.6)	0	1 (0.8)	0	0	2 (0.8)	0	0
HYPERGLYCAEMIA	1 (0.8)	0	0	2 (1.5)	0	0	2 (0.8)	0	0
HYPOKALAEMIA	3 (2.3)	0	0	0	0	0	2 (0.8)	0	0
HYPERCALCAEMIA	1 (0.8)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
HYPERCHOLESTEROLAEMIA	0	0	0	0	0	0	1 (0.4)	0	0
HYPERMAGNESAEMIA	0	0	0	0	0	0	1 (0.4)	0	0
HYPERKALAEMIA	1 (0.8)	0	0	0	0	0	0	0	0
HYPOALBUMINAEMIA	2 (1.6)	0	0	0	0	0	0	0	0
HYPOPHAGIA	1 (0.8)	0	0	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	39 (30.2)	5 (3.9)	0	19 (14.5)	0	0	43 (17.3)	2 (0.8)	0
RASH	11 (8.5)	2 (1.6)	0	9 (6.9)	0	0	24 (9.7)	1 (0.4)	0
PRURITUS	0	0	0	3 (2.3)	0	0	10 (4.0)	1 (0.4)	0
DRY SKIN	3 (2.3)	0	0	2 (1.5)	0	0	4 (1.6)	0	0
HYPERHIDROSIS	0	0	0	3 (2.3)	0	0	3 (1.2)	0	0
ACTINIC KERATOSIS	0	0	0	0	0	0	1 (0.4)	0	0
HAIR GROWTH ABNORMAL	0	0	0	0	0	0	1 (0.4)	0	0
LIVEDO RETICULARIS	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0
NAIL DISORDER	5 (3.9)	1 (0.8)	0	0	0	0	1 (0.4)	0	0
NIGHT SWEATS	1 (0.8)	1 (0.8)	0	1 (0.8)	0	0	1 (0.4)	0	0
PAIN OF SKIN	0	0	0	0	0	0	1 (0.4)	0	0
SKIN EXFOLIATION	2 (1.6)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
SKIN FISSURES	2 (1.6)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
URTICARIA	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
XERODERMA	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
ALOPECIA	29 (22.5)	1 (0.8)	0	0	0	0	0	0	0
NAIL DISCOLOURATION	2 (1.6)	0	0	0	0	0	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (0.8)	0	0	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	29 (22.5)	3 (2.3)	0	17 (13.0)	0	0	35 (14.1)	1 (0.4)	0
MUSCULOSKELETAL PAIN	23 (17.8)	3 (2.3)	0	8 (6.1)	0	0	19 (7.7)	1 (0.4)	0
ARTHRALGIA	9 (7.0)	0	0	7 (5.3)	0	0	13 (5.2)	0	0
MUSCLE SPASMS	1 (0.8)	0	0	1 (0.8)	0	0	3 (1.2)	0	0

	CA209017						CA209017+CA209063		
	DOCETAXEL N = 129			NIVOLUMAB 3 mg/kg N = 131			NIVOLUMAB 3 mg/kg N = 248		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
MUSCULAR WEAKNESS	1 (0.8)	0	0	1 (0.8)	0	0	3 (1.2)	0	0
HYPERCREATINAEMIA	0	0	0	2 (1.5)	0	0	2 (0.8)	0	0
JOINT STIFFNESS	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
MUSCLE TIGHTNESS	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
MUSCULOSKELETAL STIFFNESS	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
POLYMYALGIA RHEUMATICA	0	0	0	0	0	0	1 (0.4)	0	0
JOINT SWELLING	1 (0.8)	0	0	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13 (10.1)	2 (1.6)	2 (1.6)	17 (13.0)	1 (0.8)	0	33 (13.3)	5 (2.0)	0
DYSPNOEA	4 (3.1)	0	0	5 (3.8)	0	0	11 (4.4)	0	0
PNEUMONITIS	1 (0.8)	0	1 (0.8)	5 (3.8)	0	0	11 (4.4)	4 (1.6)	0
COUGH	1 (0.8)	0	0	4 (3.1)	1 (0.8)	0	9 (3.6)	1 (0.4)	0
EPISTAXIS	2 (1.6)	0	0	2 (1.5)	0	0	2 (0.8)	0	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
HYPOXIA	0	0	0	0	0	0	1 (0.4)	0	0
LUNG INFILTRATION	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
NASAL CONGESTION	0	0	0	0	0	0	1 (0.4)	0	0
PLEURAL EFFUSION	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
PULMONARY EMBOLISM	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)	0	0
WHEEZING	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
HAEMOPTYSIS	1 (0.8)	0	0	0	0	0	0	0	0
HICCUPS	2 (1.6)	1 (0.8)	0	0	0	0	0	0	0
OROPHARYNGEAL PAIN	1 (0.8)	0	0	0	0	0	0	0	0
PULMONARY HAEMORRHAGE	1 (0.8)	0	1 (0.8)	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	43 (33.3)	6 (4.7)	0	13 (9.9)	1 (0.8)	0	27 (10.9)	3 (1.2)	0
NEUROPATHY PERIPHERAL	25 (19.4)	3 (2.3)	0	4 (3.1)	0	0	10 (4.0)	2 (0.8)	0
HEADACHE	3 (2.3)	0	0	4 (3.1)	0	0	7 (2.8)	0	0
DIZZINESS	7 (5.4)	0	0	2 (1.5)	0	0	5 (2.0)	0	0
DYSGEUSIA	5 (3.9)	0	0	2 (1.5)	0	0	4 (1.6)	0	0
PRESYNCOPE	0	0	0	2 (1.5)	0	0	2 (0.8)	0	0
AMNESIA	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
HYPOGEUSIA	0	0	0	0	0	0	1 (0.4)	0	0
MYASTHENIC SYNDROME	0	0	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
LETHARGY	3 (2.3)	1 (0.8)	0	0	0	0	0	0	0
NEUROTOXICITY	4 (3.1)	2 (1.6)	0	0	0	0	0	0	0
PAROSMIA	1 (0.8)	0	0	0	0	0	0	0	0
SOMNOLENCE	1 (0.8)	0	0	0	0	0	0	0	0

