22 April 2021
EMA/CHMP/260350/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yervoy	ipilimumab
Opdivo	nivolumab

Procedure No. EMEA/H/C/xxxx/WS/1881

Note

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

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List of abbreviations

1L	first line
2L	second line
1Q21	first quarter in 2021
4Q20	fourth quarter in 2020
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BICR	blinded independent central review
BLA	Biologics License Application
BMS	Bristol-Myers Squibb
BMS-936558	nivolumab
BMS-734016	ipilimumab
BOR	best overall response
chemo	chemotherapy
cHL	classical Hodgkin lymphoma
C1D1	Cycle 1 Day 1
C3D1	Cycle 3 Day 1
C5D1	Cycle 5 Day 1
CI	confidence interval
CL	clearance
Cmaxss	maximum concentration at steady state
Cminss	minimum concentration at steady state
CR	complete response
CRC	colorectal cancer
CSR	Clinical Study Report
CT	computerized tomography
CTC	Common Toxicity Criteria
CTLA-4	cytotoxic T-lymphocyte antigen-4
DBL	database lock
DC	discontinuation

DCR	disease control rate
DCN	document control number
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DOR	duration of response
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunoabsorbent assay
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
HCC	hepatocellular carcinoma
HR	hazard ratio
IFCT	Intergroupe Francophone de Cancérologie Thoracique
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune modulating medication
IND	Investigational New Drug
ipi	ipilimumab
ITT	intent-to-treat
IV	intravenous(ly)
K-M	Kaplan-Meier
LCSS	Lung Symptom Cancer Scale
LDH	lactate dehydrogenase
MAPS2	Mesothelioma Avastin Cisplatin Pemetrexed Study 2
Max	maximum
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MPM	malignant pleural mesothelioma
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MSI-H	microsatellite instability-high
NA	not available

NCCN	National Comprehensive Cancer Network
NE	not estimatable
nivo	nivolumab
nivo+ipi	nivolumab plus ipilimumab combination therapy
NR	not reported
NSCLC	non-small cell lung cancer
OESI	other event of special interest
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PFS	progression-free survival
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PS	performance status
Q3W	every 3 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCLC	small-cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease
SNP	single nucleotide polymorphism

SOC	standard of care
TMB	tumor mutational burden
TTR	time to response
UC	urothelial carcinoma
US	United States
USPI	United States prescribing information
VAS	visual analogue score
VC	Volume of distribution of central compartment
W1D1	Week 1 Day 1
W7D1	Week 7 Day 1
W13D1	Week 13 Day 1

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 25 August 2020 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

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

Extension of indication to include first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) for combination treatment of Opdivo and Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.0 for Opdivo and version 30.0 for Yervoy of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0026/2020, P/0027/2020 for Opdivo (Nivolumab) and P/0003/2017, P/0085/2015 for Yervoy (Ipilimumab) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0027/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteur for the WS procedure: Blanca Garcia-Ochoa

Timetable	Actual dates
Submission date:	25 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur's preliminary assessment report circulated on:	24 November 2020
PRAC Rapporteur's preliminary assessment report circulated on:	12 November 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	26 November 2020
CHMP Rapporteur's updated Assessment Report circulated on:	10 December 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	10 December 2020
WSA's responses submitted to the CHMP on:	19 January 2021
PRAC Rapporteur's preliminary assessment report on the WSA's responses circulated on:	26 February 2021
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on:	08 March 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	11 March 2021
CHMP Rapporteur's updated assessment report on the WSA's responses circulated on:	21 March 2021
2nd request for supplementary information and extension of timetable adopted by the CHMP on:	25 March 2021
WSA's responses submitted to the CHMP on:	30 March 2021
CHMP and PRAC Rapporteur's preliminary assessment report on the WSA's responses circulated on:	09 April 2021
CHMP Rapporteur's updated assessment report on the WSA's responses circulated on:	17 April 2021
CHMP Opinion adopted on:	22 April 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Malignant pleural mesothelioma (MPM) is a rare, locally invasive, and highly aggressive cancer of the pleura membrane. Patients with MPM usually have a very poor prognosis, and less than 10% of patients live beyond 5 years.

State the claimed therapeutic indication

At the time of submission, the MAH has proposed the following indication:

For OPDIVO:

Malignant pleural mesothelioma (MPM)

OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable malignant pleural mesothelioma.

For Yervoy:

Malignant pleural mesothelioma (MPM)

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Proposed dosage and administration

The recommended dose is nivolumab 360 mg every 3 weeks (Q3W) administered as a 30-minute intravenous (IV) infusion with ipilimumab 1 mg/kg every 6 weeks (Q6W) administered as a 30 minute IV infusion until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.

Epidemiology and risk factors, screening tools/prevention

Malignant pleural mesothelioma (MPM) is a rare and incurable disease. MPM affects approximately 31,000 people around the world, with around 30,000 new cases diagnosed annually. The annual incidence of MPM in the United States (US) is estimated to be 1 in every 100,000 with approximately 3,000 new cases per year. Total incidence is highest in the US and United Kingdom (UK) although per capita, Australia and Italy also rank highly. The global incidence of MPM has risen steadily over the past decade and is predicted to continue to an estimated peak in 2020.In Europe, about 1.6 per 100,000 inhabitants corresponding to 8,000 new diagnoses annually. Based on a 5-year survival of 5%, the complete prevalence is 1.9 per 100,000 corresponding to 10,000 prevalent cases [Gatta, 2001]; thereby fulfilling the criteria for an orphan disease. There is a large intercountry variation: the incidence is 1.25/100,000 for example in Great Britain and 1.1/100,000 in Germany. MPM occurs predominantly in men (ratio of men to women 5:1) [Larsson, 2007]. The median age of diagnosis is 68 years.

Occupational exposure to asbestos is the most important risk factor associated with MPM. The lifetime risk of developing MPM among asbestos workers is thought to be as high as 10%. The mean latency period of MPM after exposure to asbestosis is around 40 year (range 15-67 years). The ongoing, unregulated use of asbestos in industrial countries such as India, Brazil, China, and Russia means that MPM will continue to represent a significant global health concern even after peak incidence has passed. Non occupational exposure to asbestos (e.g., in areas with asbestos rich soil or inhalation of other fibrous silicates) can also contribute to an increased risk for MPM. Other potential factors are radiation, and erionite.

Clinical presentation, diagnosis and stage/prognosis

MPM is usually diagnosed at an advanced stage due to late and non-specific symptoms. Thoracoscopy, or transparietal biopsies when thoracoscopy is contra-indicated, are the best methods for obtaining the diagnosis of MPM. These procedures provide large pathological specimens which are required for the reliable diagnosis of MPM via immunohistochemical examination. Several tumour markers have been studied, for early detection or diagnosis of MPM, but none appear to be reliable.

Three major histologic subtypes of MPM are well described: epithelioid (most common), sarcomatoid, and mixed-type (biphasic), with the poorest prognosis in non-epithelioid subtypes. Gender is also a known prognostic factor in MPM, with females typically having longer survival time than males.

The optimal approach to MPM measurement requires the expertise of radiologists to identify measurement sites on computerized tomography (CT) scans as per modified Response Evaluation Criteria in Solid Tumours (mRECIST). Despite these criteria, evaluation of MPM based on imaging data is challenging given the lack of clearly demarcated margins of the lesions and progression-free survival (PFS) and objective response rate (ORR) are not reliable endpoints.

Thoracoscopy is recommended to obtain adequate histology, optimal stage and to allow pleural fluid evacuation. During thoracoscopy, multiple deep and large biopsies from both the normal and seemingly abnormal pleura should be obtained to provide sufficient and adequate samples for diagnosis. The diagnosis of MPM should be made on light microscopy combined with appropriate immunohistochemistry allowing subtyping according to histology [ESMO 2015]. When thoracoscopy is not feasible or contraindicated, ultra-sound guided true cut biopsies can be used. The use of an independent expert panel should be asked to confirm the diagnosis particularly in clinical trial or in any case where there is doubt about the diagnosis [ERS/ATS Task Force, 2010].

Management

MPM is hard to treat because most patients (80-95%) present with advanced disease.

There is limited evidence for the efficacy of surgery in patients with MPM. Due to the intricate location and relation with other organs, it is virtually impossible to obtain free resection margins. Surgery is limited to patients with stage I-III disease.

Most patients (80%) are diagnosed in stage III/IV and are not candidates for surgical cure (i.e. age or medical comorbidities). Systemic therapy is a treatment of option aimed at disease control and prolonging survival, but poor performance score and low chemo- and radio-sensitivity of the tumour result in poor prognosis. MPM is not sensitive to radiotherapy. Radiotherapy is used for a palliative intend to provide symptom relief. Without therapy progression is very rapid with a median survival time of 6 to 9 months. The overall survival has improved with cisplatin therapy.

For the past 15 years, in patients with advanced or recurrent malignant mesothelioma and fit for chemotherapy, the standard of care (SOC) 1L has been a combination of pemetrexed and cisplatin, which has been shown to be more beneficial than cisplatin monotherapy. With this SOC, patients with MPM have a median overall survival (OS) of 12 months and a 5-year survival rate less than 10%. Pemetrexed-cisplatin chemotherapy also improves the quality of life and relieves some symptoms, such as dyspnoea. Although pemetrexed plus cisplatin is the SOC in 1L unresectable MPM, carboplatin is also recommended with pemetrexed, particularly in subjects who are unable to tolerate cisplatin. Based on published data in chemotherapy-naive subjects with MPM, clinical efficacy is similar between carboplatin- and cisplatin-based regimens.

Improvement in 1L treatment has been observed by adding anti-angiogenic agents to platinum/pemetrexed chemotherapy as shown by the Phase 2 Intergroupe Francophone de Cancérologie Thoracique (IFCT)-Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) with bevacizumab in select patients. However, this bevacizumab combination is not approved by health authorities. In this study, median OS was improved in the bevacizumab combination arm to 18.8 months compared with 16.1 months in the pemetrexed and cisplatin control arm, and median PFS was 9.2 months in the bevacizumab combination arm compared with 7.3 months in the control arm. As expected, the addition of bevacizumab increased the rate of Grade 3/4 toxicity, with more Grade 3 or higher hypertension (23% vs 0) and

thrombotic events (6% vs 1%) than with control. More patients stopped treatment because of toxic effects in the bevacizumab combination arm than in the control arm (24.3% vs. 6.0%). As such, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) practice guidelines recommend that the triplet regimen of bevacizumab, cisplatin, and pemetrexed may be offered to patients with no contraindications to bevacizumab.

After failure of first line therapy, there is no current second line standard of care. No randomised study has shown the benefit of second line chemotherapy on survival of quality of life after failure of primary chemotherapy although numerical improvements were observed. The median OS for patients fit for chemotherapy after failure of first line platinum/pemetrexed is 6-7 months [Krug 2015; Kindler 2016] and it might be prolonged to 8.4 months if treated with second line chemotherapy [Jassem 2008].

Immunotherapy in second line mesothelioma

Recently, also immunotherapy has been investigated in the second line MPM. In the EU, currently no immunotherapy treatment is approved in the treatment of relapsed MPM.

Several checkpoint inhibitors (nivolumab, pembrolizumab, durvalumab, tremelimumab) have been investigated as monotherapy, in combination or in combination with chemotherapy in the treatment of relapsed MPM.

Tremelimumab is the only anti CTLA-4 monoclonal antibody that has been investigated as monotherapy in relapsed MPM. Tremelimumab did not significantly prolong overall survival compared with placebo in patients previously treated with malignant mesothelioma. In a trial including a total of patients, the median overall survival in the intention-to-treat population was 7.7 months (95% CI 6.8-8.9) in the tremelimumab group and 7.3 months (95% CI: 5.9, 8.7) in the placebo group (hazard ratio 0.92 [95% CI 0.76-1.12], p=0·41) [Majo M, et al. Lancet Oncol 2017].

Various PD-L1 agents have been investigated in relapsed MPM. Nivolumab has been investigated as monotherapy and in combination with ipilimumab. The reported ORR varies between 26-29%, with a reported OS of 11.8-17.3 months. When combined with ipilimumab, higher response rates are observed varying from 24-38% with a median OS of 15.9 months (Transl Lung Cancer 2020; 9 (Suppl1): S77-S85).

In the MAPS2 study, submitted as a supportive study within this application, a numerically larger effect with the combined treatment compared with the nivolumab monotherapy e.g. ORR 17% vs. 38% and median OS 11.9 vs. 15.9 months was observed.

2.1.2. About the product

Nivolumab and ipilimumab each have distinct, but complementary, mechanisms of action, which may enhance responsiveness to the combination regardless of baseline tumour PD-L1 expression (Hamanishi et al, 2007; Brahmer et al 2010; Pardoll, 2012; Wang et al, 2014; Das et al, 2015; Wei et al, 2018 and 2019;).

Nivolumab (OPDIVO) is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2.

Ipilimumab (Yervoy) is a human monoclonal antibody that targets CTLA-4. CTLA-4 inhibition can induce de novo T-cell responses and recruit novel/additional T cells to the tumour.

OPDIVO indications:

Melanoma: OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
Relative to nivolumab monotherapy, an increase in progression free survival (PFS) and overall survival

(OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD L1 expression (see sections 4.4 and 5.1).

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

Non-small cell lung cancer (NSCLC): OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Renal cell carcinoma (RCC): OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.
OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with intermediate/poor risk advanced renal cell carcinoma (see section 5.1).
OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1).

Classical Hodgkin lymphoma (cHL): OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

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

Urothelial carcinoma: OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Oesophageal squamous cell carcinoma (OSCC): OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Yervoy indications:

Melanoma: YERVOY as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older (see section 4.4).
YERVOY in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).

Renal cell carcinoma (RCC): YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see section 5.1).

Non-small cell lung cancer (NSCLC): YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

2.1.3. General comments on compliance with GCP

Study CA209743 was performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The active substances, nivolumab and ipilimumab are proteins and therefore no environmental risk assessment studies have been submitted, in line with guidelines.

2.2.2. Discussion on non-clinical aspects

Not applicable

2.2.3. Conclusion on the non-clinical aspects

Not applicable

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The WSA 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 1. studies of unresectable Malignant Pleural Mesothelioma with Data in this submission

Study/Phase/ Status	Population	Design	Endpoints	Test Drugs and Dose	Number of Subjects
Pivotal Study - Nivo+ipi vs chemotherapy					
CA209743/ Phase 3/ Ongoing/ BMS-sponsored	Adult (≥ 18 years) male and female subjects ECOG 0-1, with histologically proven diagnosis of advanced MPM that was unresectable and not amenable to therapy with curative intent (surgery with or without chemotherapy).	Phase 3, open-label, randomized (1:1), study comparing nivo+ipi vs chemotherapy (pemetrexed plus cisplatin or carboplatin) Stratification: tumor histology (epithelioid vs non-epithelioid) and sex (male vs female)	**Primary:** OS **Secondary:** • ORR by BICR • DCR by BICR • PFS by BICR • Efficacy (OS, PFS, ORR) by PD-L1 expression	**Nivo+Ipi**: nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W until disease progression, unacceptable toxicity, or a maximum treatment duration of 2 years **Chemo**: pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 of a 21-day cycle for 6 cycles	**Randomized:** 605 subjects 303 (nivo+ipi) 302 (chemo) **Treated:** 584 subjects 300 (nivo+ipi) 284 (chemo)
Supportive Study (Contribution of Components) - Nivo+ipi or nivo monotherapy					
IFCT-1501 MAPS2/ Phase 2/ Completed/ Investigator-sponsored (Also referred to as CA209304)	Adults (≥ 18 years) male and female subjects ECOG 0-1, with histology proven MPM that had progressed according to mRECIST criteria for mesothelioma and had already received 1 or 2 systemic chemotherapy lines, at least 1 involving a pemetrexed-platinum salt doublet line.	Phase 2, open-label, noncomparative, randomized (1:1) study assessing safety and efficacy of nivo monotherapy and nivo+ipi Stratification: histology (epithelioid vs non-epithelioid), treatment line (second line vs third line) and chemosensitivity to previous treatment (progression ≥ 3 months vs < 3 months)	**Primary:** DCR at 12 weeks[a] **Secondary:** • Safety • PFS • OS • Quality of life (LCSS-meso) • Biomarker analysis	**Nivo:** nivo 3 mg/kg Q2W **Nivo+Ipi**: nivo 3mg/kg + ipi 1 mg/kg Q6W	**Randomized:** 125 subjects 63 (nivo) 62 (nivo+ipi) **Treated:** 124 subjects 63 (nivo) 61 (nivo+ipi)

[a] Primary endpoint (DCR) was Investigator-assessed using mRECIST 1.1 criteria for mesothelioma. The IFCT retrospectively introduced a BICR to provide a re-evaluation of tumor responses by independent radiologists not involved in the study.

Abbreviations: AUC - area under the plasma drug concentration-time curve; BICR - Blinded Independent Central Review; BMS - Bristol-Myers Squibb, chemo - chemotherapy, DCR - disease control rate; ECOG - Eastern Cooperative Oncology Group; ipi - ipilimumab, Mesothelioma Avastin Cisplatin Pemetrexed Study 2 - MAPS2; LCSS-Meso - Lung Cancer Symptom Scale-mesothelioma adaptation; MPM - malignant pleural mesothelioma; mRECIST - modified Response Evaluation Criteria in Solid Tumors; nivo - nivolumab, ORR - objective response rate; OS - overall survival; PD-L1 - programmed death ligand 1; PFS - progression free survival, Q2W - every 2 weeks, Q6W - every 6 weeks

Source: Final CSR for CA209743[36] and Final CSR for MAPS2[37]

2.3.2. Pharmacokinetics

Pharmacokinetics in the target population

The PPK of nivolumab and ipilimumab in combination (nivo+ipi) has been previously characterized across multiple tumour types including 1L NSCLC. The PPK analysis in NSCLC was performed with these drugs in combination with chemotherapy. For this submission, nivolumab and ipilimumab PPK analyses were performed specifically for subjects with MPM receiving these drugs in combination.

The PPK of nivolumab or ipilimumab in Study CA209743 were well-described by a linear 2-compartment model with time-varying CL, which are consistent with a previously reported model of nivolumab and ipilimumab in their combination treatment.

Nivolumab population pharmacokinetics (nivo-PPK)

The main purpose of the current PPK analysis was to characterize the PK of nivolumab in subjects with unresectable MPM in Study CA209743 who received nivolumab in combination with ipilimumab and to determine the effects of covariates on nivolumab PK parameters.

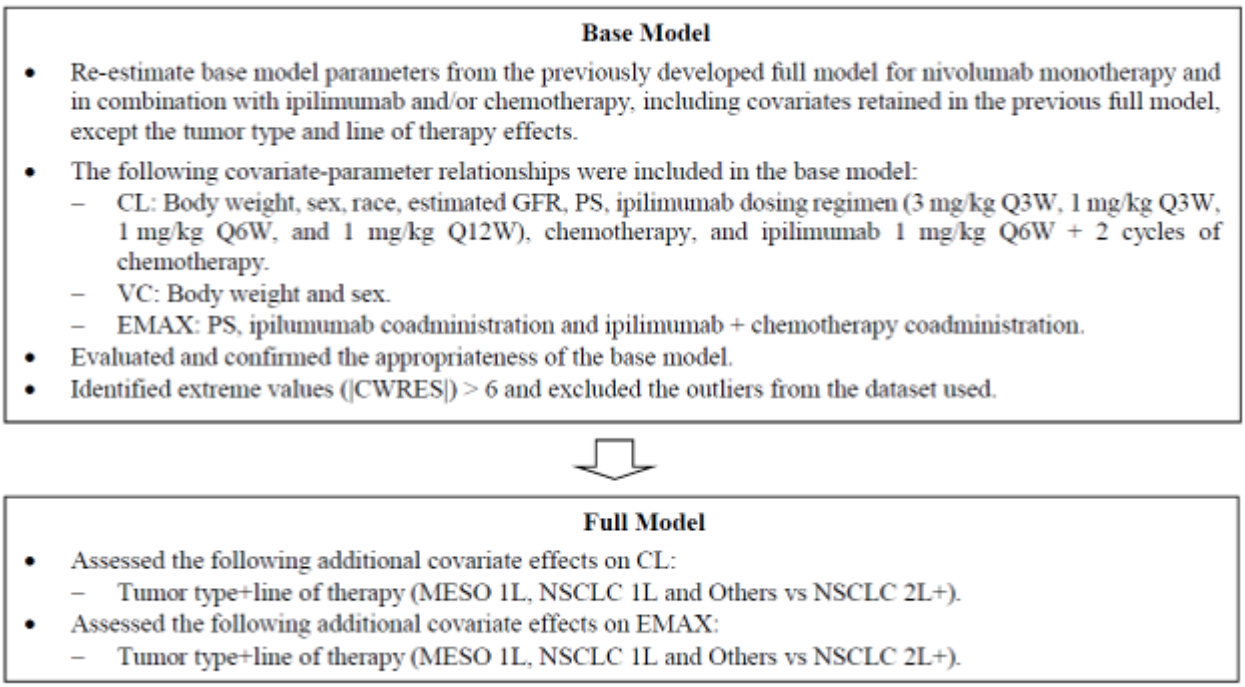
The nivolumab PPK analysis was conducted using data from 13 clinical studies conducted in subjects with MPM and other tumour types (NSCLC, melanoma, RCC, CRC, prostate cancer and HCC) who received nivolumab + ipilimumab and/or chemotherapy combination or nivolumab monotherapy. The data included are from 5 Phase 1 or 2 (MDX1106-03, CA209005 [ONO-4538-01], CA209012, CA209063, and CA209568 Parts 1 and 2), 7 Phase 3 (CA209017, CA209025, CA209026, CA209057, CA209227 Parts 1 and 2, CA2099LA, and CA209743), and 1 Phase 3b/4 (CA209817) clinical studies.

The monotherapy studies included in the analysis (MDX-1106-03, CA209005 [ONO-4538-01], CA209017, CA209025, CA209026, CA209057, and CA209063) provided data for assessment of nivolumab PK when given alone across different tumour types (MPM, SQ and NSQ NSCLC, and other tumour types). The additional studies included in the current analysis provided data on nivolumab PK administered in combination with ipilimumab in MPM (CA209743), CRC (CA209142), RCC (CA209214), or NSCLC (CA209012, CA209227, CA209568 Part 1, and CA209817) or in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy in subjects with NSCLC (CA209568 Part 2 and CA2099LA).

For the current PPK analysis in MPM and NSCLC subjects, the nivolumab PPK dataset included 19,096 nivolumab concentrations values from 4943 subjects, including 297 MPM subjects treated with nivo+ipi in Study CA209743.

Model development

Figure 1. Schematic Overview of Nivolumab Population Pharmacokinetic model development



The base model was a two-compartment, zero-order IV infusion PK model, with time-varying CL (sigmoidal-Emax function); and a proportional residual error model, with random effects on CL, Q, VC, VP, and EMAX; and correlation of random effect between CL and VC. The variance of random effect was estimated jointly for the two CL parameters (CL, Q) and for the two volume parameters (VC, VP). The base model contained BBWT, sex, race, GFR, PS, ipilimumab dosing regimen (3 mg/kg Q3W, 1 mg/kg Q3W, 1 mg/kg Q6W, and 1 mg/kg Q12W), chemotherapy, and ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy on CL, BBWT and sex on VC, BBWT on Q, BBWT on VP, and; PS, ipilimumab and ipilimumab + chemotherapy co-administration on EMAX.

Table 2. Parameter estimates of the Full Nivolumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e,BS]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	11.9	3.06E-04 (2.58)	11.2 - 12.5
VC_{REF} [L]	θ_2	4.24	0.0278 (0.656)	4.19 - 4.29
Q_{REF} [mL/h]	θ_3	33.9	0.00323 (9.53)	27.4 - 40.9
VP_{REF} [L]	θ_4	2.61	0.0809 (3.10)	2.45 - 2.78
CL_{BBWT}	θ_7	0.411	0.0292 (7.09)	0.353 - 0.470
CL_{GFR}	θ_8	0.172	0.0223 (12.9)	0.127 - 0.218
CL_{FEMALE}	θ_9	-0.224	0.0132 (5.91)	-0.251 - -0.197
CL_{PS}	θ_{10}	0.126	0.0145 (11.6)	0.0970 - 0.155
CL_{RAAA}	θ_{11}	0.0433	0.0353 (81.7)	-0.0258 - 0.121
CL_{RAAS}	θ_{12}	-0.102	0.0172 (16.8)	-0.135 - -0.0670
$V1_{BBWT}$	θ_{13}	0.573	0.0244 (4.27)	0.520 - 0.622
$V1_{FEMALE}$	θ_{14}	-0.150	0.0125 (8.31)	-0.175 - -0.125
CL_{EMAX}	θ_{15}	-0.327	0.0344 (10.5)	-0.411 - -0.250
CL_{T50}	θ_{16}	1.61E+03	66.2 (4.12)	1.48E+03 - 1.77E+03
CL_{HILL}	θ_{17}	2.08	0.172 (8.26)	1.76 - 2.47
$CL_{NSCLC\ 1L}$	θ_{18}	0.0515	0.0177 (34.3)	0.00745 - 0.0923
$CL_{MESO\ 1L}$	θ_{19}	0.148	0.0318 (21.6)	0.0764 - 0.214
CL_{OTHER}	θ_{20}	0.0456	0.0187 (41.0)	-0.00519 - 0.0929
$CL_{IPI\ 1Q3W}$	θ_{21}	0.228	0.0481 (21.1)	0.128 - 0.328

$CL_{IPI\ 1Q6W}$	θ_{22}	0.116	0.0184 (15.9)	0.0784 - 0.159
$CL_{IPI\ 1Q12W}$	θ_{23}	0.0540	0.0612 (113)	-0.0687 - 0.176
$CL_{IPI\ 3Q3W}$	θ_{24}	0.249	0.0636 (25.5)	0.127 - 0.395
CL_{CHEMO}	θ_{25}	-0.147	0.0183 (12.4)	-0.185 - -0.107
$EMAX_{IPICO}$	θ_{26}	-0.0954	0.0232 (24.3)	-0.147 - -0.0471
$EMAX_{PS}$	θ_{27}	-0.0944	0.0201 (21.3)	-0.133 - -0.0558
$CL_{IPICHEMO}$	θ_{28}	-0.0192	0.0355 (185)	-0.0849 - 0.0463
$EMAX_{IPICHEMO}$	θ_{29}	-0.0550	0.0435 (79.1)	-0.132 - 0.0290
$EMAX_{NSCLC\ 1L}$	θ_{30}	-0.0456	0.0202 (44.3)	-0.107 - 0.0236
$EMAX_{MESO\ 1L}$	θ_{31}	-0.0850	0.0441 (51.9)	-0.187 - 0.0219
$EMAX_{OTHER}$	θ_{32}	-0.0161	0.00950 (58.9)	-0.0894 - 0.0604
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.102 (0.320)	0.00468 (4.58)	0.0933 - 0.113
ZV1 [-]	$\omega_{2,2}$	0.0642 (0.253)	0.00534 (8.32)	0.0538 - 0.0744
ZEMAX [h]	$\omega_{4,4}$	0.0484 (0.220)	0.00803 (16.6)	0.0332 - 0.0639
ZCL:ZV1	$\omega_{1,2}$	0.0396 (0.489)	0.00309 (7.79)	0.0338 - 0.0461
Residual Error				
PERR [-]	θ_6	0.228	0.00336 (1.47)	0.220 - 0.235

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd
Source: Analysis-Directory/nm/full-meso-2/reports/full-meso-2_RTF.rtf

Note 1: $CL0_{REF}$ is the typical value in a reference subject with NSCLC, receiving nivolumab monotherapy as a 2L+ therapy, and weighing 80 kg. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving nivolumab monotherapy with a normal PS status (PS=0). VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note 2: Eta shrinkage (%): ETA_CL: 14.1; ETA_VC: 35.8; ETA_EMAX: 53.4 ; EPS shrinkage (%): 17.1.

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

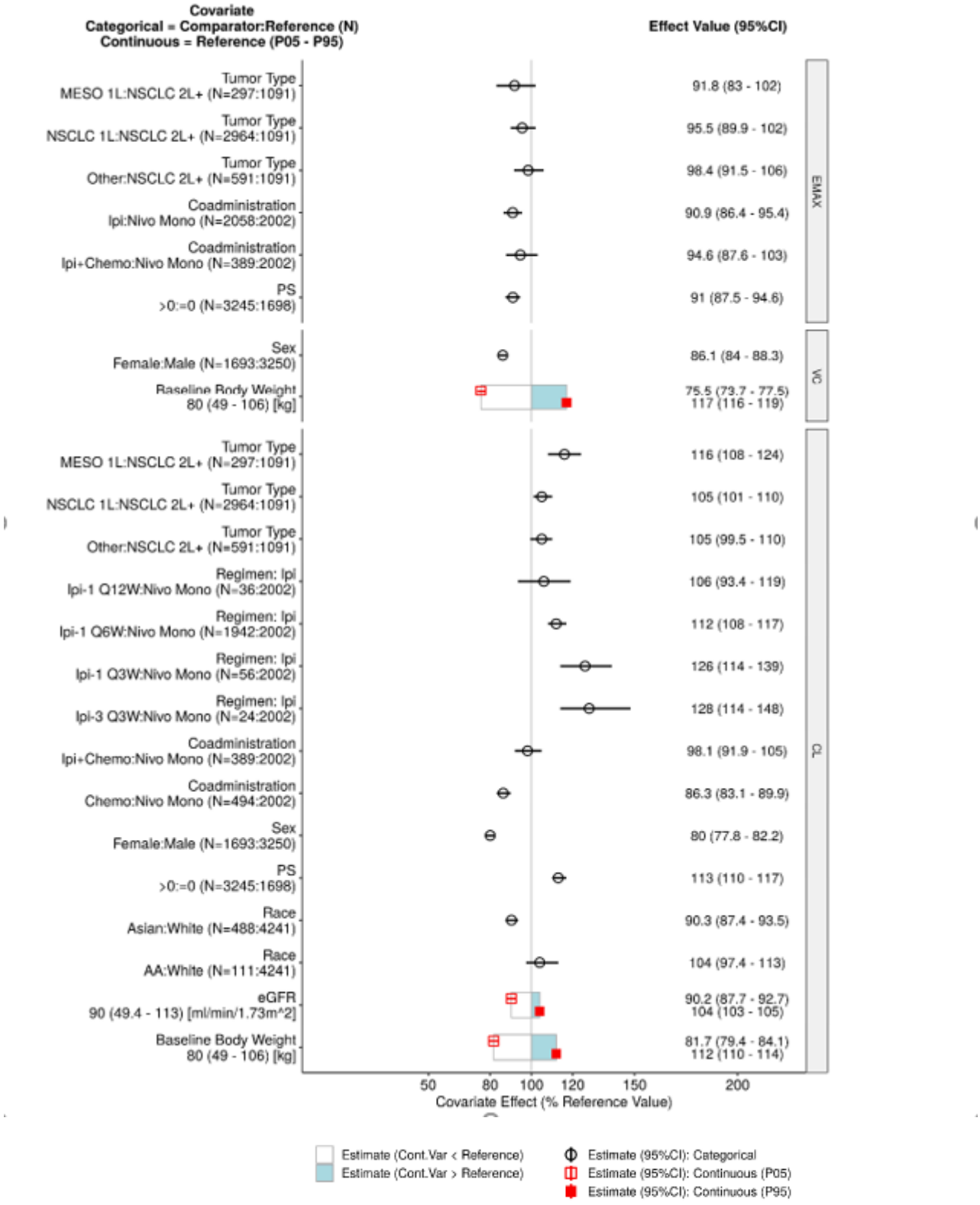
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

[BS] Confidence Interval values are taken from bootstrap calculations (571 successful out of a total of 1000).

Figure 2. Covariate on Nivolumab Pharmacokinetic Model Parameter (Full Nivolumab population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd
Source: Analysis Directory/R/plots/ggcoveff_plot.png

Note 1: CL = clearance, VC = volume of distribution of central compartment, Ipi-1 = ipilimumab 1 mg/kg, Ipi-3 = ipilimumab 3 mg/kg, 1L = first line therapy, 2L+ = second line or above therapy, MESO = mesothelioma or MPM, NSCLC = non-small cell lung cancer, PS = performance status.

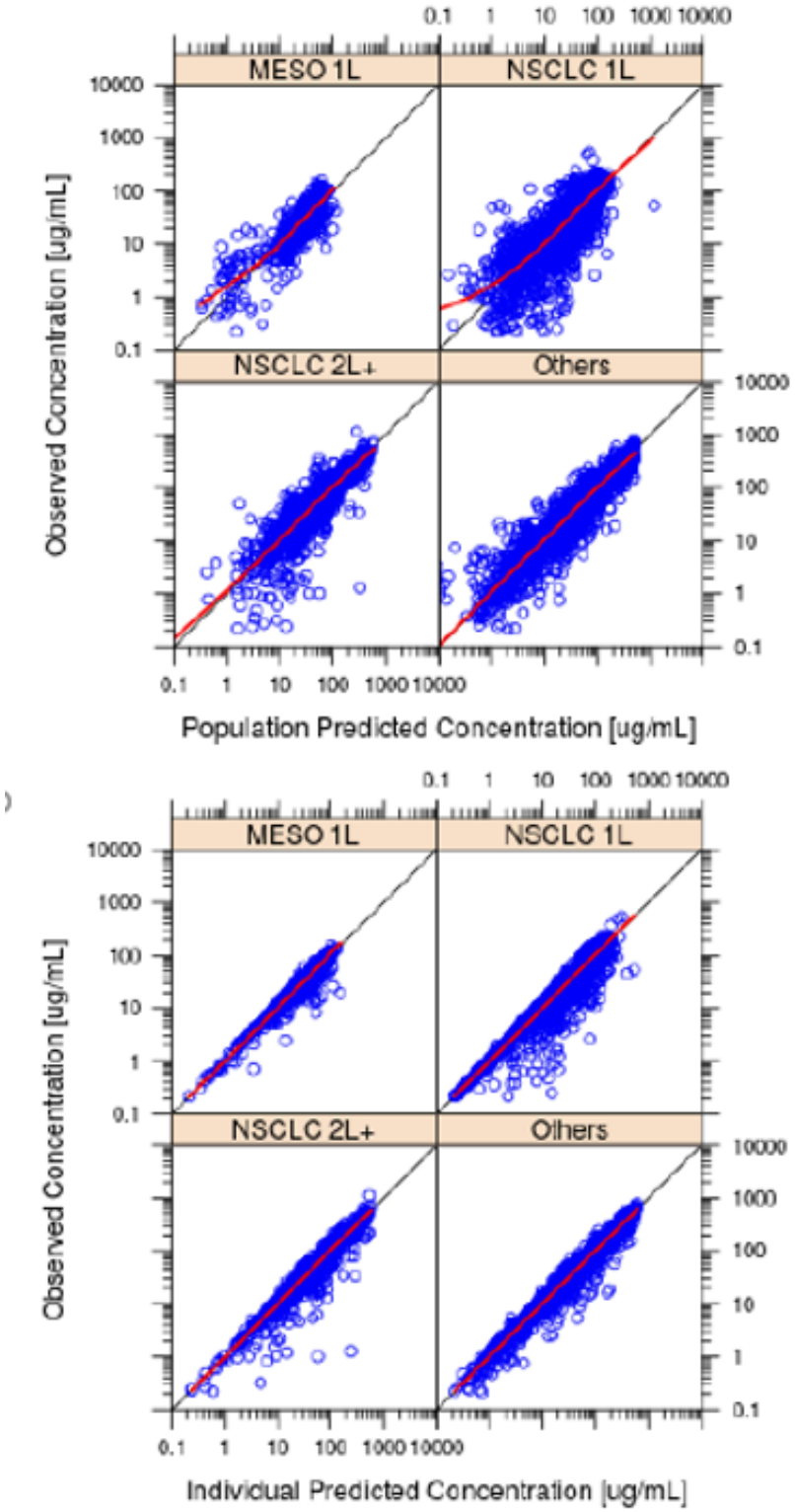
Note 2: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 3: 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 4: Reference subject is male, white/other race, body weight = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m^2,with NSCLC as tumor type and received nivolumab monotherapy as 2L+. Parameter estimate in a reference subject is considered as 100% (vertical solid line). Covariate is considered as clinical irrelevant if the covariate effect on PK parameters is within +/- 20%.

Note 5: The effect of BBWT was also added on inter-compartment clearance (Q) and volume of distribution of peripheral compartment (VP) and their estimates were fixed to be similar to that CL and VC, respectively.

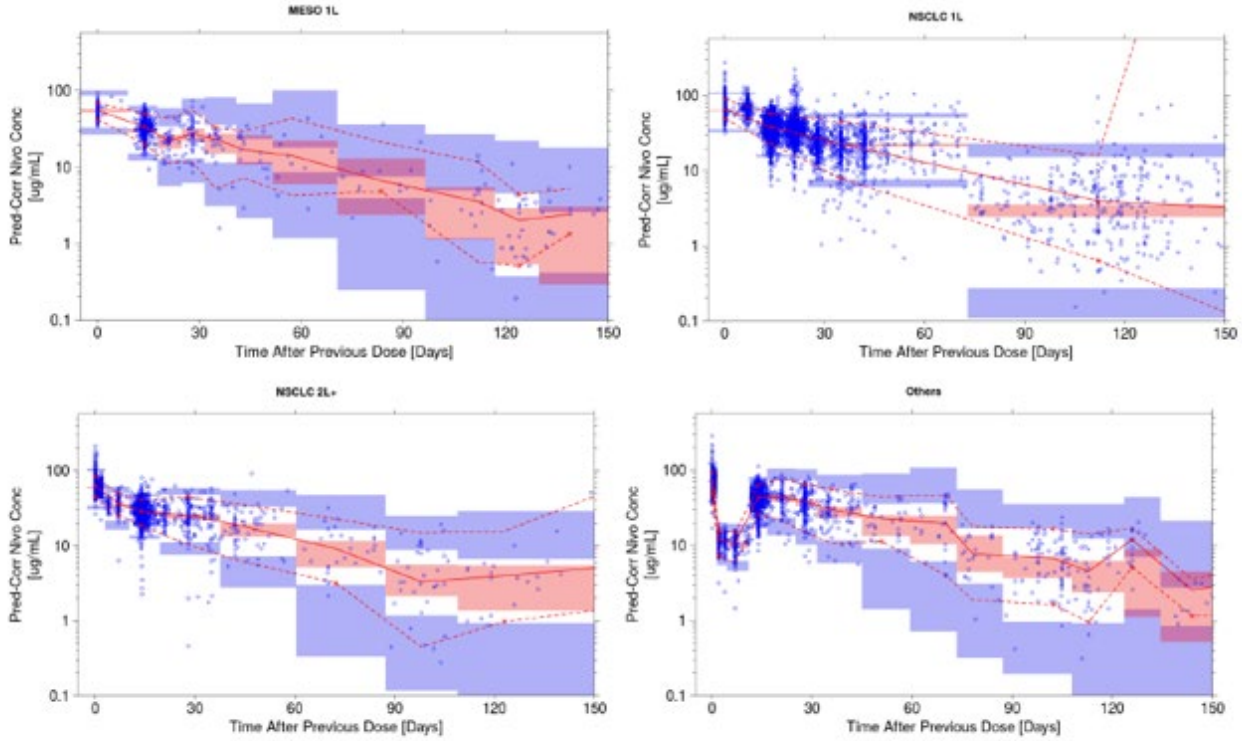
Figure 3. Observed Versus Predicted Population Average and Individual Concentration by Tumour Type (Full Nivolumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis-Directory/nm/full-meso-2/plots/obs-pred/obs-pred-ttyp.png
Source: Analysis-Directory/nm/full-meso-2/plots/obs-pred/obs-ipred-ttyp.png
Note: Solid red line represents linear regression line; Solid black line represents line of identity.

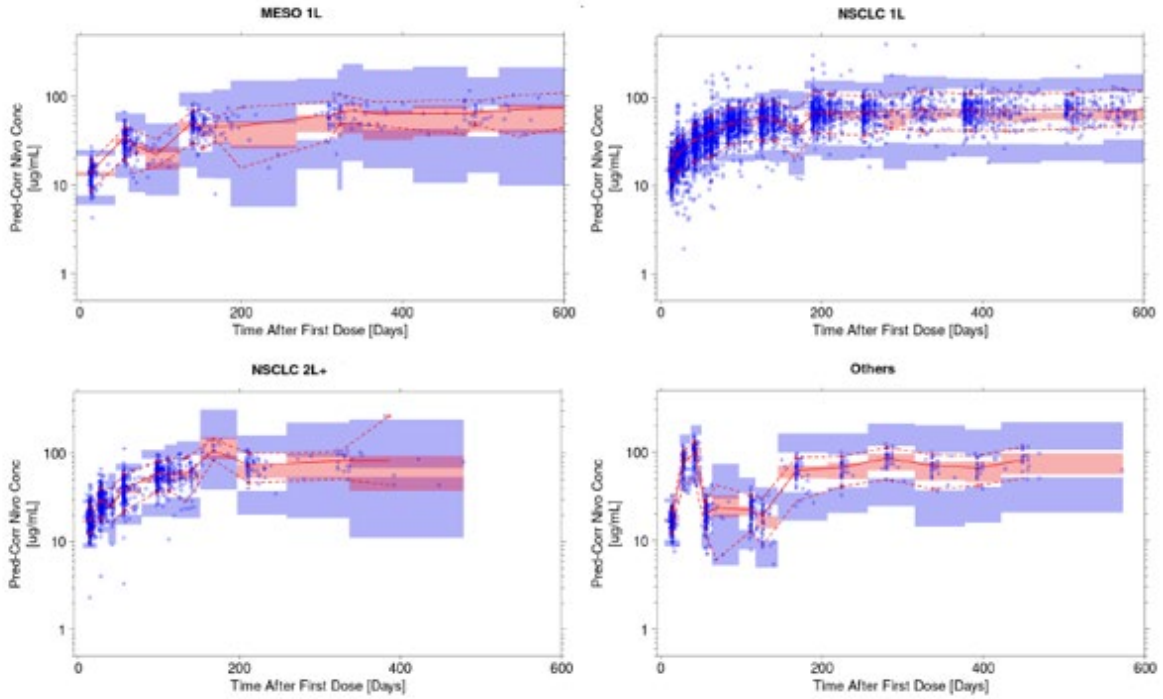
Model evaluation

Figure 4. predicted-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose by Tumour Type – Logarithmic Scale (Full Nivolumab PPK Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/psn/vpc_full_dir24/VPC-plots 1.png
Source: Analysis Directory/psn/vpc_full_dir24/VPC-plots 2.png
Source: Analysis Directory/psn/vpc_full_dir24/VPC-plots 3.png
Source: Analysis Directory/psn/vpc_full_dir24/VPC-plots 4.png
Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 5. Prediction-Corrected Visual Predictive Check of Trough Concentration versus Actual Time after First Dose Stratified by Tumour Type – Logarithmic scale (Full Nivolumab PPK Model)

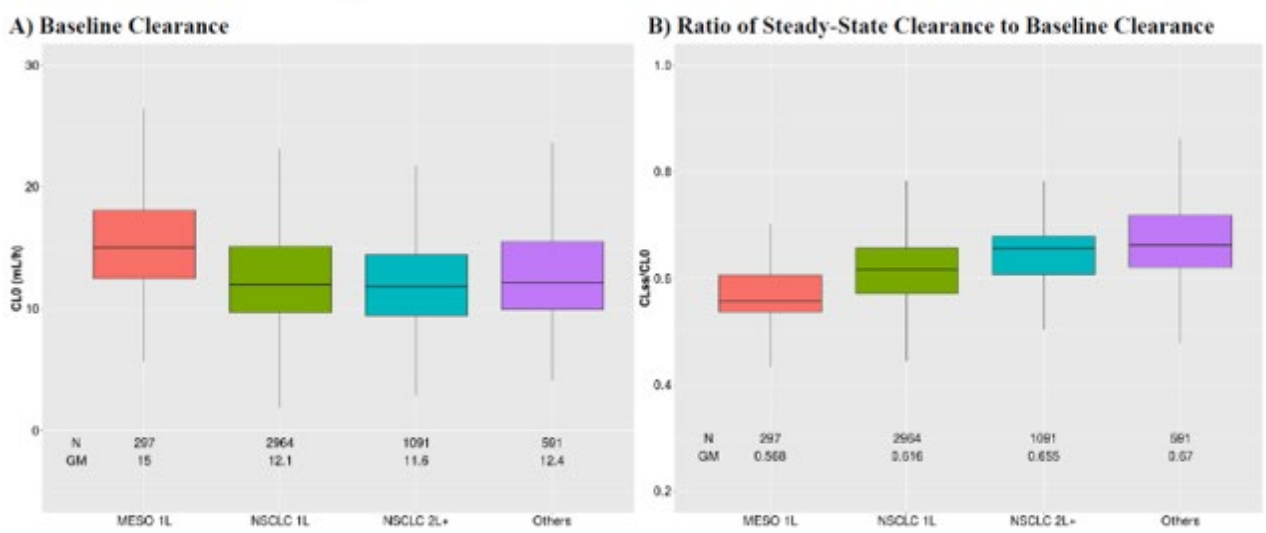


Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/psn/vpc_base_dir25/VPC-plots 1.png

Source: Analysis Directory/psn/vpc_base_dir25/VPC-plots 2.png
Source: Analysis Directory/psn/vpc_base_dir25/VPC-plots 3.png
Source: Analysis Directory/psn/vpc_base_dir25/VPC-plots 4.png
Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Model application

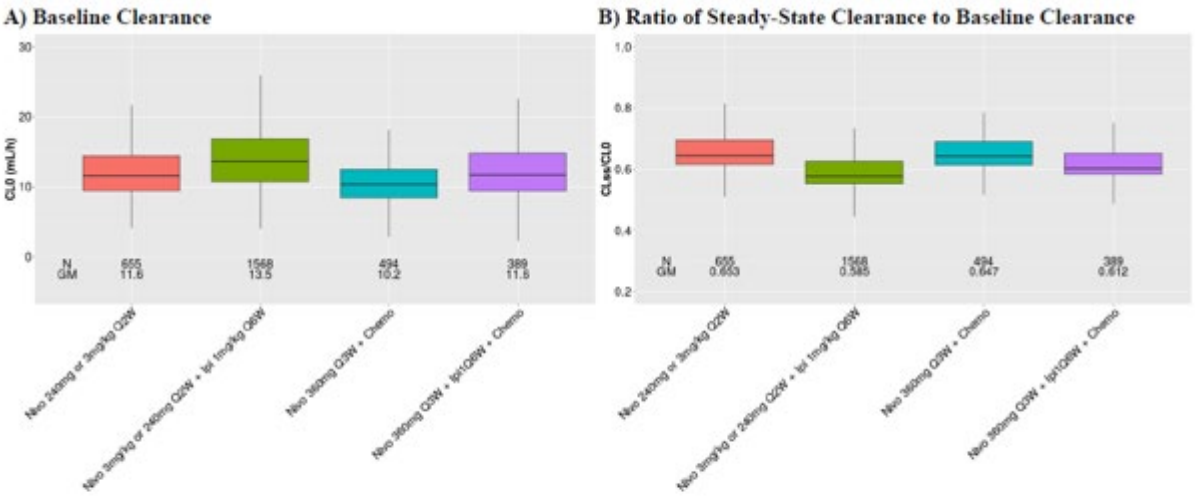
Figure 6. Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Tumour Type.



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/R/plots/CL0-tty.png
Source: Analysis Directory/R/plots/CL-ratio-tty.png

No clinically relevant difference (≤ 20%) was found between NSCLC 1L, others, and NSCLC 2L+ subjects.

Figure 7. Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Select Dosing Regimens in NSCLC 1L and Mesothelioma 1L Subjects



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/R/plots/CL0-reg.png
Source: Analysis Directory/R/plots/CL-ratio-reg.png
Note: Nivo 240 mg or 3 mg/kg Q2W includes data from NSCLC 1L subjects from Studies CA209012, CA209026, and CA209227. Nivo 240 mg or 3 mg/kg Q2W + Ipi 1 mg/kg Q6W includes data from NSCLC 1L subjects from Studies CA209012, CA209227, CA209568 Part 1, and CA209817 and MESO 1L subjects from Study CA209743. Nivo 360 mg Q3W + Ipi 1 mg/kg Q6W + chemo includes data from NSCLC 1L subjects from Studies CA209568 Part 2 and CA2099LA.

Table 3. Predictive Exposure Measure by Doing Regimen in NSCLC 1L and Mesothelioma 1L Subjects

Exposure	Nivo monotherapy Geo. Mean (CV%) N= 328	Mesothelioma 1L Nivo + Ipi Geo. Mean (CV%) N=297	NSCLC 1L Nivo + Ipi Geo. Mean (CV%) N=1271
CMIN1	18.5 (24.6)	13.7 (27)	15.9 (27.2)
CMAX1	64.1 (19)	55.6 (18.3)	59.3 (22)
CAVG1	29.5 (19.2)	23.8 (19.4)	26.3 (20.7)
CMINSS	71.4 (38.9)	56.6 (39.1)	65.9 (43.5)
CMAXSS	137 (27.4)	114 (26.2)	127 (30.4)
CAVGSS	92.7 (33.2)	74.9 (32.8)	85.5 (36.9)

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final

R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd

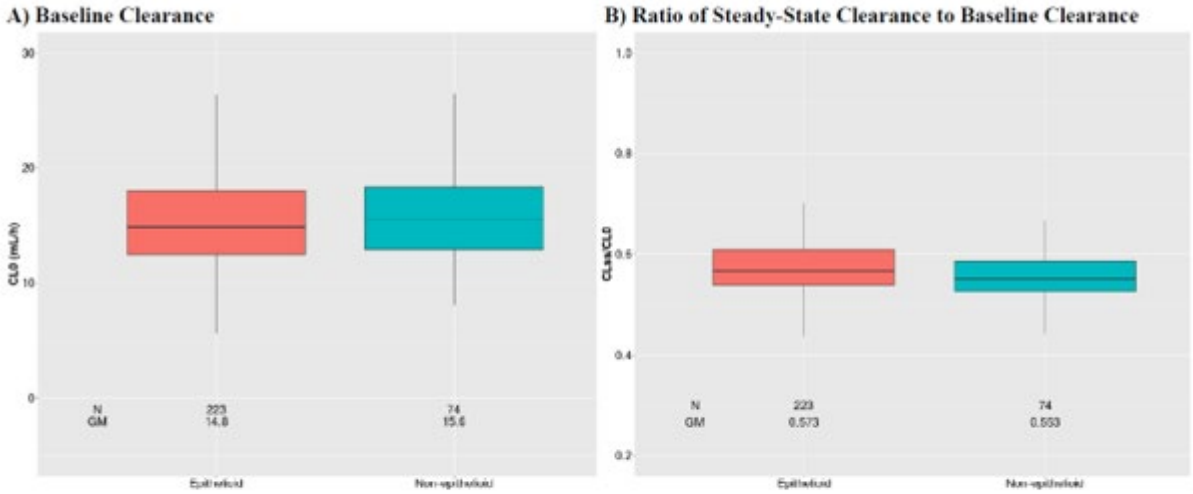
Source: Analysis Directory/R/export/expo.mono.csv

Source: Analysis Directory/R/export/expo.n3i16.csv

Source: Analysis Directory/R/export/expo.nic.csv

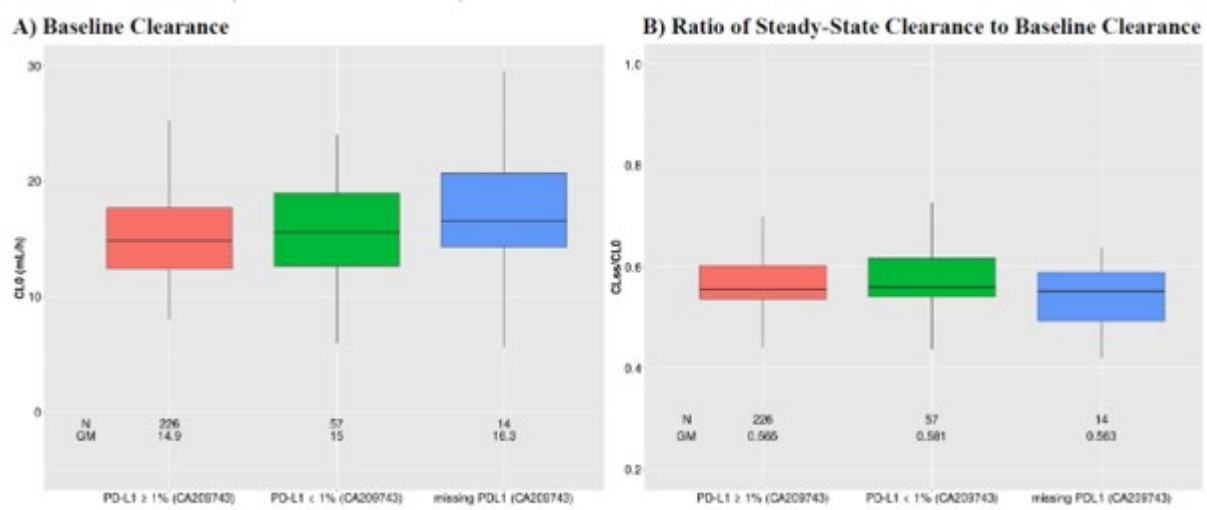
Note: Nivo monotherapy = Nivo 240 mg Q2W, which includes data from NSCLC 1L subjects from Study CA209227. NSCLC 1L Nivo + Ipi = Nivo 240 mg or 3 mg/kg Q2W + Ipi 1 mg/kg Q6W and data from NSCLC 1L subjects from Studies CA209012, CA209227, CA209568 Part 1, and CA209817. Mesothelioma 1L Nivo + Ipi = Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W and data from mesothelioma 1L subjects from Study CA209743.