System Organ Class (%) Preferred Term (%)	CA209017 DOCETAXEL N = 129 Any Grade	CA209017 DOCETAXEL N = 129 Grade 3-4	CA209017 DOCETAXEL N = 129 Grade 5	CA209017 NIVOLUMAB 3 mg/kg N = 131 Any Grade	CA209017 NIVOLUMAB 3 mg/kg N = 131 Grade 3-4	CA209017 NIVOLUMAB 3 mg/kg N = 131 Grade 5	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Any Grade	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Grade 3-4	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Grade 5
INVESTIGATIONS	14 (10.9)	6 (4.7)	0	10 (7.6)	2 (1.5)	0	18 (7.3)	2 (0.8)	0
BLOOD CREATININE INCREASED	2 (1.6)	0	0	4 (3.1)	0	0	6 (2.4)	0	0
WEIGHT DECREASED	6 (4.7)	0	0	1 (0.8)	1 (0.8)	0	4 (1.6)	1 (0.4)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	2 (1.6)	0	0	2 (1.5)	0	0	3 (1.2)	0	0
TRANSAMINASES INCREASED	1 (0.8)	1 (0.8)	0	2 (1.5)	0	0	3 (1.2)	0	0
AMYLASE INCREASED	0	0	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
BLOOD THYROID STIMULATING HORMONE DECREASED	0	0	0	0	0	0	1 (0.4)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	0	0	0	0	0	0	1 (0.4)	0	0
LIPASE INCREASED	0	0	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
WHITE BLOOD CELL COUNT DECREASED	7 (5.4)	5 (3.9)	0	0	0	0	1 (0.4)	0	0
BLOOD BILIRUBIN INCREASED	1 (0.8)	0	0	0	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	73 (56.6)	56 (43.4)	0	5 (3.8)	1 (0.8)	0	15 (6.0)	4 (1.6)	0
ANAEMIA	29 (22.5)	4 (3.1)	0	2 (1.5)	0	0	9 (3.6)	1 (0.4)	0
LYMPHOPENIA	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0	4 (1.6)	3 (1.2)	0
THROMBOCYTOPENIA	2 (1.6)	1 (0.8)	0	2 (1.5)	0	0	4 (1.6)	0	0
LEUKOPENIA	8 (6.2)	5 (3.9)	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
LYMPHADENOPATHY	0	0	0	0	0	0	1 (0.4)	0	0
NEUTROPENIA	50 (38.8)	44 (34.1)	0	1 (0.8)	0	0	1 (0.4)	0	0
FEBRILE BONE MARROW APLASIA	1 (0.8)	1 (0.8)	0	0	0	0	0	0	0
FEBRILE NEUTROPENIA	14 (10.9)	13 (10.1)	0	0	0	0	0	0	0
PANCYTOPENIA	1 (0.8)	1 (0.8)	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	19 (14.7)	5 (3.9)	1 (0.8)	5 (3.8)	1 (0.8)	0	12 (4.8)	2 (0.8)	1 (0.4)
HERPES ZOSTER	0	0	0	0	0	0	2 (0.8)	1 (0.4)	0
ORAL FUNGAL INFECTION	1 (0.8)	0	0	0	0	0	2 (0.8)	0	0
SKIN INFECTION	1 (0.8)	0	0	1 (0.8)	0	0	2 (0.8)	0	0
BRONCHITIS	0	0	0	0	0	0	1 (0.4)	0	0
CANDIDA INFECTION	3 (2.3)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
FURUNCLE	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
INFECTION	2 (1.6)	1 (0.8)	0	0	0	0	1 (0.4)	0	0
ORAL CANDIDIASIS	3 (2.3)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
PNEUMONIA	4 (3.1)	3 (2.3)	0	0	0	0	1 (0.4)	0	1 (0.4)
UPPER RESPIRATORY TRACT INFECTION	1 (0.8)	0	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
NEUTROPENIC INFECTION	1 (0.8)	1 (0.8)	0	0	0	0	0	0	0
ONYCHOMYCOSIS	1 (0.8)	0	0	0	0	0	0	0	0
PARONYCHIA	1 (0.8)	0	0	0	0	0	0	0	0
RESPIRATORY TRACT INFECTION	1 (0.8)	0	0	0	0	0	0	0	0

System Organ Class (%) Preferred Term (%)	CA209017 DOCETAXEL N = 129 Any Grade	Grade 3-4	Grade 5	CA209017 NIVOLUMAB 3 mg/kg N = 131 Any Grade	Grade 3-4	Grade 5	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Any Grade	Grade 3-4	Grade 5
SEPSIS	1 (0.8)	0	1 (0.8)	0	0	0	0	0	0
URINARY TRACT INFECTION	2 (1.6)	0	0	0	0	0	0	0	0
ENDOCRINE DISORDERS	0	0	0	5 (3.8)	0	0	10 (4.0)	1 (0.4)	0
HYPOTHYROIDISM	0	0	0	5 (3.8)	0	0	8 (3.2)	0	0
ADRENAL INSUFFICIENCY	0	0	0	0	0	0	1 (0.4)	1 (0.4)	0
THYROIDITIS	0	0	0	0	0	0	1 (0.4)	0	0
VASCULAR DISORDERS	8 (6.2)	1 (0.8)	0	5 (3.8)	0	0	10 (4.0)	1 (0.4)	0
FLUSHING	4 (3.1)	0	0	2 (1.5)	0	0	4 (1.6)	0	0
HYPOTENSION	3 (2.3)	1 (0.8)	0	2 (1.5)	0	0	3 (1.2)	0	0
HYPERTENSION	0	0	0	1 (0.8)	0	0	2 (0.8)	0	0
THROMBOSIS	0	0	0	0	0	0	1 (0.4)	0	0
VASCULITIS	0	0	0	0	0	0	1 (0.4)	1 (0.4)	0
PHLEBITIS	2 (1.6)	0	0	0	0	0	0	0	0
CARDIAC DISORDERS	1 (0.8)	1 (0.8)	0	2 (1.5)	0	0	4 (1.6)	0	0
PERICARDIAL EFFUSION	0	0	0	1 (0.8)	0	0	2 (0.8)	0	0
TACHYCARDIA	0	0	0	1 (0.8)	0	0	2 (0.8)	0	0
ATRIAL FIBRILLATION	1 (0.8)	1 (0.8)	0	0	0	0	0	0	0
IMMUNE SYSTEM DISORDERS	2 (1.6)	1 (0.8)	0	0	0	0	3 (1.2)	2 (0.8)	0
HYPERSENSITIVITY	2 (1.6)	1 (0.8)	0	0	0	0	3 (1.2)	2 (0.8)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1.6)	0	0	2 (1.5)	0	0	3 (1.2)	0	0
INFUSION RELATED REACTION	1 (0.8)	0	0	1 (0.8)	0	0	1 (0.4)	0	0
INJURY	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
PROCEDURAL NAUSEA	0	0	0	0	0	0	1 (0.4)	0	0
RADIATION PNEUMONITIS	1 (0.8)	0	0	0	0	0	0	0	0
RENAL AND URINARY DISORDERS	1 (0.8)	0	0	1 (0.8)	1 (0.8)	0	3 (1.2)	1 (0.4)	0
RENAL FAILURE	1 (0.8)	0	0	0	0	0	2 (0.8)	0	0
TUBULOINTERSTITIAL NEPHRITIS	0	0	0	1 (0.8)	1 (0.8)	0	1 (0.4)	1 (0.4)	0
EAR AND LABYRINTH DISORDERS	1 (0.8)	0	0	0	0	0	2 (0.8)	0	0
EAR DISORDER	0	0	0	0	0	0	1 (0.4)	0	0
TINNITUS	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0
EYE DISORDERS	5 (3.9)	0	0	1 (0.8)	0	0	2 (0.8)	0	0
DRY EYE	0	0	0	0	0	0	1 (0.4)	0	0
SCLERAL HYPERAEMIA	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
DACRYOSTENOSIS ACQUIRED	1 (0.8)	0	0	0	0	0	0	0	0
LACRIMATION INCREASED	4 (3.1)	0	0	0	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	1 (0.8)	0	0	2 (0.8)	0	0

System Organ Class (%) Preferred Term (%)	CA209017 DOCETAXEL N = 129 Any Grade	Grade 3-4	Grade 5	CA209017 NIVOLUMAB 3 mg/kg N = 131 Any Grade	Grade 3-4	Grade 5	CA209017+CA209063 NIVOLUMAB 3 mg/kg N = 248 Any Grade	Grade 3-4	Grade 5
HISTIOCYTIC NECROTISING LYMPHADENITIS	0	0	0	1 (0.8)	0	0	1 (0.4)	0	0
SEBORRHOEIC KERATOSIS	0	0	0	0	0	0	1 (0.4)	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0
ERECTILE DYSFUNCTION	1 (0.8)	0	0	0	0	0	1 (0.4)	0	0
PSYCHIATRIC DISORDERS	2 (1.6)	0	0	0	0	0	0	0	0
MENTAL STATUS CHANGES	1 (0.8)	0	0	0	0	0	0	0	0
SLEEP DISORDER	1 (0.8)	0	0	0	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.
Some preferred terms are re-mapped or deleted based on BMS medical review.