Figure 8. Distribution of Nivolumab baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Histology Status in Study CA209743



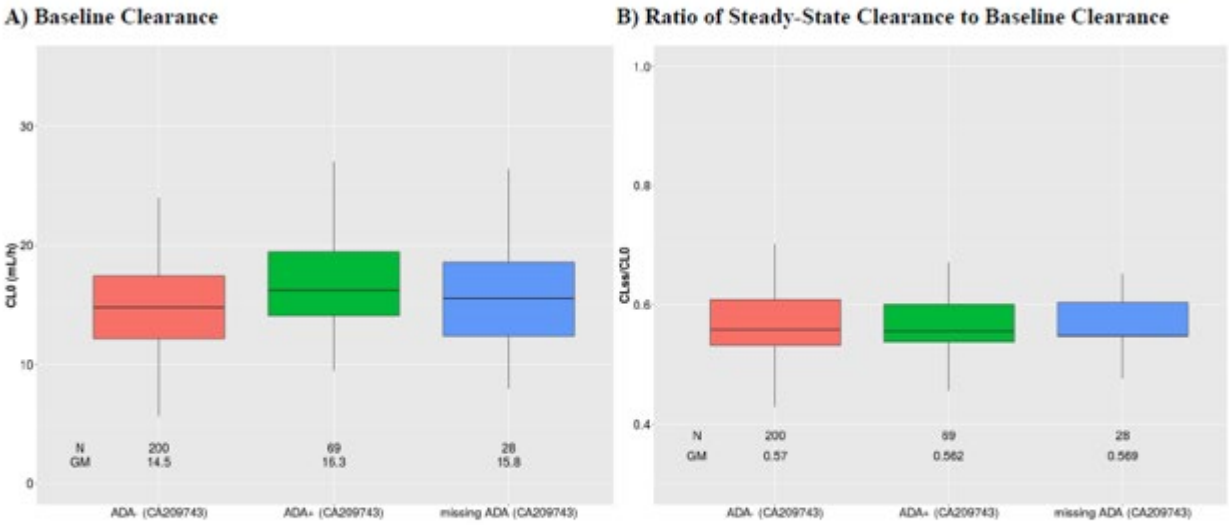
Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/R/plots/CL0-hist.png
Source: Analysis Directory/R/plots/CL-ratio-hist.png

Figure 9. Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by PD-L1 Status in Study CA209743



Baseline CL and the ratio of CLss/CL0 were similar (<3% difference) between PD-L1+ and PD-L1- subjects.

Figure 10. Distribution of Nivolumab Baseline Clearance and ratio of Steady State Clearance to Baseline Clearance in ADA+ and ADA+Subject in Study CA209743

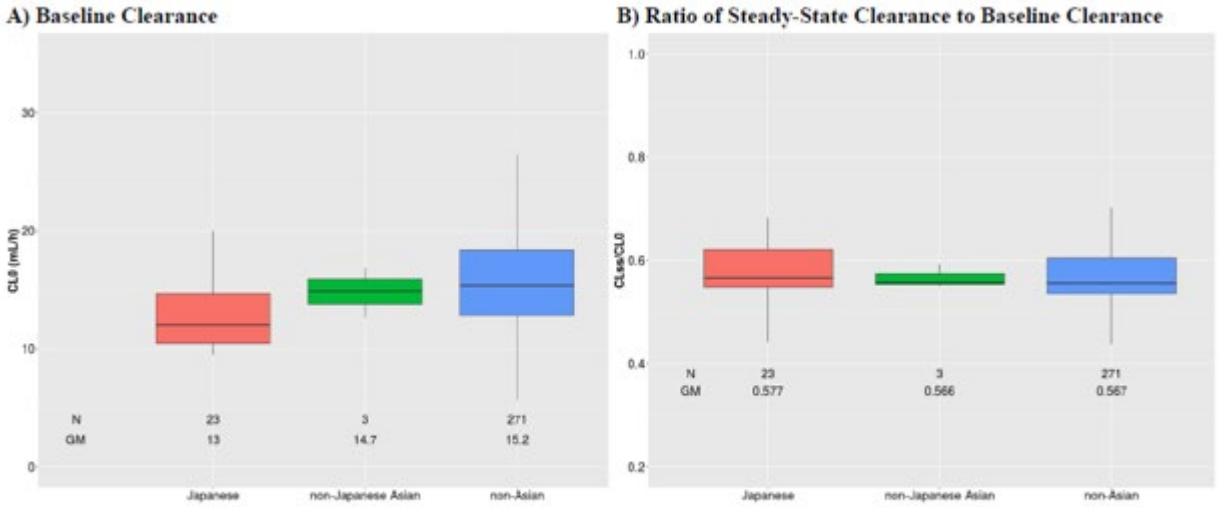


Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/R/plots/CL0-ADA.png
Source: Analysis Directory/R/plots/CL-ratio-ADA.png

The ratio CLss/CL0 was similar between ADA+ and ADA- subjects (<2% difference). No clinically relevant difference (≤ 20%) in nivolumab CL was found between ADA+ and ADA- subjects in Study CA209743.

Figure 11. Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance in Japanese, Non-Japanese Asian, Non-Asian Subjects in Study

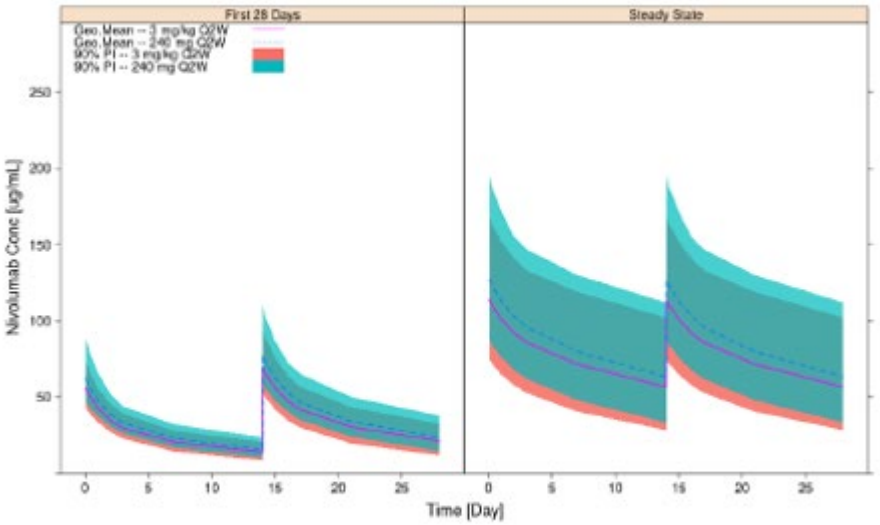
CA209743



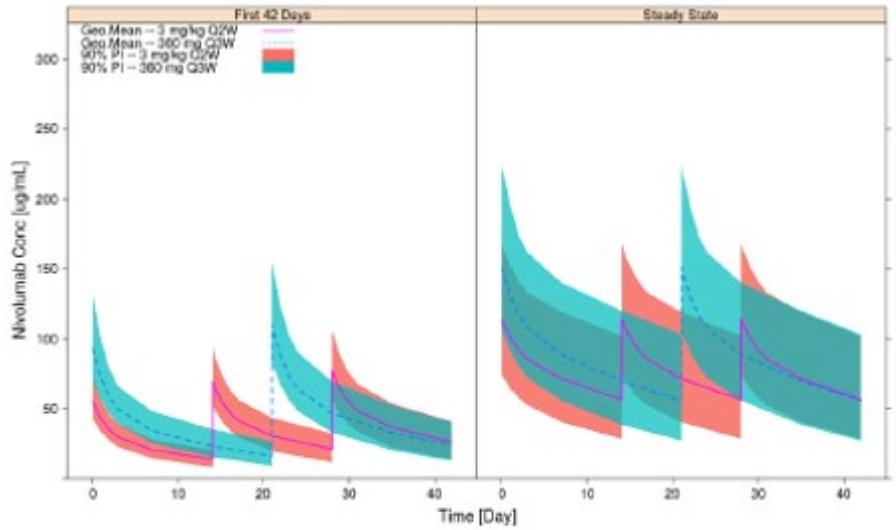
Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final
R-Program Source: Analysis-Directory/R/scripts/5-model-eval-app.Rmd
Source: Analysis Directory/R/plots/CL0-JP.png
Source: Analysis Directory/R/plots/CL-ratio-JP.png

Figure 12. Predicted Geometric Mean (With 90% PI) Nivolumab Concentration Time Profiles by Dosing Regimen (3 mg/Kg Q2W vs 240 mg Q2W/360 mg Q3W) in Subject with Mesothelioma

A) 3 mg/kg vs 240 mg Q2W



B) 3 mg/kg vs 360 mg Q3W



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final/
R-Program Source: Analysis Directory/R/scripts/3-simulation-flatdose.Rmd
Source: Analysis-Directory/R/plots/CT.plot1a-overall-meso.png
Source: Analysis-Directory/R/plots/CT.plot1b-overall-meso.png
Abbreviations: PI = prediction interval

Ipilimumab population pharmacokinetics (ipi-PPK)

The main purpose of the current PPK analysis was to characterize the PK of ipilimumab in subjects with unresectable MPM in Study CA209743 who received nivolumab in combination with ipilimumab and to determine the effects of covariates on ipilimumab PK parameters.

The ipilimumab PPK analysis was conducted using the data from 12 clinical studies conducted in subjects with MPM and other tumour types (NSCLC, melanoma) who received ipilimumab either as monotherapy or in combination with nivolumab. The data included are from 7 Phase 1 or 2 (CA184004, CA184007, CA184008, CA184022, CA184396, CA209012, and CA209568 Parts 1 and 2), 4 Phase 3 (CA184169, CA209227 Part 1, CA2099LA, and CA209743), and 1 Phase 3b/4 (CA209817) clinical studies.

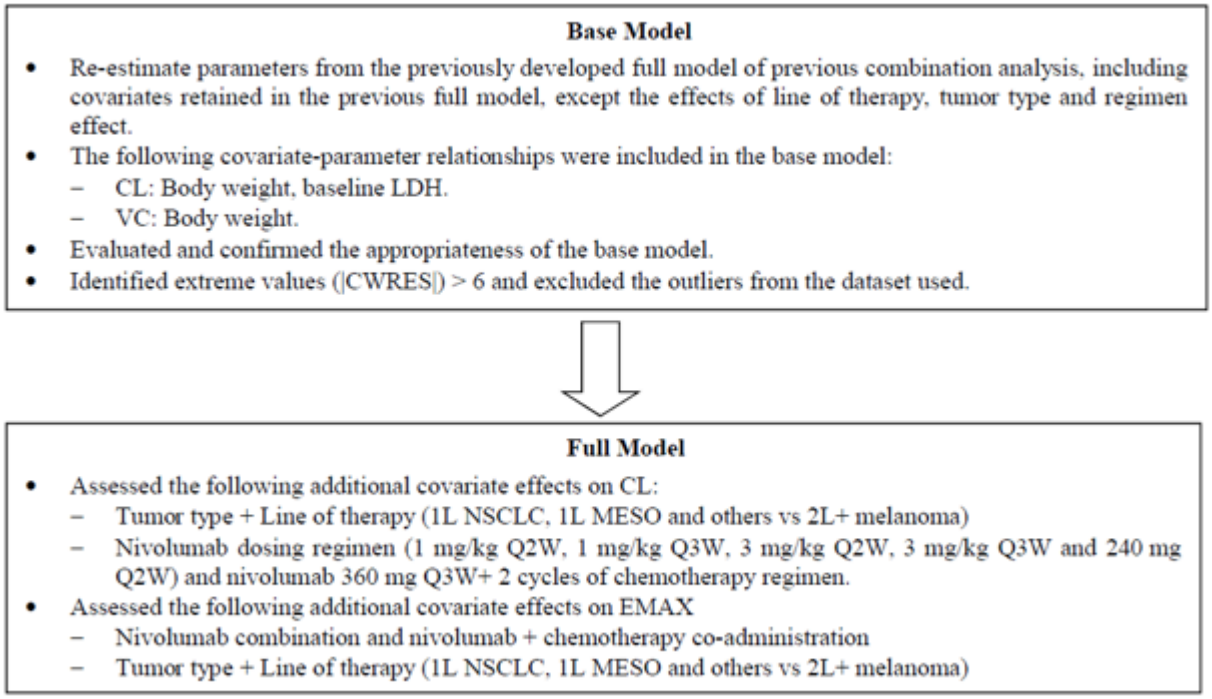
The monotherapy studies included in the analysis (CA184004, CA184007, CA184008, CA184022, and CA184396) provided data for assessment of ipilimumab PK when given alone across different tumour types (MPM and melanoma). The additional studies included in the current analysis provided data on ipilimumab PK administered in combination with nivolumab in MPM (CA209743) or NSCLC (CA209012, CA209227 Part 1, CA209568 Part 2, and CA209817) or in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy in subjects with NSCLC (CA209568 Part 2 and CA2099LA).

For the current PPK analysis, the ipilimumab PPK dataset included 11,602 ipilimumab concentration values from 3689 subjects, including 295 MPM subjects treated with nivo+ipi in Study CA209743.

Model development

The ipilimumab PPK model was developed in two steps: base and full models. Base model development consisted of re-estimating parameters of the previously developed final model (with line of therapy, tumour type and nivolumab combination effects removed), which was developed to characterize PK for ipilimumab combination therapy in subjects with NSCLC. The previous full PPK model was developed to characterize PK in ipilimumab combination in previously untreated NSCLC.

Figure 13. Schematic Overview of Ipilimumab Population Pharmacokinetic Model Development



The base model was a linear, two compartment model with zero order IV infusion and first order elimination; and a combined proportional and additive residual error model, with random effects on CL, VC and EMAX; and correlation of random effect between CL and VC. The base model contained BBWT and BLDH on CL, BBWT on VC, Q and VP.

Table 4. Parameter Estimates of the Full Ipilimumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e, f]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	13.8	0.333 (2.41)	13.1 - 14.5
VC_{REF} [L]	θ_2	4.30	0.0382 (0.889)	4.22 - 4.37
Q_{REF} [mL/h]	θ_3	26.3	1.98 (7.55)	22.4 - 30.6
VP_{REF} [L]	θ_4	3.58	0.0840 (2.35)	3.41 - 3.74
CL_{BW} [power]	θ_7	0.622	0.0342 (5.49)	0.540 - 0.681
V_{BW} [power]	θ_8	0.578	0.0347 (6.00)	0.506 - 0.648
CL_{LDH} [power log]	θ_9	0.748	0.0768 (10.3)	0.444 - 0.742
$EMAX_{REF}$	θ_{10}	0.184	0.0535 (29.1)	0.0793 - 0.290
T50	θ_{11}	2.20E+03	283 (12.8)	1.65E+03 - 2.86E+03
HILL	θ_{12}	1.82	0.182 (10.0)	1.50 - 2.32
$CL_{1L\ NSCLC}$	θ_{13}	2.26E-04	0.0444 (1.97E+04)	-0.0996 - 0.0649
$CL_{1L\ MESO}$	θ_{14}	0.170	0.0518 (30.5)	0.0511 - 0.246
CL_{Others}	θ_{15}	-0.0468	0.0265 (56.7)	-0.100 - 0.00480
CL Nivo1mg/kg Q2W	θ_{19}	0.153	0.0590 (38.5)	0.0630 - 0.294
CL Nivo1mg/kg Q3W	θ_{20}	-0.0417	0.0655 (157)	-0.140 - 0.103
CL Nivo3 mg/kg Q2W	θ_{21}	0.154	0.0444 (28.7)	0.0861 - 0.255
CL Nivo3mg/kg Q3W	θ_{22}	-0.0164	0.0751 (458)	-0.150 - 0.143
CL Nivo360 mg Q3W+Chemo	θ_{23}	0.101	0.0486 (48.3)	0.0310 - 0.212
CL Nivo240 mg Q2W	θ_{24}	0.323	0.0814 (25.3)	0.0946 - 0.438
$EMAX_{COMBO}$	θ_{26}	-0.475	0.0902 (19.0)	-0.697 - -0.313
$EMAX_{Triple}$	θ_{27}	-0.506	0.103 (20.3)	-0.743 - -0.312
$EMAX_{1L\ NSCLC}$	θ_{28}	0.0144	0.0975 (678)	-0.161 - 0.211
$EMAX_{1L\ Meso}$	θ_{29}	0.0204	0.105 (516)	-0.183 - 0.225
$EMAX_{Others}$	θ_{30}	-0.120	0.0613 (51.3)	-0.247 - -0.00143
CL_BLDH_{NA}	θ_{31}	-0.0510	0.0769 (151)	-0.209 - 0.104
Random Effects		2.26E-04	0.0444 (1.97E+04)	-0.0996 - 0.0649
ZCL[-]	$\omega_{1,1}$	0.118 (0.344)	0.00494 (4.18)	0.109 - 0.129
ZVC [-]	$\omega_{2,2}$	0.143 (0.378)	0.0161 (11.3)	0.111 - 0.176
ZEMAX	$\omega_{3,3}$	0.104 (0.323)	0.0170 (16.3)	0.0717 - 0.143
ZCL[-]:ZVC	$\omega_{1,2}$	0.0552 (0.424)	0.00484 (8.78)	0.0445 - 0.0638
Residual Error				
Proportional [-]	θ_5	0.204	0.00542 (2.66)	0.190 - 0.214
Additive [ug/mL]	θ_6	0.372	0.0301 (8.09)	0.308 - 0.455

Analysis Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final

Program Source: Analysis Directory/nm/full2/full2.lst

Source: Analysis Directory/nm/full2/reports/full2_RTF1.rtf

Note 1: CL_{REF} is the typical value in a reference subject weighing 80 kg and BLDH of 217 U/L. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note 2: *CL_BLDHNA* is the categorical effect of the subjects with missing BLDH value.

Note 3: The unit of CL_{REF} and Q_{REF} was converted to mL/h from L/h in the source.

Note 4: Eta shrinkage (%): ETA_CL:14.3; ETA_VC:30.6; ETA_EMAX: 54.3; EPS shrinkage (%):22.4

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

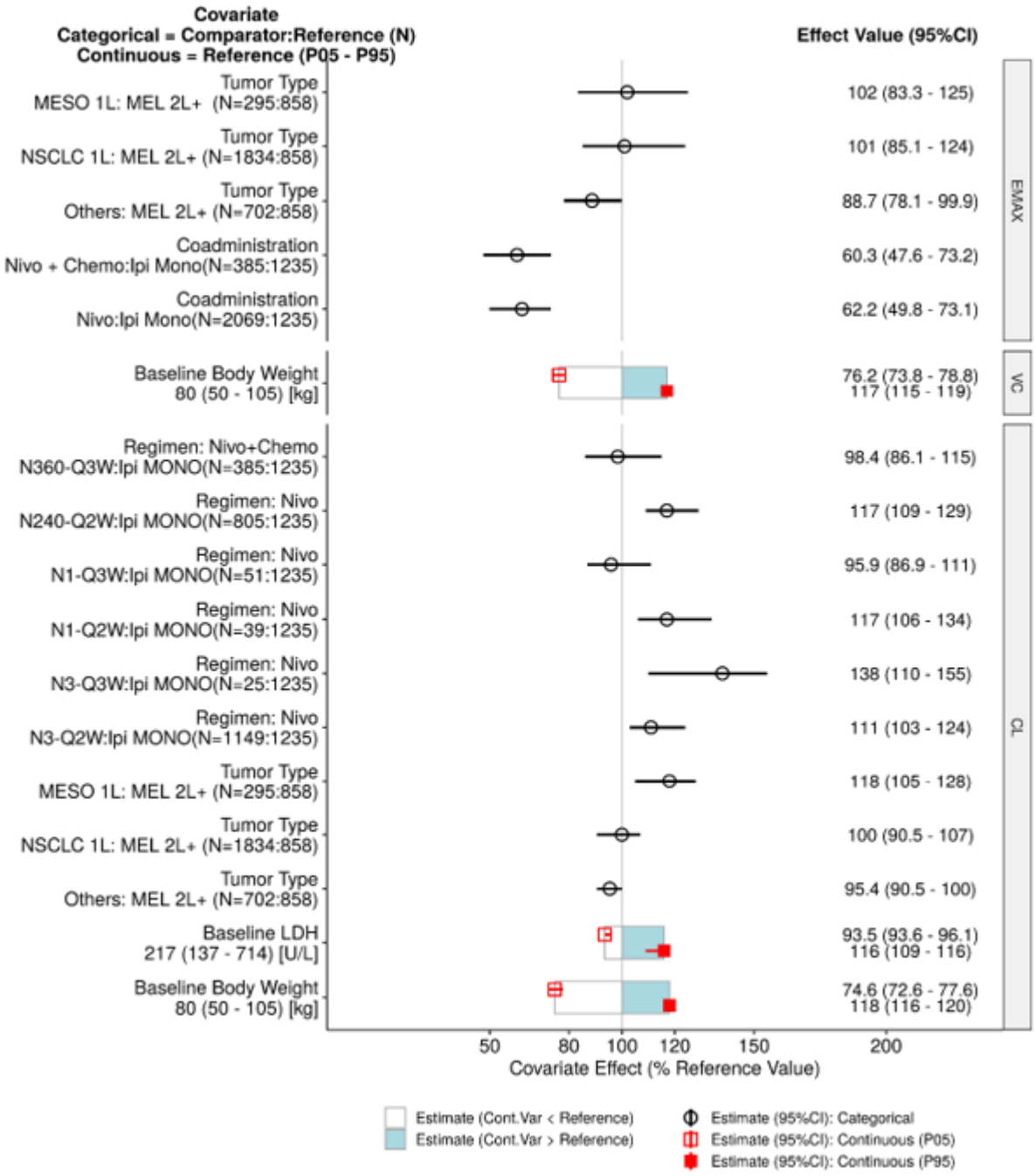
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

[f] Confidence Interval values are taken from bootstrap calculations (545 successful out of a total of 1000).

Figure 14. Covariate Effects on ipilimumab Pharmacokinetic Model Parameter (Full Ipilimumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final/

R-Program Source: Analysis Directory/R/scripts/2-model-dev.Rmd

Source: Analysis Directory/R/plots/ggcoveff_plot_full.png

Note 1: CL0 = baseline clearance, CLss = clearance at steady-state, Q = inter-compartment clearance, VC = volume of distribution of central compartment, VP = volume of distribution of peripheral compartment

Note 2: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 3: 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 4: Reference subject with 2L melanoma as tumor type, receiving ipilimumab monotherapy as a 2nd line (and plus) therapy, weighing 80 kg and BLDH of 217 U/L. Parameter estimate in a reference subject is considered as 100% (vertical solid line). Covariate is considered as clinically irrelevant if the covariate effect on PK parameters is within +/- 20%.

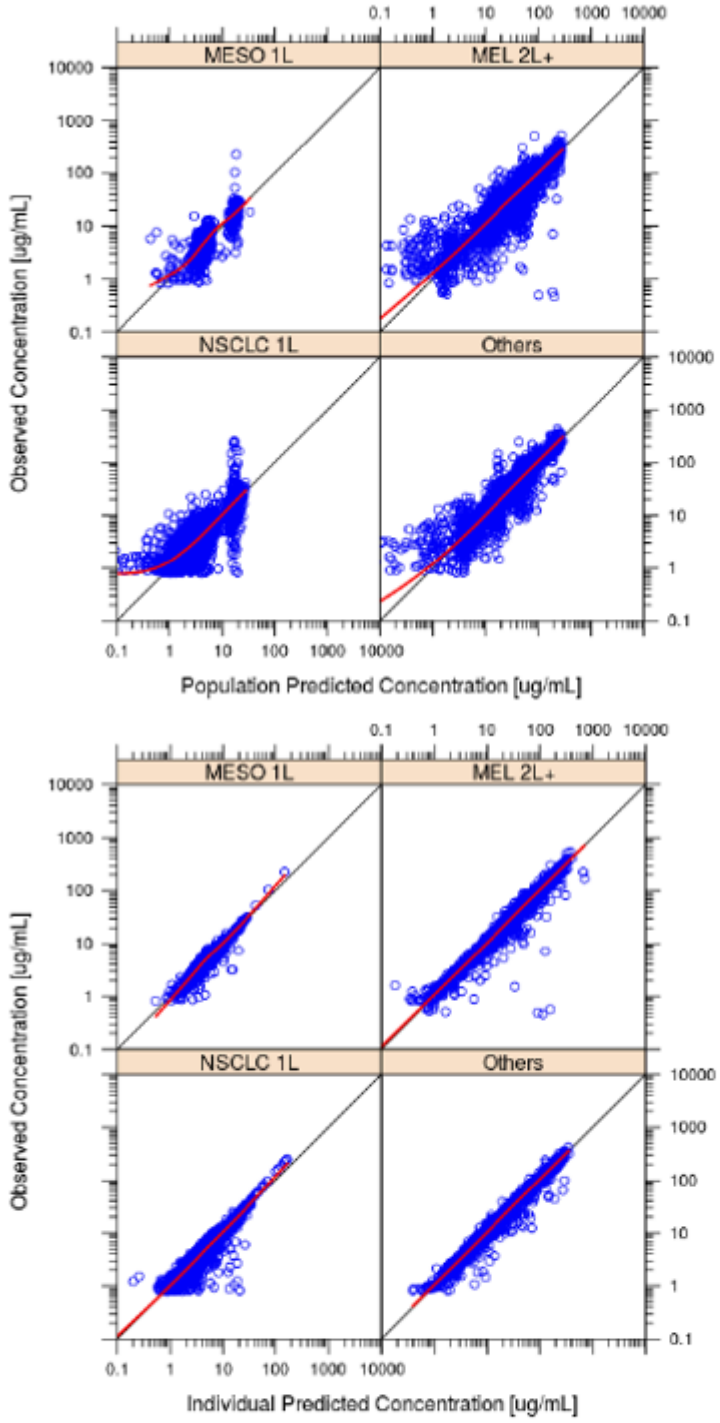
Note 5: Covariate effects on CL apply to both CL0 and CLss.

Note 6: Effects of baseline body weight on Q and VP are same as that of baseline body weight on CL and VC.

Note 7: N360 = Nivo 360 mg, N240 = Nivo 240 mg, N1 = Nivo 1 mg/kg, N3 = Nivo 3 mg/kg

The conditional number of the full model was found to be 891.9, indicating that the full model was stable (as the value is <1000).

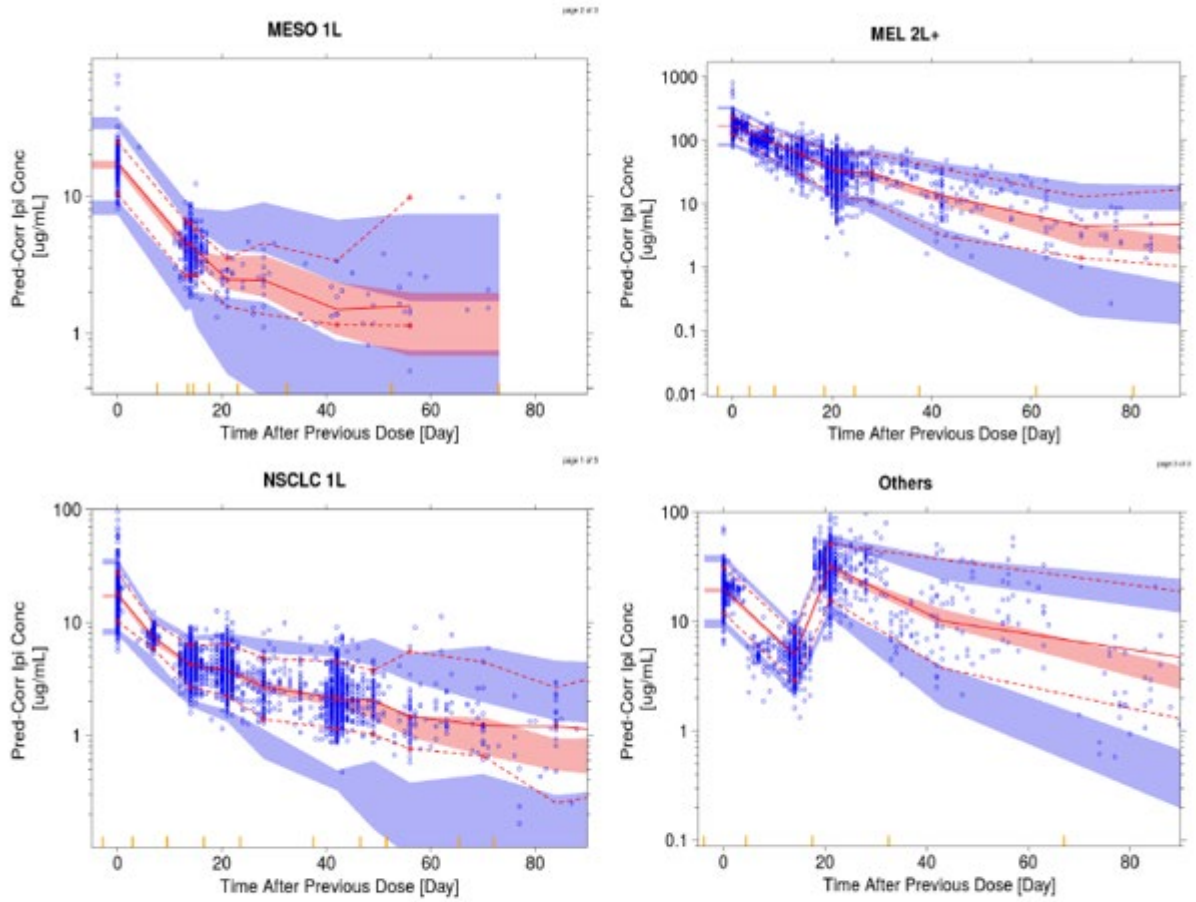
Figure 15. Observed versus Predicted Population Average and Individual Concentration in Ipilimumab by Tumour Type (Full Ipilimumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd
Source: Analysis Directory/R/scripts/ 4-model-eval-app.docx
Note: Solid red line represents linear regression line; Solid black line represents line of identity

Model evaluation

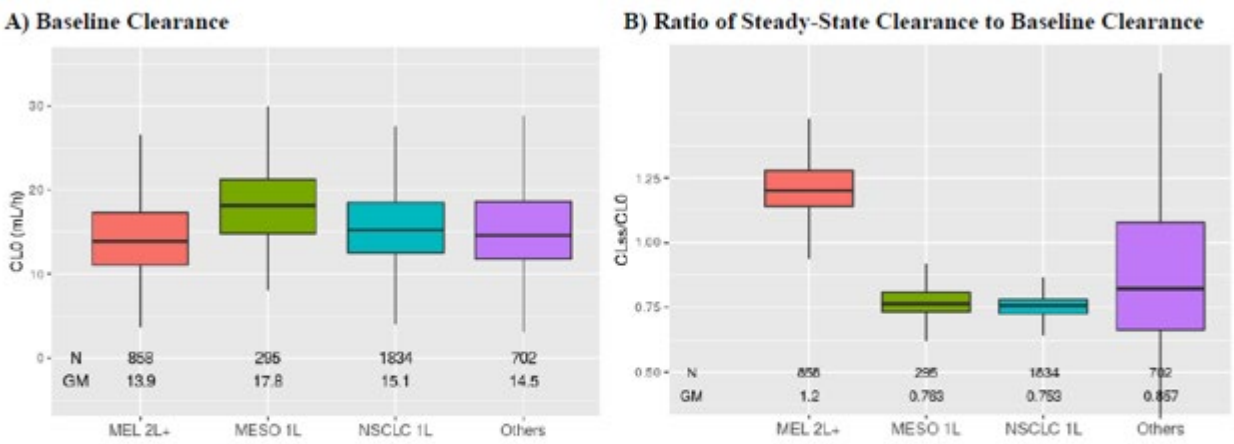
Figure 16. Prediction-Corrected Visual Predictive Check of Concentration versus Actual Time after Previous Dose in Logarithmic Scale Stratified by Tumour Type (Full Ipilimumab PPK Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd
Source: Analysis Directory/R/scripts/ 4-model-eval-app.docx

Model application

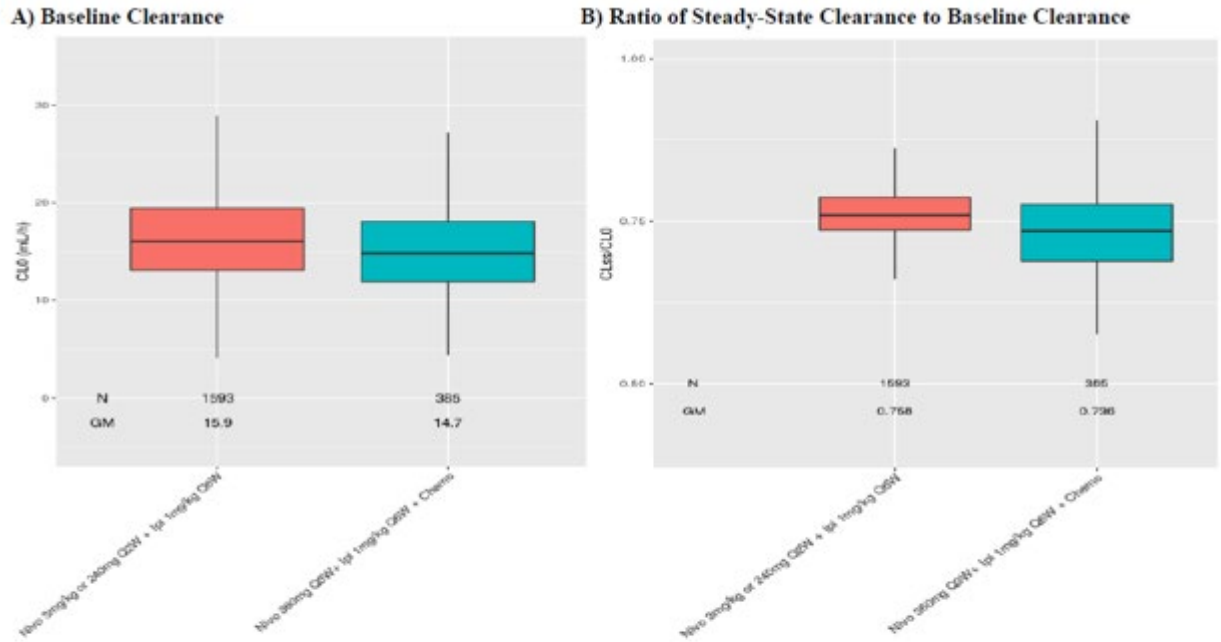
Figure 17. Distribution of Ipilimumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Tumour Type.



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd
Source: Analysis Directory/R/scripts/ 4-model-eval-app.docx

Ipilimumab CL0 was higher in 1L mesothelioma subjects compared to 2L+ melanoma subjects by~28% (geometric mean). No clinically relevant difference (≤ 20%) was found between NSCLC 1L, others and melanoma 2L+ subjects.

Figure 18. Distribution of Ipilimumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Select Dosing Regimens of Ipilimumab in Combination with Nivolumab.



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd

Source: Analysis Directory/R/scripts/ 4-model-eval-app.docx

Note: Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W includes data from 1L Meso subjects from CA209743 and 1L NSCLC subjects from Studies CA209227, CA209568 Part 1, and CA209817. Nivo 360 mg Q3W + Ipi 1 mg/kg Q6W + chemo includes data from 1L NSCLC subjects from Studies CA209568 Part 2 and CA2099LA

Table 5. Predicted Exposure Mesures in NSCLC 1L and Mesothelioma 1L Subjects

Exposure	Mesothelioma 1L Nivo + Ipi Geo. Mean (CV%) N=295	NSCLC 1L Nivo + Ipi Geo. Mean (CV%) N=552
CMIN1	0.897(45.5)	1.19(46.2)
CMAX1	17.7(51.9)	17.7(18.2)
CAVG1	3.57(23.3)	3.98(23)
CMINSS	1.75(63.4)	2.38(71.1)
CMAXSS	19.8(47.5)	20.4(20.9)
CAVGSS	5.24(34.2)	6.1(38.1)

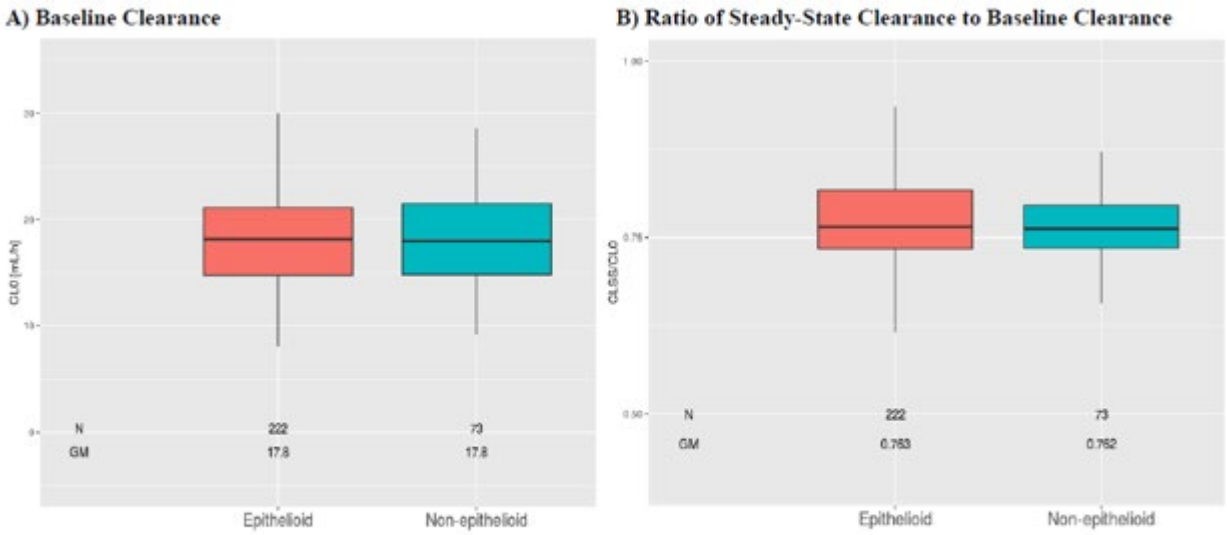
Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd

Source: Analysis Directory/R/export/Ipi-exp-summary-by-tumor.csv

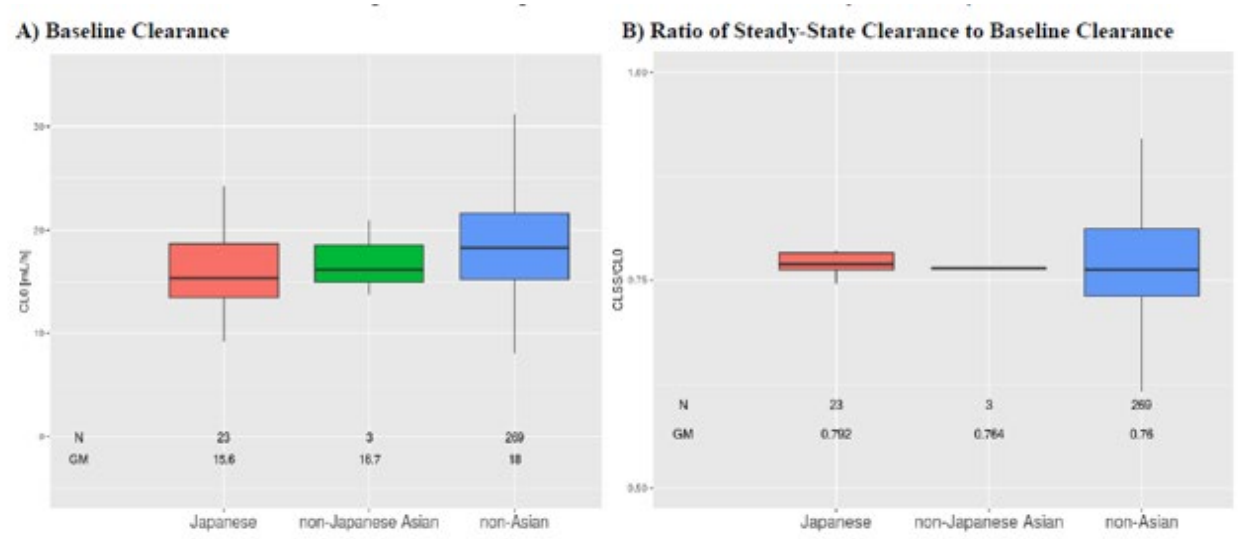
Note: Nivo+Ipi= 3 mg/kg Q2W + Ipi 1 mg/kg Q6W and includes data from 1L NSCLC subjects from Studies CA209012, CA209227 and 1L Meso subjects from Study CA209743.

Figure 19. Distribution fo Ipilimumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Histology Status in Study CA209743



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd
Source: Analysis Directory/R/scripts/ 4-model-eval-app.docx

Figure 20. Distribution of Ipilimumab baseline Clearance and Ratio of Steady State Clearance to baseline Clearance in Japanese, Non-Japanese Asian, and Non-Asian Subject in study CA209743



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd
Source: Analysis Directory/R/scripts/ 4-model-eval-app.docx

Table 6. Prediction Ipilimumab Exposure measures in Japanese, Non-Japanese and Non-Asian Subjects after Nivolumab 3 mg/Kg Q2W + Ipilimumab 1 Mg/Kg Q6W (In study CA209743)

Exposure	Japanese Geo. Mean (CV%) N = 23	non-Japanese Asian Geo. Mean (CV%) N = 3	Non-Asian Geo. Mean (CV%) N = 269
CMIN1	0.874 (44.6)	0.754 (25.8)	0.9 (45.7)
CMAX1	13.8 (37)	11 (42.3)	18.2 (51.9)
CAVG1	3.15 (28)	2.71 (25.8)	3.62 (22.6)
CMINSS	1.61 (52.9)	1.48 (25.8)	1.77 (63.9)
CMAXSS	15.6 (34.6)	12.5 (39.7)	20.3 (47.4)
CAVGSS	4.54 (31.6)	4 (25.3)	5.32 (34)

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ 4-model-eval-app.Rmd
Source: Analysis Directory/R/export/Ipi-exp-summary-by-race.csv

Immunogenicity

Table 7. Anti-Drug Antibody Assessment Summary, All Nivolumab + Ipilimumab Treated Subjects with Baseline and at Least One Post-Baseline Assessment

	Nivolumab + Ipilimumab	
Subject ADA Status (%)	Nivolumab ADA N = 269	Ipilimumab ADA N = 271
BASELINE ADA POSITIVE	17 (6.3)	12 (4.4)
ADA POSITIVE	69 (25.7)	37 (13.7)
PERSISTENT POSITIVE (PP)	5 (1.9)	3 (1.1)
NOT PP - LAST SAMPLE POSITIVE	24 (8.9)	13 (4.8)
OTHER POSITIVE	40 (14.9)	21 (7.7)
NEUTRALIZING POSITIVE	2 (0.7)	1 (0.4)
ADA NEGATIVE	200 (74.3)	234 (86.3)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment; **Persistent Positive (PP):** ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart; **Not PP-Last Sample Positive:** Not persistent but with ADA-positive sample at the last sampling timepoint; **Other Positive:** Not persistent but some ADA-positive samples with the last sample being negative; **Neutralizing Positive:** At least one ADA-positive sample with neutralizing antibodies detected post-baseline; **ADA Negative:** A subject with no ADA-positive sample after initiation of treatment.
Post-baseline assessments are assessments reported after initiation of treatment.
Source: Table S.7.5 of the CA209743 Final CSR

Dose and schedule selection and confirmation

Table 8. geometric Mean Exposure for Nivolumab after 3 mg/Kg Q2W, 240 mg Q2W, or 360 mg Q3W in subjects with Mesothelioma in Study CA209743

Summary Exposure	N	3 mg/kg Q2W GM (µg/mL) (%CV)	240 mg Q2W GM (µg/mL) (%CV)	360 mg Q3W GM (µg/mL) (%CV)	% Diff GM (G2-G1)[a]	% Diff GM (G3-G1)[b]
Cmax1	297	55.6 (18.3)	62.1 (21.6)	93.1 (21.6)	11.7	67.4
Cmin1	297	13.7 (27)	15.3 (27.9)	16.0 (33.2)	11.7	16.8
Cavg1	297	23.8 (19.4)	26.6 (20.9)	33.1 (22.4)	11.8	39.1
Cmaxss	297	114 (26.2)	127 (25.5)	151 (24.1)	11.4	32.5
Cminss	297	56.6 (39.1)	63.2 (37.3)	55.8 (40.2)	11.7	-1.41
Cavgss	297	74.9 (32.8)	83.7 (31.1)	83.7 (31.1)	11.7	11.7

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final/

R-Program Source: Analysis Directory/R/scripts/3-simulation-flatdose.Rmd

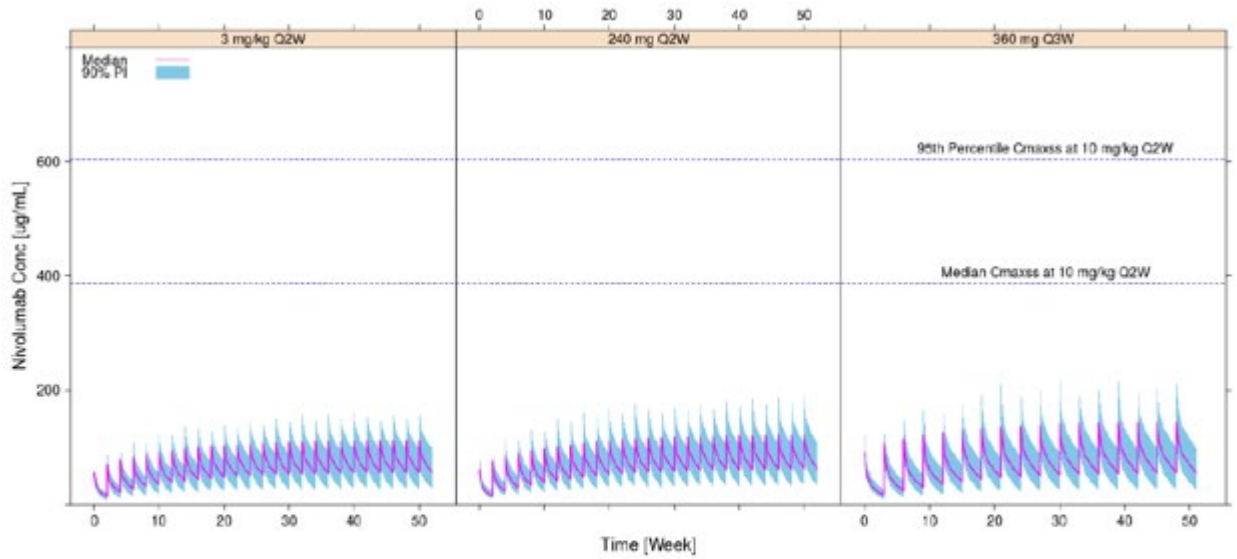
Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-3-240.csv
Analysis-Directory/R/export/sumstat-exps-bygeomean-3-360.csv

Abbreviations: Cavg1: nivolumab concentration over the first dosing interval (Cavg1 is equivalent to Cavgd14 for Q2W and Cavgd21 for Q3W), Cmax1: maximum nivolumab serum concentration after the first dose; Cmin1: trough concentration after the first nivolumab dose (Cmin1 is equivalent to Cmind14 for Q2W and Cmind21 for Q3W); Q2W = every 2 weeks; Q4W = every 4 weeks; SS = steady state.

[a] Percent difference in geometric mean of 240 mg Q2W (G2) relative to 3 mg/kg Q2W (G1).

[b] Percent difference in geometric mean of 360 mg Q3W (G3) relative to 3 mg/kg Q2W (G1).