Adverse drug reactions

Related adverse events from Table 34 were excluded from the product information because of 1 or more of the following reasons:

- Overly general/non-specific
- No suspected causal relationship to nivolumab per BMS medical review
- Single case events with limited data
- Medical concept captured under a different term
- Covered in a separate label output of laboratory abnormalities

Adverse reactions reported in subjects with SQ NSCLC who were treated with nivolumab 3 mg/kg in CA209017 and CA209063 (N = 248, pooled population), including laboratory measurements worsened from baseline, are presented in Table. Adverse reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 37: Adverse reactions in patients with squamous NSCLC treated with nivolumab 3 mg/kg (CA209017 and CA209063)

Infections and infestations	
Uncommon	bronchitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	histocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Immune system disorders	
Uncommon	anaphylactic reaction, hypersensitivity, infusion related reaction
Endocrine disorders	
Common	Hypothyroidism
Uncommon	adrenal insufficiency, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	myasthenic syndrome, polyneuropathy
Cardiac disorders	
Uncommon	Tachycardia
Vascular disorders	
Uncommon	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	Nausea
Common	diarrhoea, stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	colitis, duodenal ulcer
Skin and subcutaneous tissue disorders	
Common	rash, pruritus
Uncommon	Urticaria
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain,[a] arthralgia
Uncommon	polymyalgia rheumatica
Renal and urinary disorders	
Uncommon	tubulointerstitial nephritis, renal failure
General disorders and administration site conditions	
Very common	Fatigue
Common	pyrexia, oedema
Investigations	
Very common	increased AST,[b] increased ALT,[b] increased alkaline phosphatase,[b] increased creatinine,[b] decreased lymphocytes,[b] decreased platelet count,[b] decreased haemoglobin,[b] hypercalcaemia,[b] hypocalcaemia,[b] hyperkalaemia,[b] hypokalaemia,[b] hypomagnesaemia,[b] hyponatraemia[b]
Common	increased total bilirubin,[b] decreased absolute neutrophil count,[b] hypermagnesaemia,[b] hypernatraemia[b]
Uncommon	Increased lipase, increased amylase

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

[b] Frequencies reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements.

Adverse events of special interest:

In order to characterise AEs of special clinical interest, the Sponsor identified selected AEs based on the following 4 guiding principles:

- AEs which may differ in type frequency, or severity from AEs caused by non-immunotherapies
- AEs which may require immunosuppression (eg, corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms maybe used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization

Endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, and rash are currently considered to be select AEs.

Endocrine AEs:

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

In the pooled analyses of study CA209017 and CA209063, nivolumab showed an incidence of thyroid disorders, including hypothyroidism or thyroiditis, of 4.4% (11/248). Grade 2 cases were reported in 3.6% (9/248) of patients. No Grade 3- 5 thyroid disorders were reported. The incidence of adrenal insufficiency was 0.4% (1/248; Grade 3). There were no reports of hypophysitis, diabetes mellitus, or diabetic ketoacidosis in these studies (see section 4.8 of the SmPC).

- Median time to onset of endocrine select AEs was 17.8 weeks (range: 6.1 to 33.1 weeks).
- Resolution occurred in 6 of 12 subjects (50.0%), 5 of 11 thyroid disorders and the adrenal insufficiency, and median time to resolution was 20.6 weeks (range: 0.4 to 47.6^{+} weeks); $^{+}$ denotes a censored observation.
- Three subjects required high dose of corticoids (at least 40 mg prednisone equivalents) at a median initial dose of 1.1 mg/kg (range: 0.5-1.3) for 2.7 weeks (range: 0.6-4.6). One subject required permanent discontinuation of nivolumab due to Grade 3 adrenal insufficiency.

Gastrointestinal AEs:

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

The pooled analysis of CA209017 and CA209063, showed a frequency of diarrhoea or colitis was 9.3% (23/248). Grade 2 and Grade 3 cases were reported in 2% (5/248) and 1.6% (4/248) of patients, respectively. No Grade 4 or 5 cases were reported (see section 4.8 of the SmPC).

- Median time to onset of GI selected AEs was 5.6 weeks (range: 0.1 to 91.0 weeks).
- Three patients, including 2 patients with a Grade 3 case, received high dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.6 mg/kg (range: 0.4-1.3), for a median duration of 2.0 weeks (range: 1.4 to 14.1 weeks). One patient required permanent discontinuation of nivolumab due to Grade 3 diarrhoea.
- Resolution occurred in 19 of 23 subjects (82.6%) with a median time to resolution of 2.0 weeks (range: 0.1 to 31.0 weeks).

Hepatic AEs:

The hepatic selected AE category included the following terms: acute hepatic failure, ALT increased, AST increased, bilirubin conjugated increased, blood bilirubin increased, gamma-glutamyl-transferase (GGT) increased, hepatic enzyme increased, hepatic failure, hepatitis, hepatitis acute, hyperbilirubinemia, liver disorder, liver function test abnormal, liver injury, and transaminases increased.

The pooled analysis of CA209017 and CA209063, showed a frequency of drug-related hepatic selected AEs of 1.2% (3/248). Grade 2 cases were reported in 0.4% (1/248) of patients. No Grade 3-5 cases were reported and no patient had blood bilirubin increased (see section 4.8 of the SmPC).

- Median time to onset of hepatic select AEs was 25.1 weeks (range: 4.1 to 31.1 weeks).
- None of these subjects received high-dose corticosteroids (at least 40 mg prednisone equivalents).
- One patient required permanent discontinuation of nivolumab due to Grade 2 increases in transaminases.
- Resolution occurred in 2 patients (67%) with a median time to resolution of 4.1 weeks (range: 2.9 to 22.3^{+} weeks); $^{+}$ denotes a censored observation.

Only 1 subject in the SQ NSCLC 3 mg/kg cohort of MDX1106-03 experienced an AE belonging to the hepatic select AE category; Grade 3 transaminase increased considered drug-related by the investigator which led to study discontinuation.

Pulmonary AEs:

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 pooled analysis of CA209017 and CA209063 studies, the incidence of pneumonitis, including interstitial lung disease, was 5.2% (13/248). Grade 2 and Grade Grade 3 cases were reported in 2.8% (7/248) and 1.6% (4/248) of patients, respectively. No Grade 4 or 5 cases reported in these studies. In the phase 1 study MDX1106-03, pneumonitis, including a Grade 4 case in 1 patient, was reported in 3/37 patients (8.1%) with NSCLC receiving nivolumab 3 mg/kg (see section 4.8 of the SmPC).

Median time to onset was 11.6 weeks (range: 2.6-85.1). Eleven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.1 mg/kg (range: 0.5-4.0) for a median total duration of 4.3 weeks (range: 0.6-13.1). Eight patients, including the 4 patients with a Grade 3 case, required permanent discontinuation of nivolumab due to pneumonitis. Resolution occurred in all 13 patients with a median time to resolution of 3.9 weeks (range: 0.6-13.4).

Renal AEs:

The renal select AE category to describe an interstitial nephritis 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 pooled analysis of studies CA209017 and CA209063, the frequency of drug-related renal select AEs was 3.2% (8/248). Grade 2 and Grade 3 cases were reported in 1.2% (3/248) and 0.4% (1/248) of patients, respectively. No Grade 4 or 5 nephritis or renal dysfunction was reported in these studies (see section 4.8 of the SmPC).

- Median time to onset of renal select AEs was 10.5 weeks (range: 2.1 to 27.0 weeks).

- Two subjects, including the 1 subject with Grade 3 tubulointerstitial nephritis, received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.8 mg/kg (range: 0.5-1.2) for a median duration of 5.3 weeks (range: 0.9 to 9.7 weeks); no renal AEs led to permanent discontinuation of nivolumab.
- Resolution occurred in 5 of 7 subjects (71.4%), including the Grade 3 tubulointerstitial nephritis, with a median time to resolution of 5.9 weeks (range: 0.7 to 37.6^{+} weeks); $^{+}$ denotes a censored observation.

Skin AEs:

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 maculopapular, rash papular, rash pruritic, skin exfoliation, skin hypopigmentation, skin irritation, Steve-Johnson Syndrome, toxic epidermal necrolysis, urticaria, and vitiligo

In the pooled analysis of studies CA209017 and CA209063, the incidence of rash was 12.1% (30/248). Grade 2 and Grade 3 cases were reported in 1.6% (4/248) and 0.8% (2/248) of patients, respectively. No Grade 4 or 5 rash was reported in these studies (see section 4.8 of the SmPC).

- Median time to onset of skin select AEs was 8.1 weeks (range: 0.3 to 51.9 weeks).
- None of these patients received high-dose corticosteroids.
- Two patients required permanent discontinuation of nivolumab (1 with Grade 2 rash and 1 with Grade 3 rash).
- Resolution occurred in 24 patients (83%) and median time to resolution was 5.7 weeks (range: 0.1 to 46.9^{+} weeks); $^{+}$ denotes a censored observation.

Hypersensitivity/infusion reactions AEs:

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

In the pooled analysis of studies CA209017 and CA209063, the frequency of drug-related hypersensitivity/infusion reactions was 1.6% (4/248). There was 1 Grade 3 anaphylactic reaction and 1 Grade 4 hypersensitivity (both required permanent discontinuation of nivolumab) (see section 4.8 of the SmPC).

- Median time to onset of hypersensitivity/infusion reactions was 1.2 weeks (range: 0.1 to 27.9 weeks).
- Two subjects received high dose corticosteroids (at least 40 mg prednisone equivalents), each for a duration of 0.1 weeks.
- Resolution occurred in all 4 subjects and median time to resolution was 0.1 weeks (range: 0.1 to 0.3 weeks).

Serious adverse event / deaths / other significant events

The following table summarises the frequency of serious adverse events and deaths in study CA209017 and in the pooled analysis of studies CA209017 and CA209063.

Table 38: SAEs and deaths - All Treated Subjects - CA209017 and CA209017 + CA209063

	CA209017			CA209017 + CA209063		
	Docetaxel (N = 129)			Nivolumab (N = 131)			Nivolumab (N = 248)		
DEATHS									
NUMBER OF SUBJECTS WHO DIED (%)	106 (82.2)			82 (62.6)			154 (62.1)		
PRIMARY REASON FOR DEATH (%)									
DISEASE PROGRESSION	86 (66.7)			73 (55.7)			136 (54.8)		
STUDY DRUG TOXICITY	3 (2.3)			0			2 (0.8)		
UNKNOWN	4 (3.1)			1 (0.8)			1 (0.4)		
OTHER	13 (10.1)			8 (6.1)			15 (6.0)		
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	20 (15.5)			16 (12.2)			30 (12.1)		
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	54 (41.9)			46 (35.1)			88 (35.5)		
	CA209017						CA209017 + CA209063		
	Docetaxel (N = 129)			Nivolumab (N = 131)			Nivolumab (N = 248)		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL SAES									
TOTAL SUBJECTS WITH AN EVENT	70 (54.3)	42 (32.6)	17 (13.2)	61 (46.6)	36 (27.5)	15 (11.5)	129 (52.0)	78 (31.5)	30 (12.1)
MOST FREQUENT (017 + 063, > 2%)									
MALIGNANT NEOPLASM PROGRESSION	9 (7.0)	2 (1.6)	6 (4.7)	18 (13.7)	4 (3.1)	10 (7.6)	26 (10.5)	4 (1.6)	17 (6.9)
PNEUMONIA	10 (7.8)	8 (6.2)	0	7 (5.3)	7 (5.3)	0	14 (5.6)	12 (4.8)	2 (0.8)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1 (0.8)	1 (0.8)	0	2 (1.5)	2 (1.5)	0	6 (2.4)	6 (2.4)	0
DYSPNOEA	2 (1.6)	2 (1.6)	0	2 (1.5)	2 (1.5)	0	9 (3.6)	7 (2.8)	0
PNEUMONITIS	0	0	0	2 (1.5)	1 (0.8)	0	7 (2.8)	5 (2.0)	0
HYPERCALCAEMIA	0	0	0	4 (3.1)	2 (1.5)	0	9 (3.6)	4 (1.6)	0
DRUG-RELATED SAES									
TOTAL SUBJECTS WITH AN EVENT	31 (24.0)	25 (19.4)	3 (2.3)	9 (6.9)	3 (2.3)	0	21 (8.5)	12 (4.8)	1 (0.4)
MOST FREQUENT (017 + 063, > 1%)									
PNEUMONITIS	0	0	0	1 (0.8)	0	0	6 (2.4)	4 (1.6)	0

In study CA209063, two subjects (1.7%) died due to study drug toxicity within 100 days of last dose in CA209063; one due to hypoxic pneumonia and one due to ischemic stroke.

Laboratory findings

In the pooled analysis of studies CA209017 and CA209063, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 13.2% for decreased lymphocytes, 9% for hyponatraemia, 2.9% for hypercalcaemia and hyperkalaemia, 2.5% for decreased haemoglobin (all Grade 3), 2.0% for hypokalaemia, 1.6% for decreased neutrophil count, 1.3% for hypomagnesaemia, 1.2% for hypocalcaemia, 0.8% for increased total bilirubin, and 0.4% for increased AST, decreased platelet, hypomagnesaemia, and hypernatremia. There was no worsening to Grade 3 or 4 in increased ALT, increased alkaline phosphatase, and increased creatinine (see section 4.8 of the SmPC).

A summary of laboratory parameters that worsened relative to baseline for study CA209017 and pooled analysis from studies CA209017 and CA209063 is summarised in the following table.