Figure 21. Predicted Nivolumab Concentration (with 90 % PI) versus Time by Dosing Regimen in Subjects with Mesothelioma



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/ppk-nivo/final/
R-Program Source: Analysis Directory/R/scripts/3-simulation-flatdose.Rmd
Source: Analysis-Directory/R/plots/CT.plot3-overall-ADJ.png
Abbreviations: PI = prediction interval

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

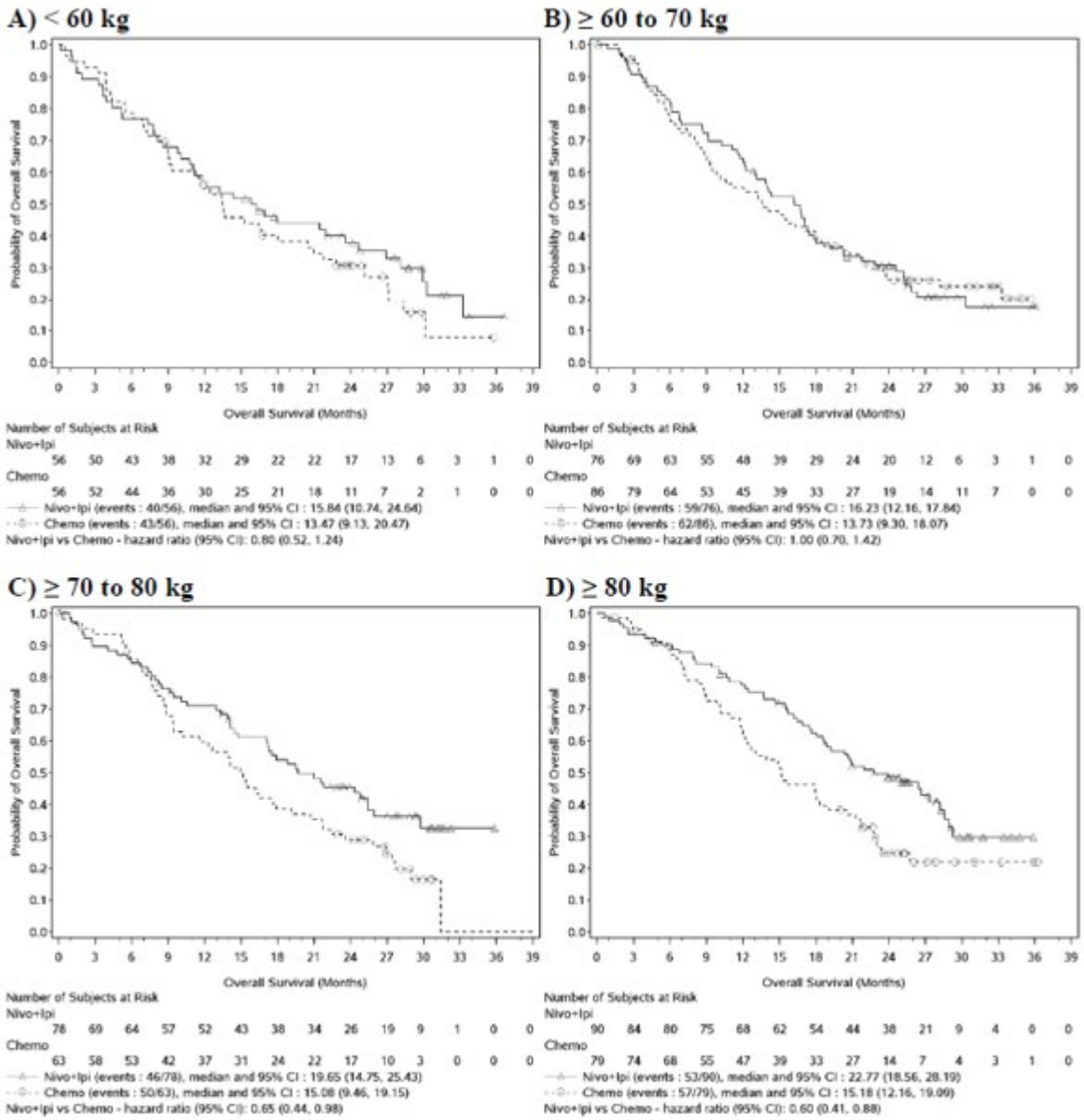
Further, clinical subgroup efficacy (OS) across body weight categories in Study CA209743 demonstrated that higher body weight subjects may have lower exposures compared with weight-based dosing which could be potentially associated with poorer survival. However, the subjects with higher body weight demonstrated better survival than those with lower body weight.

Table 9. Overall Survival in Study CA209743 Baseline Body Weight Category Summary

	Nivolumab + Ipilimumab N = 300	Chemotherapy N = 284	HR (1) (95% CI)
BASELINE BODY WEIGHT			
< 60 KG			
# EVENTS / # SUBJECTS (%)	40/ 56 (71.4)	43/ 56 (76.8)	0.80
MEDIAN OS (MONTHS) (1) (95% CI)	15.84 (10.74, 24.64)	13.47 (9.13, 20.47)	(0.52, 1.24)
>= 60-< 70 KG			
# EVENTS / # SUBJECTS (%)	59/ 76 (77.6)	62/ 86 (72.1)	1.00
MEDIAN OS (MONTHS) (1) (95% CI)	16.23 (12.16, 17.84)	13.73 (9.30, 18.07)	(0.70, 1.42)
>= 70-< 80 KG			
# EVENTS / # SUBJECTS (%)	46/ 78 (59.0)	50/ 63 (79.4)	0.65
MEDIAN OS (MONTHS) (1) (95% CI)	19.65 (14.75, 25.43)	15.08 (9.46, 19.15)	(0.44, 0.98)
>= 80 KG			
# EVENTS / # SUBJECTS (%)	53/ 90 (58.9)	57/ 79 (72.2)	0.60
MEDIAN OS (MONTHS) (1) (95% CI)	22.77 (18.56, 28.19)	15.18 (12.16, 19.09)	(0.41, 0.88)

(1) Based on Kaplan-Meier estimate
Unstratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Chemotherapy
Program Source: /opt/zfs001/prd/bms242187/stats/ebr2075/prog/tables/rt-ef-os-bywt-ebr2075-sas.sas

Figure 22. Kaplan-Meier Plot of Overall Survival in Study CA209743 by Baseline Body Weight Category



Statistical model for hazard ratio: unstratified Cox proportional hazards model

Symbols represent censored observations.

Program Source: /opt/zfs001/prd/bms242187/stats/ebr2075/prog/figures

Program Name: rg-ef-osby-ebr2075.sas

Table 10. Summary of Adverse Events by Weight Category – Nivolumab 3 mg/Kg Q2W + Ipilimumab 1 Mg/Kg Q6W Treated Subject with MPM in Study CA209743

Subjects with an Event: N (%) [95% CI	< 60 kg N = 56	≥ 60 to < 70 kg N = 76	≥ 70 to < 80 kg N = 78	≥ 80 kg N = 90	Total N = 300
Grade 3-4 AEs					
N (%)	27 (48.2)	40 (52.6)	40 (51.3)	52 (57.8)	159 (53.0)
95% CI	34.7, 62.0	40.8, 64.2	39.7, 62.8	46.9, 68.1	-
All SAEs					
N (%)	33 (58.9)	37 (48.7)	44 (56.4)	50 (55.6)	164 (54.7)
95% CI	45.0, 71.9	37.0, 60.4	44.7, 67.6	44.7, 66.0	-
Grade 2+ IMAEs					
Non-endocrine					
Pneumonitis	4 (7.1)	3 (3.9)	6 (7.7)	6 (6.7)	19 (6.3)
Diarrhea/colitis	6 (10.7)	5 (6.6)	7 (9.0)	5 (5.6)	23 (7.7)
Hepatitis	2 (3.6)	2 (2.6)	4 (5.1)	9 (10.0)	17 (5.7)
Nephritis and renal dysfunction	1 (1.8)	2 (2.6)	0	3 (3.3)	6 (2.0)
Rash	3 (5.4)	9 (11.8)	5 (6.4)	8 (8.9)	25 (8.3)
Hypersensitivity	1 (1.8)	0	1 (1.3)	2 (2.2)	4 (1.3)
Endocrine					
Adrenal insufficiency	1 (1.8)	0	3 (3.8)	3 (3.3)	7 (2.3)
Hypothyroidism/thyroiditis	2 (3.6)	1 (1.3)	2 (2.6)	12 (13.3)	17 (5.7)
Diabetes mellitus	0	0	0	1 (1.1)	1 (0.3)
Hyperthyroidism	0	0	2 (2.6)	0	2 (0.7)
Hypophysitis	3 (5.4)	3 (3.9)	3 (3.8)	1 (1.1)	10 (3.3)

Source: Table 3.1, Table 3.2, Table 4.1, Table 5.1, and Table 6.1

MedDRA Version: 22.1, CTC Version 4.0

Values are subjects with an event (%) (95% CI). Exact 95% CI on incidence rate based on Clopper and Pearson method.
Grade 3-4 AEs and SAEs include events reported between first dose and 30 days after last dose of study therapy.

Gr 2+ IMAEs include events reported between first dose and 100 days after last dose of study therapy.

Table 11. Summary of Gr2+IMAEs by Cavg Quartiles – Nivolumab + ipilimumab Treated Subjects with MPM or NSCLC in Studies CA209743, CA209227 Part 1, CA209817 Cohort A, and CA2099LA with Exposure Data Available

Subjects with an Event	Q1 < 70.1 µg/mL	Q2 ≥ 70.1 to < 86.6 µg/mL	Q3 ≥ 86.6 to < 109.8 µg/mL	Q4 ≥ 109.8 µg/mL	Total
Study CA209743, N	**98**	**92**	**66**	**41**	**297**
Non-endocrine					
Pneumonitis	11 (11.2)	5 (5.4)	1 (1.5)	2 (4.9)	19 (6.4)
Diarrhea/colitis	7 (7.1)	6 (6.5)	6 (9.1)	4 (9.8)	23 (7.7)
Hepatitis	2 (2.0)	6 (6.5)	6 (9.1)	3 (7.3)	17 (5.7)
Nephritis and renal dysfunction	2 (2.0)	3 (3.3)	1 (1.5)	0	6 (2.0)
Rash	10 (10.2)	4 (4.3)	7 (10.6)	4 (9.8)	25 (8.4)
Hypersensitivity	1 (1.0)	2 (2.2)	1 (1.5)	0	4 (1.3)
Endocrine					
Adrenal insufficiency	1 (1.0)	2 (2.2)	2 (3.0)	2 (4.9)	7 (2.4)
Hypothyroidism/thyroiditis	3 (3.1)	4 (4.3)	6 (9.1)	4 (9.8)	17 (5.7)
Diabetes mellitus	0	1 (1.1)	0	0	1 (0.3)
Hyperthyroidism	0	1 (1.1)	1 (1.5)	0	2 (0.7)
Hypophysitis	2 (2.0)	2 (2.2)	3 (4.5)	3 (7.3)	10 (3.4)
Study CA209227 Part 1, N	**121**	**125**	**115**	**123**	**484**
Non-endocrine					
Pneumonitis	13 (10.7)	3 (2.4)	10 (8.7)	9 (7.3)	35 (7.2)
Diarrhea/colitis	6 (5.0)	13 (10.4)	8 (7.0)	11 (8.9)	38 (7.9)
Hepatitis	5 (4.1)	16 (12.8)	7 (6.1)	12 (9.8)	40 (8.3)
Nephritis and renal dysfunction	0	2 (1.6)	1 (0.9)	1 (0.8)	4 (0.8)
Rash	9 (7.4)	11 (8.8)	10 (8.7)	24 (19.5)	54 (11.2)
Hypersensitivity	0	1 (0.8)	0	3 (2.4)	4 (0.8)
Endocrine					
Adrenal insufficiency	4 (3.3)	5 (4.0)	9 (7.8)	5 (4.1)	23 (4.8)
Hypothyroidism/thyroiditis	8 (6.6)	9 (7.2)	9 (7.8)	16 (13.0)	42 (8.7)
Diabetes mellitus	0	2 (1.6)	1 (0.9)	3 (2.4)	6 (1.2)
Hyperthyroidism	4 (3.3)	3 (2.4)	4 (3.5)	7 (5.7)	18 (3.7)
Hypophysitis	0	1 (0.8)	3 (2.6)	8 (6.5)	12 (2.5)

Table 12. Summary of Gr2+ IMAE by CAvg Quartiles – Nivolumab + Ipilimumab Treated Subjects with MPM or NSCLC in Studies CA209743, CA209227 Part1, CA209817 Cohort A, and CA2099LA with Exposure Data Available

Subjects with an Event	Q1 < 70.1 µg/mL	Q2 ≥ 70.1 to < 86.6 µg/mL	Q3 ≥ 86.6 to < 109.8 µg/mL	Q4 ≥ 109.8 µg/mL	Total
Study CA209817 Cohort A, N	**88**	**88**	**105**	**92**	**373**
Non-endocrine					
Pneumonitis	7 (8.0)	14 (15.9)	5 (4.8)	7 (7.6)	33 (8.8)
Diarrhea/colitis	2 (2.3)	5 (5.7)	11 (10.5)	10 (10.9)	28 (7.5)
Hepatitis	5 (5.7)	1 (1.1)	7 (6.7)	5 (5.4)	18 (4.8)
Nephritis and renal dysfunction	1 (1.1)	0	1 (1.0)	0	2 (0.5)
Rash	6 (6.8)	7 (8.0)	6 (5.7)	4 (4.3)	23 (6.2)
Hypersensitivity	0	3 (3.4)	4 (3.8)	1 (1.1)	8 (2.1)
Endocrine					
Adrenal insufficiency	0	1 (1.1)	1 (1.0)	6 (6.5)	8 (2.1)
Hypothyroidism/thyroiditis	4 (4.5)	4 (4.5)	12 (11.4)	12 (13.0)	32 (8.6)
Diabetes mellitus	1 (1.1)	0	1 (1.0)	0	2 (0.5)
Hyperthyroidism	2 (2.3)	2 (2.3)	4 (3.8)	2 (2.2)	10 (2.7)
Hypophysitis	1 (1.1)	2 (2.3)	2 (1.9)	1 (1.1)	6 (1.6)
Study CA2099LA, N	**71**	**69**	**92**	**121**	**353**
Non-endocrine					
Pneumonitis	3 (4.2)	3 (4.3)	8 (8.7)	3 (2.5)	17 (4.8)
Diarrhea/colitis	4 (5.6)	4 (5.8)	5 (5.4)	4 (3.3)	17 (4.8)
Hepatitis	3 (4.2)	3 (4.3)	6 (6.5)	5 (4.1)	17 (4.8)
Nephritis and renal dysfunction	1 (1.4)	1 (1.4)	1 (1.1)	1 (0.8)	4 (1.1)
Rash	5 (7.0)	6 (8.7)	8 (8.7)	8 (6.6)	27 (7.6)
Hypersensitivity	0	1 (1.4)	0	1 (0.8)	2 (0.6)
Endocrine					
Adrenal insufficiency	2 (2.8)	1 (1.4)	3 (3.3)	5 (4.1)	11 (3.1)
Hypothyroidism/thyroiditis	3 (4.2)	8 (11.6)	13 (14.1)	11 (9.1)	35 (9.9)
Diabetes mellitus	0	0	0	0	0
Hyperthyroidism	0	4 (5.8)	0	5 (4.1)	9 (2.5)
Hypophysitis	2 (2.8)	1 (1.4)	1 (1.1)	4 (3.3)	8 (2.3)

Source: Table 9.1, Table 9.2, Table 9.3, Table 9.4, Table 10.1, Table 10.2, Table 10.3, and Table 10.4
MedDRA Version: 22.1 (Study CA209743) or 22.0 (Studies CA209227, CA209817, and CA2099LA), CTC Version 4.0
Includes events reported between first dose and 100 days after last dose of study therapy.

Table 13. Summary of Grade 3-4 AEs and SAEs by Cavg quartiles - Nivolumab + Ipilimumab Treated Subjects with MPM or NSCLC in Studies CA209743, CA209227 Part1, CA209817 Cohort A, and CA2099LA with Exposure Data Available

Subjects with an Event	Q1 < 68.5 µg/mL	Q2 ≥ 68.5 to < 84.6 µg/mL	Q3 ≥ 84.6 to < 106.7 µg/mL	Q4 ≥ 106.7 µg/mL	Total
Grade 3-4 AEs					
Study CA209743, N	**92**	**89**	**69**	**47**	**297**
N (%)	46 (50.0)	46 (51.7)	41 (59.4)	26 (55.3)	159 (53.5)
95% CI	39.4, 60.6	40.8, 62.4	46.9, 71.1	40.1, 69.8	-
Study CA209227 Part 1, N	**115**	**117**	**115**	**137**	**484**
N (%)	74 (64.3)	75 (64.1)	67 (58.3)	85 (62.0)	301 (62.2)
95% CI	54.9, 73.1	54.7, 72.8	48.7, 67.4	53.4, 70.2	-
Study CA209817 Cohort A, N	**82**	**81**	**107**	**103**	**373**
N (%)	48 (58.5)	51 (63.0)	69 (64.5)	58 (56.3)	226 (60.6)
95% CI	47.1, 69.3	51.5, 73.4	54.6, 73.5	46.2, 66.1	-
All SAEs					
Study CA209743, N	**92**	**89**	**69**	**47**	**297**
N (%)	61 (66.3)	47 (52.8)	39 (56.5)	16 (34.0)	163 (54.9)
95% CI	55.7, 75.8	41.9, 63.5	44.0, 68.4	20.9, 49.3	-
Study CA209227 Part 1, N	**115**	**117**	**115**	**137**	**484**
N (%)	76 (66.1)	67 (57.3)	62 (53.9)	74 (54.0)	279 (57.6)
95% CI	56.7, 74.7	47.8, 66.4	44.4, 63.2	45.3, 62.6	-
Study CA209817 Cohort A, N	**82**	**81**	**107**	**103**	**373**
N (%)	50 (61.0)	55 (67.9)	62 (57.9)	56 (54.4)	223 (59.8)
95% CI	49.6, 71.6	56.6, 77.8	48.0, 67.4	44.3, 64.2	-

Source: Table 7.1, Table 7.2, Table 7.3, Table 7.4, Table 7.5, Table 7.6, Table 8.1, Table 8.2, and Table 8.3

MedDRA Version: 22.1, CTC Version 4.0

Grade 3-4 AEs and SAEs include events reported between first dose and 30 days after last dose of study therapy.

Note: For Study CA2099LA, the rates of Grade 3-4 AEs and SAEs are confounded by the addition of 2 cycles of platinum-based chemotherapy to the nivolumab + ipilimumab regimen and are therefore not included in this analysis.

2.3.4. PK/PD modelling

Exposure-response (E-R) analyses of efficacy (OS) and safety (Grade ≥ 2 immune-mediated adverse events [IMAEs]) were conducted to assess the relationship between nivolumab and ipilimumab exposure (including potential synergistic interactions between exposure/treatment effects) and efficacy and safety in subjects with MPM.

Exposure-efficacy

The Exposure-Response (E-R) analysis of efficacy included data from 579 subjects with untreated unresectable MPM in Study CA209743, including 295 subjects who received nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W and for whom estimates of both nivolumab and ipilimumab exposures (Cavg1) were available, and 284 subjects who received 6 cycles of pemetrexed 500 mg/m2 + cisplatin 75 mg/m2 or carboplatin area under the curve (AUC) 5+ (chemotherapy arm).

Table 14. Summary of Events in the Exposure-Response of OS Analysis Dataset

Study CA209743 Treatment Regimen	Number of Subjects		
	Included in Analysis	Number of Events (%)	Number Censored (%)
Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	295	195 (66.1)	100 (33.9)
Chemotherapy	284	212 (74.6)	72 (25.4)
Total	**579**	**407 (70.3)**	**172 (29.7)**

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final.

Program Source: Analysis-Directory/sas/subj_er_efficacy.sas.

Source: Analysis-Directory/reports/Table3.2.1.2-1.rtf.

Abbreviations: Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; Q2W = every 2 weeks; Q6W = every 6 weeks.

Chemotherapy: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5+.

Model development

Figure 23. Schematic Overview of the Exposure Response of OS Model Development

Full Model

- Selected log-linear functional form of nivolumab Cavg1 (ie, nivo Cavg[0-3 wk]) and linear functional form of ipilimumab Cavg1 (ie, ipi Cavg[0-6 wk]) in E-R OS full model
- The interactions of nivolumab and ipilimumab exposure effects were not a significant predictor of OS therefore were not included in the full model
- The full model including the interactions of histology and nivolumab exposure (log-linear function of nivolumab Cavg1) had lowest BIC compared to all other tested models.
- Assess impact of the following covariates on OS:
  - Continuous covariates: age, body weight, baseline LDH, baseline albumin, baseline nivolumab clearance (sensitivity analysis), and baseline tumor size
  - Categorical covariates: PD-L1 status (1% cutoff), sex, PS, disease stage, smoking status, and histology
- Baseline albumin, age, baseline tumor size, histology (chemotherapy), PS, and disease stage (IV vs I/II) were significant predictors of OS in the full model
- Sensitivity analyses were conducted to assess the E-R relationship after accounting of baseline nivolumab CL effect on OS.

Abbreviations: BIC = Bayesian information criterion; Cavg = simulated average concentration; Cavg1 = average concentration after the first dose; CL = clearance; E-R = exposure-response; LDH = lactate dehydrogenase; nivo = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1; PS = performance status.

The relationship between nivolumab and ipilimumab exposure (Cavg1) and OS was described by a semi-parametric Cox Proportional-Hazards (CPH) model and included assessments of the modulatory effect of pre-specified covariates (Table 15) on the E-R relationship.

Table 15. Parameter Estimates of the Exposure-response of the OS (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Cavg1_ipi [μg/mL]	-0.1429	0.11	76.97	0.8668 (0.6987, 1.075)
Log_Cavg1_nivo [μg/mL]	0.02555	0.04068	159.2	1.026 (0.9473, 1.111)
Log_Cavg1_nivo*Histology [Non-Epithelioid:Epithelioid] (interaction)	-0.09985	0.02439	24.43	0.905 (0.8627, 0.9493)
Histology [Non-Epithelioid:Epithelioid]	0.05374	0.1376	256	1.055 (0.8058, 1.382)
Age [yr]	0.01327	0.005797	43.69	1.013 (1.002, 1.025)
Body Weight [kg]	-0.00514	0.00381	74.14	0.9949 (0.9875, 1.002)
Log(LDH) [xULN]	0.05195	0.1652	318.1	1.053 (0.7619, 1.456)
Albumin [g/L]	-0.467	0.08934	19.13	0.6269 (0.5262, 0.7469)
Baseline Tumor Size [cm]	0.05896	0.009829	16.67	1.061 (1.04, 1.081)
Disease Status [Stage III:I/II]	0.1648	0.1756	106.6	1.179 (0.8358, 1.664)
Disease Status [Stage IV:I/II]	0.4289	0.1707	39.8	1.536 (1.099, 2.146)
Performance Score [≥ 1:0]	0.2713	0.108	39.8	1.312 (1.062, 1.621)
Smoking Status [Smoker:Non-smoker]	-0.05784	0.105	181.5	0.9438 (0.7683, 1.159)
Sex [Male:Female]	0.1383	0.1359	98.28	1.148 (0.8797, 1.499)
PD-L1 [≥ 1%:< 1%]	-0.08055	0.1199	148.9	0.9226 (0.7294, 1.167)

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/export/os-param-cph-full.csv.

Abbreviations: Cavg = simulated average concentration; Cavg1 = average concentration after the first dose; CI = confidence interval; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1; PS = performance status; RSE = relative standard error; SE = standard error; ULN = upper limit of normal.

Note: Baseline tumor size: Sum of longest diameters of all target and pleural lesions.

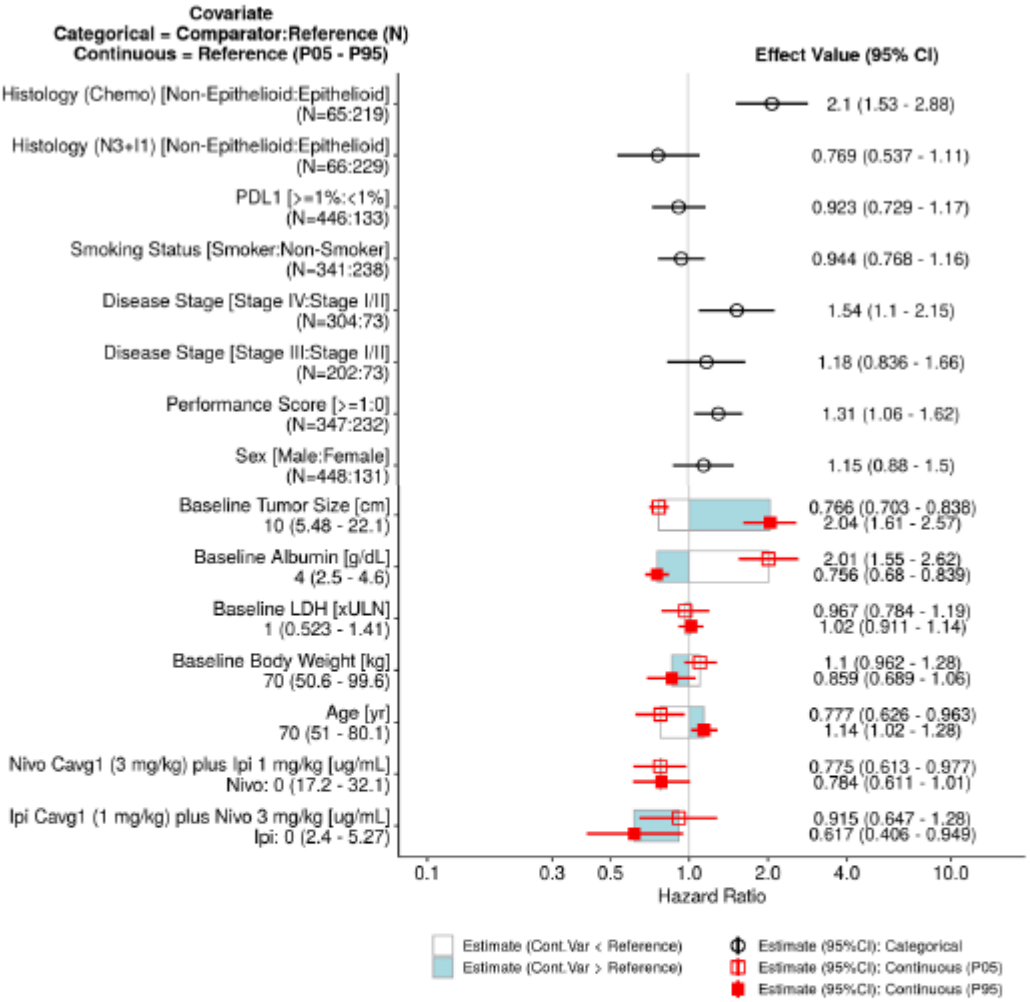
Note: Smoking status: Non-smoker = never smoked, and all others were defined as smoker (ie, current / former).

a Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference].

b RSE: Relative Standard Error = (100* SE/|Estimate|).

c Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group: Disease Stage I/II, PD-L1 <1%, PS= 0, epithelioid, non-smoker, and female subject.

Figure 24. Estimated Covariate effects of the Exposure-response of OS (Full Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/scripts/2-er-os-model-dev.html.

Abbreviations: Cavg1 = average concentration after the first dose; chemo = platinum-doublet chemotherapy; CI = confidence interval; Ipi = ipilimumab; LDH = lactate dehydrogenase; Nivo = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1; ULN = upper limit of normal.

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

Note: Baseline tumor size: Sum of longest diameters of all target and pleural lesions.

Table 16. Parameter Estimates of the Exposure-response of OS in the Sensitivity Analysis 1

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Cavg1_ipi [μg/mL]	0.07801	0.1284	164.5	1.081 (0.8407, 1.39)
Log_Cavg1_nivo [μg/mL]	-0.05478	0.04767	87.01	0.9467 (0.8623, 1.039)
Log_Cavg_nivo*Histology [Non-Epithelioid:Epithelioid]	-0.1029	0.02446	23.78	0.9023 (0.86, 0.9466)
Log(Baseline nivo CL) [mL/h]	1.196	0.3625	30.3	3.308 (1.626, 6.733)
Age [yr]	0.01434	0.005832	40.67	1.014 (1.003, 1.026)
Body Weight [kg]	-0.01337	0.004655	34.81	0.9867 (0.9778, 0.9958)
Log(LDH) [xULN]	0.03601	0.1649	457.9	1.037 (0.7504, 1.432)
Albumin [g/L]	-0.4455	0.0901	20.22	0.6405 (0.5368, 0.7642)
Tumor Size [cm]	0.05659	0.009814	17.34	1.058 (1.038, 1.079)
Disease Status [Stage III:I/II]	0.1717	0.1758	102.4	1.187 (0.8412, 1.676)
Disease Status [Stage IV:I/II]	0.424	0.1709	40.31	1.528 (1.093, 2.136)
Performance Score [≥1:0]	0.1396	0.1151	82.45	1.15 (0.9176, 1.441)
Smoking Status [Smoker:Non-smoker]	-0.08128	0.1053	129.5	0.9219 (0.7501, 1.133)
Sex [Male:Female]	-0.05265	0.1457	276.7	0.9487 (0.7131, 1.262)
PD-L1 [≥ 1%:< 1%]	-0.04671	0.1205	257.9	0.9544 (0.7537, 1.209)
Histology [Non-Epithelioid:Epithelioid]	0.05651	0.1374	243.1	1.058 (0.8083, 1.385)

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/export/ os-param-cph-sen1.csv.

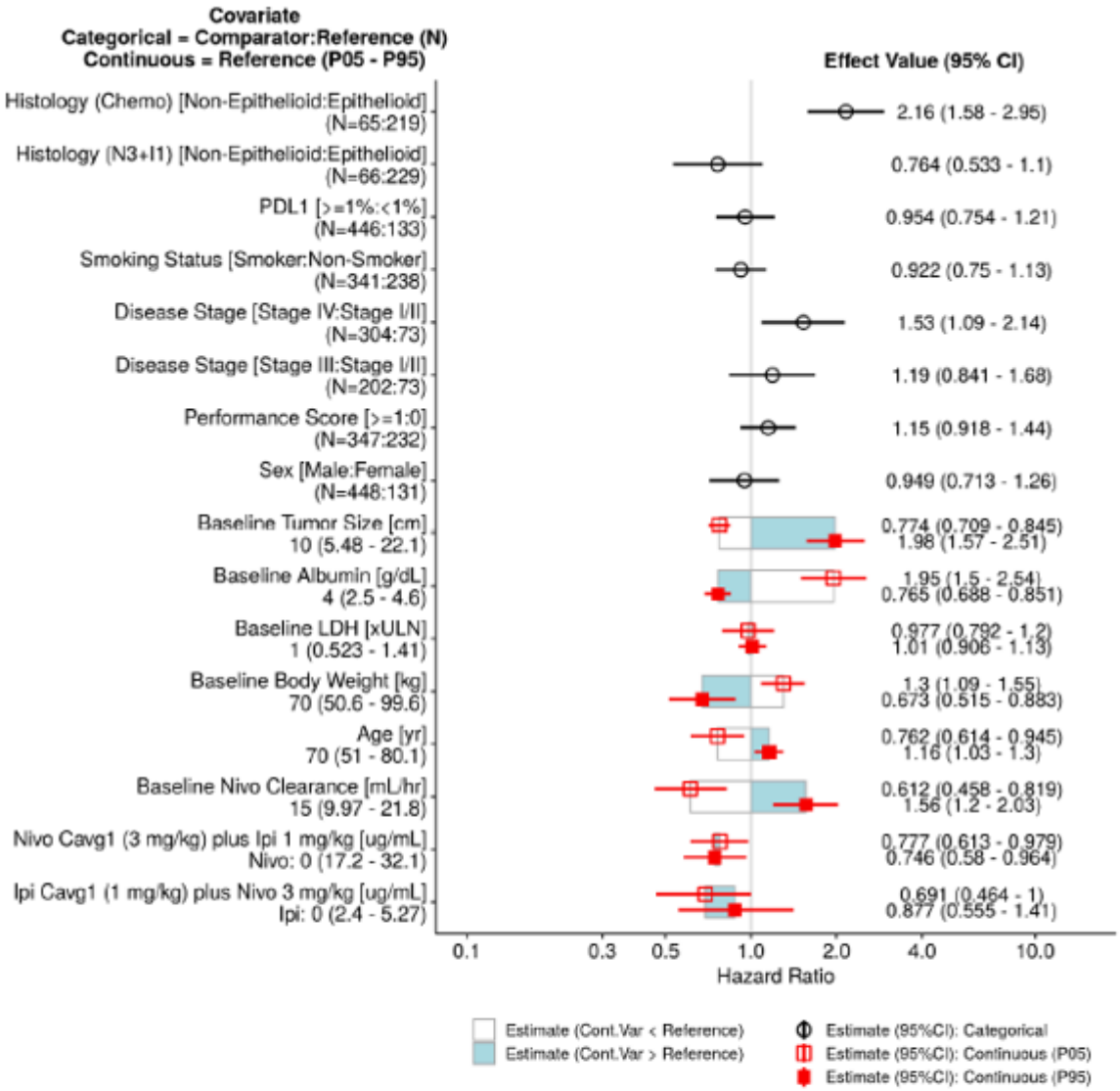
Abbreviations: Cavg = simulated average concentration; Cavg1 = average concentration after the first dose; CI = confidence interval; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1; PS = performance status; RSE = relative standard error; SE = standard error; ULN = upper limit of normal.

a Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference].

b RSE: Relative Standard Error = (100* SE/|Estimate|).

c Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group: Disease Stage I/II, PD-L1 <1%, PS = 0, epithelioid, non-smoker, and female subject.

Figure 25. Estimated Covariate Effects of the Exposure-Response of OS in the Sensitivity Analysis 1



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/scripts/2-er-os-model-dev.html.

Abbreviations: Cavg1 = average concentration after the first dose; CI = confidence interval; CL = clearance; Ipi = ipilimumab; LDH = lactate dehydrogenase; Nivo = nivolumab; OS = overall survival; PD-L1 = programmed death-ligand 1; PPK = population pharmacokinetics; ULN = upper limit of normal.

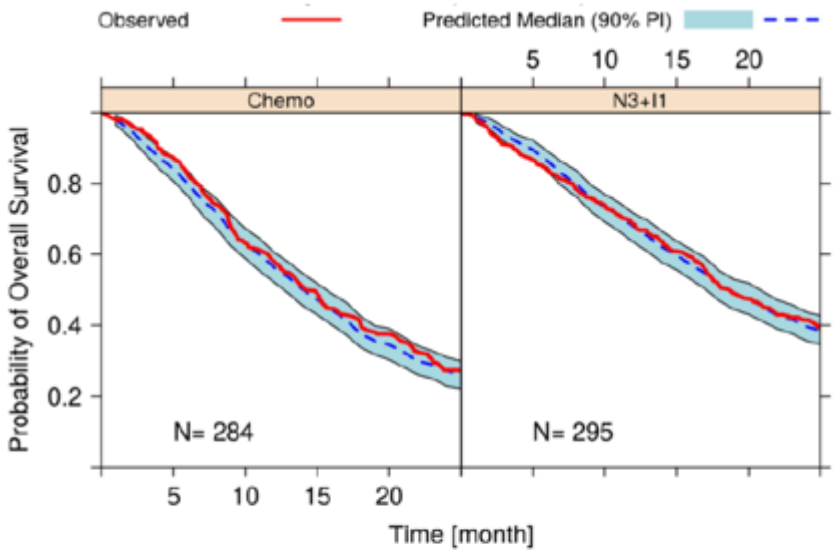
Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.

Model evaluation

The CPH model fit was evaluated by comparing the model-predicted cumulative time-to-event distributions with the corresponding distribution determined by non-parametric K-M analysis. Model evaluation of the full model shows that the model-predicted mean (90% CI) of OS is consistent with the observed K-M of OS of both treatment arms in CA209743 (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W and chemotherapy) as well as histology, as shown in Figure 26 and Figure 27, respectively.

The K-M curve was in agreement with the CPH model predictions, indicating adequate model performance.

Figure 26. Kaplan-Meier of Observed and Predicted Median (90% PI) of OS, by Treatment (Full Model)



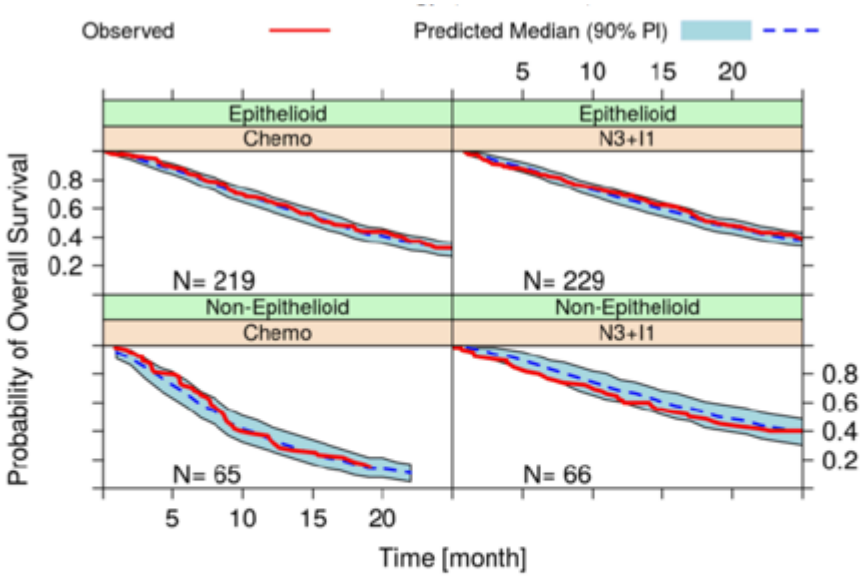
Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/scripts/2-er-os-model-dev.html.

Abbreviations: Chemo = platinum-doublet chemotherapy; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; OS = overall survival; PI = prediction interval.

Figure 27. Kaplan-Meier of Observed and Predicted Median (90% PI) of OS, by Treatment and Histology (Full Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

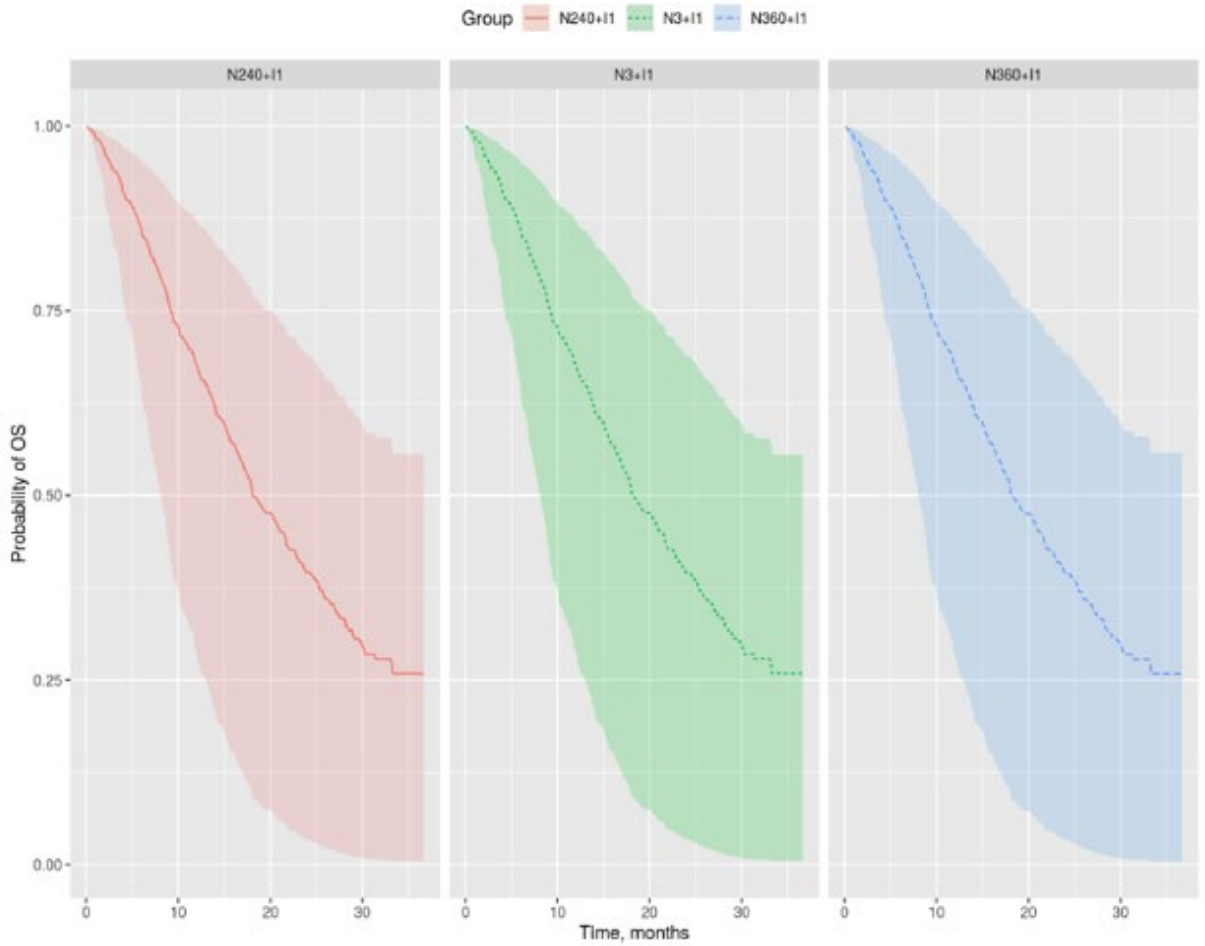
Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/scripts/2-er-os-model-dev.html.

Abbreviations: Chemo = platinum-doublet chemotherapy; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; OS = overall survival; PI = prediction interval.

Model application

Figure 28. Predicted Mean probability of OS Using Predicted Cavg for N3+I1, N240+I1, and N360+I1 in study CA209743



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

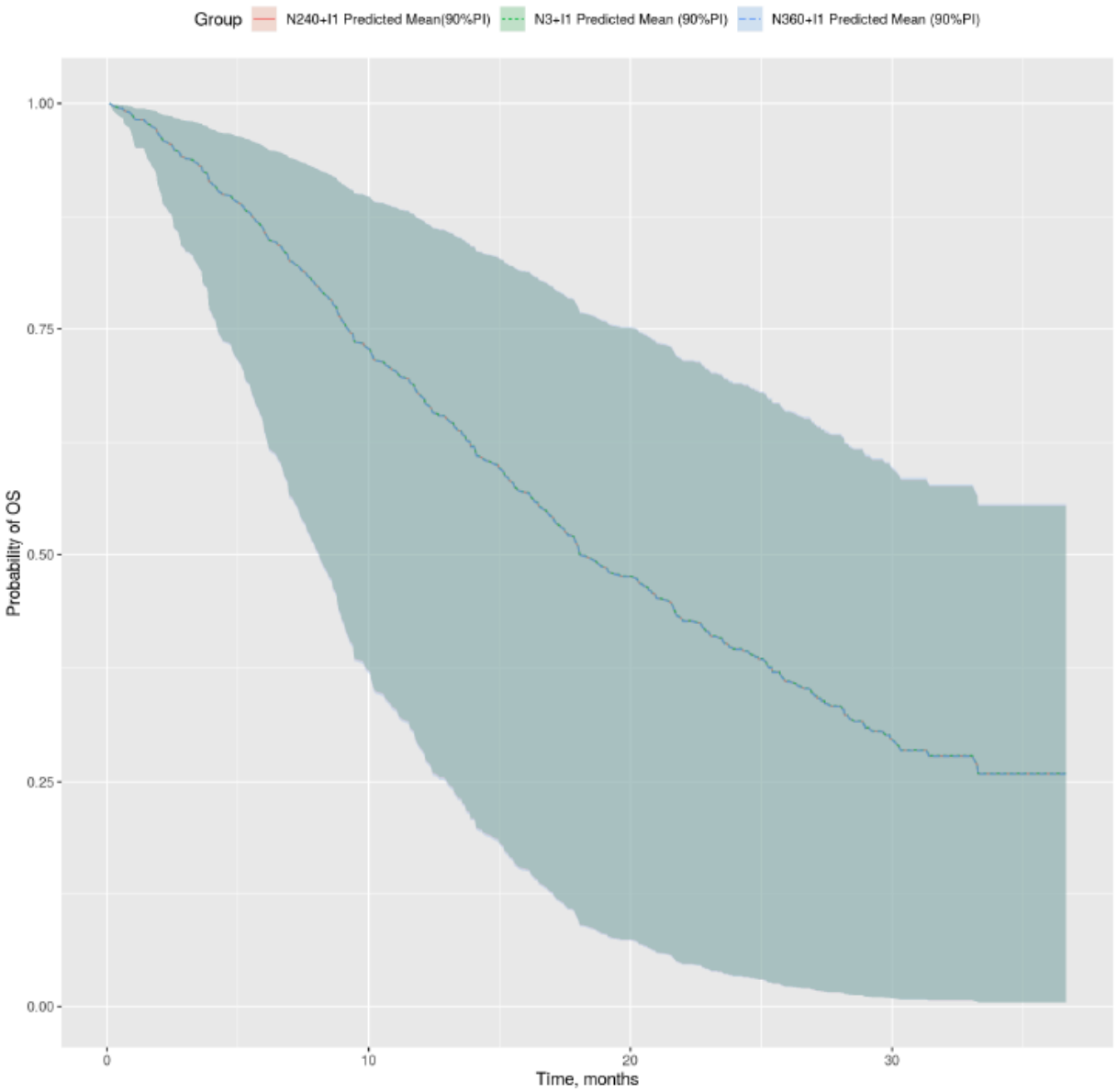
Source: Analysis-Directory/scripts/2-er-os-model-dev.html.

Abbreviations: Cavg1 = average concentration after the first dose; N240 + I1= nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; N360 + I1= nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W; OS = overall survival.

Note: Line and shaded area: model predicted mean and 90% Prediction interval.

Note: The overlapping plot of this figure is included in Appendix 5.1.3.

Figure 29. predicted Mean Probability of OS using Predicted Cavg1 for N3+I1, N240+I1, and N360+I1 in study CA209743



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-os/final/R.

Program Source: Analysis-Directory/scripts/2-er-os-model-dev.Rmd.

Source: Analysis-Directory/scripts/2-er-os-model-dev.html.

Abbreviations: N240 + I1= nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; N360 + I1= nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W; OS = overall survival; PI = prediction interval.

Exposure-safety

The E-R analysis of safety included data from the CA209743 analysis population identified for the E-R analysis of efficacy, as well as data from Study CA209227 (Parts 1 and 2), and Study CA2099LA.

Time to first Gr2+ IMAE was defined as the time between the day of the first dose of treatment and the onset date of the IMAE. The IMAEs were all causality IMAEs within 100 days of last dose. If subjects did

not experience any Gr2+ IMAE within 100 days of receiving their last treatment, they were censored at either the last dosing date +100 days, or the last known alive date, whichever occurred first. Table 17 shows there were 925 subjects with reported Gr2+ IMAEs in the analysis dataset.

Table 17. summary of Events in the Exposure Response of Gr1+ IMAs Analysis Dataset

Study	Number of Subjects		
	Included in Analysis	Number of Events (%)	Number Censored (%)
CA209743 Treatment Regimen			
Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	295	136 (46.1)	159 (53.9)
Chemotherapy	284	26 (9.2)	258 (90.8)
CA209227 Treatment Regimen			
Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	475	243 (51.2)	232 (48.8)
Nivo 240 mg Q2W	328	125 (38.1)	203 (61.9)
Nivo 360 mg Q3W + Pt-DC x 4 cycles	153	58 (37.9)	95 (62.1)
Chemotherapy	570	95 (16.7)	475 (83.3)
CA2099LA Treatment Regimen			
Nivo 360 mg Q3W + ipi 1 mg/kg Q6W + Pt-DC x 2 cycles	348	177 (50.9)	171 (49.1)
Chemotherapy	349	65 (18.6)	284 (81.4)
Total	**2802**	**925 (33.0)**	**1877 (67.0)**

Source: Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final.

Program Source: Analysis-Directory/sas/subj_er_safety.sas.

Source: Analysis-Directory/reports/Table3.2.2.2-1.rtf.

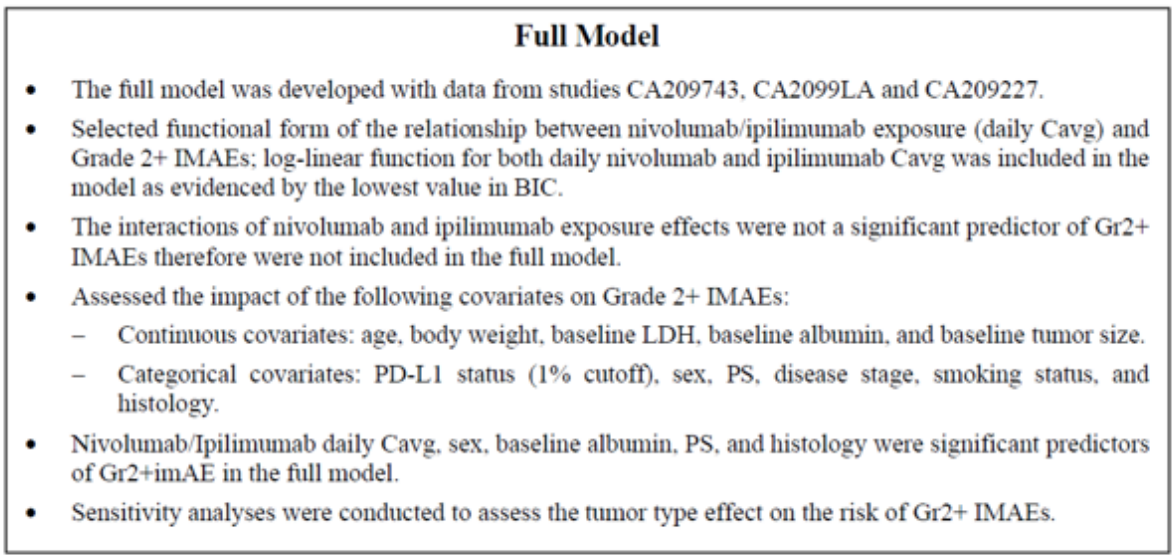
Abbreviations: Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse events; Ipi = ipilimumab; Nivo = nivolumab; Pt-DC = platinum doublet chemotherapy; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks.

Note: Chemotherapy: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5+.

The proportion of subjects with Gr2+ IMAEs over time plotted by the K-M curve is provided in Appendix 3.2.2.2-2.

Model development

Figure 30. Schematic Overview of the Exposure-Response of Gr2+ IMAEs Model Development



Abbreviations: BIC = bayesian information criterion; Cavg = simulated average concentration; Gr2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; LDH = lactate dehydrogenase; PD-L1 = programmed death-ligand 1.

The relationship between nivolumab and ipilimumab exposure (daily Cavg) and time to first occurrence of Gr2+ IMAEs was described by a semi-parametric CPH model and included assessments of the modulatory effect of covariates on the E-R relationship.

Table 18. Parameter Estimates of the Exposure Response of Gr2+ IMAEs (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Log nivo daily Cavg [μg/mL]	0.06561	0.009675	14.75	1.068 (1.048, 1.088)
Log ipi daily Cavg [μg/mL]	0.0642	0.01038	16.17	1.066 (1.045, 1.088)
Age [yr]	0.001996	0.003697	185.2	1.002 (0.9948, 1.009)
Body Weight [kg]	0.002087	0.002325	111.4	1.002 (0.9975, 1.007)
Albumin [g/L]	-0.1307	0.06708	51.34	0.8775 (0.7694, 1.001)
Tumor Size [cm]	-0.00376	0.007319	194.8	0.9962 (0.9821, 1.011)
Sex [Female:Male]	0.3023	0.0779	25.77	1.353 (1.161, 1.576)
Smoking Status [Non-smoker:Smoker]	-0.3111	0.09739	31.3	0.7326 (0.6053, 0.8867)
Disease Status [Stage III:I/II]	-0.1443	0.248	171.9	0.8656 (0.5324, 1.408)
Disease Status [Stage IV/Recurrent:I/II]	-0.2168	0.2382	109.8	0.8051 (0.5047, 1.284)
Performance Score [≥ 1:0]	-0.1485	0.06866	46.25	0.862 (0.7535, 0.9862)
Histology [Epithelioid:SQ/NSQ]	-0.2833	0.1358	47.95	0.7533 (0.5773, 0.9831)
Histology [Non-Epithelioid:SQ/NSQ]	0.08396	0.1881	224.1	1.088 (0.7522, 1.573)
PD-L1 Status [≥ 1%:< 1%]	0.04121	0.07277	176.6	1.042 (0.9036, 1.202)
Log(LDH) [×ULN]	-0.02743	0.08724	318.1	0.9729 (0.82, 1.154)

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.

Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.

Source: Analysis-Directory/R/export/fullmodel-param-imae.csv.