Table 39: Summary of On-Treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters that Worsened Relative to Baseline - All Treated Subjects

	Number (%) of Subjects								
	CA209017						CA209017+CA209063		
	Docetaxel			Nivolumab			Nivolumab		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	126	72 (57.1)	7 (5.6)	130	42 (32.3)	3 (2.3)	244	74 (30.3)	6 (2.5)
PLATELET COUNT	125	17 (13.6)	0	130	14 (10.8)	1 (0.8)	244	30 (12.3)	1 (0.4)
LEUKOCYTES	128	103 (80.5)	66 (51.6)	130	16 (12.3)	4 (3.1)	244	30 (12.3)	4 (1.6)
LYMPHOCYTES (ABSOLUTE)	125	79 (63.2)	35 (28.0)	129	59 (45.7)	14 (10.9)	243	113 (46.5)	32 (13.2)
ABSOLUTE NEUTROPHIL COUNT	126	92 (73.0)	73 (57.9)	130	11 (8.5)	4 (3.1)	244	17 (7.0)	4 (1.6)
ALKALINE PHOSPHATASE	124	22 (17.7)	2 (1.6)	129	31 (24.0)	0	240	47 (19.6)	0
ASPARTATE AMINOTRANSFERASE	123	14 (11.4)	2 (1.6)	129	32 (24.8)	0	242	50 (20.7)	1 (0.4)
ALANINE AMINOTRANSFERASE	124	25 (20.2)	1 (0.8)	129	23 (17.8)	0	242	36 (14.9)	0
BILIRUBIN, TOTAL	124	11 (8.9)	0	129	7 (5.4)	0	242	10 (4.1)	2 (0.8)
CREATININE	124	14 (11.3)	1 (0.8)	130	22 (16.9)	0	244	47 (19.3)	0
HYPERCALCEMIA	124	9 (7.3)	2 (1.6)	130	31 (23.8)	4 (3.1)	244	54 (22.1)	7 (2.9)
HYPOCALCEMIA	124	27 (21.8)	1 (0.8)	130	27 (20.8)	1 (0.8)	244	47 (19.3)	3 (1.2)
HYPERKALEMIA	123	29 (23.6)	8 (6.5)	130	35 (26.9)	2 (1.5)	244	55 (22.5)	7 (2.9)
HYPOKALEMIA	123	14 (11.4)	2 (1.6)	130	17 (13.1)	2 (1.5)	244	40 (16.4)	5 (2.0)
HYPERMAGNESEMIA	120	7 (5.8)	0	125	7 (5.6)	1 (0.8)	237	12 (5.1)	1 (0.4)
HYPOMAGNESEMIA	120	23 (19.2)	0	125	31 (24.8)	2 (1.6)	237	55 (23.2)	3 (1.3)
HYPERNATREMIA	125	3 (2.4)	0	130	8 (6.2)	1 (0.8)	244	13 (5.3)	1 (0.4)
HYPONATREMIA	125	46 (36.8)	12 (9.6)	130	43 (33.1)	11 (8.5)	244	86 (35.2)	22 (9.0)

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

Immunogenicity

A pooled analysis of nivolumab anti-drug antibody (ADA) assessments was performed with data available from the following 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, and CA209017). The confirmed ADA positive samples were then tested with a neutralizing antibody assay.

Table 40: Integrated Summary of anti-nivolumab anti-drug antibody (ADA) assessments – Studies CA209037, CA209063, CA209066, and CA209017

	Number of Patients (%)				
	CA209063 (N=101)	CA209037 (N=180)	CA209066 (N=107)	CA209017[a] (N=109)	Pooled Summary (N=497)
Baseline ADA Positive	11 (10.9)	9 (5.0)	3 (2.8)	8 (7.3)	31 (6.2)
ADA Positive	12 (11.9)	12 (6.7)	6 (5.6)	21 (19.3)	51 (10.3)
Persistent Positive	0	2 (1.1)	0	2 (1.8)	4 (0.8)
Only Last Sample Positive	6 (5.9)	4 (2.2)	2 (1.9)	3 (2.8)	15 (3.0)
Other Positive	6 (5.9)	6 (3.3)	4 (3.7)	16 (14.7)	32 (6.4)
Neutralizing ADA Positive	0	2 (1.1)	0	3 (2.8)	5 (1.0)
ADA Negative	89 (88.1)	168 (93.3)	101 (94.4)	88 (80.7)	446 (89.7)

Overall, a total of 497 patients (from CA209063, CA209037, CA209066, and CA209017 studies) were treated with nivolumab 3 mg/kg every 2 weeks and had available ADA assessments at baseline and post-baseline. Out of 497 patients, 51 patients (10.3%) were tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay after initiation of nivolumab (relative to baseline), of whom:

- Four patients (0.8%) were considered persistent positive
- Neutralizing antibodies were detected in only 5 patients (1%), out of which 4 subjects were negative for neutralizing ADA at subsequent samples.
- The observed titers in the ADA positive samples were low (≤ 512)

Safety in special populations

The safety profile of nivolumab was similar between the subgroups based on intrinsic (race, gender) and extrinsic (geographical location) factors.

A summary of adverse events in the elderly population is presented below.

Table 41: Summary of Adverse Events by Age Groups – Pooled studies CA209017 and CA209063

MedDRA Terms	Age < 65 years (N=134) n (%)	Age 65 - 74 years (N=87) n (%)	Age 75-84 years (N=25) n (%)	Age 85+ years (N=2) n (%)
Total AEs	130 (97.0)	87 (100.0)	25 (100.0)	2 (100.0)
Serious AEs – Total	67 (50.0)	46 (52.9)	14 (56.0)	2 (100.0)
- Fatal	18 (13.4)	11 (12.6)	5 (20.0)	0
- Hospitalization/prolong existing hospitalization	55 (41.0)	42 (48.3)	12 (48.0)	2 (100.0)
- Life-threatening	1 (0.7)	1 (1.1)	0	0
- Disability/incapacity	1 (0.7)	0	0	0
- Other (medically significant)	6 (4.5)	6 (6.9)	0	0
AE leading to drop-out	31 (23.1)	14 (16.1)	6 (24.0)	0
Psychiatric disorders	18 (13.4)	10 (11.5)	3 (12.0)	2 (100.0)
Nervous system disorders	40 (29.9)	29 (33.3)	9 (36.0)	1 (50.0)
Accidents and injuries	5 (3.7)	8 (9.2)	2 (8.0)	1 (50.0)
Cardiac disorders	15 (11.2)	14 (16.1)	2 (8.0)	1 (50.0)
Vascular disorders	18 (13.4)	14 (16.1)	2 (8.0)	1 (50.0)
Cerebrovascular disorders	0	2 (2.3)	0	0
Infections and infestations	40 (29.9)	37 (42.5)	10 (40.0)	2 (100.0)
Anticholinergic syndrome	48 (35.8)	28 (32.2)	10 (40.0)	1 (50.0)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	13 (9.7)	9 (10.3)	4 (16.0)	0

MedRA Version: 17.1; CTC Version: 4.0. Abbreviations: AEs = adverse events; HLGT = high level group terms; MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event, SOC = system organ class; SMQ = Standardized MedDRA Queries

Source: Appendix Q66.1.eu (AEs by Age Group), Appendix Q66.2.eu (SAEs by Age group), Appendix Q66.3.eu (AE Leading to Discontinuation), Appendix Q66.4.eu (AE by Selected SOC/HLGT/SMQ), Appendix Q66.5.eu (Sum of Postural Hypotension, Falls, Black Outs, Syncope, Dizziness, Ataxia, Fractures), Appendix Q66.6.eu (SAEs by Category), and Appendix Q66.7.eu (QOL Decreased).

Safety related to drug-drug interactions and other interactions

The applicant did not submit studies on drug-drug interaction (see safety discussion).

Discontinuation due to adverse events

In the pooled analysis of studies CA209017 and CA209063, pneumonitis and malignant disease progression were the most frequently reported AE leading to discontinuation of the study.