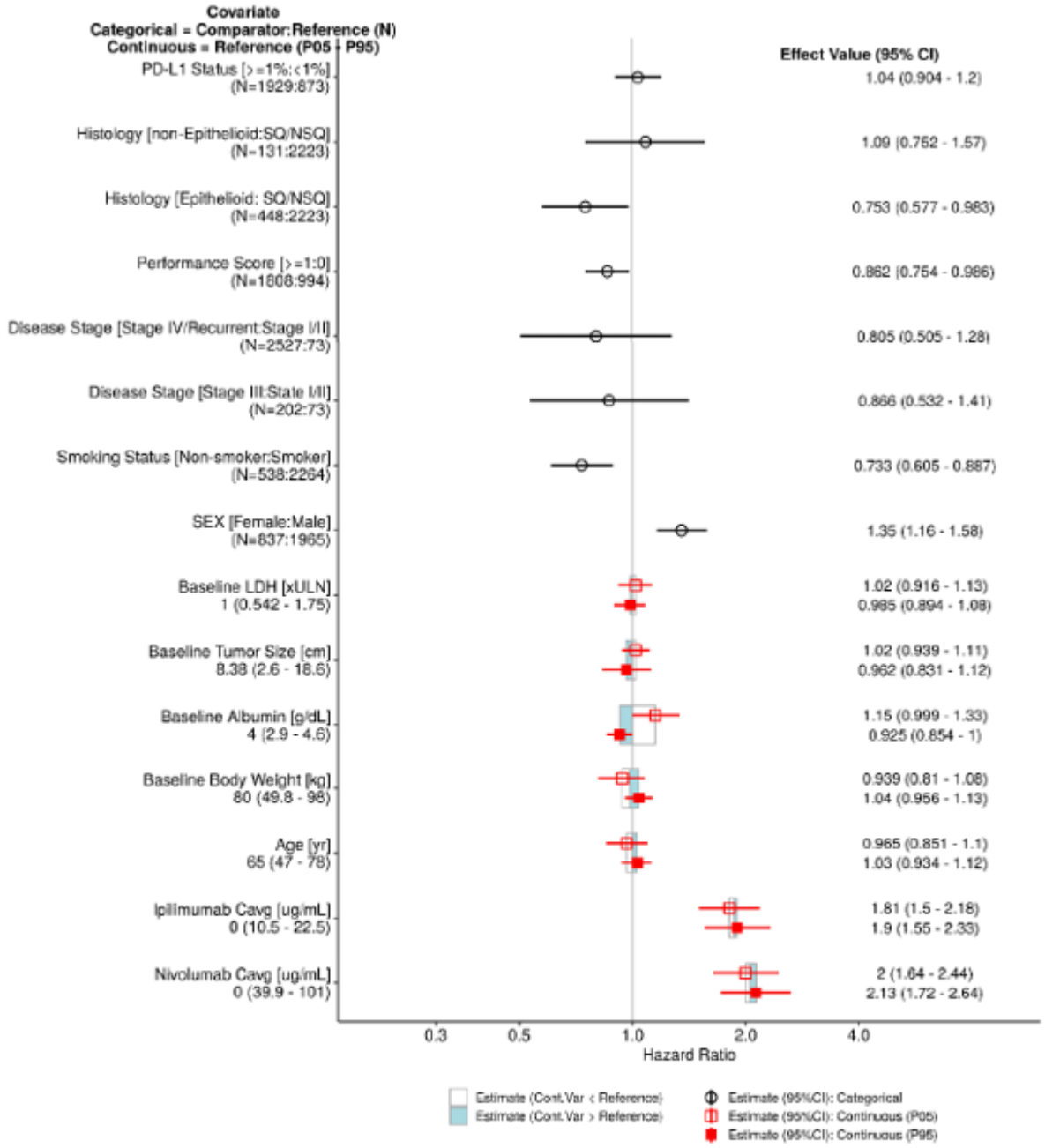
Abbreviations: Cavg = simulated average concentration; CI = confidence interval; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; PD-L1 = programmed death-ligand 1; RSE = relative standard error; SE = standard error; SQ/NSQ = squamous/non-squamous; ULN = upper limit of normal.

a Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference].

b RSE: Relative Standard Error = (100* SE/|Estimate|).

c Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group.

Figure 31. Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Full Model)



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.
Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.
Source: Analysis-Directory/R/export/coveff-full-imaegr2.png.

Abbreviations: Cavg = simulated average concentration; CI = confidence interval; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; LDH = lactate dehydrogenase; PD-L1 = programmed death-ligand 1; SQ/NSQ = squamous/non-squamous; ULN = upper limit of normal.

Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate. Cavg indicates averaged concentration from Day 1 to the event/censor.

Note: Reference subject: subject who received chemotherapy in Study CA209743 and had median value of LDH, albumin, body weight, baseline tumor size, NSCLC, male, smoker, PS = 0, PD-L1 < 1% and disease stage I/II subjects.

Table 19. Parameter Estimates of the Exposure-response of Gr2+IMAEs in the Sensitivity Analysis

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Log nivo daily Cavg [μg/mL]	0.06561	0.009675	14.75	1.068 (1.048, 1.088)
Log ipi daily Cavg [μg/mL]	0.0642	0.01038	16.17	1.066 (1.045, 1.088)
Age [yr]	0.001996	0.003697	185.2	1.002 (0.9948, 1.009)
Body Weight [kg]	0.002087	0.002325	111.4	1.002 (0.9975, 1.007)
Albumin [g/L]	-0.1307	0.06708	51.34	0.8775 (0.7694, 1.001)
Tumor Size [cm]	-0.00376	0.007319	194.8	0.9962 (0.9821, 1.011)
Sex [Female:Male]	0.3023	0.0779	25.77	1.353 (1.161, 1.576)
Smoking Status [Non-smoker:Smoker]	-0.3111	0.09739	31.3	0.7326 (0.6053, 0.8867)
Disease Status [Stage III:I/II]	-0.1443	0.248	171.9	0.8656 (0.5324, 1.408)
Disease Status [Stage IV/Recurrent:I/II]	-0.2168	0.2382	109.8	0.8051 (0.5047, 1.284)
Performance Score [≥ 1:0]	-0.1485	0.06866	46.25	0.862 (0.7535, 0.9862)
Tumor type [Mesothelioma:NSCLC]	0.08396	0.1881	224.1	1.088 (0.7522, 1.573)
Histology [Epithelioid:Others]	-0.3672	0.1826	49.73	0.6927 (0.4843, 0.9908)
PD-L1 Status [≥1%:<1%]	0.04121	0.07277	176.6	1.042 (0.9036, 1.202)
Log(LDH) [×ULN]	-0.02743	0.08724	318.1	0.9729 (0.82, 1.154)

Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.

Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.

Source: Analysis-Directory/R/export/senmodel-param-imae.csv.

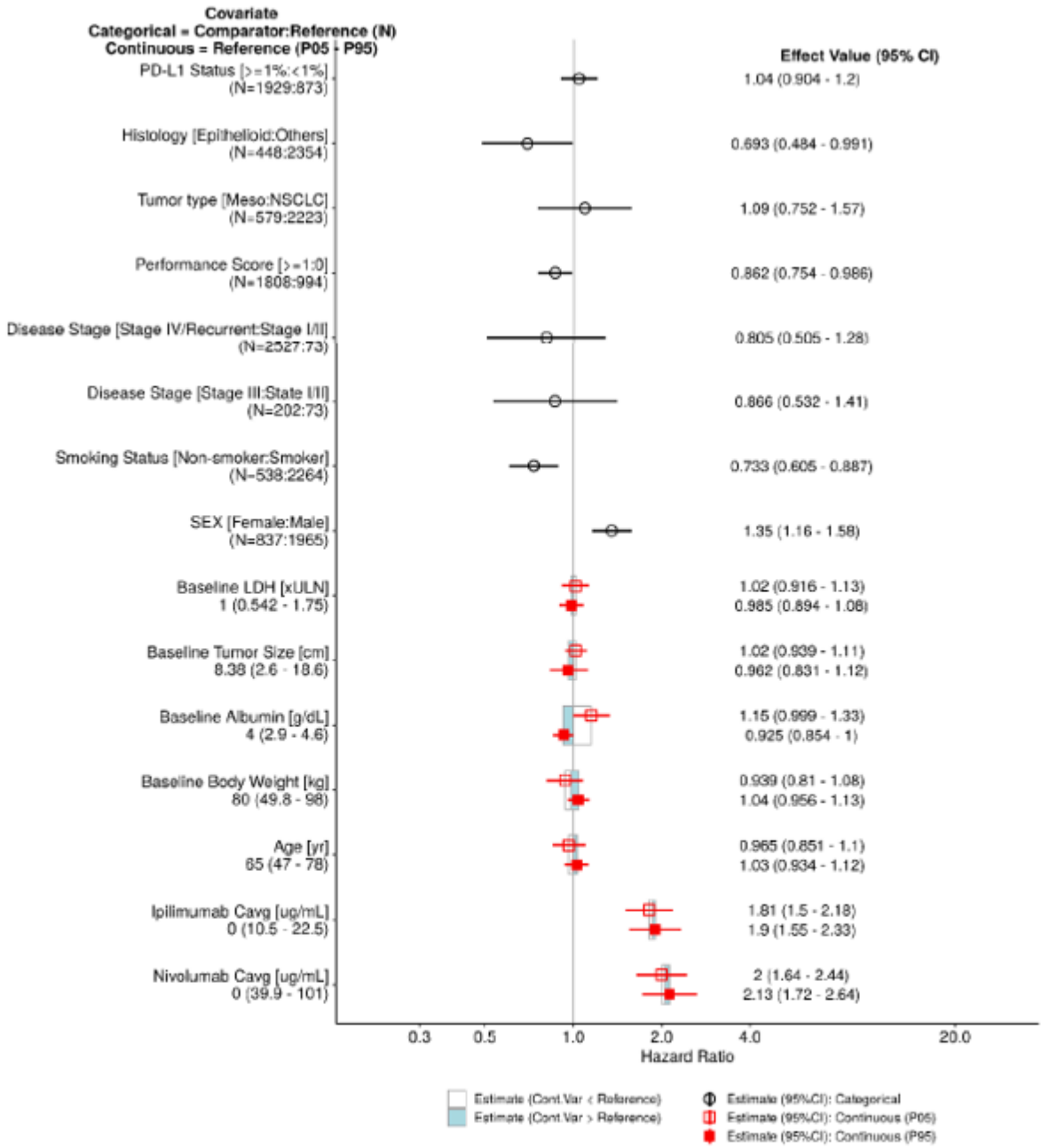
Abbreviations: Cavg = simulated average concentration; CI = confidence interval; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; HR = hazard ratio; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; RSE = relative standard error; SE = standard error; ULN = upper limit of normal.

a Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference].

b RSE: Relative Standard Error = (100* SE/|Estimate|).

c Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the HR of the comparator group to reference group.

Figure 32. Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs in the sensitivty Analysis



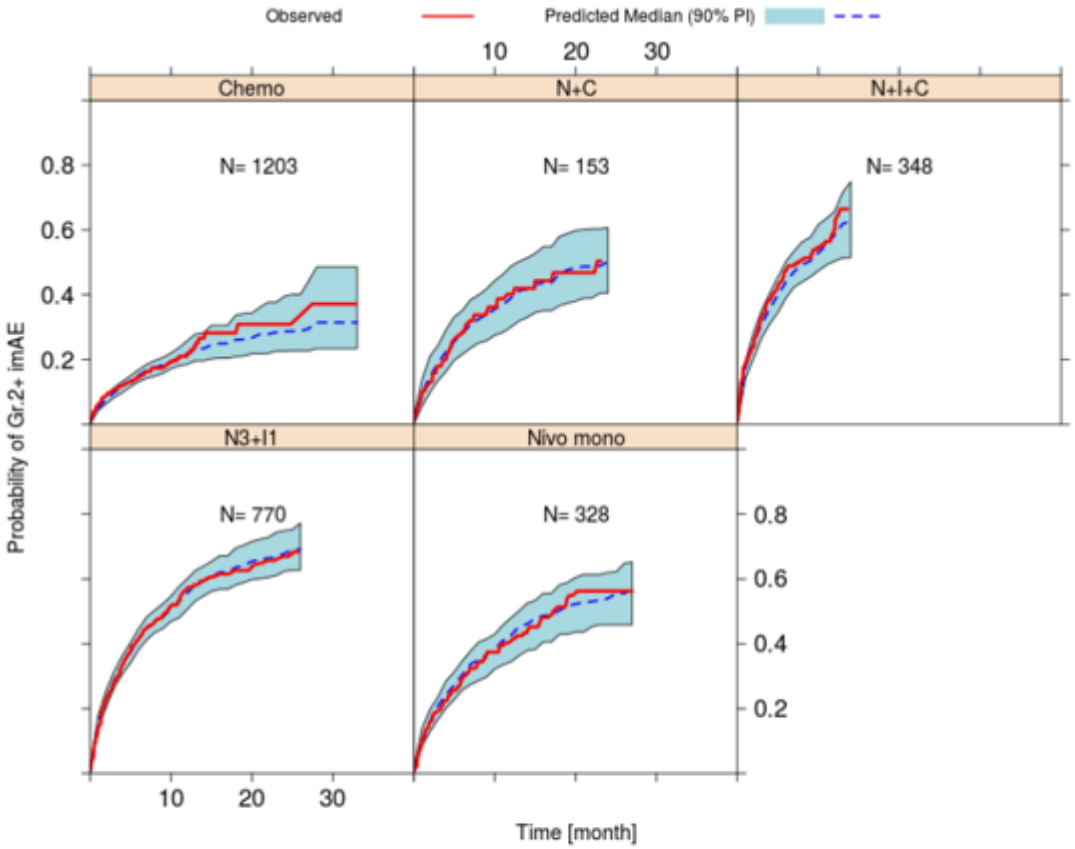
Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.
Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.
Source: Analysis-Directory/R/export/coveff-sen-imaegr2.png.

Model evaluation

The full CPH model was evaluated by a visual predictive check of the cumulative probability of the first occurrence of a Gr2+ IMAE. Figure 33 presents an evaluation of full model prediction of time-to-event of Gr2+ IMAEs by treatment. The model-predicted cumulative probabilities were in agreement with the model predictions for all of the treatments in the analysis data set. Figure 34 presents an evaluation of the

full model by histology and treatment in CA209743. This indicates that the model provides a good characterization of the probability of Gr2+ IMAEs for both the treatment arm and histology in CA209743.

Figure 33. Model Evaluation of Exposure- response of Gr2+ IMAE (Full Model), by Treatment Regimen



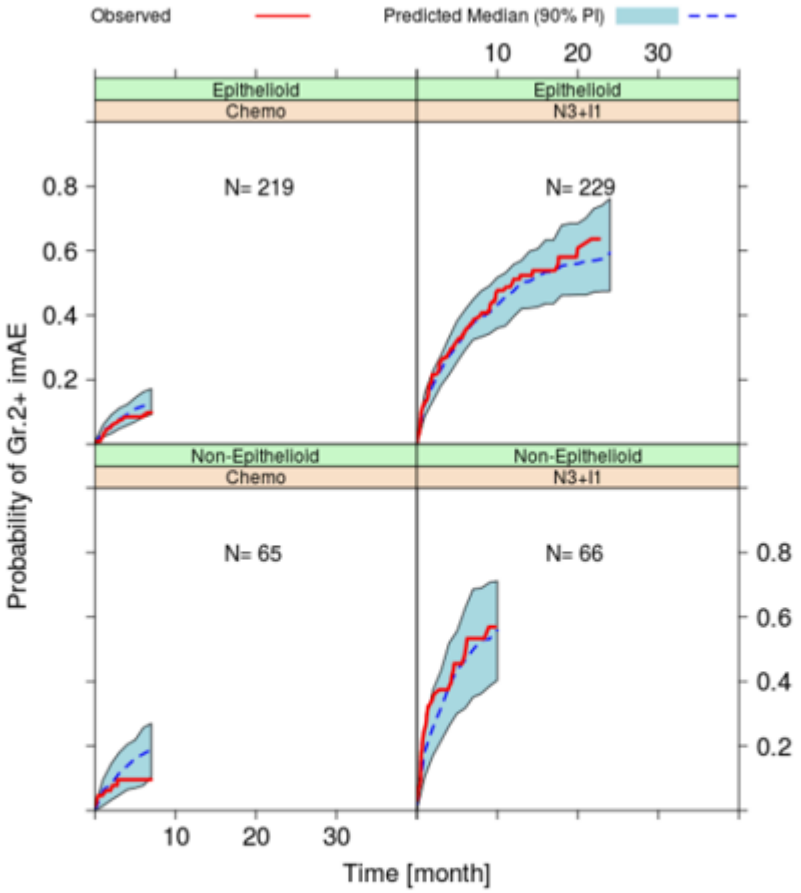
Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.

Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.

Source: Analysis-Directory/R/export/vpc-imgr2-full-trt.png.

Abbreviations: Chemo = platinum-doublet chemotherapy; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; N mono = nivolumab 240 mg; N+C = nivolumab 360 mg Q3W + 4 cycles of histology-based platinum-doublet chemotherapy; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; N+I+C = nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy; PI = prediction interval.

Figure 34. Model Evaluation of the Exposure-Response of Gr1+ IMAE (Full Model), by Histology and treatment Regimen in CA209743



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.

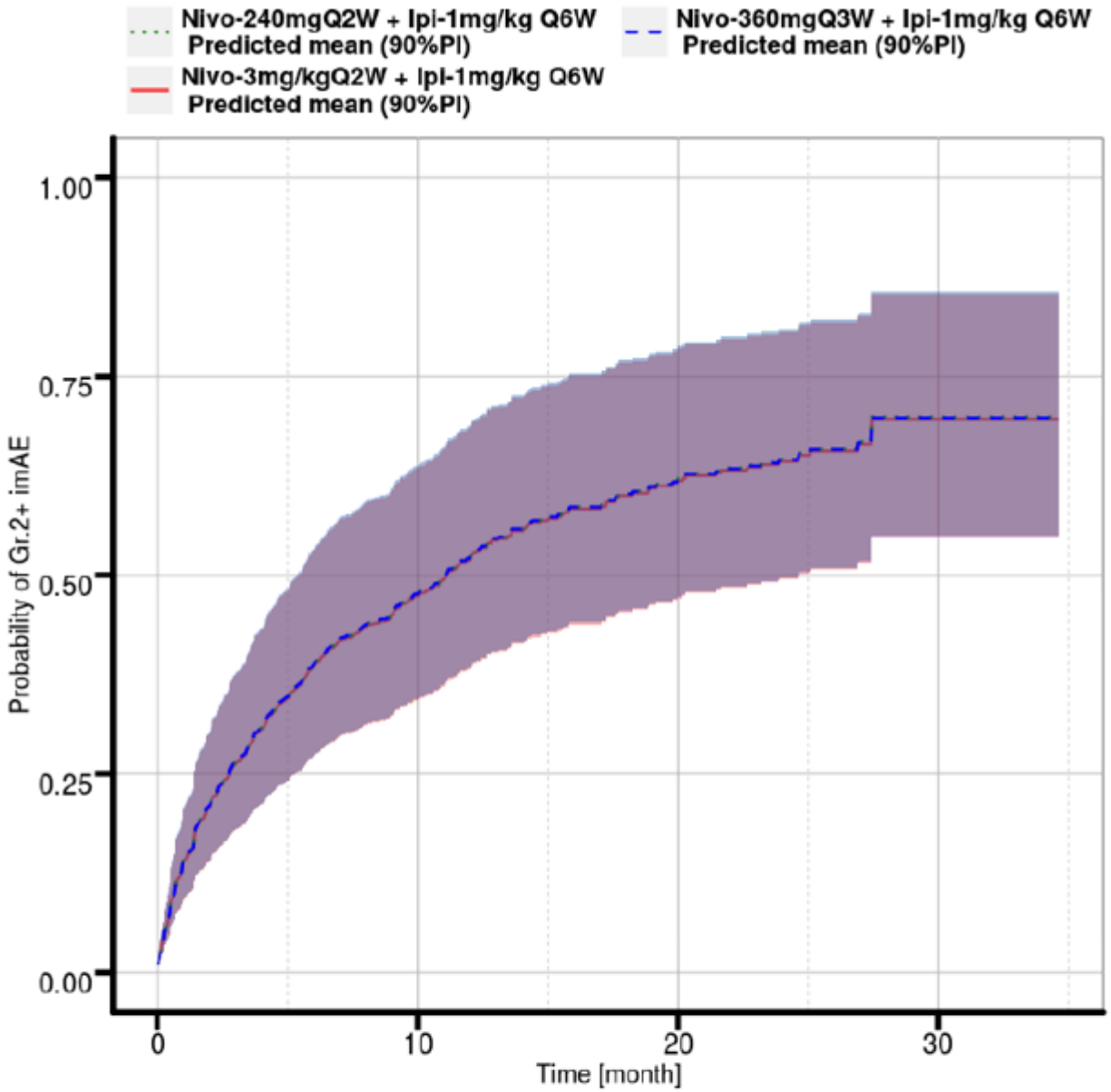
Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.

Source: Analysis-Directory/R/export/vpc-imgr2-full-his-743.png.

Abbreviations: Chemo = platinum-doublet chemotherapy; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; PI = prediction interval.

Model application

Figure 35. Predicted Mean Probability of Gr2+ IMAEs Using Predicted Exposures for N3+I1, N240+I1, and 360+I1 in study CA209743



Analysis-Directory: /global/pkms/data/CA/209/meso-1L-combo/prd/er-imae/final/R.

Program Source: Analysis-Directory/R/scripts/2-model-dev-apps-743-erimae.Rmd.

Source: Analysis-Directory/R/export/plot-pred-flat-ae.png.

Abbreviations: Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse events; Ipi = ipilimumab; N240 + I1= nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W; N3+I1 = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; N360 + I1= nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W; Nivo = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q6W = every 6 weeks.

2.3.5. Discussion on clinical pharmacology

The MAH has characterized the clinical pharmacology properties of nivolumab and ipilimumab in patients with unresectable malignant pleural mesothelioma. The modelling strategy, which applied the previously developed population PK model across multiple tumour types (base model) and the effects of covariates on nivolumab and ipilimumab PK parameters was assessed (final model), is endorsed.

Nivolumab population PK model

The base model was a two-compartment, zero-order IV infusion PK model, with time-varying CL (sigmoidal-Emax function); a proportional residual error model, with random effects on CL, VC, VP, and EMAX; and correlation of random effect between CL and VC. The final population PK model incorporates additional covariates representing the effect of tumour type + line of therapy (MPM 1L, NSCLC 1L and other vs. NSCLC 2L+) on the CL and EMAX of nivolumab. In general, adequate description of the data was observed based on the GOF and pc-VPC, which showed a slight over-prediction of the inter-individual random effects causing a wider prediction of exposure in the extreme percentiles compared to the experimental data.

The impact of the covariates selected in the final population PK model were assessed in the forest plot (Figure 2). The results suggest a clinically relevant change in Vc and CL in patients with extreme low body weights (~20%). Cmin1, Cavg1, Cminss, Cmaxss and Cavgss were >20% lower compared to the reference patient, demonstrating that patients with very low body weight would show a clinically relevant change in exposure, which may lead to a >20% less exposure with the proposed dosing regimen. The concern regarding lower expected exposure in patients with very low body weight (<50kg) is partially visible in the exposure-efficacy analysis, which suggested a statistical efficacy improvement in patients with higher body weight compared to patients with lower body weight (<70kg). It is agreed that the exposure-efficacy relationship is not only driven by the exposure metrics considered throughout the range of body weight but suggests a trend of slightly lower efficacy in patients with low body weights with the current regimen. In spite of that, it is not expected that a change in the administration regimen in patients with body weight ≤50kg could provide a significant improvement in terms of efficacy.

Ipilimumab population PK model

The base model was a two-compartment model with zero order IV infusion and first order elimination; and a combined proportional and additive residual error model, with random effects on CL, VC and EMAX; and correlation of random effect between CL and VC. The base model contained BBWT (baseline body weight) and BLDH (baseline lactate dehydrogenase) effect on CL, BBWT on VC, Q and VP. An adequate description of the data has been presented based on the GOF and pc-VPC. In addition, the pc-VPC stratified in MESO patients reflects and over-estimation of the inter-individual random effects, which might be of relevance in the prediction of PK exposure metrics in the exposure-response analyses and dose selection.

Exposure-efficacy relationship

A time-to-event model was developed to characterize the probability of overall survival in patients with MPM. This strategy is highly appreciated and endorsed. However, the time-to-event analysis revealed no clinical improvement when nivolumab 360 mg Q3W was selected over 3 mg/kg Q2W, which allows to conclude that a flat exposure-efficacy relationship was present.

Exposure-safety relationship

A time-to-event model was developed to characterize the probability of adverse events in patients with MPM. This strategy is highly appreciated and endorsed. The model is able to characterize the observed behaviour and predicted probabilities of Gr2+ IMAEs (immune mediated AEs) using the three dosing

strategies that have been shown. The results suggest negligible impact of Nivo 360 mg Q3W + Ipi 1 mg/kg 6QW compared to Nivo 240 mg Q2W + Ipi 1 mg/kg 6QW and Nivo 3 mg/kg Q2W + Ipi 1 mg/kg 6QW, demonstrating the lack of an exposure-safety relationship.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab and ipilimumab in patients with unresectable malignant pleural mesothelioma (MPM) have been provided. The modelling strategy to characterize the pharmacokinetic properties and the exposure-response analyses are endorsed. A previously developed population PK model in NSCLC and other types of tumours has been used to predict the time-course of nivolumab and ipilimumab in MPM patients.

2.4. Clinical efficacy

The studies submitted to support this application are:

- Study CA209743 "CheckMate 743" (main study)
- Study IFCT-1501 MAPS 2 (phase II, supportive study)

2.4.1. Dose response study(ies)

No specific dose response studies were included in this application.

2.4.2. Main study

Title of Study

CA209743: *A Phase III, Randomized, Open Label Trial of Nivolumab in Combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma*

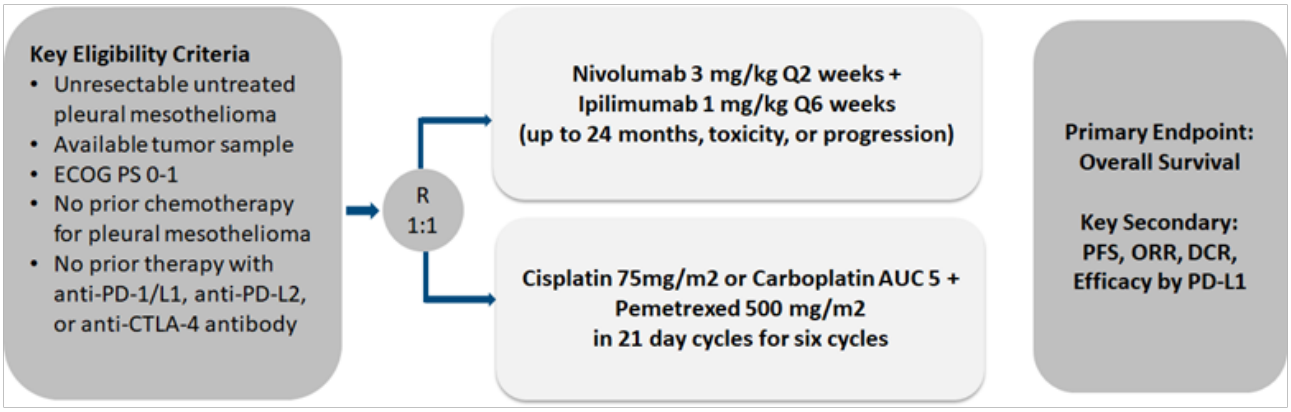
Methods

Protocol CA209743 was a randomized (1:1), open-label, Phase 3 clinical trial evaluating nivolumab 3 mg/kg every 2 weeks (Q2W) combined with ipilimumab 1 mg/kg every 6 weeks (Q6W) versus 6 cycles of pemetrexed plus cisplatin or carboplatin as a first line treatment in adults (18 years and older) with untreated, unresectable MPM.

Randomization was stratified according to tumour histology: epithelioid vs. non-epithelioid (sarcomatoid or mixed histology subtypes), and gender (male vs. female). A tumour sample was required to be sent to the central laboratory for PD-L1 status testing prior to randomization, but the results were not needed for randomization.

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

Figure 36. CA209743 Study Design Schematic



Stratification factors: histology (epithelioid vs non-epithelioid) and gender

Study participants

The study population included adult (≥ 18 years) male and female subjects, ECOG 0-1, with histologically proven diagnosis of advanced MPM that was unresectable and not amenable to therapy with curative intent (surgery with or without chemotherapy). Determination of epithelioid vs non-epithelioid histology was required. No prior therapy for MPM was allowed, nor were prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways permitted.

- Inclusion criteria:
    - Histologically proven diagnosis of MPM.
    - Advanced unresectable disease that is not amenable to therapy with curative intent. Subjects that refuse potentially curative salvage surgery are ineligible.
    - Available pathological samples for centralized PD-L1 IHC testing during the screening period. Subjects cannot randomize until the tumour tissue has been received at the central laboratory that will confirm if the sample is appropriate for PD-L1 expression testing, and contains a minimum of 100 evaluable tumour cells. Testing result is not required prior to randomization, and subjects can initiate therapy before the result of PD-L1 testing.
    - Prior palliative radiotherapy is acceptable. At least, 14 days must have passed and all signs of early toxicity must have remitted.
    - ECOG 0-1
    - Measurable disease, defined as:
        - Mesothelioma tumour thickness perpendicular to the chest wall or mediastinum, that can be measured in up to two positions at three separate levels on transverse cuts of CT scan (cuts must be at least 10 mm apart), for a total of up to 6 measurements. Each single tumour measurement must be at least 10 mm to qualify as measurable disease and contribute to the sum that defines the pleural measurement.
        - Non-pleural metastatic target lesions measured uni-dimensionally as per RECIST 1.1 criteria.

        - Patients who present without pleural lesions that can be considered measurable, but with metastatic lesions meeting criteria for target lesion by RECIST 1.1 criteria may be considered for inclusion after consultation with the Medical Monitor.
    - Subjects with a history of pleurodesis are allowed.
- Exclusion criteria:
    - Primitive peritoneal, pericardial, testis or tunica vaginalis mesothelioma.
    - Brain metastasis, except if surgically resected or treated with no evolution within 3 months before inclusion, and asymptomatic subject. Subjects must be either off corticosteroids, or on a stable decreasing dose of ≤10 mg daily prednisone for at least 2 weeks prior to first treatment.
    - Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any drug targeting T-cell co-stimulation or checkpoint pathways.
    - Prior systemic therapy for MPM.
    - Prior intraoperative intracavitary chemotherapy for MPM.
    - Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
    - Other active malignancy, active autoimmune disease or any condition requiring systemic corticosteroids or other immunosuppressive medications.
    - VIH, any positive result for hepatitis B or C indicating presence of virus.
    - Inadequate hematologic, renal or hepatic function defined by any of the following:
        - WBC < 2000/µL
        - Neutrophils < 1500/µL
        - Platelets < 100 x 10^3/µL
        - Haemoglobin < 9.0 g/dL
        - Serum creatinine > 1.5 x ULN or creatinine clearance < 60 mL/min (Cockcroft Gault)
        - AST/ALT > 3.0 x ULN (> 5 x ULN if liver metastases)
        - Total bilirubin > 1.5 x ULN

Subject enrolment

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by an interactive web response system (IWRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. Once enrolled in IWRS, subjects that have met all eligibility criteria will be ready to be randomized through IWRS. Subjects will be randomized in a 1:1 ratio to one of two treatment arms. Enrolment will stop once approximately 600 subjects have been randomized.

This study permitted the re-enrolment of a subject that had discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated).

Treatments

Arm A (Nivolumab/Ipilimumab Combination):

Note: 1 cycle= 6 weeks

- Nivolumab 3 mg/kg IV was administered every 2 weeks (Q2W).
- Ipilimumab 1 mg/kg IV was administered every 6 weeks (Q6W) on the same day as the administration of nivolumab.
- On the day of infusion of both nivolumab and ipilimumab, nivolumab was to be administered first. The infusion time for nivolumab was 30 minutes. Ipilimumab was always infused after nivolumab and would start at least 30 minutes after the completion of the nivolumab infusion. The infusion time for ipilimumab was 30 minutes.
- Nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W could continue up to 24 months, or until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure. Subjects could discontinue ipilimumab only and continue treatment with nivolumab if requirements were met. No dose modifications or dose reductions of nivolumab or ipilimumab were allowed. Subjects receiving ipilimumab in combination with nivolumab that had drug-related toxicities that met the criteria for dose delay, had both drugs delayed until retreatment criteria were met.
- Treatment beyond initial investigator-assessed and BICR confirmed progression as defined by adapted modified Response Evaluation Criteria in Solid Tumours (m-RECIST) for pleural mesothelioma and RECIST 1.1, was permitted if the subject had investigator-assessed clinical benefit and was tolerating treatment.

Arm B (Control Arm):

Note: 1 cycle= 3 weeks

- Pemetrexed (500 mg/m2), as a 10-min IV infusion plus cisplatin (75 mg/m2) or carboplatin (AUC of 5 mg/mL/min) on day 1 of a 21-day cycle, for 6 cycles or until disease progression and unacceptable toxicity. The use of cisplatin was preferred, however carboplatin could be used at the discretion of the investigator, and the reason for using carboplatin instead of cisplatin had to be reported in the case report form (CRF) and switching was allowed. Arm B dose calculations were administered according to label and/or local policy in terms of infusion schema (including but not limited to hydration protocols). Dose reductions were permitted for chemotherapy, per protocol.
- Vitamins B12 and B9 supplementation and dexamethasone premedication were required for all subjects receiving pemetrexed. Dexamethasone could be administered as IV infusion on the day of treatment as required by pemetrexed label and/or local SoC.

Dosing schedules for both groups are detailed in Table 20 The first dose of study drug was to be administered within 3 days of randomization.

Table 20. Dosing schedule

	Week1 ± 3 days	Week2	Week3 ± 3 days	Week4	Week5 ± 3 days	Week6
Arm A[a,b,c] Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W	**Cycle 1 Day 1** Nivo+Ipi		**Cycle 1 Day 15** Nivo		**Cycle 1 Day 29** Nivo	
Arm B[c,d,e] Pem 500 mg/m^2 + Cis 75mg/m^2 (or Carbo AUC 5)	**Cycle 1 Day 1** Pem+Cis or Carbo			**Cycle 2 Day 1** Pem+Cis or Carbo		

Objectives

Primary Objective:

- To compare overall survival (**OS**) of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in subjects with unresectable malignant pleural mesothelioma (MPM).

Secondary Objectives:

- To assess the objective response rate (**ORR**) as determined by blinded independent central review (BICR), of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable MPM.
- To assess the Disease Control Rate (**DCR**) as determined by BICR, of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable MPM.
- To assess progression-free survival (**PFS**) as determined by BICR of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable MPM.
- To evaluate whether programmed death ligand 1 (PD-L1) expression is a predictive biomarker for ORR, PFS, and OS.

Key exploratory objectives:

To assess safety and tolerability of nivolumab + ipilimumab (nivo+ipi) combination, and platinum doublet chemotherapy; to characterize immunogenicity of nivo+ipi; to assess overall health status and health utility using EuroQol Group's self-reported health status measure 3 level version (EQ-5D-3L) visual analog scale and utility index, and to assess cancer-related symptoms and quality of life using Lung Cancer Symptom (LCSS)- Meso scale, in subjects with unresectable MPM.

Outcomes/endpoints

Primary endpoint:

- **OS**: defined as the time from randomization to the date of death from any cause. OS was followed up at FU visits 1 and 2 and then every 3 months thereafter (via visit, phone or email). A subject who had not died was censored at the date of last contact (or "last known alive date"). OS was censored at the date of randomization for subjects who were randomized but had no follow-up.

Secondary endpoints:

- **PFS**: (primary definition) defined as the time between the date of randomization and the date of first documented tumour progression, based on BICR assessment (mRECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first.
    - Subjects who died without a reported progression were considered to have progresses on the date of their death.
    - Subjects who did not progress or die were censored on the date of their last evaluable tumour assessment.
    - Subjects who received subsequent anticancer therapy prior to documented progression were censored at the date of the last evaluable tumour assessment conducted on or prior to the date of initiation of the subsequent anticancer therapy.
    - Subjects who did not have a documented progression and received subsequent anticancer therapy were censored at the date of the last evaluable tumour assessment conducted on or prior to the initiation of the subsequent anticancer therapy.
    - **PFS** (PFS2, secondary definition) was irrespective of subsequent therapy and did not account for subsequent therapy.
- **ORR**: was defined as the number of randomized subjects who achieve a best response of CR or PR based on BICR assessments (m-RECIST and/or RECIST v1.1) divided by the number of all randomized subjects. As part of the evaluation of ORR, DoR and TTR were evaluated:
    - **DoR**: was defined as the time between the date of first documented response (CR or PR) to the date of the first documented tumour progression as determined by the BICR (per adapted m-RECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Subjects who started subsequent therapy without a prior reported progression were censored at the last evaluable tumour assessments prior to initiation of the subsequent anticancer therapy. DoR was evaluated for responders (confirmed CR or PR) only.
    - **TTR**: was defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the BICR. TTR was evaluated for responders (confirmed CR or PR) only.
- **DCR**: was defined as the proportion of all randomized subjects whose BOR was CR, PR or SD per adapted m-RECIST and/or RECIST 1.1 criteria as assessed by BICR.
- **PD-L1**: PD-L1 expression was defined as the percent of tumour cells membrane staining in a minimum of 100 evaluable tumour cells per validated Dako PD-L1 IHC assay. This was referred to as quantifiable PD-L1 expression.

Exploratory Endpoints:

- Safety: the assessment of safety was based on the incidence of AEs, SAEs, AEs leading to discontinuation, AEs leading to dose modification, select AEs for EU Submission, IMAEs for US

Submission, OESIs, and deaths. In addition, clinical laboratory tests, and immunogenicity (ie, development of anti-drug antibody) were analyzed.

- Serum anti-drug antibody (ADA) and neutralizing anti-drug antibody (NAb) response to nivo+ipi.
- EQ-5D-3LLCSS-Meso ASBI score

Sample size

The study accounted for a primary endpoint: OS. Overall two-sided alpha (type I error rate) was set at 0.05 for evaluating OS. Approximately 600 subjects were to be randomized with 1:1 ratio to 2 treatment arms (actual was 605 randomized). 473 OS events were needed for the final analysis. The sample size was calculated to compare OS between nivolumab combined with ipilimumab (Arm A) vs pemetrexed plus cisplatin or carboplatin regimen (Arm B). One formal interim analysis was planned for OS at 403 OS events. Table 2 summarizes the key parameters of trial design.

Overall survival: The key design parameters are shown in Table 2, where OS endpoint utilized a group sequential design (GSD) with one interim analysis at 403 OS events and final analysis at 473 OS events. Stopping boundaries of GSD at the interim and final OS analyses were derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Given an accrual rate of 34 subjects per month, it was estimated that it would take approximately 38/56 months to observe the required number of events for the interim/final OS analysis.

An exponential distribution was assumed for the OS time of control Arm B with a median OS time of 16 months and hazard rate of 0.043. To capture some observed features on the survival curves of immunotherapies, a piecewise exponential model was assumed for the survival time on nivolumab plus ipilimumab arm. In particular, a piecewise exponential with hazard rates of 0.043, 0.033, and 0.0001 in the following post first dose time windows: first 6-months, 6 months to 34 months, and after 34 months, provided a delay of treatment effect in the first 6 months, an exponential distribution of OS from 6 months to 34 months, and a long term survival rate plateau starting approximately at 34 months. Simulation evaluation of trial design show that the above piecewise exponential distribution would produce a 90% power in log-rank test with 606 randomized subjects. The numerical value of type one error rate in simulation was 0.05.

The above sample size calculation was based on a simulation model incorporating aspects of immuno-oncology therapies like delayed separation and long-term benefit using EAST 6.

Table 21. Summary of Key Design Parameters

Primary Endpoints	OS
Targeted Power	90%
Target Hazard Ratio 0-6 months 6-34 months after 34 months	0.72 1 0.767 0.002
Alpha	0.05 2-sided (0.03 at IA; 0.041 at FA)
Sample Size	606
Expected number of events for IA (% of target event)	403 (85%)
Target number of events	473
Duration (monthly accrual rate = 34 subjects)	56 months

Source: Table 5-1 of the CA209743 Statistical Analysis Plan (Appendix 1.11).
Abbreviations: FA - final analysis, IA - interim analysis, OS - overall survival

Randomisation

Once enrolled in IWRS, subjects that have met all eligibility criteria will be ready to be randomized through IWRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender at birth
- Tumour histology: epithelioid vs sarcomatoid or mixed histology

Subjects will be randomized in a 1:1 ratio to one of two treatment arms. Enrollment will stop once approximately 600 subjects have been randomized. The exact procedures for using the IWRS will be detailed in the IWRS manual.

Blinding (masking)

CA209743 was an open-label study. The study team only utilized subject-level data listings for the purpose of fulfilling Sponsor responsibilities for routine monitoring, safety assessment, and data review in accordance with the Data Review Plan. Measures to preclude dissemination of clinical trial data included procedural and technical access controls and use of independent third-parties for the Data Monitoring Committee (DMC) and the preparation of analysis datasets. The personnel who conducted the PD-L1 testing were blinded to treatment group assignment of individuals during the conduct of the study.

Statistical methods

Before the analyses for this study report were conducted, the protocol-defined statistical analyses were detailed in the statistical analysis plan (SAP) as follow:

Population for Analyses:

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IVRS
- All randomized subjects: all subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, and efficacy.
- All treated subjects: all randomized subjects who received at least one dose of any study medication. This is the primary dataset for drug exposure and safety analysis.
- Immunogenicity evaluable subjects: All nivolumab combined with ipiliumab treated subjects with baseline and at least 1 post-baseline immunogenicity assessment.
- Outcome research analyses evaluable subjects: All randomized subjects who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment.

Analyses

Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects

Efficacy

Primary endpoint analyses

The distribution of OS will be compared in two randomized arms at the interim and final analysis via a two-sided, log-rank test stratified by histology and gender with an overall significance level of 0.05. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses. The hazard ratio (HR) and the corresponding two-sided 100x (1-adjusted α) % confidence intervals (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method (using log-log transformation). Survival rates at 6, 12, 18, 24, 36, 48 months and 5 year will be estimated using KM estimates on the OS curve for each randomized arm provided minimum follow-up is longer than time-point to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

Secondary endpoints analyses

ORRs or DCRs and their corresponding 95% exact CIs will be calculated using the Clopper- Pearson method for each treatment group.

The PFS curves for each randomized arm will be estimated using the KM product-limit method. Two-sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method (using log-log transformation). PFS rates at 6, 12, 18, 24, 36, 48 months and 5 year will be estimated using KM estimates on the PFS curve for each randomized arm provided minimum follow-up is longer than timepoint to generate the rate. Associated two-sided 95% Cis will be calculated using the Greenwood formula (using log-log transformation).

Interim Analyses

A formal interim analysis for the OS is planned after 403 deaths have been observed, which are expected to occur approximately 38 months after study initiation. This formal comparison of OS will allow for early stopping for superiority. Lan-DeMets α spending function with O'Brien and Fleming type of boundary will

be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. However, if the analysis were performed exactly at 403 deaths, the study could be stopped by the DMC for superiority if the p-value is < 0.03. An independent statistician external to BMS will perform the analysis. If the study continues beyond the interim analysis the nominal significance level for the final look after 473 deaths would be 0.041. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol (473 deaths), final boundary will not be recalculated using updated information fraction at interim. In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. No formal test will be performed and the study will not stop for superiority.

Safety

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All on-treatment AEs, drug-related AEs, late emergent drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst Grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including haematology, chemistry, liver function and renal function will be summarized using worst Grade per NCI CTCAE v 4.0 criteria.

Results

The clinical cut-off (LPLV) for this report was 15-Jan-2020. Database lock (DBL) for this report was 03-Apr-2020.

Participant flow and recruitment

Table 22. Subject disposition

Status (%)	Nivo+Ipi	Chemo	Total
RANDOMIZED	303	302	605
TREATED	300 (99.0)	284 (94.0)	584 (96.5)
NOT TREATED	3 (1.0)	18 (6.0)	21 (3.5)
REASON FOR NOT TREATED			
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	3 (1.0)	3 (0.5)
SUBJECT WITHDREW CONSENT	1 (0.3)	11 (3.6)	12 (2.0)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (0.7)	3 (1.0)	5 (0.8)
NOT REPORTED	0	1 (0.3)	1 (0.2)

Status (%)	Nivo+Ipi N = 300	Chemo N = 284	Total N = 584
CONTINUING IN THE TREATMENT PERIOD	5 (1.7)	0	5 (0.9)
NOT CONTINUING IN THE TREATMENT PERIOD	295 (98.3)	284 (100.0)	579 (99.1)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD			
DISEASE PROGRESSION	182 (60.7)	44 (15.5)	226 (38.7)
STUDY DRUG TOXICITY	59 (19.7)	24 (8.5)	83 (14.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	12 (4.0)	9 (3.2)	21 (3.6)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	4 (1.3)	10 (3.5)	14 (2.4)
SUBJECT WITHDREW CONSENT	6 (2.0)	3 (1.1)	9 (1.5)
LOST TO FOLLOW-UP	0	1 (0.4)	1 (0.2)
MAXIMUM CLINICAL BENEFIT	10 (3.3)	2 (0.7)	12 (2.1)
POOR/NON-COMPLIANCE	1 (0.3)	0	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	4 (1.3)	0	4 (0.7)
ADMINISTRATIVE REASON BY SPONSOR	2 (0.7)	0	2 (0.3)
OTHER	11 (3.7)	2 (0.7)	13 (2.2)

NOT REPORTED [A]	4 (1.3)	189 (66.5)	193 (33.0)
CONTINUING IN THE STUDY	261 (87.0)	265 (93.3)	526 (90.1)
NOT CONTINUING IN THE STUDY	39 (13.0)	19 (6.7)	58 (9.9)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	24 (8.0)	10 (3.5)	34 (5.8)
SUBJECT WITHDREW CONSENT	11 (3.7)	6 (2.1)	17 (2.9)
LOST TO FOLLOW-UP	1 (0.3)	2 (0.7)	3 (0.5)
OTHER	3 (1.0)	1 (0.4)	4 (0.7)

Percentages based on subjects entering period.
[A] Includes subjects who achieved max duration of therapy per protocol, i.e: Chemo: 6 cycles, Nivo+Ipi: 2 years

The CRF did not have an option for treatment discontinuation due to subjects completing the maximum duration of treatment per protocol (2 years of nivo+ipi or 6 cycles of chemotherapy) and therefore, this action was captured as "not reported" on the CRF as a reason for treatment discontinuation. The majority of subjects discontinuing treatment for reason "not reported", had actually completed treatment. For example, of the 189 chemotherapy-treated subjects with reason off treatment "not reported", 176 (93.1%) subjects received all 6 cycles (the maximum allowed duration of chemotherapy per protocol).

Per protocol, nivolumab could be continued alone as monotherapy in the event ipilimumab was discontinued. However, if nivolumab was discontinued, ipilimumab could not be continued alone. In the nivo+ipi arm, 28 (9.3%) subjects discontinued ipilimumab early (Table 23).

Table 23. Ipilimumab Partial Discontinuation Summary- All treated subjects

	Nivolumab + Ipilimumab N = 300
SUBJECTS WHO DISCONTINUED IPILIMUMAB EARLIER	28 (9.3)
ADVERSE EVENT (A)	18 (64.3)
OTHER (A)	10 (35.7)
NUMBER OF NIVOLUMAB DOSES RECEIVED AFTER IPILIMUMAB IS STOPPED	
MEAN (SD)	13.1 (15.9)
MEDIAN (MIN - MAX)	4.5 (1 - 48)
DURATION OF NIVOLUMAB AFTER IPILIMUMAB IS STOPPED (DAYS) (B)	
MEAN (SD)	217.1 (243.0)
MEDIAN (MIN - MAX)	112.5 (13 - 750)

(A) Percentages are computed out of the total number of subjects who discontinued Ipilimumab earlier
(B) Duration of Nivolumab after Ipilimumab is stopped = Last dose of Nivolumab - Last dose of Ipilimumab

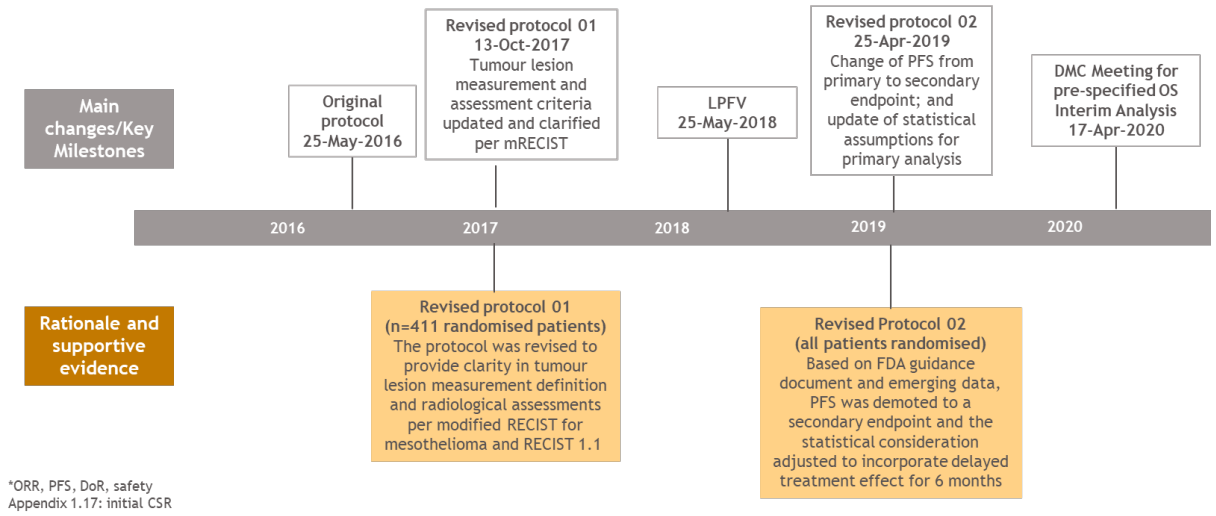
Source: Table S.4.4

A majority of subjects in both treatment arms received ≥ 90% of planned doses. The median duration of therapy was longer in the nivo+ipi arm, 5.55 months, compared with 3.48 months in the chemotherapy arm. 23.7% of subjects received more than 12 months nivo+ipi treatment. The maximum duration of treatment per protocol was 24 months for nivo+ipi, and 6 cycles of chemotherapy.

Conduct of the study

The original protocol for this study was dated 25-May-2016. There were 2 global revisions to the protocol as summarized in Table 24 and the figure 37 below. In addition, a total of 8 administrative letters were issued for this study.

Figure 37. Overview of conduct of trial CA209743



The trial was subject to 2 amendments dated 13-Oct-2017 and 25-Apr-2019 according to the figure above.

Within the first amendment (revised protocol 01) the protocol was revised to provide clarity in tumour lesion measurement definition and radiological assessments per modified RECIST for mesothelioma and RECIST 1.1.

The second amendment (revised Protocol 02) included two major changes:

- Change of PFS from co-primary to secondary endpoint and removal of hierarchical testing of secondary endpoints.
- Update of statistical assumption for primary analysis
    - Change in delay in treatment effect assumption from 4 months to 6 months in piecewise exponential model for OS in Arm A
    - Assumption for median OS of Arm B changed from 15 months to 16 months

Rationale for the changes

There were two distinct reasons for changing PFS from primary to secondary endpoint:

- Disease-specific reason: Based on FDA guidance (Dec-2018) that ORR and PFS assessments could be imprecise in tumours where there was a lack of demarcated margins, as in mesothelioma.
- Experience and observation with immuno-oncology regimens: PFS and ORR may not adequately characterize the long-term benefit of immune-oncology treatment. There was increased evidence in immunotherapy trials showing that PFS was quite often not a very reliable endpoint to assess clinical benefit, particularly when the comparator was chemotherapy.

The statistical assumptions were modified (changed delayed separation from 4 to 6 months, and median chemotherapy from 15 to 16 months) for the following reasons:

- Data with IO including nivo + ipi vs. chemotherapy in NSCLC showing ≈ 6 months delayed separation.
- Recently published data of median OS in mesothelioma studies (MAPS and LUME), indicated better survival outcome for platinum-based chemotherapy.