Table 42: AEs leading to discontinuation - All Treated Subjects - CA209017 and CA209017 + CA209063

	CA209017						CA209017 + CA209063		
	Docetaxel (N = 129)			Nivolumab (N = 131)			Nivolumab (N = 248)		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL AES LEADING TO DISCONTINUATION									
TOTAL SUBJECTS WITH AN EVENT	26 (20.2)	16 (12.4)	4 (3.1)	14 (10.7)	7 (5.3)	2 (1.5)	51 (20.6)	31 (12.5)	11 (4.4)
MOST FREQUENT (017 + 063, > 2%)									
PNEUMONITIS	0	0	0	3 (2.3)	1 (0.8)	0	8 (3.2)	5 (2.0)	0
MALIGNANT NEOPLASM PROGRESSION	2 (1.6)	2 (1.6)	0	4 (3.1)	2 (1.5)	1 (0.8)	8 (3.2)	2 (0.8)	5 (2.0)
DRUG-RELATED AES LEADING TO DISCONTINUATION									
TOTAL SUBJECTS WITH AN EVENT	13 (10.1)	8 (6.2)	1 (0.8)	4 (3.1)	2 (1.5)	0	18 (7.3)	14 (5.6)	0
MOST FREQUENT (017 + 063, > 1%)									
PNEUMONITIS	0	0	0	2 (1.5)	0	0	7 (2.8)	4 (1.6)	0

Post marketing experience

The applicant did not submit post-marketing experience.

2.6.1. Discussion on clinical safety

A total of 1826 patients have been exposed to nivolumab 3 mg Q2W, but most of the results are still blinded. The unblinded results include the melanoma population and mainly the SQ-NSCLC population.

The safety profile for the intended indication is mainly based on the open label studies CA 209017 and CA209063. Nivolumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions resolved following initiation of appropriate medical therapy or withdrawal of nivolumab.

The pooled analyses of study CA 20917 and CA 209063 show an incidence of adverse events of 98.4%, with an incidence of 14.5% of grade 3-4 AE"S and 12% of grade 5 AE.

The most frequently reported adverse events are fatigue (39.5%), dyspnoea (37.1%), cough (31.5%) decreased appetite (29.4%) and nausea (21.8)

The most frequents grade 3-4 AEs are dyspnoea, (6.9%), fatigue (4.4%), nausea (2.0%), cough (1.6%) and decreased appetite (1.6%)

Selected AEs on the basis of its mechanism of action and rate of frequency include endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, rash and hypersensitivity/infusion reactions, with the

multiple event terms that may describe each of these grouped into endocrine, GI, hepatic, pulmonary, renal, and skin selected AE categories, respectively.

According to the data submitted, the immunological ADRs related to nivolumab (pooled studies CA209017, CA209063) and identified as important identified risks include skin, gastrointestinal, endocrine, hepatic, pulmonary, and renal events, with the following terms reported: rash (12.1%), diarrhoea or colitis (9.3%), pneumonitis (5.2%), thyroid disorders (4.4%), nephritis or renal dysfunction (3.2%), hypersensitivity/infusion reactions (1.6%) and liver function abnormalities (1.2%). The SmPC sections 4.2 and 4.4 and 4.8 contain the recommendations on how to manage the immunologic ADRs.

Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of NSCLC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis. In addition, these populations have been included in the RMP as missing information.

The time -related adverse event data base is obtained from the 129 patients participating in trial CA209017.

With regards to duration, the endocrine system selected AEs took the longest time to resolve. Most of the events in this category were thyroid gland disorders.

In study CA209017, almost all of the patients reported at least one AE during the study (96.9% in both treatment groups). The most common AEs in the nivolumab treatment group CA209017 were dyspnoea (36.6%), cough (31.3%), and fatigue (30.5%), while in the docetaxel group were fatigue (39.5%), neutropenia (33.3%) and dyspnoea (29.5%). Nivolumab showed a lower incidence than docetaxel of grade 3 adverse events (51% vs 73%), serious adverse events (47% vs. 54%, grade 3 AE 39% vs. 46%) and AEs leading to discontinuation (11% vs. 20%). Drug-related SAEs were reported for 6.9 % and 24.0% of patients in the nivolumab and docetaxel groups, respectively. The reduction in incidence of adverse events between nivolumab and docetaxel was mainly due but not limited to the large difference in haematological events like lymphopenia and neutropenia.

The adverse events favouring docetaxel (≥5% difference) were dyspnoea, cough and hypercalcaemia; however, the adverse events favouring nivolumab were fatigue, anaemia, asthenia, diarrhoea, nausea, neutropenia and alopecia.

The adverse events ≥ grade 3 favouring nivolumab (≥5% difference) were fatigue, asthenia, diarrhoea and neutropenia. No adverse events ≥ grade 3 was reported with ≥5% difference in the nivolumab arm indicating that nivolumab could be better tolerated

The majority of on-study deaths were due to disease progression (55.7% nivolumab, 66.7% docetaxel). No deaths occurring in nivolumab-treated patients were considered drug-related, while in the docetaxel group, 3 deaths (2.3%) were attributed to study drug toxicity.

Pneumonitis was identified in the early studies as a potential drug-related lethal adverse event. In general, the outcomes and severity of pneumonitis AEs occurred in the phase II and Phase III studies were more favourable than those observed during the phase I study. This is probably explained by the implementation of standardized clinical management of NSCLC patients treated with nivolumab in the later studies. Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease related aetiologies should be ruled out (see sections 4.2, 4.4 and 4.8 of the SmPC).

Regarding special populations, elderly subjects were underrepresented, since literature suggests that one third of NSCLC patients are over 65 years old. According to safety data broken down by age (Age 65-74, Age 75-84, and Age 85+), an increasing trend in frequency could be seen for most AEs of special interest in the elderly (e.g. those affecting the CNS). However, for drug-related AEs by Age, frequencies seemed very similar for patients <65 and those ≥65 and <75 years of age and lower for patients over the age of 75. Considering the limited number of patients over 75 (n=27, and 2 >85), no sound conclusions can be drawn regarding the potential relationship between nivolumab toxicity and age. Safety of nivolumab in the elderly will be followed up in the post-marketing setting.

Data in subjects with severe renal impairment and moderate or severe hepatic impairment is limited; caution should be exercised when using nivolumab in these patient populations.

In study CA209017, hypercalcaemia was more frequently reported in the nivolumab group (31/130, 24%) than in the docetaxel group (9/124, 7%). This is most likely due to the malignancy and/or presence of bone metastases (more frequently reported for nivolumab patients at baseline) although the exact cause is not known. Immune-related hyperparathyroidism might be considered especially if associated with hypophosphataemia (reported in 6 hypercalcaemic patients in this study). Although hypercalcaemia is usually a sign of poor prognosis, the overall nivolumab treated population showed an improved overall survival. Monitoring and managing of hypercalcaemia in clinical practice is considered feasible and should not add additional burden to the patients' care.

Severe infusion reactions have been reported in clinical trials. In case of a severe infusion reaction, nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring (see section 4.4 and 4.8 of the SmPC). This risk has been included in the RMP as an important identified risk.

A low percentage of patients were positive for nivolumab ADA, most of them with low titers. A small number of patients had detectable neutralizing antibodies, and very few patients had persistent ADA throughout the treatment period. There was no evidence of altered pharmacokinetic or toxicity profile associated with anti product antibody development. Based on these facts, the CHMP considers that nivolumab shows a low immunogenicity potential. Given the low number of patients tested, the risk of developing ADA was considered not yet fully investigated. For suspected immune related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered. Upon improvement, nivolumab may be resumed after corticosteroid taper. Nivolumab must be permanently discontinued for any severe immune related adverse reaction that recurs and for any life threatening immune related adverse reaction (see sections 4.4 and 4.8 of the SmPC). The risk of immunogenicity has been included in the RMP as an important potential risk.

The Applicant has provided a comparison of the safety profile between the melanoma (pooled data from studies CA209003/037/066) and NSCLC populations (pooled data from studies CA209063 and CA209017). Although in general the safety profile is consistent with data previously provided, some differences in incidence of drug-related adverse events can be observed between both tumour types. For instance, drug-related pulmonary adverse events are more frequently observed in the NSCLC population (4.5%) than in the melanoma population (2.5%), while skin related selected AE and endocrine selected AE were more frequently observed in the melanoma population, (skin melanoma vs. NSLCL: 36.5% vs. 12.4%). These differences in incidence of drug-related adverse events might be due to the locally elicited immune response.

Like most therapeutic proteins, nivolumab is not metabolised by liver cytochrome (CYP) P450 metabolising enzymes or other drug-metabolising enzymes, and is not expected to have an effect on cytochrome P450 or other drug-metabolising enzymes in terms of inhibition or induction. In addition, nivolumab treatment did not result in any meaningful change in cytokines known to have indirect effect on CYP enzymes across the dose range 0.3 to 10 mg/kg. The lack of cytokine modulation suggests nivolumab has no or low potential for modulating CYP enzymes and therefore, there is a low risk of a therapeutic protein-drug interaction. Therefore, the lack of studies investigating the safety related to drug-drug interaction is acceptable. There is missing information for patients below 18 years of age, patients with severe hepatic and/or renal impairment. The missing information has been included as part of the RMP and is also described in sections 4.2 and 5.2 of the SmPC.

Based on its pharmacodynamic properties, nivolumab is unlikely to affect the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see sections 4.7 and 4.8 from the SmPC), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

The ADRs reported for patients being treated with nivolumab appear to be mostly of low grade and manageable. It was noted that immunological ADRs include skin, gastrointestinal, endocrine, hepatic, pulmonary and renal events. These are managed appropriately with the recommendations as stated in the SmPC and are also addressed in the RMP. Therefore, the CHMP considers that the safety and tolerability of nivolumab has been described appropriately and is acceptable.

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

- To generate additional information on AEs of special interest (e.g. immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions and infusion reactions) in routine oncology practice during post-marketing use. The study protocol will be discussed at PRAC within 3 months after the EC decision. The applicant should submit study CA209234, a non-interventional PASS. This post-authorisation measure is included in the RMP.

In addition, the CHMP recommends the following the following measure to address issues related to safety:

- To further evaluate the immunogenicity and the impact of ADA on efficacy and safety.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

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
Missing information	Paediatric 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

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/ renal dysfunction, endocrinopathies, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, and myasthenic syndrome), and severe infusion reactions.	Planned	Final CSR submission: 4Q2024

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis or renal dysfunction Immune-related endocrinopathies	The SmPC warns the risks of immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies, immune-related rash, and other immune-related adverse reactions in Section 4.4 (Special warnings and precautions for use), and provides specific guidance on their monitoring and management, including treatment delay or discontinuation and	To further raise awareness of HCPs on important risks of immune-related ARs and their appropriate management, additional risk minimization activity includes a Communication Plan. The Plan comprising 2 tools to be distributed to potential

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Immune related rash Other immune-related ARs	intervention with corticosteroids in Sections 4.2, 4.4 and 4.8. Further ADRs are included in Section 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important safety information in the language suitable for patients.	prescribers at launch by BMS: Adverse Reaction Management Guide Patient Alert Card
Severe infusion reactions	The SmPC warns the risk of severe infusion reactions in Section 4.4 and ADR in Section 4.8.	None
Important Potential Risks		
Embryofetal Toxicity	SmPC includes Embryofetal Toxicity in Section 4.6 Fertility, pregnancy and lactation, Section 5.3 Preclinical safety data The package leaflet also includes specific description on the safety information in the language suitable for patients.	None
Immunogenicity	SmPC Section 4.8 Immunogenicity	None
Missing Information		
Paediatric patients	SmPC Section 4.2 Posology and method of administration, subsection on Pediatric population	None
Severe hepatic and/or renal impairment	SmPC Section 4.2 Posology and method of administration: Patients with hepatic or renal impairment; SmPC Section 5.2 Pharmacokinetic properties: Hepatic or renal impairment	None
Patients with autoimmune disease	SmPC Section 4.4 provides warning and cautionary information for patients with a history of autoimmune disease	None
Patients already receiving systemic immunosuppressants before starting nivolumab	SmPC Sections 4.4 Special populations and 4.5 Systemic Immunosuppressants	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

In a phase III study in patients with documented histologically or cytologically advanced or metastatic SQ NSCLC whose disease had progressed during or after a platinum doublet-based chemotherapy regimen, Nivolumab showed a median overall survival (OS) of 9.2 months vs 6.0 months for docetaxel HR 0.59 (95%CI; (0.44-0.79), p=0.0025. Forty two (42) % vs 24% of patients were alive at 12 months for nivolumab vs docetaxel, respectively.

Treatment differences in terms of PFS were more modest, with a 0.65 month gain for nivolumab over docetaxel HR 0.62 (95 % CI 0.47-0.81) p=0.0004.

Other additional efficacy endpoints (ORR, BOR, and DOR) and an early separation in the Kaplan-Meier OS estimates also favour nivolumab treatment.

The results are supported by the single arm phase II study CA209063, including 117 patients with SQ-NSCLC after at least 2 previous chemotherapy treatments. The updated results show an ORR of 14.5% (95% CI 8.7, 22.2). The median PFS (per IRC) was 1.87 months (95% CI 1.77, 3.15), median OS was 8.21 months (range 6.05 to 10.91 months) with 62% of reported events.

Uncertainty in the knowledge about the beneficial effects.

In the elderly population, the benefit in the age group ≥75 years of age seems smaller (OS [HR 1.85; 95% CI: 0.76, 4.51], PFS [HR=1.76; 95%-CI: 0.77, 4.05]) than in the overall population although it is acknowledged that the number of patients is limited (11 nivolumab vs 18 docetaxel) (see sections 4.2 and 5.1 of the SmPC).

The role of the biomarkers PD-L1 or PD-L2 expression as potential predictive or prognostic biomarkers remains undetermined. The CHMP has imposed a condition to the marketing authorization in Annex II to perform further analyses to ascertain the potential role of the PD-L2 biomarker and other markers, to further explore the relationship between PD-L1 and PD-L2 expression on the efficacy of nivolumab, to continue the exploration of the optimal cut-off for PD-L1 positivity and to further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression.

Risks

Unfavourable effects

The pooled analyses of study CA 209017 and CA 209063 show an incidence of adverse events of 98.4%, with an incidence of 14.5% of grade 3-4 AEs and 12% of grade 5 AE.

The most frequently reported adverse events are fatigue (39.5%), dyspnoea (37.1%), cough (31.5%) decreased appetite (29.4%) and nausea (21.8)

The most frequents grade 3-4 AEs are dyspnoea, (6.9%), fatigue (4.4%), nausea (2.0%), cough (1.6%) and decreased appetite (1.6%)

In general, AEs and drug-related AEs were frequently reported in the studies, mostly of mild-moderate severity, and no clear indications of cumulative toxicity have been observed.

Several AE of special interest ("selected AEs") have been identified for nivolumab. These include endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, rash and hypersensitivity/infusion reactions.

Nivolumab has been associated with study-drug related pneumonitis/ ILD. A total of 14 cases of pneumonitis have been reported in the two main studies (8 in study CA209063, 6 in study CA209017), most of them considered study drug-related (n=13).