Other changes and revisions to the main protocol are summarized in Table 24.

Table 24: Summary of Changes to Protocol CA209743

Document	Date of Issue	Summary of Changes
Original Protocol	25-May-2016	• Not applicable
Revised Protocol 01	13-Oct-2017	• Addition of 2-year maximum treatment duration • Clarification of tissue submission requirements • Mesothelioma disease measurement updated • Radiographic assessment criteria of modified RECIST and RECIST 1.1 updated and imaging assessments were updated • Study design, assessments, and dosing schedule were clarified for consistency • Inclusion and exclusion criteria were updated • Language updated for prohibited treatments, treatment schedule, • Dose delay criteria for study treatment and discontinuation criteria were updated as per program standards • Management Algorithms for Immuno-Oncology were updated as per program standards • Typographical and formatting errors were corrected and wording updated for consistency
Revised Protocol 02	25-Apr-2019	Key changes: • Change of PFS from co-primary to secondary endpoint. • Removal of hierarchical testing of secondary endpoints, based on the above. • Update of the statistical assumptions for the primary analysis in light of emerging data from external studies Other changes: • Clarification of BICR assessed progression • Language updated for vaccines for prohibited treatment • Updated outcome assessments • Updated adverse event definitions • Updated Appendix 2 Management Algorithms • Updated Appendix 3 Women of Child Bearing Potential Definition and Methods of Contraception

Changes to the planned analyses

In addition to the planned analysis in the SAP, the following ad hoc analyses performed after the interim analysis, were included in the CSR:

- End of Study Status, Subjects who Completed Maximum Duration of Treatment per Protocol
- Baseline Disease Characteristics: Frequency of PD-L1 Tumour Cell Expression Status by Tumour Histology
- 24 months OS and PFS Rates, Time to Objective Response and DoR

Protocol deviations

Significant protocol deviations

Significant protocol deviations were defined as study conduct that differed significantly from the protocol, including GCP noncompliance. A summary of significant protocol deviations is provided in Table 25.

Table 25. Significant protocol deviations (all enrolled)

	Nivo+Ipi	Chemo	Total
Failure to obtain written informed consent prior to each subject's participation in the study	**1**	**1**	**2**
Failure to report all SAEs in accordance with the time period required by GCP, the protocol, BMS and applicable regulations	**20**	**20**	**40**
Implementation of protocol changes prior to review by IRB/IEC (except when necessary to eliminate an immediate hazard(s) to trial subjects)	**6**	**4**	**10**
Use of prohibited concomitant medications	**1**	**0**	**1**
Inclusion or exclusion deviations	**20**	**14**	**34**
Baseline assessments out of window	14	10	24
Baseline lab value out of required range	3	3	6
No measurable disease at baseline	2	0	2
Screening labs not collected	1	1	2
Incorrect dosing or study treatment assignment	**14**	**0**	**14**
Other	**32**	**43**	**75**
D1 dose given >5 days post randomization	4	3	7
Pregnancy Tests not performed as per protocol specified schedule prior to dosing	1	3	4
Required labs not performed prior to dosing	7	10	17
Tumour assessments were not done in accordance with the protocol allowed window +/-7 days and repeated every 6 weeks up to week 48 and every 12 weeks thereafter until progression	18	20	38
Consistent issues with tumour measurements	0	2	2
Tumour measurements only evaluated using RECIST1.1 criteria	2	5	7
Grand Total	**94**	**82**	**176**

Relevant protocol deviations

Relevant protocol deviations are those that are related to inclusion or exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results.

Table 26. Relevant protocol deviations summary (all randomized subjects)

	Number of Subjects (%)		
	Niv+Ipi N = 303	Chemo N = 302	Total N = 605
SUBJECTS WITH AT LEAST ONE DEVIATION	3 (1.0)	1 (0.3)	4 (0.7)
AT ENTRANCE			
SUBJECTS WITHOUT MEASURABLE DISEASE AT BASELINE AS PER INVESTIGATOR	2 (0.7)	0	2 (0.3)
SUBJECTS WITH BASELINE ECOG PS>1	0	1 (0.3)	1 (0.2)
SUBJECTS WHO RECEIVED PRIOR TREATMENT WITH AN ANTI-PD-1, ANTI-PD-L1, ANTI-PD-L2, ANTI-CTLA-4 ANTIBODY OR ANY OTHER ANTIBODY/DRUG SPECIFICALLY TARGETING T-CELL CO-SIMULATION OR CHECKPOINT PATHWAYS	0	0	0
SUBJECTS WHO RECEIVED PRIOR CHEMOTHERAPY FOR PLEURAL MESOTHELIOMA	0	0	0
ON-TREATMENT DEVIATIONS			
SUBJECTS RECEIVING ANTICANCER THERAPY WHILE ON STUDY THERAPY	1 (0.3)	0	1 (0.2)
SUBJECTS TREATED DIFFERENTLY THAN AS RANDOMIZED	0	0	0

Baseline data

Demographics and baseline disease characteristics are presented in Table 27 and Table 88, respectively.

Table 27. Demographics Characteristics Summary - All Randomized Subjects

	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302	Total N = 605
AGE (YEARS)			
N	303	302	605
MEAN	68.7	67.8	68.2
MEDIAN	69.0	69.0	69.0
MIN, MAX	32, 85	25, 89	25, 89
Q1, Q3	65.0, 75.0	62.0, 75.0	64.0, 75.0
SD	8.5	9.7	9.1
AGE (%)			
< 65	71 (23.4)	96 (31.8)	167 (27.6)
>= 65	232 (76.6)	206 (68.2)	438 (72.4)
>= 65 AND < 75	154 (50.8)	127 (42.1)	281 (46.4)
>= 75 AND < 85	75 (24.8)	76 (25.2)	151 (25.0)
>= 85	3 (1.0)	3 (1.0)	6 (1.0)
SEX (%)			
MALE	234 (77.2)	233 (77.2)	467 (77.2)
FEMALE	69 (22.8)	69 (22.8)	138 (22.8)
RACE (%)			
WHITE	266 (87.8)	250 (82.8)	516 (85.3)
ASIAN	26 (8.6)	39 (12.9)	65 (10.7)
AMERICAN INDIAN OR ALASKA NATIVE	2 (0.7)	4 (1.3)	6 (1.0)
OTHER	9 (3.0)	9 (3.0)	18 (3.0)
ETHNICITY (%)			
HISPANIC OR LATINO	19 (6.3)	19 (6.3)	38 (6.3)
NOT HISPANIC OR LATINO	122 (40.3)	136 (45.0)	258 (42.6)
NOT REPORTED	162 (53.5)	147 (48.7)	309 (51.1)
COUNTRY BY GEOGRAPHIC REGION (%)			
NORTH AMERICA	32 (10.6)	27 (8.9)	59 (9.8)
EUROPE	177 (58.4)	175 (57.9)	352 (58.2)
ASIA	26 (8.6)	39 (12.9)	65 (10.7)
ROW	68 (22.4)	61 (20.2)	129 (21.3)

Abbreviations: ROW = rest of world, US = United States

Sex per CRF source

Table 28. Baseline Disease Characteristics - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302	Total N = 605
DISEASE STAGE AT STUDY ENTRY			
STAGE I	12 (4.0)	20 (6.6)	32 (5.3)
STAGE II	23 (7.6)	22 (7.3)	45 (7.4)
STAGE III	103 (34.0)	106 (35.1)	209 (34.5)
STAGE IV	160 (52.8)	149 (49.3)	309 (51.1)
NOT REPORTED	5 (1.7)	5 (1.7)	10 (1.7)
ECOG PERFORMANCE STATUS			
0	114 (37.6)	128 (42.4)	242 (40.0)
1	189 (62.4)	173 (57.3)	362 (59.8)
2	0	1 (0.3)	1 (0.2)
TUMOUR HISTOLOGY			
EPITHELIOID	229 (75.6)	227 (75.2)	456 (75.4)
NON-EPITHELIOID	74 (24.4)	75 (24.8)	149 (24.6)
SMOKING STATUS			
NEVER	127 (41.9)	122 (40.4)	249 (41.2)
FORMER	155 (51.2)	163 (54.0)	318 (52.6)
CURRENT	18 (5.9)	8 (2.6)	26 (4.3)
UNKNOWN	3 (1.0)	9 (3.0)	12 (2.0)
TIME FROM INITIAL DIAGNOSIS TO RANDOMIZATION (YEARS)			
N	303	302	605
MEDIAN	0.15	0.15	0.15
MIN - MAX	0.0 - 4.8	0.0 - 7.5	0.0 - 7.5
TIME FROM INITIAL DIAGNOSIS TO RANDOMIZATION (%)			
< 1 YEAR	296 (97.7)	291 (96.4)	587 (97.0)
>= 1 YEAR	7 (2.3)	11 (3.6)	18 (3.0)

Abbreviations: ECOG = Eastern Cooperative Oncology Group, PD-L1 = programmed death ligand 1
Histology per CRF source

Baseline demographics and disease characteristics were balanced between the nivo+ipi and chemotherapy arms, and were representative of a first-line mesothelioma population. Overall, 24.6% of subjects had non-epithelioid tumour histology, which included tumours with mixed (8.9%), sarcomatoid (11.7%) or other (4.0%) histology.

Table 29: IRT Stratification Summary - All Randomized Subjects

	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302	Total N = 605
HISTOLOGY			
EPITHELIOID	236 (77.9)	235 (77.8)	471 (77.9)
NON-EPITHELIOID	67 (22.1)	67 (22.2)	134 (22.1)
SEX			
MALE	235 (77.6)	234 (77.5)	469 (77.5)
FEMALE	68 (22.4)	68 (22.5)	136 (22.5)

Note, the term IRT (interactive response technologies) is used in the listings. IRT is interchangeable with IWRS. Regarding cell type distribution for non-epithelioid histology among both treatment arms, 26

(8.6%) subjects in the nivo+ipi arm and 28 (9.3%) in the chemo arm presented mixed histology, 35 (11.6%) patients from the nivo+ipi arm and 36 (11.9%) from the chemotherapy treatment arm had sarcomatoid histology and, for other histologies, these figures were 13 (4.3%) subjects in the nivo+ipi arm and 11 (3.6%) patients in the chemotherapy treatment arm.

Baseline PD-L1 Tumour Cell Expression

Subjects were required to provide a tumour sample (archival or current formalin fixed paraffin embedded [FFPE] tumour tissue) to central laboratory for PD-L1 (Dako 28-8 IHC) testing during the Screening period. Testing result was not required prior to randomization. Subjects were randomized regardless of PD-L1 status.

Table 30. Frequency of PD-L1 Tumour Cell Expression Status - All Randomized Subjects

Population PD-L1 Expression Category	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302	Total N = 605
OVERALL	303	302	605
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	3 (1.0)	0	3 (0.5)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	289 (95.4)	297 (98.3)	586 (96.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	232/289 (80.3)	219/297 (73.7)	451/586 (77.0)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	57/289 (19.7)	78/297 (26.3)	135/586 (23.0)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	0	0	0
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	11 (3.6)	5 (1.7)	16 (2.6)

Source: Table S.10.2

Subjects with non-epithelioid MPM had higher PD-L1 expression than subjects with epithelioid MPM (data not shown).

Subjects with "PD-L1 expression missing" were subjects with no tumour tissue sample available for evaluation.

Previous treatments

Table 31: Prior Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302	Total N = 605
PRIOR SURGERY RELATED TO CANCER			
YES	156 (51.5)	163 (54.0)	319 (52.7)
NO	147 (48.5)	139 (46.0)	286 (47.3)
PRIOR RADIOTHERAPY			
YES	29 (9.6)	28 (9.3)	57 (9.4)
NO	274 (90.4)	274 (90.7)	548 (90.6)
PRIOR SYSTEMIC THERAPY			
YES	1 (0.3) [A]	0	1 (0.2)
NO	302 (99.7)	302 (100.0)	604 (99.8)

Source: Table S.3.6
[A] The subject is miscategorized as having received prior systemic therapy. Medical Monitor confirmed the subject received bevacizumab as part of subsequent therapy following nivo+ipi

discontinuation, but an incorrect start date for bevacizumab was reported in the database at the time of the CSR DBL. A correction will be reflected in the next safety update.

Based on clinical review, the majority of the prior surgeries listed were diagnostic procedures and/or biopsies of tumour as mandated by the protocol, or palliative surgery.

Treatment beyond progression

Subjects in the nivo+ipi arm were permitted to continue on nivo+ipi treatment beyond initial adapted m-RECIST for mesothelioma and/or RECIST 1.1 defined PD as long as they provided consent and met all protocol criteria for clinical benefit and tolerance of study drug.

The study included BICR for imaging assessment by a vendor, ERT [Previously BioMedical Systems] (Seattle, Washington). Per protocol, BICR-confirmed PD was required prior to treatment discontinuation. ERT imaging charter and Site Procedure Manual outlined the expectation of the turnaround time (TAT), ie, imaging scans submission from sites to occur within 3 days of imaging collection, and BICR imaging assessment to be sent to sites within 5 days. Protocol and protocol guidance documents allowed the Principal Investigator to make the initial assessment of progression and the treatment beyond progression decision (with Medical Monitor's approval), to ensure the safety and risk benefit assessment for the subjects on the trial. Additional protocol guidance included an algorithm for decision making after Investigator assessment of PD to ensure the process to determine Medical Monitor approval for Treatment beyond Progression was taken into consideration.

Following the report of delayed BICR PD reporting, the MAH assessed the impact of turnaround delays on patient safety:

- Five subjects on nivo+ipi arm (Arm A) with confirmed BICR PD and a BICR PD TAT delay were treated beyond progression without Medical Monitor's approval. All of the safety assessments were reviewed for these subjects and there was no significant impact overall on patient safety.
- Forty-eight subjects that did not have confirmed BICR PD, and no BICR PD delay, came off treatment due to investigator assessed PD; this included 34 subjects on Arm A and 14 subjects on control Arm B. There was no impact on patient safety.
- Seven subjects that did not have confirmed BICR PD, and had BICR PD TAT delay, came off treatment due to investigator assessed PD; this included 5 subjects on treatment arm A and 2 subjects on the chemotherapy arm (Arm B). There was no impact on patient safety.
- No subjects with confirmed BICR PD and without BICR PD TAT delay were treated beyond progression. There was no impact on patient safety.

Despite the BICR PD reporting delay, there was no critical impact to the validity of study data. Concordance between BICR and Investigator PFS assessments was high, with a concordance rate of 82.5% in the nivo+ipi arm and 80.8% on the chemotherapy arm. Ultimately, investigator-assessed PD and subject risk benefit for treatment beyond progression were the basis of clinical decisions for all subjects.

Discontinuation of Study Therapy

At DBL, 98.3% of subjects in the nivo+ipi arm and 100% of subjects in the chemotherapy arm had discontinued treatment as of the DBL.

Subjects treated with nivolumab and ipilimumab could discontinue ipilimumab and continue to receive nivolumab (partial discontinuation); however, if nivolumab was discontinued, ipilimumab could not be continued alone as monotherapy.

Table 32. Ipilimumab Partial Discontinuation Summary- All treated subjects

	Nivolumab + Ipilimumab N = 300
SUBJECTS WHO DISCONTINUED IPILIMUMAB EARLIER	28 (9.3)
ADVERSE EVENT (A)	18 (64.3)
OTHER (A)	10 (35.7)
NUMBER OF NIVOLUMAB DOSES RECEIVED AFTER IPILIMUMAB IS STOPPED	
MEAN (SD)	13.1 (15.9)
MEDIAN (MIN - MAX)	4.5 (1 - 48)
DURATION OF NIVOLUMAB AFTER IPILIMUMAB IS STOPPED (DAYS) (B)	
MEAN (SD)	217.1 (243.0)
MEDIAN (MIN - MAX)	112.5 (13 - 750)

(A) Percentages are computed out of the total number of subjects who discontinued Ipilimumab earlier
(B) Duration of Nivolumab after Ipilimumab is stopped = Last dose of Nivolumab - Last dose of Ipilimumab

Subsequent Anti-Cancer Therapy

Table 33. Subsequent Anti-Cancer Therapy- All randomized subjects.

	Number of Subjects (%)	
	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	145 (47.9)	136 (45.0)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	23 (7.6)	28 (9.3)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	1 (0.3)	3 (1.0)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	134 (44.2)	123 (40.7)
IMMUNOTHERAPY	10 (3.3)	61 (20.2)
ANTI-PD1	9 (3.0)	59 (19.5)
ANTI PD 1	0	1 (0.3)
NIVOLUMAB	7 (2.3)	41 (13.6)
PEMBROLIZUMAB	2 (0.7)	17 (5.6)
ANTI-PDL1	0	2 (0.7)
ATEZOLIZUMAB	0	1 (0.3)
AVELUMAB	0	1 (0.3)
ANTI-CTLA4	2 (0.7)	3 (1.0)
IPILIMUMAB	2 (0.7)	3 (1.0)
OTHER IMMUNOTHERAPY	1 (0.3)	1 (0.3)
EPACADOSTAT	0	1 (0.3)
RITUXIMAB	1 (0.3)	0
TARGETED THERAPY	20 (6.6)	10 (3.3)
VEGFR INHIBITORS	20 (6.6)	8 (2.6)
BEVACIZUMAB	20 (6.6)	8 (2.6)
OTHER TARGETED THERAPY	0	2 (0.7)
NINTEDANIB	0	2 (0.7)
OTHER SYSTEMIC CANCER THERAPY - EXPERIMENTAL DRUGS	2 (0.7)	12 (4.0)
ABBV-428	0	1 (0.3)
ANTI-ICOS AGONIST ANTIBODY	0	1 (0.3)
CELECOXIB	0	1 (0.3)
CRS 207	0	1 (0.3)
ELEMENE	1 (0.3)	0
HERBS	0	1 (0.3)
INCB001158	0	1 (0.3)
INVESTIGATIONAL ANTINEOPLASTIC DRUG	0	2 (0.7)
MK-2118	0	1 (0.3)
PLATINUM	1 (0.3)	0
RAD-INTERFERON (STUDY PROTOCOL)	0	1 (0.3)
RAMUCIRUMAB/PLACEBO	0	4 (1.3)
RIMO-301	0	1 (0.3)
OTHER SYSTEMIC CANCER THERAPY - CHEMOTHERAPY	131 (43.2)	95 (31.5)
ANTINEOPLASTIC	2 (0.7)	0
CARBOPLATIN	89 (29.4)	39 (12.9)
CARPLA/PEME	1 (0.3)	0

CISPLATIN	40 (13.2)	8 (2.6)
DICANTH/PYRDX	0	1 (0.3)
DOCETAXEL	1 (0.3)	1 (0.3)
DOXORUBICIN	2 (0.7)	1 (0.3)
GEMCITABINE	25 (8.3)	45 (14.9)
GIMER/OTERA/TEGFUR	0	1 (0.3)
IRINOTECAN	0	2 (0.7)
METHOTREXATE	1 (0.3)	2 (0.7)
PACLITAXEL	0	2 (0.7)
PEMETREXED	121 (39.9)	48 (15.9)
PEVONEDISTAT	0	2 (0.7)
RALTITREXED	1 (0.3)	0
TOPOTECAN	0	1 (0.3)
VINORELBINE	15 (5.0)	25 (8.3)
UNASSIGNED	2 (0.7)	1 (0.3)
VALPROATE	2 (0.7)	1 (0.3)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

Numbers analysed

Table 34: Analysis Populations in this Clinical Study Report

Population	Nivo+Ipi	Chemo	Total
Enrolled: All enrolled subjects who signed the ICF and were registered in IWRS. This population was used for pre-treatment disposition.	--	--	713
Randomized: All subjects who were randomized to either treatment group. This population was used for demography, protocol deviations, baseline characteristics, and efficacy.	303	302	605
Treated: All randomized subjects who received at least one dose of study drug. This population was used for drug exposure and safety	300	284	584
Immunogenicity Subjects: All treated subjects with baseline and at least one post-baseline assessment for ADA. This population was used for analysis of immunogenicity.	269	271	540
All PD-L1 Evaluable Subjects: All PD-L1 tested subjects with quantifiable PD-L1 expression	289	297	586

Outcomes and estimation

Primary Efficacy Endpoint

OS

Study CA209743 met the primary endpoint of OS. The minimum follow-up for OS was 22.1 months (Table 35). The median follow-up (time between randomization date and last known alive date) was 17.35 months for nivo+ipi arm, and 13.27 months for chemotherapy arm.

Table 35: Overall Survival - All Randomized Subjects - CA209743

	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
# EVENTS / # SUBJECTS (%)	200/303 (66.0)	219/302 (72.5)
MEDIAN OS (MONTHS) (1) (95% CI)	18.07 (16.82, 21.45)	14.09 (12.45, 16.23)

HR	0.74 (A)
(95% CI)	(0.61, 0.89)
P-VALUE (2)	0.0020

(1) Based on Kaplan-Meier Estimates
(2) Log-rank test stratified by histology and sex as entered in the IRT 2-sided p values from Boundary for statistical significance p-value < 0.0345.
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Chemotherapy. 96.6% CI HR: (0.60, 0.91)

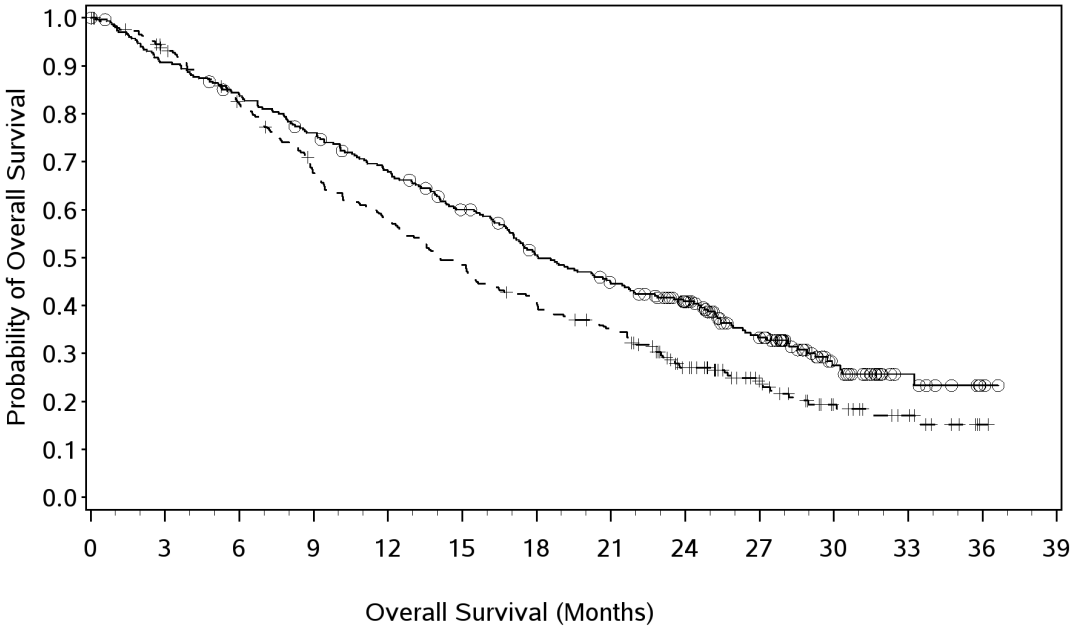
Table 36: Overall Survival Rates - All Randomized Subjects - CA209743

Overall Survival Rate (95% CI)	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
6-MONTH	84.0 (79.4, 87.7)	82.2 (77.3, 86.2)
12-MONTH	67.9 (62.3, 72.8)	57.7 (51.7, 63.2)
18-MONTH	50.5 (44.7, 56.1)	40.6 (34.8, 46.3)
24-MONTH	40.8 (35.1, 46.5)	27.0 (21.9, 32.4)

Based on Kaplan-Meier Estimates

Separation of the Kaplan-Meier curves of OS favoring nivo+ipi over chemotherapy occurred at around 5 months and was sustained. The proportional hazards assumption for OS was validated using a stratified Cox regression model with a time-dependent interaction covariate, which was not significant (Figure 38).

Figure 38: Kaplan-Meier Plot of Overall Survival - All Randomized Subjects - CA209743



Number of Subjects at Risk

Nivo + Ipi	303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemo	302	268	233	190	162	136	113	95	62	38	20	11	1	0

—○— Nivo + Ipi (events: 200/303), median and 95% CI: 18.07 (16.82, 21.45)
– + – Chemo (events: 219/302), median and 95% CI: 14.09 (12.45, 16.23)
Nivo + Ipi vs. Chemo - hazard ratio (95% CI): 0.74 (0.61, 0.89),
Nivo + Ipi vs. Chemo - hazard ratio (96.6% CI): 0.74 (0.60, 0.91),
Stratified log-rank test p-value: 0.0020

Median follow-up for OS (median time from clinical cut-off date to randomization date) was 29.7 months for all randomized subjects.

Follow-up for OS was current for the majority of subjects in both arms; 83.5% and 82.5% of subjects in the nivo+ipi and chemotherapy arms, respectively, either died or had a last known alive date on or after 15-Jan-2020.

Status of censored patients for OS primary analysis can be found on Table 37:

Table 37. Status of censored patients for OS primary analysis - All randomized subjects

	Number of Subjects (%)	
	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
NUMBER OF DEATHS (%)	200 (66.0)	219 (72.5)
NUMBER OF SUBJECTS CENSORED (%)	103 (34.0)	83 (27.5)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON TREATMENT	5 (1.7)	0
NOT PROGRESSED	2 (0.7)	0
PROGRESSED (1)	3 (1.0)	0
IN FOLLOW-UP	80 (26.4)	61 (20.2)
OFF STUDY	18 (5.9)	22 (7.3)
SUBJECT WITHDREW CONSENT	15 (5.0)	17 (5.6)
LOST TO FOLLOW-UP	2 (0.7)	2 (0.7)
OTHER	1 (0.3)	3 (1.0)

OS by IRT Stratification Factor – Histology

Nivo+ipi demonstrated an improvement in OS compared with chemotherapy, regardless of histology (Table 38 and Figure 39). The observed treatment effect of nivo+ipi vs chemotherapy was larger in subjects with non-epithelioid MPM compared with epithelioid MPM (HR: 0.46 vs 0.85).

Within the nivo+ipi arm, the median OS were similar across histologies (18.73 and 16.89 months for epithelioid and non-epithelioid, respectively). In the chemotherapy arm, subjects with non-epithelioid histology presented lower median OS than epithelioid (8.80 vs 16.23 months), confirming histology as a prognostic factor in MPM subjects receiving chemotherapy.

24-month OS rates in subjects with epithelioid histology were 41.2% and 31.8% in the nivo+ipi and chemotherapy arms, respectively. In subjects with non-epithelioid histology, 24-month OS rates were 39.5% and 9.7% in the nivo+ipi and chemotherapy arms, respectively.

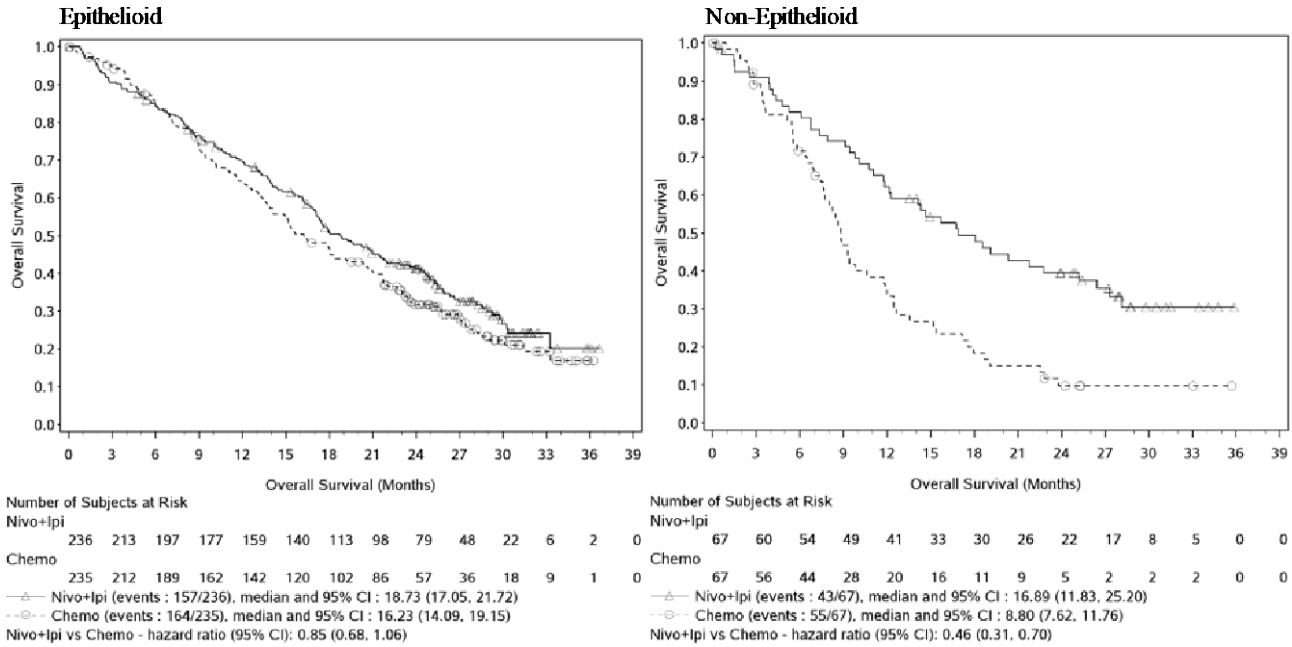
Table 38: Overall Survival of Nivolumab + Ipilimumab vs Chemotherapy by Histology - All Randomized Subjects

	Epithelioid (N = 471)		Non-epithelioid (N = 133)	
	Nivo+Ipi N = 236	Chemo N = 235	Nivo+Ipi N = 67	Chemo N = 67
OS				
Median (95% CI), mo.[a]	18.73 (17.05, 21.72)	16.23 (14.09, 19.15)	16.89 (11.83, 25.20)	8.80 (7.62, 11.76)
HR (95% CI)[b]	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Events, n	157	164	43	55

a: Based on Kaplan-Meier estimate

b: Unstratified Cox proportional hazards model

Figure 39: Kaplan-Meier Plot of Overall Survival by Histology per IRT - All Randomized Subjects



Statistical model for hazard ratio: unstratified Cox proportional hazards model
Symbols represent censored observations.
Source: Figure S.5.10

OS by IRT Stratification Factor – Sex

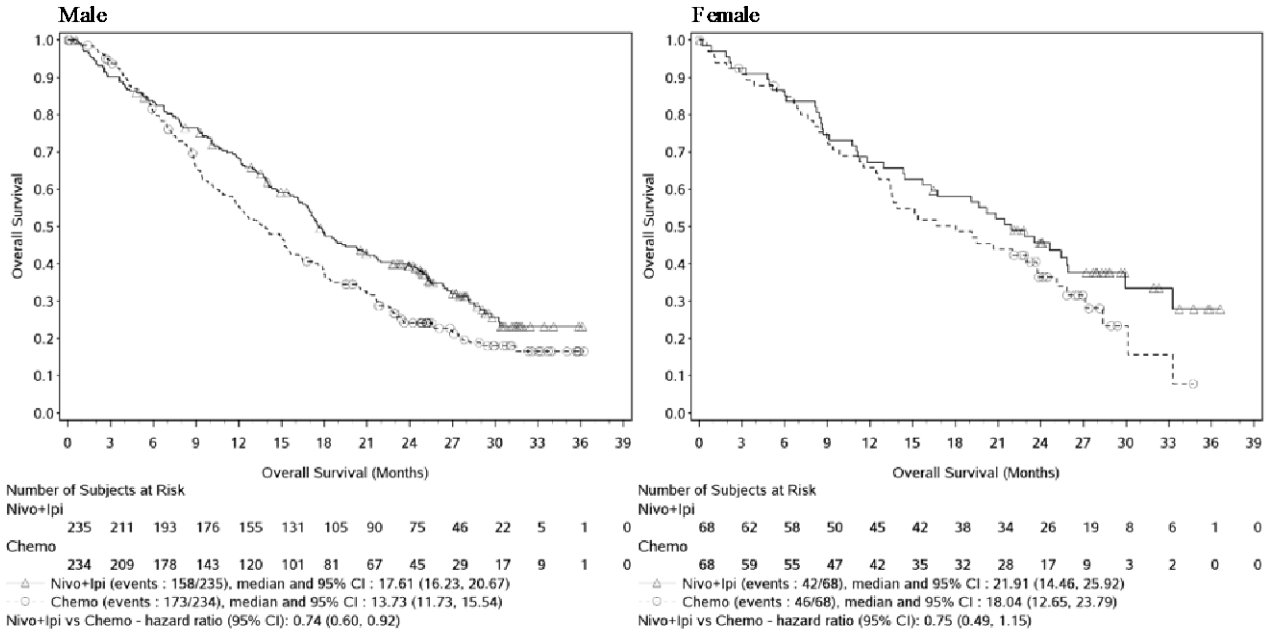
Nivo+ipi demonstrated an improvement (HR < 1) in OS over chemotherapy in both male and female subjects (Table 39).

Table 39: Overall Survival of Nivolumab + Ipilimumab vs Chemotherapy by Sex -All Randomized Subjects

	Male (N = 469)		Female (N = 136)	
	Nivo+Ipi N = 235	Chemo N = 234	Nivo+Ipi N = 68	Chemo N = 68
OS				
Median (95% CI), mo.[a]	17.61 (16.23, 20.67)	13.73 (11.73, 15.54)	21.91 (14.46, 25. 92)	18.04 (12.65, 23.79)
HR (95% CI) [,b]	0.74 (0.60, 0.92)		0.75 (0.49, 1.15)	
Events, n	158	173	42	46

a: Based on Kaplan-Meier estimate
b: Unstratified Cox proportional hazards model
Source: Figure S.5.12 (OS)

Figure 40: Kaplan-Meier Plot of Overall Survival by Sex per IRT - All Randomized Subjects



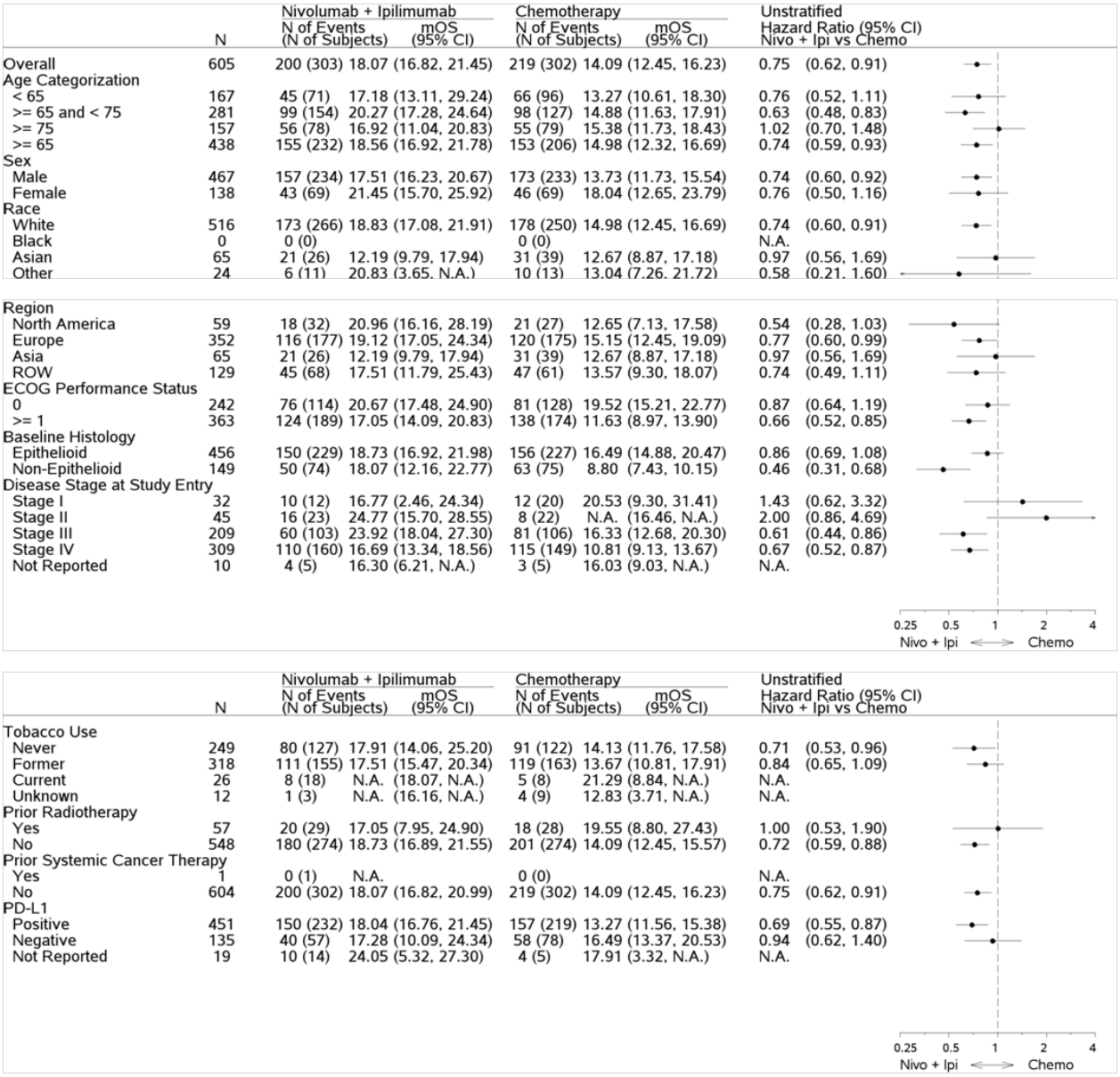
Statistical model for hazard ratio: unstratified Cox proportional hazards model
Symbols represent censored observations.
Source: Figure S.5.12

OS in Other Predefined Subsets

The HRs for OS favoured (HR <1) nivo+ipi vs chemotherapy in the majority of pre-defined subgroups with the exception of subjects with age ≥75, Stage I/II disease, and subjects who received prior radiotherapy (Figure 41).

The treatment effect of nivo+ipi vs chemotherapy was larger in subjects with PD-L1 positive tumours (≥ 1%) than in subjects with PD-L1 negative tumours (<1%) (HR: 0.69 vs 0.94). Further exploration of efficacy by PD-L1 expression is presented below.

Figure 41: Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - All Randomized Subjects

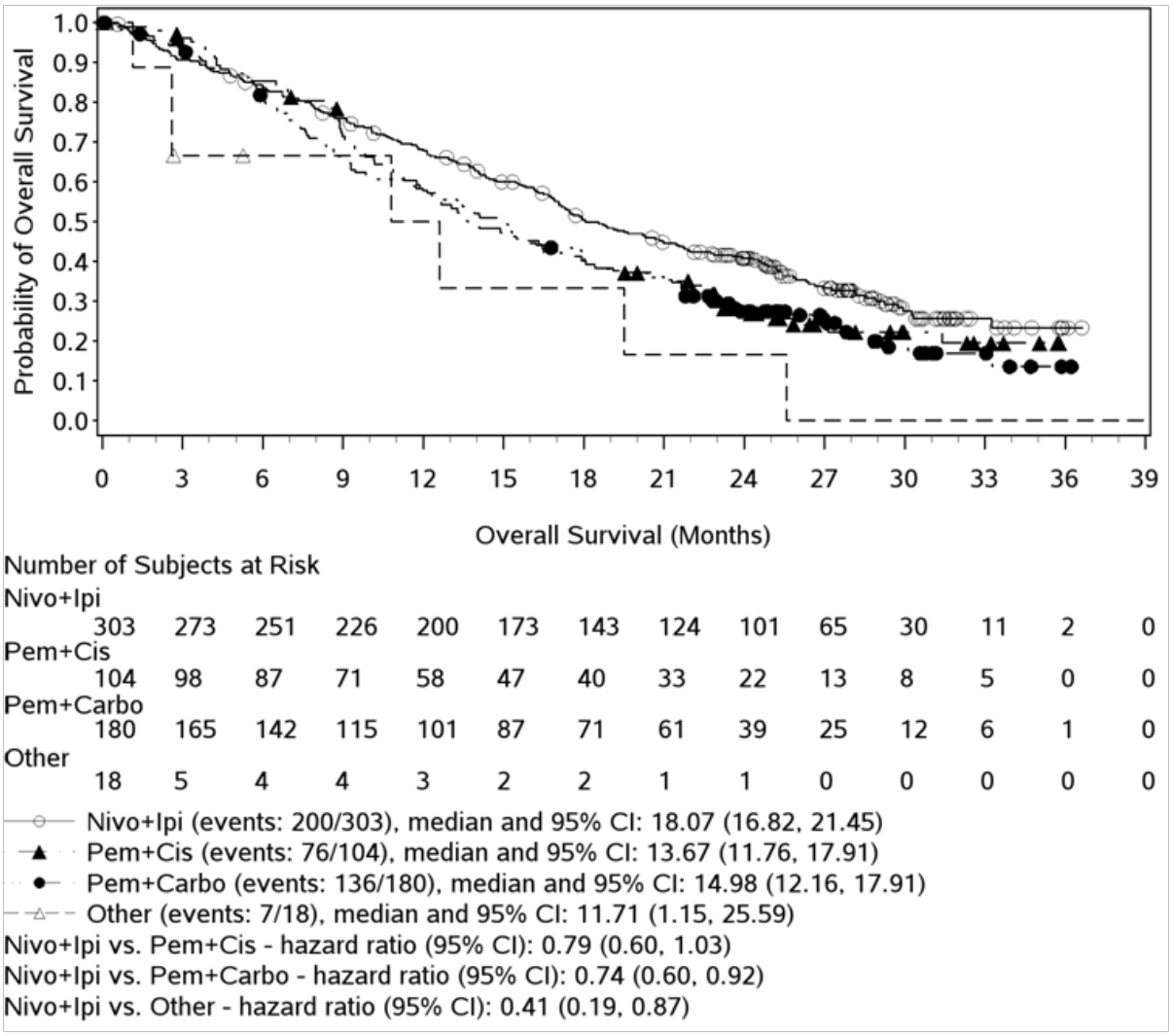


HR is not computed for subset category with less than 10 subjects per treatment group.
PD-L1: Positive (≥ 1%), Negative (< 1%)
Source: Figure 7.2.3-1 of the CA209743 Final CSR

Efficacy by Platinum Backbone (Ad hoc Analysis)

An ad hoc KM OS analysis by arm was conducted based on the 'as randomized' population with the chemotherapy arm split into 3 subgroups defined by the actual treatment received in Cycle 1 (Figure 42). The subgroup 'OTHER' referred to subjects randomized to chemotherapy but never treated (n = 18). 29/104 (28%) subjects switched from cisplatin to carboplatin after Cycle 1. The OS HR for nivo+ipi vs pemetrexed+cisplatin was similar to nivo+ipi vs pemetrexed+carboplatin (0.79 [95% CI: 0.60, 1.03] vs 0.74 [95% CI: 0.60, 0.92]). The treatment effect was similar regardless of platinum-based treatment choice.

Figure 42: Kaplan-Meier Plot of Overall Survival by Chemotherapy Regimen - All Randomized Subjects



Secondary Efficacy Endpoints

PFS

The nivo+ipi arm did not show an advantage over the chemotherapy arm in PFS. The median PFS per BICR was 6.77 (95% CI: 5.59, 7.36) months in the nivo+ipi arm and 7.20 (95% CI: 6.93, 8.05) months in the chemotherapy arm (HR = 1.00 [95% CI: 0.82, 1.21]) (Table 40).

- The 6-month Kaplan-Meier estimated PFS was lower with nivo+ipi compared with chemotherapy. After 6-months, the PFS rates were higher with nivo+ipi (Table 41),
- The Kaplan-Meier curves for PFS showed an advantage for chemotherapy during the initial part of the curve with the curves crossing at approximately 8 months and then subsequently favouring nivo+ipi (Figure 43).
- At database lock, 28.1% and 30.8% of randomized subjects in the nivo+ipi and chemotherapy arms, respectively, were censored for PFS.
- Concordance between BICR and Investigator PFS assessments was high, with a concordance rate of 82.5% in the nivo+ipi arm and 80.8% on the chemotherapy arm.

Table 40. PFS per BICR- All randomized subjects

	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
# EVENTS / # SUBJECTS (%)	218/303 (71.9)	209/302 (69.2)
MEDIAN PFS (MONTHS) (1) (95% CI)	6.77 (5.59, 7.36)	7.20 (6.93, 8.05)
HR	1.00 (A)	
(95% CI)	(0.82, 1.21)	

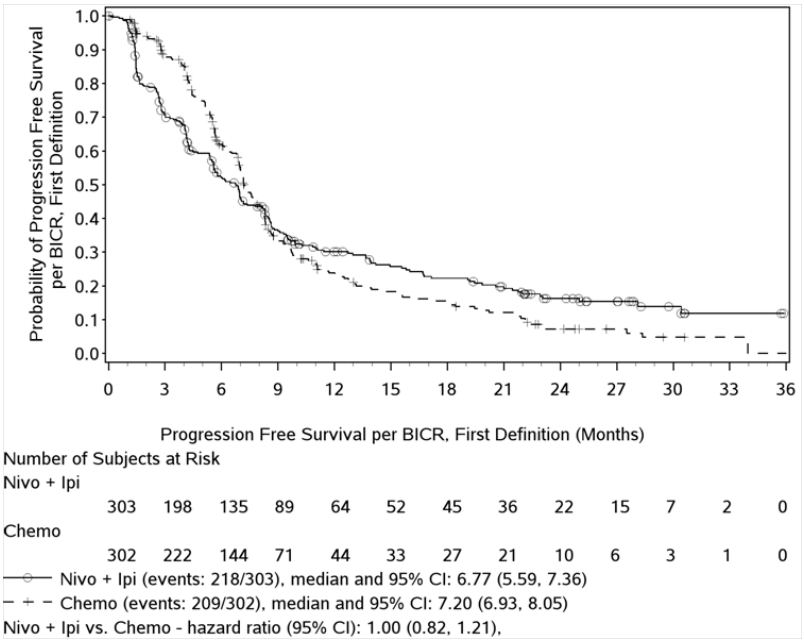
(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Chemotherapy.
Source: Table S.5.11.2

Table 41. PFS Survival Rates per BICR- All randomized subjects

Progression Free Survival Rate (95% CI)	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
6-MONTH	52.1 (46.0, 57.8)	61.9 (55.6, 67.7)
12-MONTH	30.2 (24.6, 35.9)	23.8 (18.4, 29.7)
18-MONTH	22.3 (17.2, 27.8)	15.0 (10.5, 20.3)
24-MONTH	16.3 (11.7, 21.5)	7.2 (4.0, 11.7)

Based on Kaplan-Meier Estimates
Source: Table S.5.12.2.A

Figure 43. Kaplan-Meier Plot of Progression Free Survival per BICR, Primary Definition – All Randomized Subjects



Follow-up for PFS per BICR was current for the majority of subjects in both arms; 85.1% and 85.1% of subjects in the nivo+ipi and chemotherapy arms, respectively, had a PFS event per BICR on or after the LPLV date for this DBL.

PFS by IRT Stratification Factor – Histology

Table 42. Progression-free Survival of Nivolumab + Ipilimumab vs Chemotherapy by Histology - All Randomized Subjects

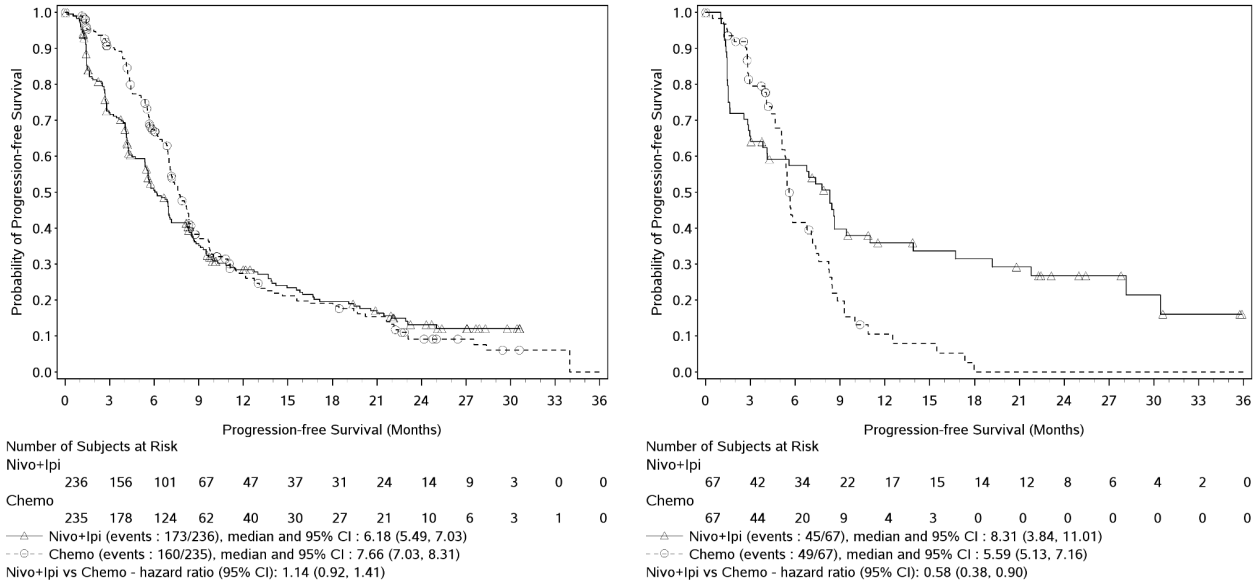
	Epithelioid (N = 471)		Non-epithelioid (N = 133)	
	Nivo+Ipi N = 236	Chemo N = 235	Nivo+Ipi N = 67	Chemo N = 67
PFS per BICR (1° Definition)				
Median (95% CI), mo.[a]	6.18 (5.49, 7.03)	7.66 (7.03, 8.31)	8.31 (3.84, 11.01)	5.59 (5.13, 7.16)
HR (95% CI)[b]	1.14 (0.92, 1.41)		0.58 (0.38, 0.90)	
Events, n	173	160	45	49

a: Based on Kaplan-Meier estimate

b: Unstratified Cox proportional hazards model

Figure 44: Kaplan-Meier Plot of PFS (Primary Definition, BICR) by Histology per IRT - All Randomized Subjects

Epithelioid *Non-Epithelioid*



Statistical model for hazard ratio: unstratified Cox proportional hazards model
Symbols represent censored observations.

PFS by IRT Stratification Factor – Sex

Similar to the all randomized population, the nivo+ipi arm did not show an advantage over the chemotherapy arm in PFS in both males and females (HR:0.96 and 1.03, respectively) (Table 43 and Figure 45).

Table 43. PFS of Nivolumab + Ipilimumab vs Chemotherapy by Sex -All Randomized Subjects

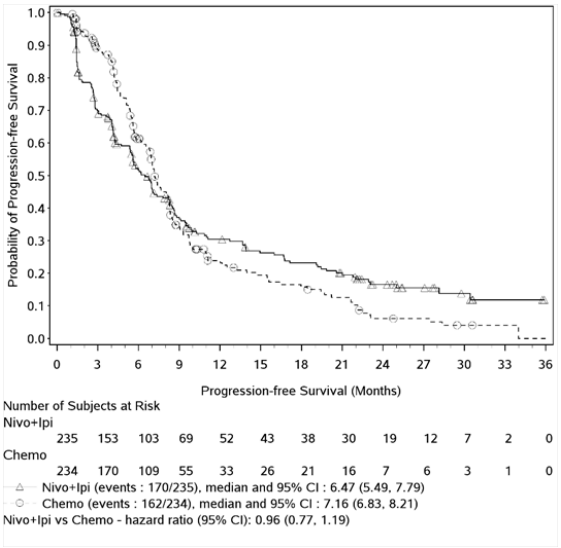
	Male (N = 469)		Female (N = 136)	
	Nivo+Ipi N = 235	Chemo N = 234	Nivo+Ipi N = 68	Chemo N = 68
PFS per BICR (1° Definition)				
Median (95% CI), mo.[a]	6.47 (5.49, 7.79)	7.16 (6.83, 8.21)	6.93 (4.27, 8.57)	7.56 (6.05, 8.48)
HR (95% CI) [b]	0.96 (0.77, 1.19)		1.03 (0.69, 1.54)	
Events, n	170	162	48	47

a: Based on Kaplan-Meier estimate

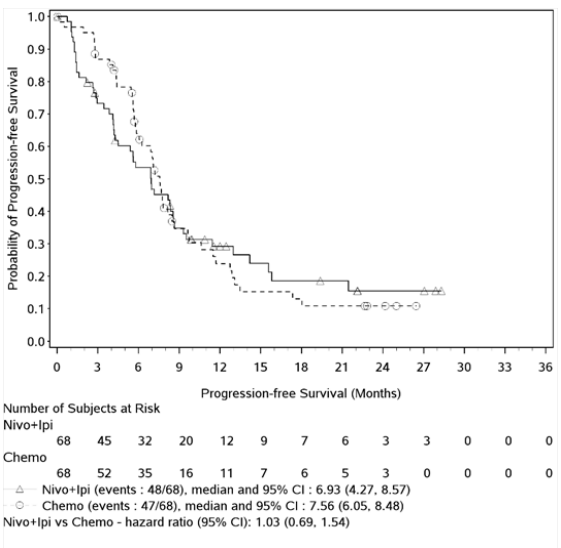
b: Unstratified Cox proportional hazards model Source: Figure S.5.11 (PFS)

Figure 45 Kaplan-Meier Plot of PFS (BICR) by Sex per IRT - All Randomized Subjects

Male



Female

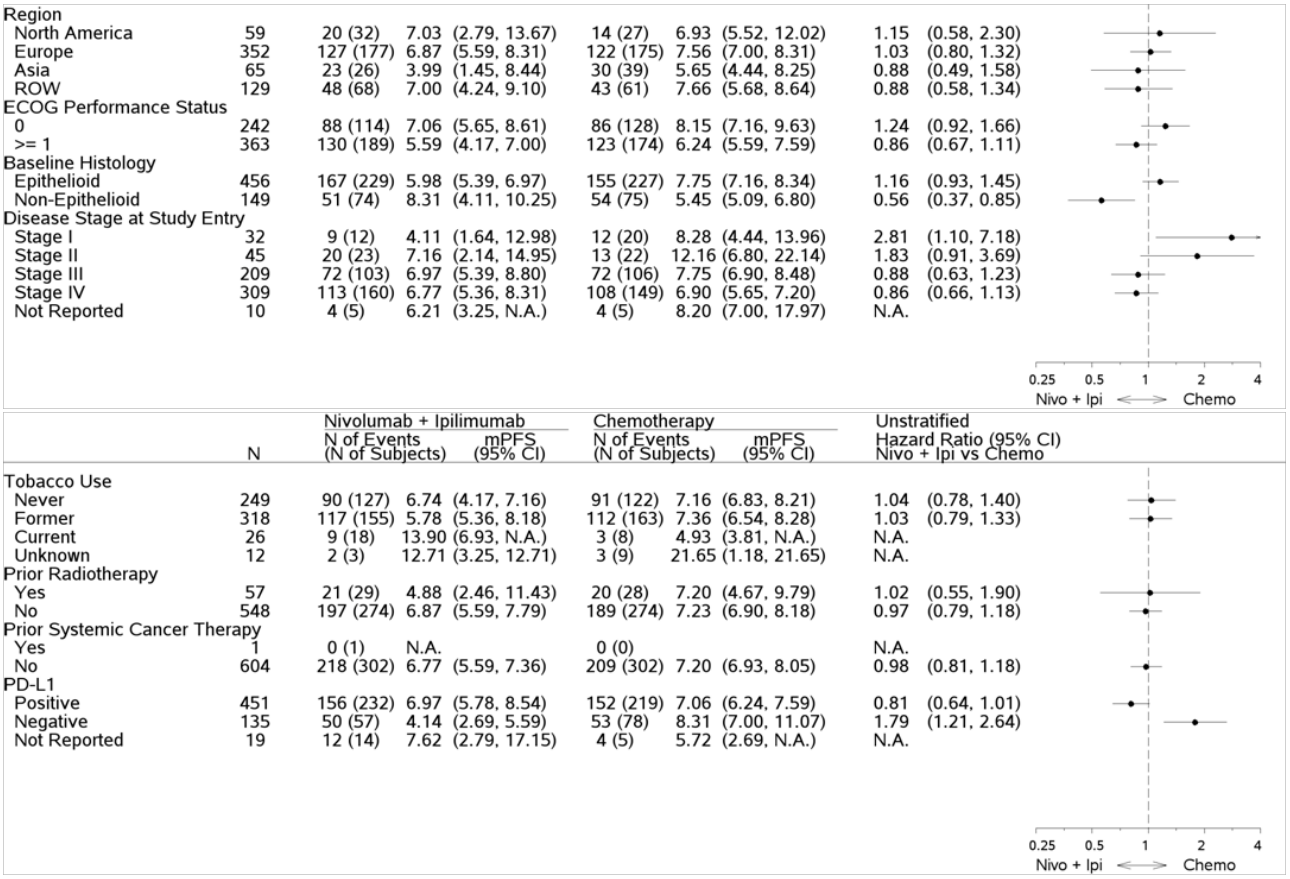


Progression-free Survival in Other Predefined Subsets

The HRs for PFS favoured (HR < 1) nivo+ipi vs chemotherapy in subjects with sarcomatoid histology and PD-L1 positive tumours (≥ 1% PD-L1). The HRs favoured (HR > 1) chemotherapy vs nivo+ipi in subjects with Stage I disease and PD-L1 negative tumours (< 1% PD-L1) (Figure 46).

Figure 46: Forest Plot of Treatment Effect on PFS in Pre-Defined Subsets - All Randomized Subjects

	N	Nivolumab + Ipilimumab N of Events (N of Subjects)	mPFS (95% CI)	Chemotherapy N of Events (N of Subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs Chemo
Overall	605	218 (303)	6.77 (5.59, 7.36)	209 (302)	7.20 (6.93, 8.05)	0.97 (0.81, 1.18)
Age Categorization						
< 65	167	50 (71)	5.65 (4.11, 8.31)	63 (96)	6.93 (5.68, 8.15)	1.02 (0.70, 1.48)
>= 65 and < 75	281	108 (154)	7.79 (5.98, 8.64)	91 (127)	7.26 (6.24, 8.28)	0.85 (0.64, 1.13)
>= 75	157	60 (78)	5.36 (4.04, 7.06)	55 (79)	8.15 (6.80, 9.69)	1.25 (0.87, 1.81)
>= 65	438	168 (232)	6.90 (5.59, 8.31)	146 (206)	7.59 (6.97, 8.25)	0.97 (0.78, 1.22)
Sex						
Male	467	169 (234)	6.21 (5.49, 7.36)	162 (233)	7.16 (6.83, 8.21)	0.96 (0.77, 1.19)
Female	138	49 (69)	6.93 (4.27, 8.57)	47 (69)	7.56 (6.05, 8.48)	1.03 (0.69, 1.53)
Race						
White	516	189 (266)	6.90 (5.62, 8.18)	170 (250)	7.39 (7.00, 8.21)	1.02 (0.83, 1.25)
Black	0	0 (0)		0 (0)		N.A.
Asian	65	23 (26)	3.99 (1.45, 8.44)	30 (39)	5.65 (4.44, 8.25)	0.88 (0.49, 1.58)
Other	24	6 (11)	19.19 (1.51, N.A.)	9 (13)	7.72 (2.56, 18.43)	0.70 (0.25, 1.98)



HR is not computed for subset category with less than 10 subjects per treatment group PD-L1: Positive (≥ 1%), Negative (< 1%)

Source: Figure S.5.8.A.2

ORR

ORR per BICR was similar in the 2 treatment arms (Table 44). Concordance between BICR and investigator-assessed BOR was high, with a concordance rate of 81.1% and 79.0% for nivo+ipi and chemotherapy arms, respectively.

Table 44. Confirmed Best Overall Response per BICR - All randomized subjects

	Number of Subjects (%)	
	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
CONFIRMED BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	5 (1.7)	0
PARTIAL RESPONSE (PR)	115 (38.0)	129 (42.7)
STABLE DISEASE (SD)	112 (37.0)	125 (41.4)
NON-CR/NON-PD	0	3 (1.0)
PROGRESSIVE DISEASE (PD)	55 (18.2)	14 (4.6)
UNABLE TO DETERMINE (UTD)	4 (1.3)	5 (1.7)
NOT REPORTED	12 (4.0)	26 (8.6)
OBJECTIVE RESPONSE RATE (1)	120/303 (39.6%)	129/302 (42.7%)
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
DISEASE CONTROL RATE (2)	232/303 (76.6%)	257/302 (85.1%)
(95% CI)	(71.4, 81.2)	(80.6, 88.9)

Per adapted m-RECIST for pleural mesothelioma and RECIST 1.1, confirmation of response required.
(1) Number of (CR+PR)/number of subjects, confidence interval based on the Clopper and Pearson method.
(2) Number of (CR + PR + SD+ Non-CR/Non-PD)/number of subjects; confidence interval based on the Clopper and Pearson method.

Median TTR per BICR was 2.69 months for all confirmed responders in the nivo+ipi arm, and 2.53 months for all confirmed responders in the chemotherapy arm (Table 45).

The median DoR was longer for confirmed responders in the nivo+ipi arm relative to the chemotherapy arm (11.01 [95% CI: 8.11, 16.49] vs 6.67 [95% CI: 5.32, 7.10] months, respectively). 69% and 53% of responders in the nivo+ipi and chemotherapy arms, respectively, had a DoR of at least 6 months.

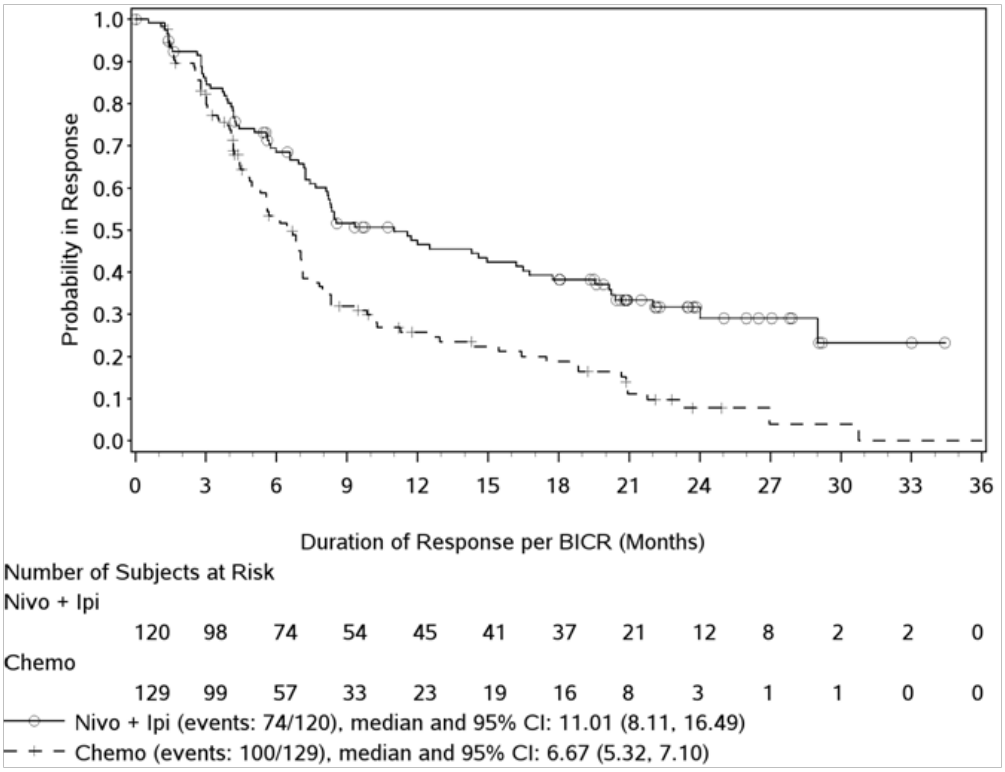
Separation of the Kaplan-Meier curves for DoR occurred at approximately 2 months and favoured nivo+ipi over chemotherapy. At DBL, 38.3% of subjects in the nivo+ipi arm and 22.5% of subjects in the chemotherapy arm were censored for DoR per BICR (Figure 47).

Table 45. Time to Objective Response and Duration of Response per BICR - All Confirmed Responders

	Nivolumab + Ipilimumab N = 120	Chemotherapy N = 129
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	2.76	2.95
MEDIAN	2.69	2.53
MIN, MAX	0.8, 13.4	0.3, 19.4
Q1, Q3	1.45, 3.27	1.41, 3.02
STANDARD DEVIATION	1.81	2.69
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	0.0+, 34.4+	0.0+, 30.8
MEDIAN (95% CI) (B)	11.01 (8.11, 16.49)	6.67 (5.32, 7.10)
N EVENT/N RESP (%)	74/120 (61.7)	100/129 (77.5)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	0.85 (0.78, 0.91)	0.82 (0.74, 0.88)
6 MONTHS	0.69 (0.59, 0.76)	0.53 (0.43, 0.61)
12 MONTHS	0.47 (0.37, 0.56)	0.26 (0.18, 0.34)
18 MONTHS	0.38 (0.29, 0.47)	0.19 (0.12, 0.27)
24 MONTHS	0.32 (0.23, 0.41)	0.08 (0.03, 0.15)

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Based on Kaplan-Meier estimates of duration of response.
Source: Table 7.4-2 of the CA209743 Final CSR

Figure 47. Kaplan-Meier Plot of Duration of Response per BICR - All Responders



Subjects in the nivo+ipi arm were permitted to continue receiving nivo+ipi treatment beyond initial adapted m-RECIST for mesothelioma and/or RECIST 1.1 defined PD as long as they provided consent and met all protocol criteria for clinical benefit and tolerance of study drug (section 4.6 of the protocol).

Best Overall Response by Predefined Subsets

In a pre-defined analysis, the ORR by BICR was similar in the nivo+ipi and chemotherapy arms in the majority of subgroups (Table 46).

Table 46: ORR per BICR by Subsets - All Randomized Subjects

	OBJECTIVE RESPONSE RATE (%)(A) 95% CI	
	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
OVERALL	120/303 (39.6%) (34.1, 45.4)	129/302 (42.7%) (37.1, 48.5)
AGE CATEGORIZATION		
< 65	25/71 (35.2%) (24.2, 47.5)	32/96 (33.3%) (24.0, 43.7)
>= 65 AND < 75	62/154 (40.3%) (32.4, 48.5)	57/127 (44.9%) (36.1, 54.0)
>= 75	33/78 (42.3%) (31.2, 54.0)	40/79 (50.6%) (39.1, 62.1)
>= 65	95/232 (40.9%) (34.6, 47.6)	97/206 (47.1%) (40.1, 54.1)
SEX		
MALE	93/234 (39.7%) (33.4, 46.3)	96/233 (41.2%) (34.8, 47.8)
FEMALE	27/69 (39.1%) (27.6, 51.6)	33/69 (47.8%) (35.6, 60.2)
RACE		
WHITE	104/266 (39.1%) (33.2, 45.2)	103/250 (41.2%) (35.0, 47.6)
BLACK	0	0
ASIAN	11/26 (42.3%) (23.4, 63.1)	20/39 (51.3%) (34.8, 67.6)
OTHER	5/11 (45.5%)	6/13 (46.2%)

	(16.7, 76.6)	(19.2, 74.9)
REGION		
NORTH AMERICA	9/32 (28.1%)	12/27 (44.4%)
	(13.7, 46.7)	(25.5, 64.7)
EUROPE	73/177 (41.2%)	70/175 (40.0%)
	(33.9, 48.9)	(32.7, 47.7)
ASIA	11/26 (42.3%)	20/39 (51.3%)
	(23.4, 63.1)	(34.8, 67.6)
ROW	27/68 (39.7%)	27/61 (44.3%)
	(28.0, 52.3)	(31.5, 57.6)
ECOG PERFORMANCE STATUS		
0	48/114 (42.1%)	58/128 (45.3%)
	(32.9, 51.7)	(36.5, 54.3)
>= 1	72/189 (38.1%)	71/174 (40.8%)
	(31.1, 45.4)	(33.4, 48.5)
BASELINE HISTOLOGY		
EPITHELIOID	88/229 (38.4%)	108/227 (47.6%)
	(32.1, 45.1)	(40.9, 54.3)
MIXED	8/26 (30.8%)	11/28 (39.3%)
	(14.3, 51.8)	(21.5, 59.4)
SARCOMATOID	19/35 (54.3%)	9/36 (25.0%)
	(36.6, 71.2)	(12.1, 42.2)

OBJECTIVE RESPONSE RATE (%)(A) 95% CI

	Nivolumab + Ipilimumab N = 303	Chemotherapy N = 302
OTHER	5/13 (38.5%)	1/11 (9.1%)
	(13.9, 68.4)	(0.2, 41.3)
DISEASE STAGE AT STUDY ENTRY		
STAGE I	5/12 (41.7%)	9/20 (45.0%)
	(15.2, 72.3)	(23.1, 68.5)
STAGE II	10/23 (43.5%)	14/22 (63.6%)
	(23.2, 65.5)	(40.7, 82.8)
STAGE III	49/103 (47.6%)	43/106 (40.6%)
	(37.6, 57.6)	(31.1, 50.5)
STAGE IV	55/160 (34.4%)	61/149 (40.9%)
	(27.1, 42.3)	(33.0, 49.3)
NOT REPORTED	1/5 (20.0%)	2/5 (40.0%)
	(0.5, 71.6)	(5.3, 85.3)
TOBACCO USE		
NEVER	53/127 (41.7%)	54/122 (44.3%)
	(33.0, 50.8)	(35.3, 53.5)
FORMER	57/155 (36.8%)	72/163 (44.2%)
	(29.2, 44.9)	(36.4, 52.1)
CURRENT	9/18 (50.0%)	2/8 (25.0%)
	(26.0, 74.0)	(3.2, 65.1)
UNKNOWN	1/3 (33.3%)	1/9 (11.1%)
	(0.8, 90.6)	(0.3, 48.2)
PRIOR RADIOTHERAPY		
YES	15/29 (51.7%)	14/28 (50.0%)
	(32.5, 70.6)	(30.6, 69.4)
NO	105/274 (38.3%)	115/274 (42.0%)
	(32.5, 44.4)	(36.1, 48.1)
PRIOR SYSTEMIC CANCER THERAPY		
YES	1/1 (100.0%)	0
	(2.5, 100.0)	
NO	119/302 (39.4%)	129/302 (42.7%)
	(33.9, 45.2)	(37.1, 48.5)
PD-L1		
POSITIVE	101/232 (43.5%)	97/219 (44.3%)
	(37.1, 50.2)	(37.6, 51.1)
NEGATIVE	12/57 (21.1%)	30/78 (38.5%)
	(11.4, 33.9)	(27.7, 50.2)
NOT REPORTED	7/14 (50.0%)	2/5 (40.0%)
	(23.0, 77.0)	(5.3, 85.3)

(A) CR+PR as per adapted m-RECIST for pleural mesothelioma and RECIST 1.1 criteria confirmation of response required (BICR Assessment), confidence interval based on the Clopper and Pearson method.

Efficacy According to PD-L1 Expression

Efficacy by PD-L1 expression was assessed as a secondary endpoint in this study. However, the study was not stratified by PD-L1; therefore it is not powered to assess treatment effect by PD-L1 expression.

Efficacy according to PD-L1 expression was explored in the PD-L1 evaluable population which represented 96.9% of the All Randomized population. OS in subjects with ≥ 1% baseline PD-L1 expression (PD-L1 positive) was consistent with the results seen in the All Randomized population. The improvement in OS with nivo+ipi treatment over chemotherapy was larger in subjects with PD-L1 positive tumours (HR for < 1% and ≥ 1% PD-L1 was 0.94 and 0.69, respectively.

For PFS per BICR, opposite treatment effects were observed by PD-L1 expression. A benefit of nivo+ipi over chemotherapy was observed in subjects with PD-L1 positive tumours (HR: 0.81), while in the subjects with PD-L1 negative tumours, the PFS HR was 1.79 favouring chemotherapy (Table 47).

Consistent with the All Randomized population, ORR per BICR was similar in both treatment arms in subjects with PD-L1 positive tumours. The ORR in subjects with PD-L1 negative tumours was numerically lower for nivo+ipi compared with chemotherapy (21.1% vs. 38.5%). However, the PD-L1 <1% subgroup has a modest sample size, providing for limited event counts in the context of time to event analyses.

Table 47: Efficacy by 1% PD-L1 Cutoff - All PD-L1 Evaluable Subjects

	< 1% (N = 135)		**≥ 1% (N = 451)**	
	Nivo+Ipi N = 57	**Chemo N = 78**	**Nivo+Ipi N = 232**	**Chemo N = 219**
Median[a] OS (95% CI), mo.	17.3 (10.1, 24.3)	16.5 (13.4, 20.5)	18.0 (16.8, 21.5)	13.3 (11.6, 15.4)
HR[b] (95% CI)	0.94 (0.62, 1.40)		0.69 (0.55, 0.87)	
No .of events	40	58	150	157
Median[a] PFS per BICR (95% CI), mo.	4.1 (2.7, 5.6)	8.3 (7.0, 11.1)	7.0 (5.8, 8.5)	7.1 (6.2, 7.6)
HR[b] (95% CI)	1.79 (1.21, 2.64)		0.81 (0.64, 1.01)	
No .of events	50	53	156	152
ORR[c] per BICR (95% CI), %	21.1 (11.4, 33.9)	38.5 (27.7, 50.2)	43.5 (37.1, 50.2)	44.3 (37.6, 51.1)
BOR				
CR	0	0	3 (1.3)	0
PR	12 (21.1)	30 (38.5)	98 (42.2)	97 (44.3)
SD	28 (49.1)	38 (48.7)	79 (34.1)	84 (38.4)
PD	16 (28.1)	6 (7.7)	37 (15.9)	8 (3.7)

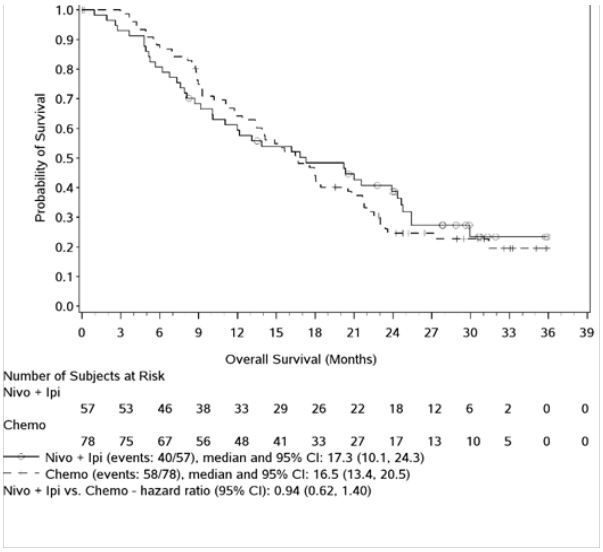
[a] Based on Kaplan-Meier Estimates.

[b] Unstratified Cox proportional hazard model.

[c] Number of (CR+PR)/number of subjects, confidence interval based on the Clopper and Pearson method.

Figure 48: Kaplan-Meier Plot of OS by 1% PD-L1 Cutoff - All PD-L1 Evaluable Subjects

Baseline PD-L1 Expression < 1%



Baseline PD-L1 Expression ≥ 1%

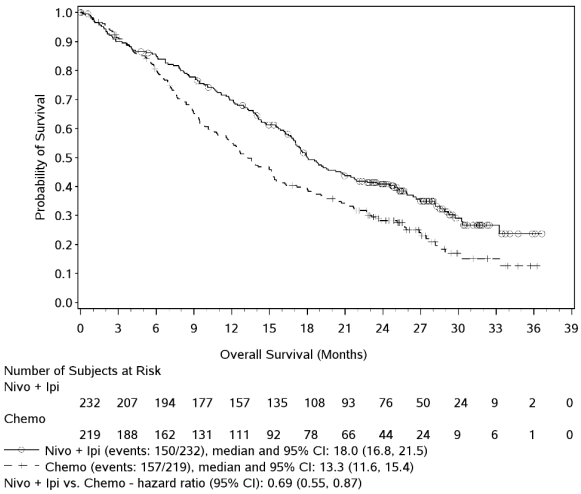
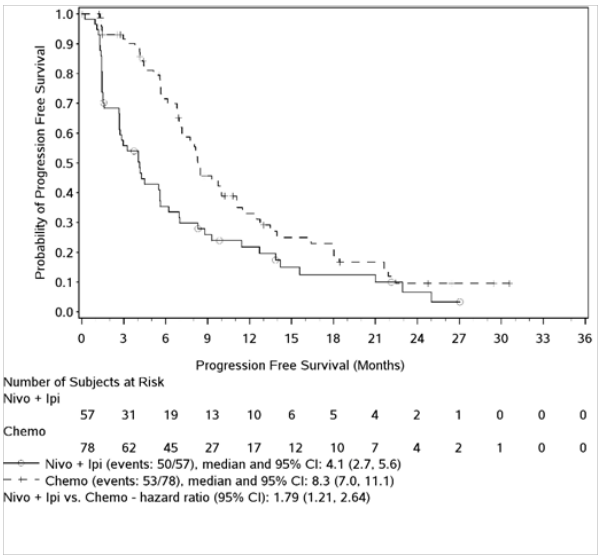
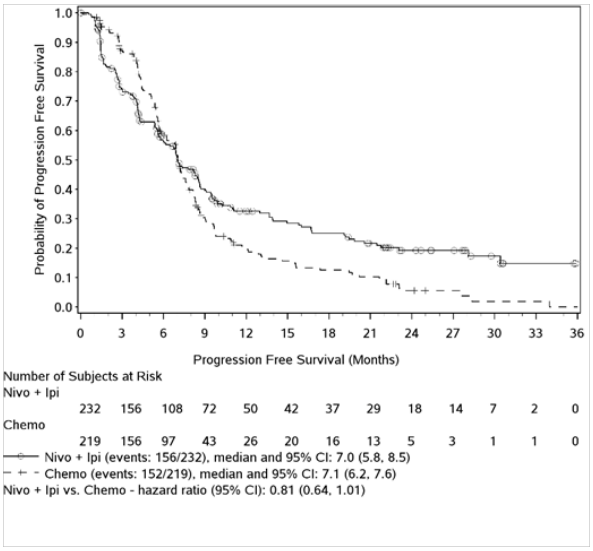


Figure 49: Kaplan-Meier Plot of PFS (Primary Definition, BICR) by 1% PD-L1 Cutoff - All PD-L1 Evaluable Subjects

Baseline PD-L1 Expression < 1%



Baseline PD-L1 Expression ≥ 1%



Ancillary analyses

Efficacy according to PD-L1 Expression and Histology (exploratory analysis)

Table 48: Subgroup Analysis by Histology and PD-L1 Expression Levels (≥ 1% and < 1%) - All PD-L1 Evaluable Subjects - CA209743

	Epithelioid		Non-epithelioid	
	PD-L1 < 1% Cut	**PD-L1 ≥ 1% Cut**	**PD-L1 < 1% Cut**	**PD-L1 ≥ 1% Cut**
Subgroup Size (nivo+ipi vs chemo)	47 vs 62	173 vs 162	10 vs 16	59 vs 57
Median OS, months (nivo+ipi vs chemo)	17.3 vs 18.1	18.0 vs 15.5	15.7 vs 11.8	16.9 vs 7.7
OS Rate, % (nivo+ipi vs chemo)				
12 Month	61.4 vs 70.3	71.2 vs 64.2	50.0 vs 40.0	65.5 vs 29.6
24 Month	41.3 vs 29.2	41.6 vs 34.7	25.0 vs 6.7	38.5 vs 9.9
OS HR (95% CI)	0.99 (0.63, 1.56)	0.81 (0.63, 1.06)	0.69 (0.28, 1.67)	0.43 (0.28, 0.66)
Median PFS, months (nivo+ipi vs chemo)	4.2 vs 8.2	6.9 vs 7.7	3.5 vs 8.5	8.6 vs 5.3
PFS HR (95%CI)	1.91 (1.24, 2.94)	0.99 (0.76, 1.28)	1.12 (0.42, 2.95)	0.46 (0.28, 0.74)
ORR, % (nivo+ipi vs chemo)	21.3 vs 41.9	42.2 vs 50.0	20.0 vs 25.0	47.5 vs 28.1
Median DOR, months (nivo+ipi vs chemo)	8.3 vs 7.1	9.3 vs 6.7	10.5 vs 8.3	20.4 vs 4.2

Abbreviations: chemo - chemotherapy, CI - confidence interval, DOR - duration of response, HR - hazard ratio, ipi - ipilimumab, nivo - nivolumab, ORR - objective response rate, OS - overall survival, PD-L1 -programmed death ligand-1, PFS - progression-free survival,

Source: Refer to Table 3.1.7-1, SCE, Module 2.7.3

Efficacy results by Region

Of the randomized subjects in CA209743, 9.8% (59/605) were from North America, 58.2% (352/605) were from Europe, 10.7% (65/605) were from Asia, and 21.3% (129/605) were from the rest of the world. Efficacy was observed across regions (HR < 1) nivo+ipi vs chemotherapy, including the subgroup of subjects from North America (HR = 0.54 [95% CI: 0.28, 1.03]), Europe (HR = 0.77 [95% CI: 0.60, 0.99]), and Asia (HR = 0.97 [95% CI: 0.56, 1.69]) however, it should be noted the Asian sample size was small.

Summary of main study

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

Table 49. Summary of Efficacy for Study CA209743

Study CA209743: A Phase III, Randomized, Open Label Trial of Nivolumab in Combination with Ipilimumab Versus Pemetrexed With Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma			
Study identifier	Eudra CT: 2016-001859-43		
Design	Randomised, parallel group, open label study		
	Duration of main phase		Nivolumab + ipilimumab arm: up to 24 months or until progressive disease, unacceptable toxicity or death, whatever occurs first. Chemotherapy arm: up to 4 cycles of chemotherapy or disease progression or death, whatever occurs first.
	Duration of Run-in phase / Duration of Extension phase		Not applicable
Hypothesis	Superiority		
Treatments groups	Nivolumab + ipilimumab		Nivolumab 3 mg/kg Q2 weeks + Ipilimumab 1 mg/kg Q6 weeks (up to 24 months, toxicity, or progression) N=303
	Chemotherapy		Cisplatin 75mg/m2 or Carboplatin AUC 5 + Pemetrexed 500 mg/m2 in 21 day cycles for six cycles N=302
Endpoints and definitions	Primary endpoint	OS	Time from randomisation to the date of death of any course
	Secondary endpoints	PFS	Time from the randomisation data to the date of first documented tumour progression (modified BICR/RECIST v1.1)

		ORR	Proportion of randomised patients who have confirmed CR or PR (modified BICR/RECIST v1.1)
		DOR	Time between the date of first documented response (CR or PR) to the date of the first documented tumour progression as determined by the BICR (per adapted m- RECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first.
Database lock	3 April 2020		
Results and Analysis			
Analysis description	**Primary Analyses** First planned interim analysis conducted on 17 April 2020, when 419 (89%) of the total OS events planned had occurred. Database lock: 3-Apr-2020. Minimum follow-up for OS was 22.1 months.		
Analysis population and time point description	All randomised patients		
Descriptive statistics and estimate variability	Treatment group	Nivolumab + ipilimumab	Chemotherapy
	Number of subjects	303	302
	Median OS (months)	18.1	14.1
	95 %CI	16.8, 21.5	12.5, 16.2
	Median PFS (months)	6.8	7.20
	95 % CI	5.6, 7.4	6.9, 8.1
	ORR (n, %)	120 (40%)	129 (43%)
	Median DOR (months) (95 % CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)
Effect estimate per comparison	Overall survival (primary outcome)	Comparison groups	Nivo+ ipi vs. chemo
		Hazard ratio	0.74
		96.6% CI	0.60-0.91
		p-value*	0.0020
	PFS	Comparison groups	Nivo+ ipi vs. chemo
		Hazard ratio	1.00
		95 % CI	0.82-1.21
		p-value	Not reported

Notes	OS: Kaplan-Meier estimates HR for OS based on Stratified Cox proportional hazard model. HR is nivo+ipi over chemo and the 2-sided p-values from stratified log-rank test. The 95% CI of the ORR is measured by Clopper and Pearson Method

Clinical studies in special populations

No specific study was conducted for patients aged ≥75 years. The results of this subgroup of elderly patients of Study CA209743 are provided below.

157 subjects aged ≥75 years were included in Study CA209743, 6 of them were ≥85. 78 subjects were randomized to the nivo+ipi arm and 79 to the chemotherapy treatment arm.

Regarding efficacy results in this population, the observed median OS was 16.92 (95% CI: 11.04, 20.83) months for the nivo+ipi arm and 15.38 (95% CI: 11.73, 18.43) months for the chemotherapy group; HR 1.02 (95% CI: 0.59, 1.48).

Median PFS in the nivo+ipi group was 5.36 (95% CI: 4.04, 7.06) months and 8.15 (95% CI: 6.80, 9.69) months for the chemotherapy treatment arm; HR 1.25 (95% CI: 0.87, 1.81).

The observed ORR was 33/78 (42.3%; 95% CI: 31.2, 54.0) for the nivo+ipi arm and 40/79 (50.6%; 95% CI: 39.1, 62.1) for the chemotherapy group. The DoR was not reported.

Supportive study

Study IFCT-1501 MAPS 2: ***A randomized Phase II Study evaluating Efficacy and Safety of 2nd or 3rd line treatment by Nivolumab monotherapy or Nivolumab plus Ipilimumab for unresectable Malignant Pleural Mesothelioma (MPM) patients.***

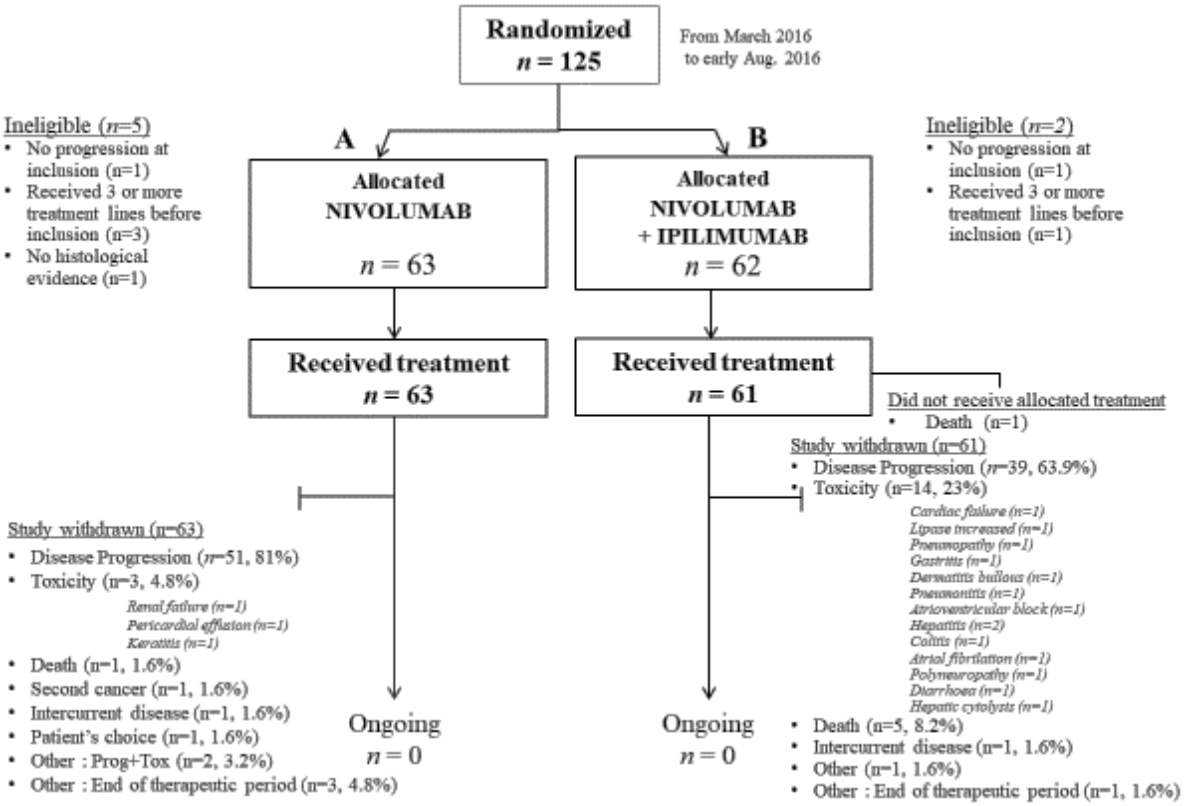
Study MAPS 2 was an interventional, multi-center, open-label, randomized and non-comparative phase II study. This study was performed in 21 active centers in France, from Mar-2016 to Aug-2018.

It evaluated nivolumab monotherapy, or nivolumab in combination with ipilimumab, for the treatment of unresectable MPM in subjects who had documented progression on or after 1 or 2 previous lines of chemotherapy, including at least 1 platinum-based chemotherapy regimen.

Subjects were randomized 1:1 into the following treatment groups and stratified by histological subtype (epithelioid vs sarcomatoid or biphasic), line of treatment (second- vs third-line), and sensitivity to platinum/pemetrexed treatment (progression ≥ 3 months vs < 3 months):

- Nivolumab (N = 63): nivolumab 3 mg/kg Q2W, over 60 min.
- Nivolumab + ipilimumab (N = 62): nivolumab 3 mg/kg Q2W over 60 min + ipilimumab 1 mg/kg Q6W over 90 min.

Subject disposition



Subjects were treated for up to 2 years from randomization or until disease progression, unacceptable toxicity, or until other protocol-specified reasons for discontinuation were met. Tumour assessments occurred every 12 weeks (± 1 week) from the first dose until progression or treatment discontinuation. Subjects could continue treatment beyond initial RECIST 1.1-defined PD – at CT-scan assessment at Week 12 – if they met all the following criteria:

- Investigator-assessed clinical benefit, and subjects did not have rapid PD
- Continued to meet all other study protocol eligibility criteria
- Good tolerance of study drug(s)
- Stable ECOG PS

The primary study endpoint, DCR at 12 weeks, was assessed by the Investigator using the modified Response Evaluation Criteria in Solid Tumours (mRECIST) 1.1 criteria for mesothelioma. The following secondary variables were also collected: PFS, OS, QOL, predictive value of PD-L1 and prognosis impact of biomarkers.

Results

Demographic and disease characteristics

125 subjects were included, 63 to the nivolumab arm and 62 to the nivo+ipi arm. Median age was 71.8 years, 80% of patients were male and 58.4% of subjects were former or current smokers. 84% of patients had epithelioid histology, 68.8% of subjects had received one prior treatment line and 28.8% two. Regarding PD-L1, 41.4% were considered positive (≥1% expression).

Table 50. Efficacy summary for the ITT population

	Nivolumab 3 mg/kg (N = 63)	Nivo 3 mg/kg + Ipi 1 mg/kg (N = 62)
DCR at 12 Weeks by BICR N (%) [95% CI] %	25 (39.7) [27.6 - 51.8]	32 (51.6) [39.2 - 64.1]
Best Overall Response by BICR, N (%)		
Complete Response (CR)	0	0
Partial Response (PR)	11 (17.5)	16 (25.8)
Stable Disease (SD)	14 (22.2)	16 (25.8)
Progressive Disease (PD)	34 (54.0)	23 (37.1)
Unable to determine/Not reported	4 (6.3)	7 (11.3)
PFS, by the Investigator		
Events, n (%)	60 (95.2)	56 (90.3)
Median (95% CI), months	3.97 [2.79-5.68]	5.44 [3.06-8.21]
Overall Survival,		
Events, n (%)	55 (87.3)	52 (83.9)
Median [95% CI], months	11.86 [6.73, 17.44]	15.93 (10.68, 22.21)
1-year OS rate [95% CI], %	49.2 (36.4, 60.8)	58.1 (44.80, 69.2)
2-year OS rate [95% CI], %	25.4 [15.5-36.5]	31.7 [20.5-43.4]

mRECIST 1.1, confirmation of response required.

Primary endpoint

In the pre-specified EP population, DCR at 12 weeks was achieved in 44.4% of subjects in the nivolumab arm and 50.0% of subjects in the nivolumab plus ipilimumab arm, as re-evaluated by the BICR according to the mRECIST 1.1 criteria. In the ITT population, 25 (39.7%; [95% CI: 27.6 - 51.8]) subjects in the nivolumab arm and 32 (51.6%; [95% CI: 39.2 - 64.1]) subjects in the nivolumab plus ipilimumab arm reached DCR at 12 weeks after re-evaluation by the BICR.

Secondary endpoints

The mPFS was 3.97 months [95% CI: 2.79 - 5.68] in the nivolumab arm and 5.44 months [95% CI: 3.06 - 8.21] in the nivolumab plus ipilimumab arm. The mOS was 11.86 months [95% CI: 6.73 - 17.44] in the nivolumab arm and 15.93 months [95% CI: 10.68 - 22.21] in the nivolumab plus ipilimumab arm.

Evaluations of QOL showed that more than 42.0% of subjects had declined at 12 weeks for the general and symptom distress in the nivolumab arm and for interference with daily activities, fatigue and anorexia in the nivolumab plus ipilimumab arm.

DCR, independently of the treatment arm, was achieved in 24 of 48 (41.4% [95% CI: 28.7 - 54.1]) PD-L1-negative subjects (i.e. IHC score <1%). vs 22 of 41 (53.7% [95% CI: 38.4 - 68.9]) PD-L1-positive subjects (i.e. IHC score ≥1%). Using a 25% cut-off as the threshold of high PD-L1 expression, DCR was achieved in 6 of 7 (85.7% [95% CI: 59.8 - 100.0]) high-PD-L1 and 40 of 92 (43.5% [95% CI: 33.3 - 53.6] low-PD-L1 subjects.

In the nivolumab arm, but not in the nivolumab plus ipilimumab arm, subjects with progression ≥ 3 months on previous chemotherapy with cisplatin/pemetrexed had a longer survival than those with progression before 3 months (HR=0.42 [0.23; 0.74]; p=0.003).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The open-label design is considered acceptable although a double-blind design is preferable; nonetheless the difficulties to blind the study due to differences in infusion regimens and toxicities of chemotherapy compared with immunotherapy are acknowledged. The chosen comparator, platinum in combination with pemetrexed up to 6 cycles, is considered adequate, as it represents the standard of care treatment for 1L MPM patients.

MPM diagnosis is difficult and it is not confirmed by central review in this study. In the inclusion criteria it is stated that subjects must have histological proven diagnosis and thoracoscopy is highly recommended, but it is not the only available method to obtain the sample and other methods were allowed. Thoracoscopy is the preferred diagnostic method, according to several guidelines, because it allows obtaining proper tissue samples for a histological diagnosis but it is acknowledged that not all patients would be candidates for this procedure and not all procedures performed would be successful in obtaining such samples, therefore, this approach is acceptable as long as the diagnosis was confirmed.

Regarding disease baseline characteristics, patients included were required to have unresectable MPM. Surgical staging based on TNM system is preferred and it is a predictor of prognosis, therefore baseline disease stage based on TNM staging system was provided upon request and they were mostly balanced between both arms.

The sample size calculations and operating characteristics of the sample size estimation are clearly described and considered acceptable. Regarding the general methods established for the statistical analyses, the assumptions are agreeable.

In the pivotal study submitted for the additional indication in MPM, nivolumab was administered as a 3 mg/kg dose 30-min infusion Q2W, in combination with ipilimumab 1 mg/kg as a 30-min infusion Q6W. Nevertheless, the proposed dosage regimen for this new indication is nivolumab 360 mg Q3W (flat dose). This 360 mg dosing was used, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy in Study CA2099LA for 1L NSCLC. In light of the provided PK-PD modelling study the proposed dose regimen approach is considered acceptable.

The comparator arm consisted of platinum based pemetrexed. In the EU, only the cisplatin combination is approved. However, the ESMO guideline mentions also carboplatin, particularly in elderly patients as cisplatin is more toxic than carboplatin. Therefore, the currently provided comparator arm is accepted.

Efficacy assessments for the secondary objectives were based on the radiological response by modified RECIST for mesothelioma or RECIST 1.1 criteria. The first amendment of study CA209743 protocol (revised protocol 01) included an update on measurement definitions for mesothelioma lesions per modified RECIST and radiographic assessment criteria per mRECIST and RECIST 1.1, aimed at providing clarity for these evaluations. There was a potential risk for inconsistency in the efficacy assessment during the conduct of the trial so the MAH was requested to provide the baseline characteristics and efficacy data (ORR, DOR, PFS, OS) of patients included before and after this amendment, which occurred when a total of 411/605 (68%) subjects had already been enrolled and 323/605 (53.4%) had been randomized. With regards to the reported efficacy results, some differences were expected to be found in secondary endpoints, as the amendment included a re-definition of the radiology assessment of these endpoints. The reported median PFS for both groups did not significantly change before and after the implementation of the amendment, i.e. the reported HR (95% CI) was 0.91 (0.69, 1.19) and 1.09 (0.82, 1.45), respectively. The reported HR for the overall population was already of 1.00 (0.82, 1.21) that, as previously discussed did not support PFS benefit and, in fact, numerically favoured the chemotherapy arm

vs. the nivo+ipi arm. The same discordance/trend was shown in the new data provided. Although the ORR results are not highly affected by the revision, there was a remarkable before/after difference for the DOR in the immunotherapy group: 14.59 vs. 8.18 months respectively. In the chemotherapy arm, the DOR was also reduced after the amendment (7.03 vs. 5.68 months) but the difference was not as worrying as in the nivo+ipi arm. The MAH was asked to discuss these results, based on the possibility that the change in radiological assessment introduced by the amendment could have led to a different assessment of the responses. The MAH clarified that the same criteria were applied during all the trial and the amendment was only intended to adapt the protocol to the criteria already used by the BICR. Unbalances regarding baseline demographic and disease characteristics for subjects randomized before and after the amendment were again analysed. Although some slight unbalances across arms before and after the amendment are observed that could have played a role (most likely differences in the distribution of patients by histology and PD-L1 expression), and although a level of uncertainty still remains, there appears to be no strong justification to question the reliability of radiologically assessed endpoints based on the differences found in the requested post-hoc analysis. In addition, it is considered that PFS, ORR and DOR results are of interest for prescribers and therefore have been included in the PI, along with an explicit reference to their descriptive nature.

Randomization was performed by IWRS and stratified according to histology and gender, which are well-known prognostic factors for MPM. Subjects were stratified in two groups: epithelioid and non-epithelioid histology, being this last one associated with poorer responses to standard chemotherapy and worse prognosis. As mentioned above, histology (epithelioid or non-epithelioid) and sex (male or female) were stratification factors in this study. Discrepancies between IRT and CRF have been observed. The rate of discrepancies between IRT and CRF was low in both the nivo+ipi (2.3% for histology and 0.3% for sex) and chemotherapy (4.0% for histology and 0.3% for sex) arms. The discrepancy rate did not exceed the limit of 10% non-concordance that would have triggered additional OS sensitivity analyses, as pre-specified in the SAP.

The PD-L1 expression was not a stratification factor nevertheless the difference between "subjects with indeterminate PD-L1 expression at baseline" and "subjects with PD-L1 expression at baseline not evaluable" is the former had tumour cell membrane staining hampered for reasons attributed to the biology of the tumour tissue sample and not because of improper sample preparation or handling, whereas the latter provided a tumour tissue sample but it was not optimally collected or prepared.

. Revised protocol 02 (issued 25-Apr-2019) included some major changes in the study endpoints and planned analyses. PFS per modified RECIST 1.1 by BICR, initially co-primary endpoint, was changed into a secondary endpoint. OS, as primary endpoint, is acceptable and the change of PFS from being a co-primary endpoint to be included as a secondary endpoint is acknowledged and accepted from a clinical point of view, also considering that PFS as well as ORR per RECIST 1.1 and DOR (collected as additional secondary endpoints) are somewhat difficult to measure in mesothelioma, because the tumour lack of demarcated margins. Of note, the hierarchical testing of secondary endpoints was removed so no formal testing of secondary objectives was done, and the results were descriptive. The reason behind the removal of the hierarchical testing of secondary endpoints was that statistically significant differences were not expected in any of those endpoints between the combination and chemotherapy which, in addition, were not expected to correlate to a survival benefit for the reasons stated above. The approach followed is understood and can be agreed to.

The included protocol deviations did not seem to have an impact on the analyses or conclusions of primary endpoint, which was OS.

Efficacy data and additional analyses

The primary efficacy endpoint (OS) and the secondary endpoint (PFS) were compared using a stratified log-rank test at the time of the interim analysis for OS that was conducted on 17 April 2020 when 419 (89%) of the total OS events planned had occurred. Study CA209743 met its primary endpoint of OS. Nivo+ipi demonstrated a statistically significant and clinically relevant 4.0 months improvement in OS compared to chemotherapy: i.e. median OS of 18.07 months (95% CI: 16.82, 21.45) for nivo+ipi vs. 14.09 months (95% CI: 12.45, 16.23) for the chemotherapy arm [HR=0.74 (95% CI: 0.61, 0.89), stratified log-rank test p value=0.0020]. Separation of the Kaplan-Meier curves of OS favouring nivo+ipi over chemotherapy occurred at around 5 months and was sustained but crossing of the curves before that point is observed.

On the contrary, PFS or ORR showed no improvement for the combination. The median PFS per BICR numerically favoured the chemotherapy combination, i.e. 6.77 (95% CI: 5.59, 7.36) months in the nivo+ipi arm and 7.20 (95% CI: 6.93, 8.05) months in the chemotherapy arm, though HR = 1.00 (95% CI: 0.82, 1.21). BICR assessed ORR was 39.6% (95% CI: 34.1, 45.4) in the nivo+ipi arm and 42.7% (95% CI: 37.1, 48.5) in the chemotherapy arm. Some durable responses were identified: the median DoR was longer for confirmed responders in the nivo+ipi arm relative to the chemotherapy arm (11.01 [95% CI: 8.11, 16.49] vs. 6.67 [95% CI: 5.32, 7.10] months, respectively).

Efficacy according to pre-specified subgroups favoured the nivo+ipi treatment arm in most of them. Particularly, improvement in OS in the non-epithelioid histology should be remarked, as this subgroup of patients is known for its chemo-resistance associated to limited responses to standard first line treatment. Results however numerically favoured chemotherapy arm in some subgroups such as ≥75 years, stage I-II and subjects with prior radiotherapy. In line with what previously said, epithelioid histology obtained worse comparative results HR=0.86 (0.69, 1.08) but, this is due to its documented better response to chemotherapy, and it is not considered enough to exclude these patients, as the results are still positive for the combination.

Regarding elderly patients (≥75 years) the findings in this study are in line with those reported in other studies with this combination. Although median OS results numerically favour the nivo+ipi combination, the HR for OS is 1.02 and the secondary endpoints showed better results for the chemotherapy arm, which is in line with the observations made for the ITT population. This analysis is not powered to reach any conclusion so results should be interpreted with caution and this information is included in the PI (section 5.1).

ORR results for predefined subsets, same as PFS, generally concurs with the overall results, but benefit for some of them seems to specially favour chemotherapy treatment. This is observed for North America and Asia region and PD-L1 expression <1%. Also, for sarcomatoid histology, quite higher ORR was reported for nivo+ipi (54.3% vs 25.0%). Once again, small sample size for these subsets and the lack of stratification factors among them precludes any firm conclusion.