In the pivotal study CA 209017, nivolumab showed a comparable incidence for the adverse events (97% v s 97%) with docetaxel. However, nivolumab reported a lower incidence of the adverse events grade ≥3 (51% vs. 73%), serious adverse events (47% vs. 54%) and events leading to discontinuation (11% vs. 20%).

Uncertainty in the knowledge about the unfavourable effects

AEs of special interest will be systematically assessed within ongoing and planned studies (see RMP).

Effects Table

		Short Description	Unit	Arm1 (Nivolumab 3mg/kg)	Arm2 (Docetaxel 75 mg/m²)	Uncertainties/ Strength of evidence
Favourable	OS	Primary endpoint	Median (months)	9.23 95% CI (7.33, 13.27) HR 95% CI: 0.59 (0.43, 0.79)	6.01 95% CI (5.13, 7.33)	Meaningful anti-tumour activity results in heavily pre-treated SQ NSCLC. Superiority over docetaxel demonstrated with a meaningful gain in terms of OS. Only 1 patient achieved CR (BOR was PR for most of the nivolumab patients) Limited data for patients >75 years old Reliability and value of PD-L1 (and PD-L2) as predictive biomarkers is uncertain. Magnitude of the effect in the phase 2 study (3rd line and beyond) is smaller
	PFS	2ndary endpoint	Median (months)	3.48, 95% CI (2.14, 4.86) HR 95% CI: 0.62 (0.47, 0.81)	2.83 95% CI (2.10, 3.52)	
	ORR	2ndary endpoint Complete + partial tumour response	Number (%)	27 (20%), 95% CI (13.6, 27.7) CR= 1 (0.7%) vs PR = 26 (19.3%)	12 (8.8%) 95% CI (4.6, 14.8) CR= 0 vs. PR = 12 (8.8%)	
Unfavourable	Dyspnoea		Proportion	AE 36.6% G3/4 5.3% SAE 1.5%	AE 29.5% G3/4 5 6.2% SAE 1.6%	Safety profile seems manageable and tolerable by patients. Safety dataset of elderly patients is limited Long-term safety data of nivolumab are limited and the relation between duration of treatment and AEs is not known. The size of the safety database might be too limited to determine the incidence of rare and immune related AEs.
	Cough		Proportion	AE 31.3% G3/4 1.5% SAE <1%	AE 18.6% G3/4 0% SAE <1%	
	Fatigue		Proportion	AE 30.5% G3/4 2.3% SAE <1%	AE 39.5% G3/4 8.5% SAE 1.6%	
	Decreased appetite		Proportion	AE 24.4% G3/4 0.8% SAE <1%	AE 27.1% G3/4 1.6% SAE <1%	
	Anaemia		Proportion	AE 16.8% G3/4 3.1% SAE 1.5%	AE 28.7% G3/4 3.1% SAE 14.7%	
	Diarrhoea		Proportion	AE 15.3% G3/4 0% SAE <1%	AE 25.6% G3/4 3.1% SAE <1%	
	Pneumonitis (drug-related)		Proportion	AE 4.6% G3/4 0.8% SAE 0.8%%	AE 0.8% G3/4 0% SAE 0%	
	Tolerability			AE 97% ≥ 1 dose delay/reduction: 27.5% ≥ 1 infusion interruption: 6.1% AE leading to discontinuations 10.7% SAE 46.6%	AE 97% ≥ 1 dose delay/reduction: 41.1% ≥ 1 infusion interruption: 6.2% AE leading to discontinuations 20.2% SAE 54.3%	

Benefit-risk balance

Importance of favourable and unfavourable effects

The superiority of nivolumab over docetaxel in terms of OS was demonstrated and is supported by the PFS data. This is an important outcome in a patient population with high unmet medical need and limited therapeutic options.

The overall frequency of adverse events was comparable but nivolumab reported a lower frequency of adverse events ≥ grade 3, serious adverse events and adverse events leading to discontinuation than for docetaxel.

Overall, the size of the safety database is considered adequate to characterise the general safety profile of nivolumab and the toxicity was considered manageable and tolerable by patients.

Benefit-risk balance

The treatment with nivolumab in SQ-NSCLC has shown an improvement over active treatment in life expectancy for patients with at least one prior treatment. The observed overall incidence of adverse events was comparable with docetaxel, but with a lower reported incidence of AE's grade ≥3, serious AE's and AE's leading to discontinuation. Importantly, nivolumab treatment is associated with less related hematological sided effects, including the potential life threatening febrile neutropenia. Given the clinically relevant improvement in OS over docetaxel and the manageable toxicity in a patient population in which there is a high unmet medical need, the benefit-risk balance of nivolumab is considered positive.

Discussion on the benefit-risk balance

The treatment options for second-line treatment for SQ-NSCLC are limited. In the pivotal study CA20917 comparing nivolumab to docetaxel, an improvement of 3.2 months in OS was demonstrated. Study CA209063 provides data regarding the use of nivolumab in the 3rd line and later setting.

For over 15 years, docetaxel has been a standard treatment for previously treated SQ NSCLC subjects who have progressed after first-line treatment. However, only a small fraction of patients respond to docetaxel: 3.3-15%, with a median response duration of approximately 6 months and median overall survival (OS) and 1-year OS of approximately 6 to 10 months and 30% to 40%, respectively. The treatment with nivolumab in SQ-NSCLC has shown an improvement over active treatment in life expectancy for patients with at least one prior treatment. Patients who were PD-L1-positive showed the best (numerical) improvements, but patients who were PD-L1-negative showed comparable or even better improvements in ORR, PFS and OS than those obtained with docetaxel. The applicant should further investigate an appropriate biomarker in order to select the most sensitive patients.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Nivolumab BMS in the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of nivolumab BMS in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness about the potential immune mediated adverse events associated with nivolumab BMS use, how to manage them and to enhance the awareness of patients or their caregivers on the signs and symptoms relevant to the early those adverse events.

The MAH shall ensure that in each Member State where nivolumab BMS is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use nivolumab BMS have access to/are provided with the following educational package:

- Physician educational material
- Patient alert car

The physician educational material should contain:

- The Summary of Product Characteristics
- Adverse Reaction Management Guide

The Adverse Reaction Management Guide shall contain the following key elements:

- Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable) for the following safety concerns:
    - 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
- Details on how to minimise the safety concern through appropriate monitoring and management

The patient alert card shall contain the following key messages:

- That nivolumab BMS treatment may increase the risk of:
    - 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
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the nivolumab BMS prescriber

- **Obligation to complete post-authorisation measures**

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

Description	Due date
Post-authorisation efficacy study (PAES): The MAH should submit an updated OS data for Study CA209017: a Phase 3, randomized study of nivolumab vs docetaxel in subjects with advanced or metastatic squamous NSCLC who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. The updated data should be submitted by	31st December 2015
The value of biomarkers to predict the efficacy of nivolumab should be further explored, specifically: 1) To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of	30th September 2015

Description	Due date
nivolumab efficacy. These analyses will be conducted in studies CA 209037 and CA209066 in patients with advanced melanoma.	
2) To further investigate the value 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. These additional biomarker analyses are occurring in the context of study CA209-038 and study CA209-066.	30th September 2017
3) To further investigate at post-approval the relation between PDL-1 and PDL-2 expression in Phase 1 (CA209009, CA209038 and CA209064).	31st March 2017
4) To further investigate the associative analyses between PDL-1 and PDL-2 expression conducted in study CA209-066.	31st December 2017
5) To further investigate at post-approval the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in studies CA209-009, CA209-038 and CA209-064.	30th September 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Nivolumab is qualified as a new active substance at the time of submission of this application.