The role of PD-L1 as a biomarker in MPM is not established, with recent studies failing to demonstrate the predictive value of PD-L1 expression to select patients who will most benefit from anti-PD-(L)1 therapy regimens. Efficacy by PD-L1 tumour cell expression was assessed as a secondary endpoint but it was not a stratification factor and efficacy results in these subgroups come from exploratory analyses and the study is therefore not powered to assess treatment effect by PD-L1 expression. Analyses were planned and performed to explore possible associations between efficacy endpoints and various levels of PD-L1 expression, according to the SAP. Even more, there were some imbalances between treatment arms, i.e. among subjects with quantifiable PD-L1 test at baseline, 80.3% of subjects in the nivo+ipi arm had tumour positive PD-L1 expression (≥1%), while only 19.7% had tumour negative PD-L1 expression (<1%), compared to 73.7% and 26.3% in the chemotherapy arm, respectively. Imbalances are also seen

in several key baseline characteristics. Efficacy according to PD-L1 expression was explored in the PD-L1 evaluable population which represented 96.9% of the All Randomized population. OS in subjects with ≥ 1% baseline PD-L1 expression (PD-L1 positive) was consistent with the results seen in the All Randomized population. The improvement in OS with nivo+ipi treatment over chemotherapy was larger in subjects with PD-L1 positive tumours (HR for < 1% and ≥ 1% PD-L1 was 0.94 and 0.69, respectively. However, the absence of stratification by PD-L1 expression, the smaller sample size of the <1% PD-L1 subgroup (compared with ≥ 1% PD-L1 subgroup), and the variability of chemotherapy performance (median OS of 16.5 and 13.3 months for chemotherapy subjects with PD-L1 negative and positive tumours, respectively), also may have contributed to the difference in performance.

Nevertheless, even if efficacy in patients with PD-L1 expression <1% appears more limited, *[OS HR=0.94 (95% CI: 0.62, 1.40), median OS was 17.28 (10.09, 24.34) months for the nivo+ipi arm and 16.49 (13.37, 20.53) months for the chemotherapy treatment arm]* and, as expected, neither PFS nor ORR results supports the small reported increase in median OS *[PFS HR=1.79 (95% CI: 1.21, 2.64), median PFS of 4.14 (95% CI: 2.69, 5.59) months for the combination group and 8.31 (7.00, 11.07) months for the chemotherapy group; ORR (95% CI) in PD-L1 negative patients was 21.1% (11.4, 33.9) for the nivo+ipi arm and 38.5% (27.7, 50.2) for the chemotherapy arm; DOR for PD-L1 <1% responders not reported]* and some caution is needed in interpreting these more 'negative' results , evidence is not considered strong enough to exclude PD-L1 <1% patients from the indication. Detailed data have however been included in section 5.1 of the SmPC to inform treating physicians.

In CA209743, PD-L1 expression was reported at a higher frequency in the non-epithelioid subgroup compared with the epithelioid subgroup in both the nivo+ipi and chemotherapy arms. This is consistent with observations from other studies showing that sarcomatoid/biphasic subtypes are more commonly PD-L1 expressors than the epithelioid subtype.
The magnitude of OS benefit comparing nivo+ipi vs chemotherapy did vary according to histology and PD-L1 expression. Given the correlation between histology subtype and PD-L1 expression an efficacy subgroup analysis by histology and PD-L1 was performed.
Results of the analysis (Table 27), show a survival benefit favouring nivo+ipi regardless of PD-L1 expression in the non-epithelioid cohort (PD-L1 ≥ 1%, HR = 0.43 [95% CI: 0.28, 0.66] and PD-L1 < 1%, HR = 0.69 [95% CI: 0.28, 1.67], respectively). In the epithelioid group, the benefit with nivo+ipi vs chemotherapy was more pronounced in PD-L1 ≥ 1% (HR = 0.81 [95% CI: 0.63, 1.06]) vs PD-L1 < 1% (HR = 0.99 [95% CI: 0.63, 1.56]). Results of other efficacy endpoints in these subgroups were consistent with the all randomized population. However, it should be noted that the subgroup sample sizes are small, defined by both histology and PD-L1 simultaneously, and therefore some estimates of benefit, particularly in the lower PD-L1 expressing group of epithelioid subjects, remain imprecise.

In the nivo+ipi arm, 28 subjects (9.3%) discontinued ipilimumab early. Out of the 28 subjects, 64.3% discontinued ipilimumab due to adverse event and 35.7% discontinued for "other" reasons. Patients who discontinued ipilimumab received a median of 4.5 (range 1-48) nivolumab doses (after stopping ipilimumab). The wide range shows high variability in the response and tolerability to nivolumab after ipilimumab was stopped. The MAH was asked to analyse the endpoints separately for patients receiving more nivolumab infusions, in order to explore the role of nivolumab in maintaining a response achieved with the combination. The limit was set at 4 additional nivolumab doses (similar to the median observed), after ipilimumab discontinuation. As expected, efficacy endpoints results were better in subjects receiving at least 4 additional nivolumab doses, which seems to confirm the benefit of maintaining treatment in patients who discontinue ipilimumab to prolong the response to treatment while controlling toxicity, known to be less with nivolumab monotherapy than with the combined treatment, although the recommendation is still continuous combination treatment until progression or unacceptable toxicity.

Supportive study – contribution of monocomponents

The results from the investigator-sponsored study MAPS2 were submitted to support the relative contribution of ipilimumab to nivolumab in the treatment of malignant MPM since study CA209743 did not include a comparator arm with nivolumab or ipilimumab monotherapy to show the additional benefit of the proposed combination strategy. In that supportive trial the addition of ipilimumab to nivolumab translated into improvement of ORR, PFS and OS, compared with nivolumab monotherapy. Also, a previous trial with a CTLA4 inhibitor (tremelimumab) failed to show superiority over placebo in the second line mesothelioma which suggests that anti CTLA4 monoclonal antibodies, like ipilimumab, might not be effective as monotherapy in the treatment of malignant mesothelioma. The proposed approach to address the contribution of monocomponents has obvious limitations, as it is based on cross study comparisons and data coming from a different line of therapy, however, it can be regarded as basically acceptable also considering that a gain in OS has been reported with the proposed combination therapy vs. current standard of care (reference is made to EMEA/H/C/WS1278).

2.4.4. Conclusions on the clinical efficacy

Data supporting this variation procedure are based on the results from Study CA209743, a phase III, open-label study, in which 605 MPM untreated patients were randomized to receive nivolumab+ipilimumab combination until progression or unacceptable toxicity or standard treatment with platinum-based chemotherapy for 6 cycles. Subjects were stratified by histology (epithelioid or non-epithelioid) and gender, known prognostic factors for MPM. The primary objective was to evaluate survival in this population and the primary endpoint was OS. The control arm is considered adequate, as platinum in combination with pemetrexed is established as the standard 1L treatment for MPM in all clinical guidelines.

The combination therapy showed an overall clinically relevant improvement in the ITT in OS of 4.0 months [HR = 0.74 (95% CI: 0.61, 0.89), stratified log-rank test p value=0.0020]. Median OS was 18.07 (95% CI: 16.82, 21.45) months and 14.09 (95% CI: 12.45, 16.23) months for nivo+ipi and chemotherapy, respectively. On the contrary, no improvement was observed for PFS and ORR, although some durable responses were identified, similar to what has been observed with immunotherapy treatment in other tumour types. This combination also showed an improved OS for both histologies included, which is remarkable for non-epithelioid MPM, traditionally associated to poor responses to chemotherapy. Indeed in non-epithelioid patients (n=133) the reported improvement in OS was larger compared to that reported in epithelioid patients (n=471), i.e. median OS of 8.80 (95% CI: 7.62, 11.76) months and of 16.23 (95% CI: 14.09, 19.15) months for the chemotherapy arm vs. 16.89 (95% CI: 11.83, 25.20) months and 18.73 (95% CI: 17.05, 21.72) for the nivo+ipi combination arm [HR = 0.46 (95% CI: 0.31, 0.70) vs. HR = 0.85 (95% CI: 0.68, 1.06)], respectively.

2.5. Clinical safety

Introduction

Primary safety data are from the **pivotal Study CA209743**, a Phase 3, randomized, open-label study of nivo+ipi versus chemotherapy (pemetrexed with cisplatin or carboplatin) in subjects with previously untreated unresectable MPM. Supportive safety results are also provided from the Intergroupe Francophone de Cancérologie Thoracique (IFCT)-Mesothelioma Avastin Cisplatin Pemetrexed Study 2 (IFCT-1501 MAPS2) study, an investigator-sponsored trial, to provide safety and tolerability data on nivolumab monotherapy and the combination of nivo+ipi in MPM. In addition, the frequency of adverse

events (AEs), immune-mediated AEs (IMAEs), and other events of special interest (OESIs) from nivo+ipi in CA209743 are assessed relative to those from nivo+ipi regimens studied in other tumour types: non-small cell lung cancer (NSCLC) study CA209227 Part 1 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q6W), renal cell carcinoma (RCC) study CA209214 and colorectal cancer (CRC) study CA209142 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W in both RCC and CRC studies).

The safety data are presented for nivo+ipi (N = 300) and chemotherapy (N = 284) treated subjects from the **pivotal study CA209743**. These data are based on the database lock (DBL) of 03-Apr-2020, with a minimum follow-up of 22.1 months for overall survival (OS). The safety analyses were conducted in all 584 treated subjects who received at least one dose of study drug.

Patient exposure

Based on the database lock of 03-Apr-2020, 584 subjects were treated (300 subjects in the nivo+ipi arm and 284 in the chemotherapy arm). The median duration of therapy was 5.55 months for the nivo+ipi arm and 3.48 months for the chemotherapy arm.

Patient disposition

Table 51 Subject Disposition - All Randomized, All Treated Subjects

Status (%)	Nivo+Ipi	Chemo	Total
RANDOMIZED	303	302	605
TREATED	300 (99.0)	284 (94.0)	584 (96.5)
NOT TREATED	3 (1.0)	18 (6.0)	21 (3.5)
REASON FOR NOT TREATED			
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	3 (1.0)	3 (0.5)
SUBJECT WITHDREW CONSENT	1 (0.3)	11 (3.6)	12 (2.0)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (0.7)	3 (1.0)	5 (0.8)
NOT REPORTED	0	1 (0.3)	1 (0.2)

Status (%)	Nivo+Ipi N = 300	Chemo N = 284	Total N = 584
CONTINUING IN THE TREATMENT PERIOD	5 (1.7)	0	5 (0.9)
NOT CONTINUING IN THE TREATMENT PERIOD	295 (98.3)	284 (100.0)	579 (99.1)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD			
DISEASE PROGRESSION	182 (60.7)	44 (15.5)	226 (38.7)
STUDY DRUG TOXICITY	59 (19.7)	24 (8.5)	83 (14.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	12 (4.0)	9 (3.2)	21 (3.6)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	4 (1.3)	10 (3.5)	14 (2.4)
SUBJECT WITHDREW CONSENT	6 (2.0)	3 (1.1)	9 (1.5)
LOST TO FOLLOW-UP	0	1 (0.4)	1 (0.2)
MAXIMUM CLINICAL BENEFIT	10 (3.3)	2 (0.7)	12 (2.1)
POOR/NON-COMPLIANCE	1 (0.3)	0	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	4 (1.3)	0	4 (0.7)
ADMINISTRATIVE REASON BY SPONSOR	2 (0.7)	0	2 (0.3)
OTHER [A]	11 (3.7)	2 (0.7)	13 (2.2)
NOT REPORTED [B]	4 (1.3)	189 (66.5)	193 (33.0)
CONTINUING IN THE STUDY	261 (87.0)	265 (93.3)	526 (90.1)
NOT CONTINUING IN THE STUDY	39 (13.0)	19 (6.7)	58 (9.9)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	24 (8.0)	10 (3.5)	34 (5.8)
SUBJECT WITHDREW CONSENT	11 (3.7)	6 (2.1)	17 (2.9)
LOST TO FOLLOW-UP	1 (0.3)	2 (0.7)	3 (0.5)
OTHER	3 (1.0)	1 (0.4)	4 (0.7)

Percentages based on subjects entering period.
[A] In the nivo+ipi arm, majority were due to completion of protocol specified 2-year treatment (Refer to Appendix 2.5 of the CA209743 Final CSR)
[B] Includes subjects who achieved maximum duration of therapy per protocol, i.e: Chemo: 6 cycles, Nivo+Ipi: 2 years

Out of the 189 chemotherapy-treated subjects with reason off treatment "not reported", 176 (93.1%) subjects did receive all 6 cycles (the maximum allowed duration of chemotherapy per protocol). The CRF did not have an option for treatment completion as reason for end of treatment.

A higher proportion of subjects in the nivo+ipi arm than in the chemotherapy arm discontinued study therapy due to study drug toxicity (19.7% vs 8.5%). These data should be evaluated taking into consideration the planned treatment duration for each regimen. 36 (61.0%) subjects in the nivo+ipi arm discontinued due to study drug toxicity after 3 months of treatment vs. 6 (25.0%) subjects in the chemotherapy arm (mDOT among those who discontinued due to study drug toxicity in nivo+ipi arm was 4.37 months [0.95, 9.95 interquartile range (IQR)] vs. 2.45 months [2.09, 2.99 IQR] in chemotherapy arm), although 22.0% of subjects in the nivo+ipi arm discontinued after 12 months of treatment.

Discontinuation due to study drug toxicity did not seem to impact overall survival based on an exploratory post-hoc analysis. In subjects who discontinued due to study drug toxicity, median OS was 24.64 (95% CI: 17.08, N.A.) months and 9.79 (95% CI: 7.72, 20.99) months for nivo+ipi and chemotherapy, respectively (HR = 0.47 [95% CI: 0.27, 0.81]). However, since the two regimens had different treatment duration, subjects in the nivo+ipi arm could discontinue later than subjects in the chemotherapy arm, and therefore, the mOS for these subjects could be artificially longer.

Ten subjects in the nivo+ipi arm and 2 subjects in the chemotherapy arm discontinued due to maximum clinical benefit which was defined by the Investigator. Of the 10 subjects in nivo+ipi arm, 9 subjects were discontinued for PR and 1 subject was discontinued for SD. The maximum number of cycles on nivo+ipi could be 18 (6 week/cycle over 2 years), and 4 subjects have received 2 years of treatment. Of the 2 subjects in the chemotherapy arm, both received 4 cycles of chemotherapy with a best response of SD.

Patient exposure

The maximum duration of treatment per protocol was 24 months for nivo+ipi, and 6 cycles of chemotherapy. A total of 300 subjects received at least 1 infusion of nivo+ipi, and 284 subjects received at least 1 infusion of chemotherapy. In this study, the proportion of subjects who received ≥ 90% of the planned dose intensity was as follows in each treatment arm:

- Nivo+ipi: 69.0% for nivolumab, 83.6% for ipilimumab
- Chemotherapy: 65.5% for pemetrexed, 77.9% for cisplatin, and 64.6% for carboplatin

The median number of doses received was as follows in each arm:

- Nivo+ipi: 12.0 doses for nivolumab, 4.0 doses for ipilimumab
- Chemotherapy: 6.0 doses for pemetrexed, 5.0 doses for cisplatin, and 6.0 doses for carboplatin

The median (95% CI) duration of therapy was 5.55 (4.63, 6.70) months for the nivo+ipi arm and 3.48 (N.A, N.A.) months for the chemotherapy arm.

Table 52: Cumulative Dose and Relative Dose Intensity - All Treated Subjects

	Nivolumab + Ipilimumab N = 300	
	Nivolumab N = 300	Ipilimumab N = 300
NUMBER OF DOSES RECEIVED		
MEAN (SD)	16.5 (14.5)	5.4 (4.6)
MEDIAN (MIN - MAX)	12.0 (1 - 55)	4.0 (1 - 19)
Q1, Q3	5.0, 23.5	2.0, 7.0
CUMULATIVE DOSE (UNIT) (A)		
MEAN (SD)	49.12 (43.07)	5.43 (4.67)

MEDIAN (MIN - MAX)	35.93 (2.9 - 165.4)	4.00 (1.0 - 21.0)
Q1, Q3	14.7, 69.7	2.0, 7.3
RELATIVE DOSE INTENSITY (%)		
>= 110%	1 (0.3)	4 (1.3)
90% TO < 110%	206 (68.7)	247 (82.3)
70% TO < 90%	77 (25.7)	43 (14.3)
50% TO < 70%	13 (4.3)	6 (2.0)
< 50%	3 (1.0)	0
NOT REPORTED	0	0

		Chemotherapy N = 284	
	Pemetrexed N = 284	Cisplatin N = 104	Carboplatin N = 209
NUMBER OF DOSES RECEIVED			
MEAN (SD)	5.1 (1.4)	4.3 (1.9)	4.8 (1.6)
MEDIAN (MIN - MAX)	6.0 (1 - 6)	5.0 (1 - 6)	6.0 (1 - 6)
Q1, Q3	4.0, 6.0	3.0, 6.0	4.0, 6.0
CUMULATIVE DOSE (UNIT) (A)			
MEAN (SD)	2403.89 (756.05)	377.07 (319.88)	23.20 (7.95)
MEDIAN (MIN - MAX)	2743.80 (83.8 - 3294.0)	375.56 (71.1 - 2442.4)	25.01 (4.9 - 35.9)
Q1, Q3	1997.3, 2997.6	221.9, 446.6	19.3, 29.7
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	8 (7.7)	10 (4.8)
90% TO < 110%	186 (65.5)	73 (70.2)	125 (59.8)
70% TO < 90%	73 (25.7)	20 (19.2)	65 (31.1)
50% TO < 70%	20 (7.0)	3 (2.9)	9 (4.3)
< 50%	4 (1.4)	0	0
NOT REPORTED	1 (0.4)	0	0

(A) Dose units: Nivolumab in mg/kg; Ipilimumab in mg/kg; Cisplatin and Pemetrexed in mg/m^2 and Carboplatin in AUC

Partial discontinuation

Subjects treated with nivolumab and ipilimumab could discontinue ipilimumab and continue to receive nivolumab (i.e. partial discontinuation); however, if nivolumab was discontinued, ipilimumab could not be continued alone as monotherapy.

In the nivo+ipi arm, 28 subjects (9.3%) discontinued ipilimumab early. Out of the 28 subjects, 64.3% discontinued ipilimumab due to adverse event and 35.7% discontinued for "other" reasons. Following ipilimumab discontinuation, subjects continued receiving nivolumab monotherapy for a median of 112.5 days (range 13-750 days).

Dose Delay, Dose Reductions, Infusion Interruptions and Infusion Rate Reductions of Study Therapy

Most treated subjects received all doses of study medication without infusion interruptions or infusion rate reductions; however, dose delays were common in both arms.

Dose delays of study drug (proportion of subjects with at least 1 dose delay) were reported as follows:

- Nivo+ipi: 55.0% for nivolumab and 44.3% for ipilimumab
- Chemotherapy: 29 - 39% of subjects experienced a delay in chemotherapy (pemetrexed, cisplatin, and/or carboplatin)

The primary reason for nivolumab delay was due to adverse events (55.2%); for ipilimumab, the primary reason was "not reported", which included adjustment of dosing schedule to resynchronize ipilimumab with nivolumab dosing (54.5%). The primary reason for dose delay in the chemotherapy arm was due to adverse events (68.6% pemetrexed, 58.5% cisplatin, 67.3% carboplatin).

Omitted Doses: Dose omissions were not permitted for nivolumab and ipilimumab. In the chemotherapy arm, 2 subjects missed 1 dose of pemetrexed and 1 dose of carboplatin due to adverse events.

Dose reductions were not permitted with nivolumab or ipilimumab treatment, but they were permitted with chemotherapy. Dose reductions of chemotherapy (proportion of subjects with at least 1 dose reduction) were reported as follows:

- Chemotherapy: 31.3% for pemetrexed, 17.3% for cisplatin, and 40.7% for carboplatin

Infusion interruptions: 6.7% and 1.3% of subjects had at least one infusion interruption during nivolumab or ipilimumab administration, respectively. Out of the nivolumab interruptions, 60.7% of occurrences were due to hypersensitivity reaction. For ipilimumab, the main reason for the few interruptions (4 occurrences) was due to "other" reasons (75.0%).

In the chemotherapy arm, infusion interruptions occurred infrequently during pemetrexed (0.4%) and carboplatin (1.4%) administration. 9.6% of subjects who received cisplatin experienced an infusion interruption, due to "other" reasons.

Infusion rate reductions: 9.0% and 2.3% of subjects required a reduction in nivolumab or ipilimumab infusion rate, respectively. When nivolumab or ipilimumab IV infusion rates were reduced, the primary reason was "other" (79.8% and 50.0%, respectively).

In the chemotherapy arm, few subjects required an infusion rate reduction. The highest incidence occurred with carboplatin (7.7%), mainly due to "other" reasons.

Switch from cisplatin to carboplatin: In the chemotherapy arm, 29 subjects switched from cisplatin to carboplatin at some point in the study.

Adverse events

Safety data are presented for nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg IV Q6W and of pemetrexed plus cisplatin or carboplatin chemotherapy (Table 53). The nivo+ipi regimen was administered for up to 24 months in the absence of disease progression or toxicity, whereas chemotherapy was limited to 6 cycles. The median duration of therapy and follow-up were longer in nivo+ipi arm than in chemotherapy arm.

Table 53: Summary of Safety - All Treated Subjects

	No. of Subjects (%)			
Safety Parameters	**Nivo + Ipi (N = 300)**		**Chemotherapy (N = 284)**	
Number of Subjects Who Died	198 (66.0)		212 (74.6)	
Within 30 days of last dose	28 (9.3)		14 (4.9)	
Within 100 days of last dose	55 (18.3)		50 (17.6)	
Primary Reason for Death				
Disease	183 (61.0)		199 (70.1)	
Study Drug Toxicity	3 (1.0)		1 (0.4)	
Unknown	3 (1.0)		2 (0.7)	
Other[a]	9 (3.0)		10 (3.5)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	164 (54.7)	103 (34.3)	72 (25.4)	54 (19.0)
Drug-related SAEs	64 (21.3)	46 (15.3)	22 (7.7)	17 (6.0)
All-causality AEs leading to DC	88 (29.3)	59 (19.7)	58 (20.4)	28 (9.9)
Drug-Related AEs leading to DC	69 (23.0)	45 (15.0)	45 (15.8)	21 (7.4)
All-causality AEs	299 (99.7)	159 (53.0)	277 (97.5)	121 (42.6)
Drug-related AEs	240 (80.0)	91 (30.3)	233 (82.0)	91 (32.0)
≥ 15% of Subjects in Any Treatment Group				
Diarrhoea	62 (20.7)	10 (3.3)	21 (7.4)	2 (0.7)
Pruritus	49 (16.3)	3 (1.0)	1 (0.4)	0
Fatigue	41 (13.7)	3 (1.0)	55 (19.4)	5 (1.8)
Nausea	30 (10.0)	1 (0.3)	104 (36.6)	7 (2.5)
Decreased appetite	29 (9.7)	2 (0.7)	50 (17.6)	2 (0.7)
Asthenia	25 (8.3)	0	44 (15.5)	12 (4.2)
Anaemia	6 (2.0)	1 (0.3)	102 (35.9)	32 (11.3)
Neutropenia	2 (0.7)	2 (0.7)	71 (25.0)	43 (15.1)
All-causality Select AEs				
Endocrine	62 (20.7)	6 (2.0)	7 (2.5)	1 (0.4)
Gastrointestinal	97 (32.3)	18 (6.0)	34 (12.0)	3 (1.1)
Hepatic	54 (18.0)	19 (6.3)	9 (3.2)	0
Pulmonary	26 (8.7)	6 (2.0)	2 (0.7)	1 (0.4)
Renal	33 (11.0)	6 (2.0)	25 (8.8)	3 (1.1)
Skin	136 (45.3)	11 (3.7)	42 (14.8)	1 (0.4)
Hypersensitivity/Infusion Reactions	37 (12.3)	4 (1.3)	7 (2.5)	0
Drug-Related Select AEs				
Endocrine	52 (17.3)	4 (1.3)	0	0
Gastrointestinal	66 (22.0)	16 (5.3)	23 (8.1)	3 (1.1)
Hepatic	36 (12.0)	16 (5.3)	6 (2.1)	0
Pulmonary	20 (6.7)	2 (0.7)	0	0
Renal	15 (5.0)	4 (1.3)	19 (6.7)	1 (0.4)
Skin	108 (36.0)	9 (3.0)	28 (9.9)	1 (0.4)
Hypersensitivity/Infusion Reactions	36 (12.0)	4 (1.3)	7 (2.5)	0

Table 53: Summary of Safety - All Treated Subjects

Safety Parameters	No. of Subjects (%) Nivo + Ipi (N = 300)		Chemotherapy (N = 284)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Diarrhea/Colitis	26 (8.7)	12 (4.0)	1 (0.4)	1 (0.4)
Hepatitis	18 (6.0)	14 (4.7)	0	0
Pneumonitis	20 (6.7)	6 (2.0)	0	0
Nephritis/Renal Dysfunction	8 (2.7)	5 (1.7)	0	0
Rash	39 (13.0)	8 (2.7)	3 (1.1)	0
Hypersensitivity/Infusion Reactions	5 (1.7)	1 (0.3)	0	0
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Adrenal Insufficiency	7 (2.3)	2 (0.7)	0	0
Hypophysitis	12 (4.0)	3 (1.0)	0	0
Hypothyroidism/Thyroiditis	35 (11.7)	0	1 (0.4)	0
Hyperthyroidism	11 (3.7)	0	1 (0.4)	0
Diabetes Mellitus	1 (0.3)	1 (0.3)	0	0
All-causality OESIs within 100 days of last dose				
With or Without Immune Modulating Medication				
Pancreatitis	4 (1.3)	1 (0.3)	0	0
Encephalitis	3 (1.0)	1 (0.3)	1 (0.4)	1 (0.4)
Myositis	2 (0.7)	2 (0.7)	0	0
Myasthenic Syndrome	2 (0.7)	2 (0.7)	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0
Uveitis	2 (0.7)	1 (0.3)	0	0
Myocarditis	1 (0.3)	1 (0.3)	0	0
Rhabdomyolysis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

MedDRA version 22.1; CTC version 4.0. Includes events reported between first dose and 30 days after the last dose of study drug, unless otherwise indicated.

Abbreviations: AEs - adverse events, DC - discontinuation, OESIs - other events of special interest, SAEs - serious adverse events

Common Adverse Events

The overall frequencies of any-grade all causality AEs and drug-related AEs were similar between the nivo+ipi and chemotherapy arms; the overall frequencies of Grade 3-4 all causality AEs were higher with nivo+ipi compared with chemotherapy (Table 53).

All-causality Adverse Events

Any-grade all-causality AEs were reported in 299 (99.7%) subjects in the nivo+ipi arm, and 277 (97.5%) subjects in the chemotherapy arm (Table 53 and Table 54).

The most frequently reported AEs (regardless of causality) were:

- Nivo+ipi: diarrhoea (31.3%), fatigue (28.7%), dyspnoea (26.0%), nausea (24.3%), and decreased appetite (23.7%).
- Chemotherapy: nausea (43.3%), anaemia (41.9%), constipation (29.6%), neutropenia (27.8%), fatigue (27.1%), and decreased appetite (25.4%).

Exposure adjusted AE incidence rates: When incidence rates were exposure-adjusted, AE incidence rates (per 100 person-years) were 1485.0 with nivo+ipi treatment and 2306.4 with chemotherapy treatment.

Grade 3-4 all-causality AEs were reported in 159 (53.0%) subjects in the nivo+ipi arm, and 121 (42.6%) subjects in the chemotherapy arm.

The most frequently reported Grade 3-4 AEs (regardless of causality) were:

- Nivo+ipi: increased lipase (5.3%), diarrhoea (4.0%), fatigue, increased amylase, and malignant neoplasm progression (3.0%, each)
- Chemotherapy: neutropenia (15.8%), anaemia (13.7%), asthenia (4.2%), thrombocytopenia (3.9%), and dyspnoea (3.2%)

Drug-related Adverse Events

Any-grade drug-related AEs were reported in 240 (80.0%) subjects in the nivo+ipi arm, and 233 (82.0%) subjects in the chemotherapy arm (Table 31).

The most frequently reported drug-related AEs were:

- Nivo+ipi: diarrhoea (20.7%), pruritus (16.3%), rash (14.3%), fatigue (13.7%), and hypothyroidism (10.7%).
- Chemotherapy: nausea (36.6%), anaemia (35.9%), neutropenia (25.0%), fatigue (19.4%), decreased appetite (17.6%), and asthenia (15.5%).

Exposure adjusted AE incidence rates: When incidence rates were exposure-adjusted, drug-related AE incidence rates (per 100 person-years) were 502.1 with nivo+ipi treatment and 1355.3 with chemotherapy treatment.

Grade 3-4 drug-related AEs were reported in 91 (30.3%) subjects in the nivo+ipi arm, and 91 (32.0%) subjects in the chemotherapy arm.

The most frequently reported Grade 3-4 drug-related AEs were:

- Nivo+ipi: increased lipase (4.3%), diarrhoea (3.3%), colitis (2.3%), and increased amylase (2.3%).
- Chemotherapy: neutropenia (15.1%), anaemia (11.3%), asthenia (4.2%), thrombocytopenia (3.5%), and nausea (2.5%).

Table 54: Adverse Events by Worst CTC Grade in ≥ 10% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 300			Chemotherapy N = 284		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	299 (99.7)	159 (53.0)	25 (8.3)	277 (97.5)	121 (42.6)	10 (3.5)
General disorders and administration site conditions	209 (69.7)	29 (9.7)	0	183 (64.4)	30 (10.6)	0
Fatigue	86 (28.7)	9 (3.0)	0	77 (27.1)	5 (1.8)	0
Pyrexia	55 (18.3)	4 (1.3)	0	13 (4.6)	2 (0.7)	0
Asthenia	49 (16.3)	4 (1.3)	0	57 (20.1)	12 (4.2)	0
Oedema peripheral	45 (15.0)	0	0	18 (6.3)	0	0
Non-cardiac chest pain	40 (13.3)	5 (1.7)	0	14 (4.9)	1 (0.4)	0
Gastrointestinal disorders	185 (61.7)	28 (9.3)	0	190 (66.9)	21 (7.4)	0
Diarrhoea	94 (31.3)	12 (4.0)	0	32 (11.3)	2 (0.7)	0
Nausea	73 (24.3)	2 (0.7)	0	123 (43.3)	7 (2.5)	0
Constipation	56 (18.7)	1 (0.3)	0	84 (29.6)	2 (0.7)	0
Vomiting	43 (14.3)	0	0	52 (18.3)	6 (2.1)	0
Abdominal pain	31 (10.3)	2 (0.7)	0	12 (4.2)	2 (0.7)	0
Respiratory, thoracic and mediastinal disorders	170 (56.7)	27 (9.0)	2 (0.7)	107 (37.7)	17 (6.0)	0
Dyspnoea	78 (26.0)	7 (2.3)	0	41 (14.4)	9 (3.2)	0
Cough	65 (21.7)	2 (0.7)	0	22 (7.7)	0	0
Skin and subcutaneous tissue disorders	154 (51.3)	12 (4.0)	0	64 (22.5)	1 (0.4)	0
Pruritus	62 (20.7)	3 (1.0)	0	4 (1.4)	0	0
Rash	60 (20.0)	3 (1.0)	0	21 (7.4)	0	0
Metabolism and nutrition disorders	122 (40.7)	22 (7.3)	1 (0.3)	112 (39.4)	21 (7.4)	0
Decreased appetite	71 (23.7)	3 (1.0)	0	72 (25.4)	4 (1.4)	0
Musculoskeletal and connective tissue disorders	117 (39.0)	13 (4.3)	0	39 (13.7)	2 (0.7)	0
Arthralgia	40 (13.3)	3 (1.0)	0	3 (1.1)	0	0
Blood and lymphatic system disorders	62 (20.7)	18 (6.0)	0	167 (58.8)	84 (29.6)	1 (0.4)
Anaemia	43 (14.3)	8 (2.7)	0	119 (41.9)	39 (13.7)	0
Neutropenia	5 (1.7)	3 (1.0)	0	79 (27.8)	45 (15.8)	0
Thrombocytopenia	3 (1.0)	2 (0.7)	0	31 (10.9)	11 (3.9)	0
Endocrine disorders	57 (19.0)	5 (1.7)	1 (0.3)	6 (2.1)	0	0
Hypothyroidism	38 (12.7)	0	0	3 (1.1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	42 (14.0)	12 (4.0)	19 (6.3)	18 (6.3)	5 (1.8)	8 (2.8)
Malignant neoplasm progression	32 (10.7)	9 (3.0)	19 (6.3)	14 (4.9)	5 (1.8)	8 (2.8)

Table 31: Drug-related Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 300			Chemotherapy N = 284		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	240 (80.0)	91 (30.3)	1 (0.3)	233 (82.0)	91 (32.0)	1 (0.4)
Skin and subcutaneous tissue disorders	116 (38.7)	10 (3.3)	0	38 (13.4)	1 (0.4)	0
Pruritus	49 (16.3)	3 (1.0)	0	1 (0.4)	0	0
Rash	43 (14.3)	3 (1.0)	0	15 (5.3)	0	0
Rash maculo-papular	16 (5.3)	1 (0.3)	0	2 (0.7)	0	0
Gastrointestinal disorders	101 (33.7)	17 (5.7)	0	146 (51.4)	15 (5.3)	0
Diarrhoea	62 (20.7)	10 (3.3)	0	21 (7.4)	2 (0.7)	0
Nausea	30 (10.0)	1 (0.3)	0	104 (36.6)	7 (2.5)	0
Constipation	12 (4.0)	0	0	42 (14.8)	1 (0.4)	0
Vomiting	8 (2.7)	0	0	41 (14.4)	6 (2.1)	0
General disorders and administration site conditions	89 (29.7)	3 (1.0)	0	118 (41.5)	19 (6.7)	0
Fatigue	41 (13.7)	3 (1.0)	0	55 (19.4)	5 (1.8)	0
Asthenia	25 (8.3)	0	0	44 (15.5)	12 (4.2)	0
Pyrexia	16 (5.3)	0	0	5 (1.8)	1 (0.4)	0
Investigations	60 (20.0)	22 (7.3)	0	41 (14.4)	4 (1.4)	0
Lipase increased	20 (6.7)	13 (4.3)	0	1 (0.4)	1 (0.4)	0
Amylase increased	17 (5.7)	7 (2.3)	0	1 (0.4)	0	0
Alanine aminotransferase increased	16 (5.3)	5 (1.7)	0	2 (0.7)	0	0
Endocrine disorders	51 (17.0)	5 (1.7)	0	1 (0.4)	0	0
Hypothyroidism	32 (10.7)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	44 (14.7)	6 (2.0)	0	4 (1.4)	0	0
Arthralgia	22 (7.3)	1 (0.3)	0	0	0	0
Myalgia	15 (5.0)	0	0	3 (1.1)	0	0
Metabolism and nutrition disorders	37 (12.3)	7 (2.3)	0	65 (22.9)	7 (2.5)	0
Decreased appetite	29 (9.7)	2 (0.7)	0	50 (17.6)	2 (0.7)	0
Injury, poisoning and procedural complications	26 (8.7)	3 (1.0)	0	2 (0.7)	0	0
Infusion related reaction	24 (8.0)	3 (1.0)	0	2 (0.7)	0	0
Nervous system disorders	22 (7.3)	6 (2.0)	0	44 (15.5)	2 (0.7)	0
Dysgeusia	3 (1.0)	0	0	19 (6.7)	0	0
Blood and lymphatic system disorders	17 (5.7)	6 (2.0)	0	140 (49.3)	75 (26.4)	1 (0.4)
Anaemia	6 (2.0)	1 (0.3)	0	102 (35.9)	32 (11.3)	0
Neutropenia	2 (0.7)	2 (0.7)	0	71 (25.0)	43 (15.1)	0
Thrombocytopenia	2 (0.7)	2 (0.7)	0	26 (9.2)	10 (3.5)	0
Leukopenia	0	0	0	22 (7.7)	8 (2.8)	0

Adverse Events by Standardized MedDRA Query (SMQ)

The number of subjects in CA209743 with at least 1 AE per individual SMQ occurring up to 30 days after last dose was analyzed by treatment arm using both broad scope and narrow scope SMQs. Results of these analyses did not lead to the identification of new types of clinically important events (data not shown)

Serious adverse event/deaths/other significant events

Deaths

Table 55 - Death Summary - All Treated Subjects

	Nivolumab + Ipilimumab N = 300	Chemotherapy N = 284
NUMBER OF SUBJECTS WHO DIED (%)	198 (66.0)	212 (74.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	183 (61.0)	199 (70.1)
STUDY DRUG TOXICITY	3 (1.0)	1 (0.4)
UNKNOWN	3 (1.0)	2 (0.7)
OTHER [A]	9 (3.0)	10 (3.5)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	28 (9.3)	14 (4.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	23 (7.7)	10 (3.5)
STUDY DRUG TOXICITY	0	1 (0.4)

UNKNOWN	0	0
OTHER	5 (1.7)	3 (1.1)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	55 (18.3)	50 (17.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	48 (16.0)	43 (15.1)
STUDY DRUG TOXICITY	2 (0.7)	1 (0.4)
UNKNOWN	0	0
OTHER	5 (1.7)	6 (2.1)

Deaths Attributed to Study Drug Toxicity

Three (1.0%) subjects in the nivo+ipi arm and 1 (0.4%) subject in the chemotherapy arm died due to study drug toxicity (Table 56).

Table 56: Study Drug Toxicity Deaths - All Treated Subjects

Subject ID (Age/Gender/Race)	Randomization Date	First Dose Date	Last Dose Date	Death Date	Days Since Last Dose	Cause of Death (AE/SAE)
Nivolumab + Ipilimumab						
CA209743-xx-xxx Case 1(72/M/C)	14AUG2017	15AUG2017	12SEP2017	04NOV2017	54	PNEUMONITIS
CA209743-xx-xxx Case 2 (70/M/C)	21AUG2017	22AUG2017	24JAN2018	16JUL2018	174	TOXICITY OF IMMUNOTHERAPY AND DEVELOPMENT OF NEUROLOGICAL COMPLICATIONS
CA209743-xx-xxx case 3 (66/F/C)	06FEB2018	07FEB2018	07MAR2019	21APR2019	46	ACUTE HEART FAILURE
Chemotherapy						
CA209743-xx-xxx (64/F/C)	21NOV2017	23NOV2017	01FEB2018	14FEB2018	14	MYELOSUPPRESSION DUE TO DRUGS AND SALMONELLA SEPSIS

Deaths Attributed to Other Reasons

Deaths attributed to other reasons were reported in 3.0% of treated subjects in the nivo+ipi arm and 3.5% of treated subjects in the chemotherapy arm (Table 53). The verbatim terms reported for the 'other' reasons for death in treated subjects are provided in (Table 57). These verbatim terms were consistent with events expected in the population under study.

Table 57 - Verbatim Terms for Deaths Attributed to "Other" - All Treated Subjects

Nivolumab+Ipilimumab		Chemotherapy	
Subject ID	**Verbatim Term**	**Subject ID**	**Verbatim Term**
CA209743-Case 1xx-xxx	sepsis	CA209743-case 6xx-xxx	unclear if the death is due to the known cardiac disease, the malignancy or a combination of both
CA209743-case 2xx-xxx	pulmonary thromboembolism with outcome in death	CA209743-case 7xx-xxx	pneumonia
CA209743-case 3xx-xxx	heart attack	CA209743-case 8xx-xxx	NSCLC
CA209743-case 4xx-xxx	worsening of general condition	CA209743-case 9xx-xxx	S400 SAE death induced by septic shock
CA209743- case 5xx-xxx	bronchitis	CA209743-case 10xx-xxx	self murder
CA209743-case 1xx-xxx	bronchopneumonia	CA209743-case 5xx-xxx	aspiration pneumonia after another stroke

Table 57 - Verbatim Terms for Deaths Attributed to "Other" - All Treated Subjects

Nivolumab+Ipilimumab		Chemotherapy	
Subject ID	Verbatim Term	Subject ID	Verbatim Term
CA209743-case2xx-xxx	sepsis	CA209743-case 6xx-xxx	acute myeloid leukemia discovered in December 2019
CA209743-case 3xx-xxx	superior vena cava syndrome	CA209743-case 7xx-xxx	sepsis
CA209743-case 4xx-xxx	acute respiratory failure	CA209743-case 8xx-xxx	acute myocardial infarction
		CA209743-case 9xx-xxx	acute respiratory insufficiency

Serious Adverse Events

The overall frequencies of SAEs (all-causality and drug-related) were higher in the nivo+ipi arm than in the chemotherapy arm (Table 53).

A higher frequency of drug-related SAEs with nivo+ipi relative to chemotherapy were reported in the following SOCs: GI disorders (5.3% vs 1.4%), hepatobiliary disorders (3.7% vs 0%), renal and urinary disorders (3.0% vs 0%), endocrine disorders (2.7% vs 0%), respiratory disorders (2.3% vs 0%), and injury, poisoning and procedural complications (2.0% vs 0%).

Any-grade all-causality SAEs were reported in 164 (54.7%) subjects in the nivo+ipi arm vs 72 (25.4%) subjects in the chemotherapy arm. Grade 3-4 SAEs were reported in 103 (34.3%) subjects in the nivo+ipi arm and 54 (19.0%) subjects in the chemotherapy arm (Table 57).

The most frequently reported all-causality SAEs were:

- Nivo+ipi: malignant neoplasm progression (10.7%), pyrexia (4.3%), pneumonia (3.7%), pleural effusion (3.0%), and colitis (3.0%).
- Chemotherapy: malignant neoplasm progression (4.6%), anaemia (2.8%), and dyspnoea (2.1%).

Any-grade drug-related SAEs were reported in 64 (21.3%) subjects in the nivo+ipi arm, and 22 (7.7%) subjects in the chemotherapy arm. Grade 3-4 drug-related SAEs were reported in 46 (15.3%) subjects in the nivo+ipi arm, and 17 (6.0%) subjects in the chemotherapy arm.

The most frequently reported drug-related SAEs were:

- Nivo+ipi: colitis (3.0%), infusion related reaction (2.0%), abnormal hepatic function, acute kidney injury, and pneumonitis (1.7%, each).
- Chemotherapy: anaemia (2.1%), febrile neutropenia (1.1%), and pancytopenia (1.1%).

Table 57 - Most Frequently Reported (in ≥ 2%) Serious Adverse Events - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab + Ipilimumab N = 300			Chemotherapy N = 284		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	164 (54.7)	103 (34.3)	25 (8.3)	72 (25.4)	54 (19.0)	10 (3.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38 (12.7)	11 (3.7)	19 (6.3)	13 (4.6)	5 (1.8)	8 (2.8)
Malignant neoplasm progression	32 (10.7)	9 (3.0)	19 (6.3)	13 (4.6)	5 (1.8)	8 (2.8)
Respiratory, thoracic and mediastinal disorders	35 (11.7)	17 (5.7)	2 (0.7)	14 (4.9)	12 (4.2)	0
Pleural effusion	9 (3.0)	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)	0
Pneumonitis	7 (2.3)	2 (0.7)	0	0	0	0
Dyspnoea	5 (1.7)	3 (1.0)	0	6 (2.1)	5 (1.8)	0
Infections and infestations	30 (10.0)	21 (7.0)	2 (0.7)	12 (4.2)	11 (3.9)	0
Pneumonia	11 (3.7)	8 (2.7)	0	5 (1.8)	5 (1.8)	0
Gastrointestinal disorders	28 (9.3)	18 (6.0)	0	9 (3.2)	6 (2.1)	0
Colitis	9 (3.0)	7 (2.3)	0	0	0	0
Diarrhoea	6 (2.0)	4 (1.3)	0	1 (0.4)	0	0
General disorders and administration site conditions	25 (8.3)	13 (4.3)	0	13 (4.6)	11 (3.9)	0
Pyrexia	13 (4.3)	3 (1.0)	0	2 (0.7)	2 (0.7)	0
Renal and urinary disorders	13 (4.3)	7 (2.3)	0	2 (0.7)	1 (0.4)	0
Acute kidney injury	7 (2.3)	5 (1.7)	0	1 (0.4)	0	0
Injury, poisoning and procedural complications	10 (3.3)	6 (2.0)	0	3 (1.1)	2 (0.7)	0
Infusion related reaction	7 (2.3)	4 (1.3)	0	0	0	0
Blood and lymphatic system disorders	7 (2.3)	5 (1.7)	0	15 (5.3)	11 (3.9)	1 (0.4)
Anaemia	5 (1.7)	3 (1.0)	0	8 (2.8)	5 (1.8)	0

Exposure-adjusted Adverse Events Rates

The overall frequencies of all-causality and drug-related SAEs and AEs leading to discontinuation were higher with nivo+ipi than with chemotherapy. However, when incidence rates were exposure-adjusted (analyses accounting for multiple occurrences of adverse events and total exposure time to study treatment in each arm), the overall rates of all-causality and drug-related SAEs in the nivo+ipi arm were comparable to the incidence rates in the chemotherapy arm (Table 58). In contrast, the exposure adjusted incidence rates of all-causality and drug-related AEs leading to discontinuation were higher in the chemotherapy arm relative to the nivo+ipi arm (Table 58).

Table 58 - Exposure Adjusted Adverse Event Rates for All Nivolumab + Ipilimumab and Chemotherapy Treated Subjects - CA209743

	Exposure Adjusted Rates per 100 person-years	
Safety Parameters	**Nivo+Ipi (N = 300) Total person-years of exposure: 220.3**	**Chemotherapy (N = 284) Total person-years of exposure: 94.5**
Serious Adverse Events (SAEs)	139.4	123.8
Drug-Related SAEs	39.5	40.2
Adverse Events (AEs) Leading to Discontinuation	47.7	76.2
Drug-Related AEs Leading to Discontinuation	37.7	59.2
All AEs	1485.0	2306.4
Drug-Related AEs	502.1	1355.3

Select Adverse Events

The majority of select AEs were Grade 1-2 and most were considered drug-related by the investigator. The most frequently reported drug-related select AE categories (any grade) were as follows in each treatment arm (Table 53):

- Nivo+ipi: skin (36.0%), gastrointestinal (22.0%), hepatic and hypersensitivity/infusion reaction (12.0% each)
- Chemotherapy: skin (9.9%), gastrointestinal (8.1%), renal (6.7%)

The most frequently reported drug-related select AEs by preferred term (any grade) were as follows in each treatment arm:

- Nivo+ipi: diarrhoea (20.7%), pruritus (16.3%), rash (14.3%), hypothyroidism (10.7%), and infusion related reaction (8.0%)
- Chemotherapy: diarrhoea (7.4%), rash (5.3%), blood creatinine increased (4.9%), erythema (1.8%), and hypersensitivity (1.8%)

The most frequently reported drug-related serious select AEs by PT (any grade) were as follows in each treatment arm:

- Nivo+ipi: colitis (3.0%), infusion related reaction (2.0%), pneumonitis (1.7%), and acute kidney injury (1.7%)
- Chemotherapy: diarrhoea (0.4%)

Across the select AE categories, the majority of events in the nivo+ipi arm were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic corticosteroids) were administered (Table 59). Except for endocrine events, most drug-related select AEs with nivo+ipi had resolved (ranging from 66.4% to 94.4% across categories) at the time of database lock. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 59 - Onset, Management, and Resolution of Drug-Related Select AEs - Nivolumab + Ipilimumab Treated Subjects (N = 300)

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids a	Median Timeb to Resolution of Drug-related Select AE (range), wks c,d,e	% Subj. with Drug-related Select AE that Resolved
Endocrine	17.3 / 1.3	12.07 (2.0 - 90.3)	0.3	34.6 / 9.6	N.A. (0.3 - 144.1+)	32.7
Gastrointestinal	22.0 / 5.3	16.86 (0.1 - 94.3)	5.0	36.4 / 33.3	3.14 (0.1 - 100.0+)	93.9
Hepatic	12.0 / 5.3	7.93 (2.0 - 88.1)	3.7	47.2 / 41.7	4.14 (1.0 - 78.3+)	86.1
Pulmonary	6.7 / 0.7	7.64 (1.1 - 90.3)	2.3	85.0 / 70.0	6.14 (1.1 - 113.1+)	80.0
Renal	5.0 / 1.3	15.71 (2.1 - 62.6)	1.3	53.3 / 40.0	6.14 (0.9 - 126.4+)	80.0
Skin	36.0 / 3.0	6.86 (0.1 - 97.1)	0.7	41.7 / 8.3	12.14 (0.4 - 146.4+)	66.4
Hypersensitivity/ Infusion Reaction	12.0 / 1.3	2.14 (0.1 - 51.6)	1.7	27.8 / 16.7	0.14 (0.1 - 106.4+)	94.4

[a] Denominator is based on the number of subjects who experienced the event

[b] From Kaplan-Meier estimation.

[c] + indicates a censored value.

[d] Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.
[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

Abbreviations: AE - adverse event, DC - discontinuation, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Immune-mediated Adverse Events

IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (ie, with extended follow-up). These analyses occurred on subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate etiology and an immune mediated component.

Overall, the majority of IMAEs were Grade 1-2 (Table 53). The most frequently reported IMAEs (any grade) were as follows in each treatment arm (Table 54).

- Nivo+ipi: rash (13.0%), hypothyroidism/thyroiditis (11.7%), diarrhoea/colitis (8.7%), and pneumonitis (6.7%)
- Chemotherapy: rash (1.1%)

Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered (Table 60). Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy (Table 60).

Re-challenge information was also summarized for subjects who continued to receive nivolumab treatment after the onset of an IMAE (Table 60). A re-challenge was considered as an unsuccessful or positive re-challenge if, after resolution of the IMAE, a new IMAE of the same type occurred with re-treatment. A re-challenge was considered as a successful or negative re-challenge if, after resolution of the IMAE, no new IMAEs of the same type occurred with re-treatment.

Table 60 - Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - Nivolumab + Ipilimumab Treated Subjects (N =300)

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids [a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE	Median [b] Time to Resolution (range), wks [c,d,e]	% Subj. with Recurrence after Reinitiation
Pneumonitis	6.7 / 2.0	10.14 (1.9 - 90.3)	3.0 / 3.3	100 / 80.0	12.86 (1.1 - 82.4)	65.0	17.14 (1.3 - 113.1+)	11.1 (1 / 9)
Diarrhea/Colitis	8.7 / 4.0	26.71 (1.3 - 99.6)	3.7 / 4.3	100 / 84.6	6.21 (0.4 - 50.7)	92.3	3.71 (0.4 - 63.3+)	6.7 (1 / 15)
Hepatitis	6.0 / 4.7	8.79 (2.0 - 72.0)	4.3 / 2.7	100 / 88.9	10.50 (0.1 - 61.0)	88.9	4.71 (1.0 - 35.1)	0 (0 / 8)
Nephritis/Renal Dysfunction	2.7 / 1.7	18.50 (3.3 - 46.1)	1.0 / 2.3	100 / 62.5	9.07 (2.3 - 40.4)	50.0	N.A. (0.9 - 126.4+)	0 (0 / 8)
Rash	13.0 / 2.7	11.00 (0.4 - 82.3)	0 / 2.7	100 / 23.1	10.71 (0.4 - 122.0)	61.5	17.00 (1.3 - 131.9+)	2.9 (1 / 35)
Hypersensitivity	1.7 / 0.3	2.14 (2.1 - 8.0)	0.3 / 0	100 / 60.0	0.14 (0.1 - 4.7)	100	0.14 (0.1 - 8.1)	0 (0 / 4)
Adrenal Insufficiency	2.3 / 0.7	26.00 (17.6 - 53.7)	0.7 / 1.0	85.7 / 28.6	47.14 (0.9 - 70.7)	42.9	N.A. (1.1 - 108.7+)	0 (0 / 6)
Hypophysitis	4.0 / 1.0	22.79 (2.1 - 47.6)	0 / 2.7	100 / 33.3	57.93 (2.4 - 142.9)	25.0	N.A. (0.7 - 144.1+)	0 (0 / 12)
Hypothyroidism/Thyroiditis	11.7 / 0	14.00 (4.3 - 90.3)	0 / 1.3	5.7 / 0	37.29 (19.1 - 55.4)	25.7	N.A. (2.1 - 129.9+)	0 (0 / 34)
Hyperthyroidism	3.7 / 0	6.14 (2.0 - 24.0)	0 / 0.7	9.1 / 0	6.00 (6.0 - 6.0)	90.9	5.43 (0.3 - 130.4+)	0 (0 / 9)
Diabetes Mellitus	0.3 / 0.3	56.86 (56.9 - 56.9)	0 / 0	0 / 0	N.A.	100	0.71 (0.7 - 0.7)	0 (0 / 1)

[a] Denominator is based on the number of subjects who experienced the event

[b] From Kaplan-Meier estimation.

[c] + indicates a censored value.

[d] Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

Abbreviations: AE - adverse event, DC - discontinuation, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Other Events of Special Interest

Other events of special interest (OESIs) (regardless of causality or IMM treatment) with extended follow-up are summarized by category in Table 53.

OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent in both treatment arms (Table 53). Overall, OESIs were reported in 14 (4.7%) subjects in the nivo+ipi arm and 1 (0.4%) subject in the chemotherapy arm.

12/14 OESIs in the nivo+ipi arm and 1/1 OESIs in the chemotherapy arm were resolved at the time of database lock. 12/14 and 1/1 events had resolved with IMM treatment in the nivo+ipi and chemotherapy arms, respectively.

Adverse Drug Reactions (ADRs)

For labeling purposes, some MedDRA PTs were re-mapped or deleted. Re-mapping allowed for pooling of PTs representing the same or similar clinical conditions. Some MedDRA PTs were deleted from the tables

generated to support the product information because they were overly general/non-specific. The summary table of AEs with re-mapped MedDRA PTs was used to identify ADRs for both the USPI and the SmPC.

Description of selected adverse reactions

Immune related pneumonitis: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of pneumonitis including interstitial lung disease was 6.7% (20/300). Grade 2 and Grade 3 cases were reported in 5.3% (16/300) and 0.7% (2/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.3-20.8). Resolution occurred in 16 patients (80%) with a median time to resolution of 6.1 weeks (range: 1.1-113.1).

Immune related colitis: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of diarrhoea or colitis was 22.0% (66/300). Grade 2 and Grade 3 cases were reported in 7.3% (22/300) and 5.3% (16/300) of patients, respectively. Median time to onset was 3.9 months (range: 0.0-21.7). Resolution occurred in 62 patients (93.9%) with a median time to resolution of 3.1 weeks (range: 0.1 100.0+).

Immune related hepatitis: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of liver function test abnormalities was 12.0% (36/300). Grade 2, Grade 3, and Grade 4 cases were reported in 1.7% (5/300), 4.3% (13/300), and 1.0% (3/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.5-20.3). Resolution occurred in 31 patients (86.1%) with a median time to resolution of 4.1 weeks (range: 1.0-78.3)

Immune related nephritis and renal dysfunction: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of renal dysfunction was 5.0% (15/300). Grade 2 and Grade 3 cases were reported in 2.0% (6/300) and 1.3% (4/300) of patients, respectively. Median time to onset was 3.6 months (range: 0.5-14.4). Resolution occurred in 12 patients (80.0%) with a median time to resolution of 6.1 weeks (range: 0.9-126.4).

Immune related endocrinopathies: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of thyroid disorders was 14% (43/300). Grade 2 and Grade 3 thyroid disorders were reported in 9.3% (28/300) and 1.3% (4/300) of patients, respectively. Hypophysitis occurred in 2% (6/300) of patients. Grade 2 cases were reported in 1.3% (4/300) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 1.0% (3/300) and 1.0% (3/300) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (5/300) and 0.3% (1/300) of patients, respectively. Median time to onset of these endocrinopathies was 2.8 months (range: 0.5-20.8). Resolution occurred in 17 patients (32.7%). Time to resolution ranged from 0.3 to 144.1 weeks.

Immune related skin adverse reactions: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of rash was 36.0% (108/300). Grade 2 and Grade 3 cases were reported in 10.3% (31/300) and 3.0% (9/300) of patients, respectively. Median time to onset was 1.6 months (range: 0.0-22.3). Resolution occurred in 71 patients (66.4%) with a median time to resolution of 12.1 weeks (range: 0.4-146.4).

Infusion reactions: In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of hypersensitivity/infusion reactions was 12% (36/300); Grade 2 and Grade 3 cases were reported in 5.0% (15/300) and 1.3% (4/300) of patients, respectively.

Laboratory findings

Laboratory results that were recorded regardless of causality and reported after first dose and within 30 days of last dose of study therapy are presented in the sections below for all subjects treated with nivo+ipi or chemotherapy in CA209743.

Haematology

Abnormalities in hematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2. Grade 3 or 4 hematologic abnormalities reported in ≥ 5% of subjects were as follows:

- Nivo+ipi: absolute lymphocyte count (8.1% Grade 3)
- Chemotherapy: hemoglobin (14.5% Grade 3), absolute lymphocyte count (13.4% Grade 3), and ANC (8.0% Grade 3)

On-treatment worsening of hematology parameters to Grade 3-4 was higher in the chemotherapy arm vs nivo+ipi arm (Table 61).

Table 61: Summary of On-Treatment Worst CTC Grade Hematology Tests That Worsened Relative to Baseline (SI Units) - All Treated Subjects

	Number of Subjects (%)					
	Nivo+ipi			Chemotherapy		
Lab Test Description	N(A)	Grade 1–4	Grade 3–4	N(A)	Grade 1–4	Grade 3–4
HEMOGLOBIN (B)	297	127 (42.8)	7 (2.4)	276	208 (75.4)	40 (14.5)
LEUKOCYTES	297	24 (8.1)	3 (1.0)	278	142 (51.1)	20 (7.2)
LYMPHOCYTES (ABSOLUTE),	296	128 (43.2)	25 (8.4)	276	158 (57.2)	38 (13.8)
ABSOLUTE NEUTROPHIL COUNT	297	16 (5.4)	4 (1.3)	276	131 (47.5)	34 (12.3)
PLATELET COUNT	296	26 (8.8)	3 (1.0)	277	56 (20.2)	13 (4.7)

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.

Serum Chemistry

Liver Tests

Generally, there was a higher frequency of AST and ALT elevations in the nivo+ipi arm relative to the chemotherapy arm. Most on-treatment liver tests were Grade 1-2.

A total of 3/295 (1.0%) and 4/295 (1.4%) subjects in the nivo+ipi arm and no subjects in the chemotherapy arm had concurrent alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN with total bilirubin > 2 × ULN within 1 day and within 30 days based on laboratory results reported after the first dose and within 30 days of last dose of study therapy (Table 62 [SI]).

Table 62: On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects

Abnormality (%)	Nivo+Ipi N = 300	Chemo N = 284	Total N = 584
	N = 295	N = 275	N = 570
ALT OR AST > 3XULN	34 (11.5)	8 (2.9)	42 (7.4)
ALT OR AST > 5XULN	24 (8.1)	1 (0.4)	25 (4.4)
ALT OR AST > 10XULN	15 (5.1)	0	15 (2.6)
ALT OR AST > 20XULN	7 (2.4)	0	7 (1.2)
	N = 295	N = 275	N = 570
TOTAL BILIRUBIN > 2XULN	7 (2.4)	0	7 (1.2)
	N = 295	N = 275	N = 570
ALP > 1.5XULN	65 (22.0)	25 (9.1)	90 (15.8)
	N = 295	N = 275	N = 570
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	6 (2.0)	0	6 (1.1)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	7 (2.4)	0	7 (1.2)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	3 (1.0)	0	3 (0.5)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	4 (1.4)	0	4 (0.7)

1. Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
2. Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter

The majority of subjects did not have liver function tests that worsened relative to baseline. The following hepatic abnormalities worsened to Grade 3-4 relative to baseline in ≥ 1% of subjects (Table 63).

- Nivo+ipi: increased ALT (7.1%), increased AST (7.1%), increased alkaline phosphatase (ALP) (3.1%), and increased bilirubin (1.7%)
- Chemotherapy: none

Table 63: Summary of On-Treatment Worst CTC Grade Liver Function Tests that Worsened Relative to Baseline (SI Units) - All Treated Subjects

	Number of Subjects (%)					
	Nivo+ipi			Chemotherapy		
Lab Test Description	N(A)	Grade 1-4	Grade 3-4	N(A)	Grade 1-4	Grade 3-4
ALANINE AMINOTRANSFERASE	295	108 (36.6)	21 (7.1)	275	42 (15.3)	1 (0.4)
ALKALINE PHOSPHATASE	295	91 (30.8)	9 (3.1)	275	32 (11.6)	0
ASPARTATE AMINOTRANSFERASE	294	111 (37.8)	21 (7.1)	273	45 (16.5)	0
BILIRUBIN, TOTAL	295	29 (9.8)	5 (1.7)	275	2 (0.7)	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.

Kidney Function Tests

Most subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period.

The abnormalities in creatinine (increase) were primarily reported as Grade 1 or 2. 1 subject in the nivo+ipi arm and 1 subject in the chemotherapy arm had a Grade 3-4 increased creatinine level.

The majority of subjects did not have creatinine that worsened relative to baseline. The proportions of subjects with creatinine level worsening to Grade 3-4 relative to baseline were 0.3% and 0.4% in the nivo+ipi and chemotherapy arms, respectively.

Thyroid Function Tests

Generally, there was a higher frequency of abnormal thyroid function test results in the nivo+ipi arm relative to the chemotherapy arm. Increases in TSH (>ULN) from baseline (≤ULN) were reported in 26.4% subjects in the nivo+ipi arm and 7.5% subjects in the chemotherapy arm. Decreases in TSH (< LLN) from baseline (≥LLN) were reported in 20.3% subjects in the nivo+ipi arm and 2.0% subjects in the chemotherapy arm (Table 64).

Table 64: On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects

Abnormality (%)	Nivo+Ipi N = 276	Chemo N = 255	Total N = 531
TSH > ULN	95 (34.4)	33 (12.9)	128 (24.1)
TSH > ULN WITH TSH <= ULN AT BASELINE	73 (26.4)	19 (7.5)	92 (17.3)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	47 (17.0)	4 (1.6)	51 (9.6)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	39 (14.1)	22 (8.6)	61 (11.5)
WITH FT3/FT4 TEST MISSING (A) (B)	9 (3.3)	7 (2.7)	16 (3.0)
TSH < LLN	61 (22.1)	12 (4.7)	73 (13.7)
TSH < LLN WITH TSH >= LLN AT BASELINE	56 (20.3)	5 (2.0)	61 (11.5)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	32 (11.6)	2 (0.8)	34 (6.4)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	24 (8.7)	8 (3.1)	32 (6.0)
WITH FT3/FT4 TEST MISSING (A) (B)	5 (1.8)	2 (0.8)	7 (1.3)

3. Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

4. (A) Within a 2-week window after the abnormal TSH test date.

5. (B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Pancreas Function Tests

Amylase and lipase were assessed periodically during treatment and within 30 days of last dose. Most abnormalities were Grade 1-2. Grade 3-4 abnormalities reported in ≥ 5% of treated subjects with on-treatment laboratory results were Grade 3 lipase (8.4%) in the nivo+ipi arm.

The majority of subjects did not have on-treatment worsening (increases) in amylase or lipase. The proportions of subjects with amylase and lipase worsened to Grade 3-4 relative to baseline were higher in the nivo+ipi arm than in the chemotherapy arm:

Nivo+ipi: lipase (12.8%) and amylase (5.4%)

Chemotherapy: lipase (0.8%) and amylase (0.9%)

Electrolytes

Most subjects had normal electrolyte levels during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. The following Grade 3 abnormalities in electrolytes were observed in ≥ 5% of treated subjects with on-treatment laboratory results:

- Nivo+ipi: hyponatremia (8.8% Grade 3)

Chemotherapy: none

The majority of subjects did not have electrolyte levels that worsened relative to baseline. The following electrolyte abnormalities worsened to Grade 3-4 relative to baseline in ≥ 2% of subjects:

Nivo+ipi: hyponatremia (8.1%), hyperkalemia (4.1%), hyperglycemia (2.8%), and hypokalemia (2.0%)

Chemotherapy: hyponatremia (2.9%)

Selected Laboratory Abnormalities that Worsened Relative to Baseline

In CA209743, laboratory abnormalities that worsened relative to baseline in ≥ 15% of nivo+ipi treated subjects are presented in Table 65 below.

Table 65: Selected Laboratory Abnormalities (US Units) Worsening from Baseline in ≥ 15% of Nivolumab + Ipilimumab Treated Subjects

Laboratory Abnormality	Percentage of Subjects with Worsening Laboratory Test from Baseline[a]			
	Niv+ipi		Chemotherapy	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Lymphopenia	43.2	8.4	57.2	13.8
Anemia	42.8	2.4	75.4	14.5
Chemistry				
Hyperglycemia	53.2	3.7	34.4	1.1
Increased AST	37.8	7.1	16.5	0
Increased ALT	36.6	7.1	15.3	0.4
Increased lipase	34.2	12.8	9.2	0.8
Hyponatremia	31.8	8.1	21.0	2.9
Increased alkaline phosphatase	30.8	3.1	11.6	0
Hyperkalemia	29.7	4.1	16.4	0.7
Hypocalcemia	27.9	0	16.2	0
Increased amylase	26.3	5.4	13.2	0.9
Increased creatinine	20.4	0.3	20.3	0.4
Hypomagnesemia	15.7	0	27.6	0.4

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Nivo+ ipi (range: 109 to 297 subjects); chemotherapy (range: 90 to 278 subjects).

Safety in special populations

Intrinsic and Extrinsic Factors

The frequencies of all-causality and drug-related AEs in the nivo+ipi arm for the subgroup of gender were similar to the AE frequencies reported for the overall study populations by treatment. For subgroups based on race, most participants were clustered in a single category (White). Very low sample sizes in other categories of race limit the interpretability of potential differences.

For subgroups based on age, no overall difference in AEs (all-causality) was reported in older subjects (≥ 65 and < 75, ≥ 75 and < 85, and ≥ 85 years) compared with younger subjects (< 65 years) treated with nivo+ipi; however, the frequency of drug-related AEs was higher in the older subjects (71.8%, 83.4%, 80.0%, and 100.0% in subjects aged < 65, ≥ 65 and < 75, ≥ 75 and < 85, and ≥ 85 years, respectively). The rate of discontinuation due to AEs (excluding progression terms) was higher in subjects aged 75 years or older, relative to all patients who received nivo+ipi (34.6% vs 27.7%).

For subgroups based on geographic region, the Asia region had the highest frequency of drug-related Grade 3-4 AEs compared to the other regions (Asia [50.0%], Europe [29.7%], Rest of World [26.9%], and North America [25.0%]).

The frequencies of all-causality and drug-related AEs in the chemotherapy arm for the subgroup of gender were similar to the AE frequencies reported for the overall study populations by treatment. The following numerical differences were observed in the subgroups of age and geographical region within the chemotherapy treatment group:

- Frequencies of all-causality and drug-related Grade 3-4 AEs were higher in older subjects:
  - All-causality Grade 3-4 AEs: 32.2%, 43.9%, 50.7%, and 100.0% in subjects aged < 65, ≥ 65 and < 75, ≥ 75 and < 85, and ≥ 85 years, respectively
  - Drug-related Grade 3-4 AEs: 25.3%, 30.1%, 40.8%, and 100.0% in subjects aged < 65, ≥ 65 and < 75, ≥ 75 and < 85, and ≥ 85 years, respectively
  - The rate of discontinuation due to AEs (excluding progression terms) was higher in subjects aged 75 years or older who received chemotherapy, relative to all patients (25.7% vs 19.4%).
- Frequencies of all-causality and drug-related Grade 3-4 AEs were highest in the Asia region:
  - All-causality Grade 3-4 AEs: Asia (52.6%), Europe (42.1%), Rest of Word (40.4%), and North America (36.0%).
  - Drug-related Grade 3-4 AEs: Asia (39.5%), Europe (32.9%), North America (28.0%), and Rest of Word (26.3%).

These differences do not alter the overall safety profile of nivolumab + ipilimumab in these subgroups.

Special Population - Age Groups

In CA209743, the frequencies of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented for nivo+ipi and chemotherapy treated subjects in Table 66.

In CA209743, only a small number of subjects were aged > 85 years (N =3 in both nivo+ipi and chemotherapy arms).

The frequencies for subgroups of age < 65, 65 to 74, and 75 to 84 years were similar to the frequencies reported for the overall study population by treatment, with these exceptions:

Nivo+ipi:

- Numerically higher frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs the overall population for SAEs - total (65.3% vs 54.7%) and SAEs requiring hospitalization/prolongation (62.7% vs 50.7).

Table 66: Summary of Safety Results by Age Group - Treated Subjects - CA209743

Treatment Group: Nivolumab + Ipilimumab N = 300

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 71	65–74 N = 151	75–84 N = 75	>= 85 N = 3	Total N = 300
TOTAL SUBJECTS WITH AN EVENT	71 (100.0)	150 (99.3)	75 (100.0)	3 (100.0)	299 (99.7)
SERIOUS AE - TOTAL	36 (50.7)	76 (50.3)	49 (65.3)	3 (100.0)	164 (54.7)
FATAL (DEATH)	8 (11.3)	18 (11.9)	8 (10.7)	0	34 (11.3)
HOSPITALIZATION/PROLONGATION	34 (47.9)	68 (45.0)	47 (62.7)	3 (100.0)	152 (50.7)
LIFE THREATENING	1 (1.4)	4 (2.6)	1 (1.3)	0	6 (2.0)
CANCER	0	3 (2.0)	2 (2.7)	0	5 (1.7)
DISABILITY/INCAPACITY	0	2 (1.3)	2 (2.7)	0	4 (1.3)
IMPORTANT MEDICAL EVENT	1 (1.4)	4 (2.6)	5 (6.7)	0	10 (3.3)
AE LEADING TO DISCONTINUATION	13 (18.3)	47 (31.1)	28 (37.3)	0	88 (29.3)

PSYCHIATRIC DISORDERS	14 (19.7)	28 (18.5)	12 (16.0)	1 (33.3)	55 (18.3)
NERVOUS SYSTEM DISORDERS	22 (31.0)	41 (27.2)	23 (30.7)	1 (33.3)	87 (29.0)
ACCIDENT AND INJURIES	2 (2.8)	16 (10.6)	6 (8.0)	0	24 (8.0)
CARDIAC DISORDERS	5 (7.0)	14 (9.3)	15 (20.0)	2 (66.7)	36 (12.0)
VASCULAR DISORDERS	5 (7.0)	25 (16.6)	8 (10.7)	0	38 (12.7)
CEREBROVASCULAR DISORDERS	0	3 (2.0)	3 (4.0)	0	6 (2.0)
INFECTIONS AND INFESTATIONS	31 (43.7)	64 (42.4)	33 (44.0)	1 (33.3)	129 (43.0)
ANTICHOLINERGIC SYNDROME	22 (31.0)	51 (33.8)	26 (34.7)	1 (33.3)	100 (33.3)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	6 (8.5)	20 (13.2)	8 (10.7)	0	34 (11.3)

Table 66: Summary of Safety Results by Age Group - Treated Subjects - CA209743 (continuation)

Treatment Group: Chemotherapy N = 284

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 87	65-74 N = 123	75-84 N = 71	>= 85 N = 3	Total N = 284
TOTAL SUBJECTS WITH AN EVENT	85 (97.7)	120 (97.6)	69 (97.2)	3 (100.0)	277 (97.5)
SERIOUS AE - TOTAL	24 (27.6)	26 (21.1)	20 (28.2)	2 (66.7)	72 (25.4)
FATAL (DEATH)	6 (6.9)	6 (4.9)	3 (4.2)	1 (33.3)	16 (5.6)
HOSPITALIZATION/PROLONGATION	21 (24.1)	23 (18.7)	17 (23.9)	2 (66.7)	63 (22.2)
LIFE THREATENING	0	2 (1.6)	0	0	2 (0.7)
CANCER	0	0	2 (2.8)	0	2 (0.7)
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	1 (1.1)	1 (0.8)	2 (2.8)	0	4 (1.4)
AE LEADING TO DISCONTINUATION	16 (18.4)	22 (17.9)	17 (23.9)	3 (100.0)	58 (20.4)
PSYCHIATRIC DISORDERS	7 (8.0)	18 (14.6)	12 (16.9)	0	37 (13.0)
NERVOUS SYSTEM DISORDERS	25 (28.7)	30 (24.4)	11 (15.5)	2 (66.7)	68 (23.9)
ACCIDENT AND INJURIES	1 (1.1)	3 (2.4)	2 (2.8)	0	6 (2.1)
CARDIAC DISORDERS	8 (9.2)	4 (3.3)	2 (2.8)	1 (33.3)	15 (5.3)
VASCULAR DISORDERS	7 (8.0)	6 (4.9)	2 (2.8)	0	15 (5.3)
CEREBROVASCULAR DISORDERS	0	1 (0.8)	0	0	1 (0.4)
INFECTIONS AND INFESTATIONS	21 (24.1)	35 (28.5)	14 (19.7)	1 (33.3)	71 (25.0)
ANTICHOLINERGIC SYNDROME	17 (19.5)	19 (15.4)	15 (21.1)	2 (66.7)	53 (18.7)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	7 (8.0)	6 (4.9)	2 (2.8)	0	15 (5.3)

CTC Version 4.0; MedDRA Version: 22.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Safety related to drug-drug interactions and other interactions

No formal pharmacokinetic drug interaction studies have been conducted with nivolumab or ipilimumab. This is reflected in the approved PI and no new information has been generated in support of this submission.

Discontinuation due to adverse events

The overall frequencies of all-causality AEs leading to discontinuation were higher in the nivo+ipi arm compared with the chemotherapy arm (Table 29).

Any-grade all-causality AEs leading to discontinuation were reported in 88 (29.3%) subjects in the nivo+ipi arm, and 58 (20.4%) subjects in the chemotherapy arm (Table 29). Grade 3-4 AEs leading to discontinuation were reported in 59 (19.7%) subjects in the nivo+ipi arm, and 28 (9.9%) subjects in the

chemotherapy arm. Grade 5 AEs leading to discontinuation were rare, occurring in 1.0% of nivo+ipi treated subjects and 0.7% of chemotherapy-treated subjects.

The most frequently reported all-causality AEs leading to discontinuation were:

- Nivo+ipi: colitis (2.3%), diarrhoea (2.3%), infusion-related reaction (1.7%), and pneumonitis (1.7%).
- Chemotherapy: anaemia (3.9%), asthenia (2.1%), nausea, fatigue, neutropenia, and thrombocytopenia (1.8%, each).

Any-grade drug-related AEs leading to discontinuation were reported in 69 (23.0%) subjects in the nivo+ipi arm and 45 (15.8%) subjects in the chemotherapy arm (Table 29). Grade 3-4 AEs leading to discontinuation were reported in 45 (15.0%) subjects in the nivo+ipi arm, and 21 (7.4%) subjects in the chemotherapy arm. Drug-related grade 5 AEs leading to discontinuation were rare, occurring in 0.3% of nivo+ipi treated subjects and 0.4% of chemotherapy-treated subjects.

The most frequently reported drug-related AEs leading to discontinuation were:

- Nivo+ipi: colitis (2.3%), diarrhea (2.3%), infusion related reaction (1.7%), and pneumonitis (1.7%).
- Chemotherapy: anemia (3.9%), asthenia (2.1%), nausea, neutropenia, and thrombocytopenia (1.8%, each).

Immunogenicity - CA209743

Of the 269 **nivolumab ADA evaluable** subjects in the nivo+ipi arm, 17 (6.3%) subjects were nivolumab ADA positive at baseline and 69 (25.7%) subjects were nivolumab ADA positive after the start of treatment (Table 67). Few subjects were persistent positive (1.9%) and positive for neutralizing ADA (0.7%). The highest titer value recorded was 64 which occurred in one subject.

Of the 271 **ipilimumab ADA evaluable** subjects nivo+ipi arm, 12 (4.4%) subjects were ipilimumab ADA positive at baseline and 37 (13.7%) subjects were ipilimumab ADA positive after start of treatment (Table 45). Few subjects were persistent positive (1.1%) and positive for neutralizing ADA (0.4%). The highest titer value recorded was 32 which occurred in one subject.

Table 67: ADA Assessments Summary - All Nivolumab + Ipilimumab Treated Subjects with Baseline and at Least One Post-Baseline Assessment

	Nivolumab + Ipilimumab	
Subject ADA Status (%)	Nivolumab ADA N = 269	Ipilimumab ADA N = 271
BASELINE ADA POSITIVE	17 (6.3)	12 (4.4)
ADA POSITIVE	69 (25.7)	37 (13.7)
PERSISTENT POSITIVE (PP)	5 (1.9)	3 (1.1)
NOT PP - LAST SAMPLE POSITIVE	24 (8.9)	13 (4.8)
OTHER POSITIVE	40 (14.9)	21 (7.7)
NEUTRALIZING POSITIVE	2 (0.7)	1 (0.4)
ADA NEGATIVE	200 (74.3)	234 (86.3)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment; **Persistent Positive (PP):** ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint; **Other Positive:** Not persistent but some ADA-positive samples with the last sample being negative; **Neutralizing Positive:** At least one ADA-positive sample with neutralizing antibodies detected post-baseline; **ADA Negative:** A subject with no ADA-positive sample after initiation of treatment.
Post-baseline assessments are assessments reported after initiation of treatment.

Effect of Immunogenicity on Safety

The frequency of hypersensitivity/infusion reactions was 10.1% and 12.0% in nivolumab ADA positive and ADA negative subjects, respectively. Similarly, the frequency was 10.8% and 12.0% in ipilimumab ADA positive and ADA negative subjects, respectively (Table 68). These findings suggest that neither nivolumab nor ipilimumab ADA occurrence has impact on subject safety.

Table 68: Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All Treated Subjects with ADA Positive or ADA Negative

	Nivolumab + Ipilimumab			
Preferred Term (%)	Nivo ADA Positive N = 69	Nivo ADA Negative N = 200	Ipi ADA Positive N = 37	Ipi ADA Negative N = 234
TOTAL SUBJECTS WITH AN EVENT	7 (10.1)	24 (12.0)	4 (10.8)	28 (12.0)
Hypersensitivity	2 (2.9)	9 (4.5)	1 (2.7)	9 (3.8)
Infusion related hypersensitivity reaction	0	2 (1.0)	0	2 (0.9)
Infusion related reaction	5 (7.2)	14 (7.0)	3 (8.1)	17 (7.3)

MedDRA Version: 22.1
CTC Version 4.0
Includes events between first dose and within the last dose of therapy + 100 days.

Supportive safety results from other MPM studies and other tumour types

Safety Results - MAPS2 Study in MPM

In the MAPS2 study, subjects were treated with nivolumab 3 mg/kg Q2W or nivo+ipi at the same schedule and regimen as that used in CA209743 (Table 69). The duration of the study treatment was 2 years from randomization, until disease progression, occurrence of any adverse event (AE) requiring discontinuation, or withdrawal of consent.

The population in the MAPS2 study was subjects diagnosed with unresectable MPM and previously treated by at least one line of pemetrexed-based chemotherapy.

Table 69: Summary of MAPS2 Study in Previously Treated Unresectable MPM

	Primary Study
Study/Phase/Status	IFCT-1501 MAPS2/ Phase 2/ completed
Study Design	Phase 2, multi-center, randomized open-label study. Subjects were randomized 1:1 into two arms, using minimization method, and assigned to one of the following treatment arms: • Monotherapy arm: Nivolumab was administrated intravenously (IV) over 60 minutes at 3 mg/kg Q2W • Combination arm: Nivolumab was administered IV over 90 minutes at 1 mg/kg Q2W, combined with ipilimumab administered IV over 90 minutes at 1 mg/kg Q6W. Randomization was stratified by: 1) histology: epithelioid vs sarcomatoid and biphasic previous line of treatment (2^{nd} line vs 3^{rd} line of treatment) chemosensitivity (progression >3 months vs progression ≤ 3 months)
Study Population	Subjects (≥ 18 years) with histologically proven diagnosis of unresectable MPM. Subjects received previous treatment with 1 or 2 systemic chemotherapy lines (1 line of chemotherapy considered if the patient received ≥2 cycles of this chemotherapy), including at least one line with pemetrexed in combination with platinum agent and had documented progression of the MPM, assessed by CT scan.
Primary Endpoint	Disease control rate (DCR)
Number of Treated Subjects	63 in the nivo arm and 61 in the nivo+ipi arm

6. Abbreviations: MPM: malignant pleural mesothelioma; Q2W: every 2 weeks; Q6W: every 6 weeks

According to the MAH, the routine clinical and laboratory evaluations performed in the study were appropriate and the study was conducted in accordance with the ethical principles stated in the recommendations from the 1974 Declaration of Helsinki (revised in 1975 and 1989), public health law no. 2004-806 of 09-Aug-2004 related to the protection and safety of humans, and Good Clinical Practice (GCP) requirements [International Conference on Harmonization (ICH) E6].

The toxicity was monitored at each visit for AEs according to the CTCAE v4.0. and evaluated as the number and the percentage of subjects with at least 1 AE per arm and per grade.

AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification version 21.0.

Overall Adverse Events

The safety analysis was performed on the safety population that included all recruited subjects who received at least one dose of the study drug.

All subjects (63 in the nivolumab arm and 61 in the nivolumab plus ipilimumab arm) experienced at least one AE (all-causality). Twenty-five (39.7%) subjects in the nivolumab arm and 36 (59%) subjects in the nivolumab plus ipilimumab arm had at least one SAE (all-causality). AEs leading to treatment discontinuation (all-causality) were reported in 3 (4.8%) and 14 (23%) subjects in the nivolumab and nivolumab plus ipilimumab arm, respectively. All-causality Grade 3/4 AEs were experienced in 30 (47.6%) subjects in the nivolumab arm and 32 (52.5%) subjects in the nivolumab plus ipilimumab arm, and all-causality Grade 5 AEs in 7 (11.1%) and 5 (8.2%) subjects, respectively.

A total of 57 (90.5%) subjects in the nivolumab arm and 57 (93.4%) subjects in the nivolumab plus ipilimumab arm experienced at least one treatment-related AE (any grade). The most common treatment-related AEs (>10%) included asthenia [27 (42.9%) and 34 (55.7%) subjects], diarrhoea [9 (14.3%) and 18 (29.5%) subjects] and nausea [11 (17.5%) and 11 (18%) subjects] in the nivolumab and nivolumab plus ipilimumab arms, respectively.

Grade 3-4 treatment-related AEs seemed less common in the nivolumab arm [grade 3: 8 (12.7%) subjects; grade 4: 1 (1.6%) subject] than in the nivolumab plus ipilimumab arm [grade 3: 15 (24.6%) subjects; grade 4: 2 (3.3%) subjects].

The safety profiles of nivolumab and nivolumab plus ipilimumab arms seemed consistent with other trials using immunotherapies and even more favorable compared to the safety profiles associated to platinum-based chemotherapy.

The summary of AEs is provided in Table 70.

Table 70: MAPS2 Study Safety Summary

	NIVOLUMAB (N=63)	**NIVOLUMAB + IPILIMUMAB (N=61)**
	Any Grade	**Any Grade**
	n (%)	**n (%)**
Any adverse event	63(100%)	61(100%)
All-causality Serious adverse event	25(39.7%)	36(59%)
All-causality AEs Leading to Discontinuation	3(4.8%)	14(23%)
All-causality Grade 3/4 AE	30(47.6%)	32(52.5%)
All-causality Grade 5 AE	7(11.1%)	5(8.2%)
Most Common Treatment-related AEs (≥10%)		
. Asthenia	27 (42.9%)	34 (55.7%)
. Diarrhoea	9 (14.3%)	18 (29.5%)
. Nausea	11 (17.5%)	11 (18%)
. Constipation	7 (11.1%)	9 (14.8%)
. Weight decreased	6 (9.5%)	8 (13.1%)
. Alanine aminotransferase increased	1 (1.6%)	8 (13.1%)
. Aspartate aminotransferase increased	2 (3.2%)	7 (11.5%)
. Pruritus	6 (9.5%)	15 (24.6%)
. Dry skin	3 (4.8%)	9 (14.8%)
. Anaemia	10 (15.9%)	19 (31.1%)
. Decreased appetite	14 (22.2%)	11 (18%)

Deaths

Grade 5 treatment-related AEs, were reported in 3 (4.9%) subjects in the nivolumab plus ipilimumab arm only, including one patient with hepatitis, one patient with encephalitis and one patient with acute kidney failure.

The 3 deaths considered treatment related in the nivolumab plus ipilimumab arm were reported during the first 4 months. However, no additional treatment-related deaths were reported for the next 20 months. This could be related to the experience that investigators gained in identifying immune-related AEs and optimizing the treatment for the patients, throughout the study.

Serious Adverse Events

Twenty-five (39.7%) subjects in the nivolumab arm and 36 (59%) subjects in the nivolumab plus ipilimumab arm had at least one SAE (all-causality).

In total, 123 SAEs (all-causality) have been reported to IFCT, including 56 SAEs in the nivolumab arm, 65 SAEs in the nivolumab plus ipilimumab arm and 2 SAEs reported before the beginning of the treatment.

Among these events, 29 SAEs were defined as possibly related to the study treatment, including 4 SAEs in the nivolumab arm and 25 SAEs in the nivolumab plus ipilimumab arm. Most of the treatment-related SAEs observed during the study were expected, except for 3 suspected unexpected serious adverse reactions (SUSARs), including one atrioventricular block, one encephalitis and one bullous pemphigoid, which were all reported in the nivolumab plus ipilimumab arm.

Safety Results of Nivolumab + Ipilimumab in First-line MPM and Other Tumour Types

Safety data of nivo+ipi from CA209743 in first-line MPM subjects are presented side-by-side with safety data of nivolumab 3 mg/kg + ipilimumab 1 mg/kg from first-line NSCLC study CA209227 Part 1, RCC study CA209214, and CRC study CA209142. While all studies had a ipilimumab dose of 1 mg/kg, ipilimumab was administered less frequently in the MPM study than in the RCC and CRC studies (Q6W vs Q3W), but over a longer duration (up to 2 years vs for 4 doses).

The intended dose and schedule of nivolumab + ipilimumab were as follows:

- MPM (CA209743): nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
- NSCLC (CA209227 Part 1): nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
- RCC (CA209214): nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W
- CRC (CA209142): nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W

The DBL dates and minimum follow-ups of these studies are as follows:

- MPM (CA209743): 03-Apr-2020, with a minimum follow-up of 22.1 months for OS and median follow-up of 17.35 months for all other data
- NSCLC (CA209227 Part 1): 02-Jul-2019, with a minimum follow-up of 29.3 months for OS and 28.3 months for all other data
- RCC (CA209214): 07-Aug-2017, with a minimum follow-up of 17.5 months
- CRC (CA209142): 18-Aug-2017, with a minimum follow-up of 9 months

Overall, the safety profile of nivo+ipi in first-line MPM (CA209743) was consistent with the safety profile of the nivo+ipi in first-line NSCLC (CA209227 Part 1), RCC (CA209214), and CRC (CA209142) (Table 71). It should be noted that there were differences in follow-up across 4 studies.

- No new safety concerns were identified with nivo+ipi in CA209743 MPM, relative to nivo+ipi in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC.
- Death attributed to study drug toxicity was rare with nivo+ipi across tumour types.
- All-causality and drug-related SAEs, all-causality and drug-related AEs leading to discontinuation, and all-causality AEs were reported at similar frequencies with nivo+ipi in CA209743 MPM relative to CA209227 NSCLC, CA209214 RCC, and CA209142 CRC.
- Drug-related AEs (any-grade and Grade 3-4) were reported at similar frequencies with nivo+ipi in CA209743 MPM relative to CA209227 NSCLC, CA209214 RCC, and CA209142 CRC.

- IMAEs were reported at similar or lower frequencies with nivo+ipi in CA209743 MPM relative to nivo+ipi in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC in most IMAE categories.
- Most drug-related select AEs were reported at lower or similar frequencies with nivo+ipi in CA209743 MPM relative to nivo+ipi in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC in most select AE categories. Hypersensitivity/infusion reactions select AEs occurred at a higher frequency in CA209743 MPM than in CA209227 NSCLC (12.0% vs 4.0%), CA209214 RCC (12.0% vs 4.0%), and CA209142 CRC (12.0% vs 3.4%).
- OESIs (regardless of causality or immune-modulating medication) within 100 days after the last dose were reported at lower or similar frequencies with nivo+ipi in CA209743 MPM relative to nivo+ipi in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC.

Table 71: Summary of Safety of Nivolumab + Ipilimumab in MPM, NSCLC, RCC, and CRC

	MPM CA209743		NSCLC CA209227		RCC CA209214		CRC CA209142	
	Nivo 3 Q2W + Ipi 1 Q6W N = 300		Nivo 3 Q2W + Ipi 1 Q6W N = 576		Nivo 3 + Ipi 1 Q3W N = 547		Nivo 3 + Ipi 1 Q3W N = 119	
DEATHS	198 (66.0)		372 (64.6)		159 (29.1)		33 (27.7)	
WITHIN 30 DAYS OF LAST DOSE	28 (9.3)		75 (13.0)		23 (4.2)		3 (2.5)	
WITHIN 100 DAYS OF LAST DOSE	55 (18.3)		154 (26.7)		50 (9.1)		13 (10.9)	
PRIMARY REASON FOR DEATH								
DISEASE PROGRESSION	183 (61.0)		304 (52.8)		124 (22.7)		29 (24.4)	
STUDY DRUG TOXICITY	3 (1.0)		8 (1.4)		7 (1.3)		0	
UNKNOWN	3 (1.0)		14 (2.4)		6 (1.1)		1 (0.8)	
OTHER	9 (3.0)		46 (8.0)		22 (4.0)		3 (2.5)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
ALL-CAUSALITY SAEs	164 (54.7)	103 (34.3)	355 (61.6)	259 (45.0)	305 (55.8)	227 (41.5)	63 (52.9)	49 (41.2)
DRUG-RELATED SAEs	64 (21.3)	46 (15.3)	141 (24.5)	106 (18.4)	162 (29.6)	121 (22.1)	27 (22.7)	24 (20.2)
ALL-CAUSALITY AEs LEADING TO DC	88 (29.3)	59 (19.7)	190 (33.0)	141 (24.5)	168 (30.7)	118 (21.6)	19 (16.0)	13 (10.9)
DRUG-RELATED AEs LEADING TO DC	69 (23.0)	45 (15.0)	104 (18.1)	71 (12.3)	118 (21.6)	84 (15.4)	16 (13.4)	12 (10.1)
ALL-CAUSALITY AEs	299 (99.7)	159 (53.0)	568 (98.6)	360 (62.5)	544 (99.5)	357 (65.3)	118 (99.2)	71 (59.7)
DRUG-RELATED AEs	240 (80.0)	91 (30.3)	442 (76.7)	189 (32.8)	509 (93.1)	250 (45.7)	95 (79.8)	38 (31.9)
Most Frequent Drug-related AEs (≥ 15% of Any Grade in any treatment group)								
DIARRHOEA	62 (20.7)	10 (3.3)	98 (17.0)	10 (1.7)	145 (26.5)	21 (3.8)	30 (25.2)	3 (2.5)
PRURITUS	49 (16.3)	3 (1.0)	82 (14.2)	3 (0.5)	154 (28.2)	3 (0.5)	24 (20.2)	2 (1.7)
RASH	43 (14.3)	3 (1.0)	98 (17.0)	9 (1.6)	118 (21.6)	8 (1.5)	18 (15.1)	2 (1.7)
FATIGUE	41 (13.7)	3 (1.0)	83 (14.4)	10 (1.7)	202 (36.9)	23 (4.2)	22 (18.5)	2 (1.7)
HYPOTHYROIDISM	32 (10.7)	0	72 (12.5)	2 (0.3)	85 (15.5)	2 (0.4)	21 (17.6)	1 (0.8)
NAUSEA	30 (10.0)	1 (0.3)	57 (9.9)	3 (0.5)	109 (19.9)	8 (1.5)	16 (13.4)	1 (0.8)
LIPASE INCREASED	20 (6.7)	13 (4.3)	43 (7.5)	23 (4.0)	90 (16.5)	56 (10.2)	14 (11.8)	6 (5.0)
PYREXIA	16 (5.3)	0	43 (7.5)	2 (0.3)	79 (14.4)	2 (0.4)	18 (15.1)	0
DRUG-RELATED SELECT AEs, BY CATEGORY								
ENDOCRINE	52 (17.3)	4 (1.3)	137 (23.8)	24 (4.2)	178 (32.5)	38 (6.9)	38 (31.9)	7 (5.9)
GASTROINTESTINAL	66 (22.0)	16 (5.3)	105 (18.2)	14 (2.4)	154 (28.2)	27 (4.9)	30 (25.2)	4 (3.4)
HEPATIC	36 (12.0)	16 (5.3)	91 (15.8)	47 (8.2)	101 (18.5)	45 (8.2)	28 (23.5)	14 (11.8)
PULMONARY	20 (6.7)	2 (0.7)	48 (8.3)	19 (3.3)	34 (6.2)	6 (1.1)	7 (5.9)	1 (0.8)
RENAL	15 (5.0)	4 (1.3)	25 (4.3)	4 (0.7)	48 (8.8)	7 (1.3)	7 (5.9)	2 (1.7)
SKIN	108 (36.0)	9 (3.0)	196 (34.0)	24 (4.2)	267 (48.8)	20 (3.7)	42 (35.3)	5 (4.2)
HYPERSENSITIVITY/INFUSION REACTIONS	36 (12.0)	4 (1.3)	23 (4.0)	0	22 (4.0)	0	4 (3.4)	0

Table 71: Summary of Safety of Nivolumab + Ipilimumab in MPM, NSCLC, RCC, and CRC (continuation)

	MPM CA209743		NSCLC CA209227		RCC CA209214		CRC CA209142	
	Nivo 3 Q2W + Ipi 1 Q6W N = 300		Nivo 3 Q2W + Ipi 1 Q6W N = 576		Nivo 3 + Ipi 1 Q3W N = 547		Nivo 3 + Ipi 1 Q3W N = 119	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
ALL-CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY								
Immune-mediated AEs Treated with Immune-modulating medication								
PNEUMONITIS	20 (6.7)	6 (2.0)	50 (8.7)	23 (4.0)	24 (4.4)	9 (1.6)	3 (2.5)	0
DIARRHEA/COLITIS	26 (8.7)	12 (4.0)	48 (8.3)	17 (3.0)	52 (9.5)	25 (4.6)	8 (6.7)	4 (3.4)
HEPATITTIS	18 (6.0)	14 (4.7)	46 (8.0)	37 (6.4)	38 (6.9)	32 (5.9)	12 (10.1)	10 (8.4)
NEPHRITIS AND RENAL DYSFUNCTION	8 (2.7)	5 (1.7)	6 (1.0)	2 (0.3)	25 (4.6)	9 (1.6)	2 (1.7)	2 (1.7)
RASH	39 (13.0)	8 (2.7)	106 (18.4)	21 (3.6)	91 (16.6)	18 (3.3)	20 (16.8)	5 (4.2)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (1.7)	1 (0.3)	4 (0.7)	0	7 (1.3)	0	3 (2.5)	0
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications								
ADRENAL INSUFFICIENCY	7 (2.3)	2 (0.7)	27 (4.7)	13 (2.3)	41 (7.5)	17 (3.1)	10 (8.4)	3 (2.5)
HYPOPHYSITTIS	12 (4.0)	3 (1.0)	20 (3.5)	9 (1.6)	25 (4.6)	15 (2.7)	5 (4.2)	3 (2.5)
HYPOTHYROIDISM/THYROIDITTIS	35 (11.7)	0	81 (14.1)	4 (0.7)	119 (21.8)	4 (0.7)	23 (19.3)	3 (2.5)
HYPERTHYROIDISM	11 (3.7)	0	50 (8.7)	0	66 (12.1)	4 (0.7)	18 (15.1)	0
DIABETES MELLITUS	1 (0.3)	1 (0.3)	6 (1.0)	5 (0.9)	15 (2.7)	6 (1.1)	1 (0.8)	0
ALL-CAUSALITY OESIs WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY								
with or without Immune-Modulating Medications								
Myasthenic Syndrome	2 (0.7)	2 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0

Guillain-Barre Syndrome	0	0	0	0	0	0	0	0
Pancreatitis	4 (1.3)	1 (0.3)	6 (1.0)	4 (0.7)	13 (2.4)	6 (1.1)	1 (0.8)	1 (0.8)
Uveitis	2 (0.7)	1 (0.3)	2 (0.3)	0	2 (0.4)	0	1 (0.8)	1 (0.8)
Encephalitis	3 (1.0)	1 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.8)	1 (0.8)
Myocarditis	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	0	0
Myositis	2 (0.7)	2 (0.7)	2 (0.3)	1 (0.2)	3 (0.5)	1 (0.2)	2 (1.7)	1 (0.8)
Rhabdomyolysis	0	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0

MedDRA version 22.1 for CA209743, MedDRA version 22.0 for CA209227, MedDRA version 20.0 for CA209214, and MedDRA version 21.1 for CA209142; CTC version 4.0

All events are within 30 days of the last dose of study drug, unless otherwise indicated. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Abbreviations: AE - adverse event; CRC - colorectal cancer; DC - discontinuation; Ipi - ipilimumab; Nivo - nivolumab; NSCLC - non-small cell lung cancer; QXW- every X weeks; RCC - renal cell carcinoma; SAE - serious adverse event

Post marketing experience

Based on pharmacovigilance activities conducted by Bristol Myers Squibb (BMS) Worldwide Patient Safety, review of post-marketing safety data is consistent with, and confirms the nivolumab + ipilimumab clinical trial safety data. The safety profile of nivolumab + ipilimumab in the post-marketing setting remains favourable.

2.5.1. Discussion on clinical safety

The safety profile of nivolumab 360 mg administered every 3 weeks in combination with 1 mg/kg ipilimumab administered every 6 weeks is based mainly on the pivotal study CA209743, a Phase 3, randomized, open label study of nivolumab plus ipilimumab versus chemotherapy in subjects with previously untreated unresectable MPM. However, the posology used in this study differed from the one proposed to be included in the SmPC for the applied indication. In the CA209743 study subjects were randomized to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (N = 300) or pemetrexed 500mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin (AUC of 5 mg per millilitre per minute), on day 1 of a 21-days cycle for 6 cycles or until disease progression or unacceptable toxicity (N = 284). Therefore, this section should be read in conjunction with the PK/PD section.

Supportive safety results are also provided from the Intergroupe Francophone de Cancérologie Thoracique (IFCT)-Mesothelioma Avastin Cisplatin Pemetrexed Study 2 (IFCT-1501 MAPS2), an investigator-sponsored trial, to provide safety and tolerability data on nivolumab monotherapy and the combination of nivolumab and ipilimumab in MPM.

The study CA209743 was comprised by patients with previously untreated MPM with a median age of 69 years (range: 25, 89). Most of them were white (85.3%), male (77.2%), with an ECOG performance status of 0 (40.0%) or 1 (59.8%). Most of the patients had PD-L1 ≥ 1% (80%) and epithelioid histology (75%). Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotactic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the trial.

Safety data from study CA209743 are based on the database lock of 03-Apr-2020. The study stopped for superiority of OS at the planned interim analysis after crossing the boundary for statistical significance. From the 605 subjects who were randomized, the safety analyses were conducted in 584 treated subjects (300 subjects in the nivolumab plus ipilimumab arm and 284 in the chemotherapy arm) who received at least one dose of study drug.

At the time of database lock, 99.1% of patients did not continue in the treatment period. The main reason for not continuing in the treatment period other than disease progression was study drug toxicity (19.7% and 8.5% for nivolumab plus ipilimumab and chemotherapy, respectively). The maximum duration of treatment per protocol was 24 months for nivolumab plus ipilimumab, and 6 cycles of chemotherapy. The median (95% CI) duration of therapy was 5.55 (4.63, 6.70) months for the nivolumab plus ipilimumab

arm with a median number of doses of 12 for nivolumab and 4 for ipilimumab. The median (95% CI) duration of therapy was 3.48 (N.A, N.A.) months for the chemotherapy arm with a median number of doses of 6 for pemetrexed, 5 for cisplatin, and 6 for carboplatin. The proportion of patients who received at least 90% of the planned dose intensity were 68.7% for nivolumab, 82.3% for ipilimumab, 65.5% for pemetrexed, 70.2% for cisplatin, and 59.8% for carboplatin.

There was a minimum follow-up (date of the last subject randomized to clinical data cut-off) of 22.1 months for overall survival and a median follow-up for survival (median for all randomized subjects between the date of randomization to the clinical cut-off date) of 29.7 months.

It is relevant to mention that the different figures between the safety profiles of nivolumab plus ipilimumab versus chemotherapy can be related to a longer treatment duration of the nivolumab plus ipilimumab administration. However, this more prolonged treatment is required to obtain the observed efficacy results. Therefore, the unadjusted data is considered the main piece of information for the safety assessment.

The overall frequencies of any-grade all causality AEs (> 95%) and drug-related AEs (≥80.0%) were similar between the nivolumab plus ipilimumab and chemotherapy arms. Frequencies of grade 3-4 all-causality AEs were higher with nivolumab plus ipilimumab (53.0%) compared to chemotherapy (42.6%), although frequencies of drug-related grade 3-4 AEs were similar between the 2 arms (30.3% and 32.0% for nivolumab plus ipilimumab and chemotherapy, respectively).

The most frequently reported all-causality AEs in the nivolumab plus ipilimumab arm were diarrhoea (31.3%), fatigue (28.7%), dyspnoea (26.0%), nausea (24.3%), and decreased appetite (23.7%). Whilst those in the chemotherapy arm were nausea (43.3%), anaemia (41.9%), constipation (29.6%), neutropenia (27.8%), fatigue (27.1%), and decreased appetite (25.4%). The most frequently reported grade 3-4 all-causality AEs in the nivolumab plus ipilimumab arm were increased lipase (5.3%), diarrhoea (4.0%), fatigue, increased amylase, and malignant neoplasm progression (3.0%, each). Whilst in the chemotherapy arm were neutropenia (15.8%), anaemia (13.7%), asthenia (4.2%), thrombocytopenia (3.9%), and dyspnoea (3.2%).

The overall frequency of all-causality SAEs and drug-related SAEs was higher with nivolumab plus ipilimumab (54.7% | 21.3%) compared to chemotherapy (25.4% | 7.7%). Grade 3-4 all causality SAEs were also more frequent for the nivolumab plus ipilimumab arm (34.3%) compared to the chemotherapy arm (19.0%). In the same way, the frequency of grade 3-4 drug-related SAEs was higher in the nivolumab plus ipilimumab arm (15.3%) compare to the chemotherapy arm (6.0%).

The most frequently reported all-causality SAEs for the nivolumab plus ipilimumab arm were malignant neoplasm progression (10.7%), pyrexia (4.3%), pneumonia (3.7%), pleural effusion (3.0%), and colitis (3.0%). Whilst those in the chemotherapy were malignant neoplasm progression (4.6%), anemia (2.8%), and dyspnoea (2.1%). The most frequently reported any-grade drug-related SAEs in the nivolumab plus ipilimumab arm were colitis (3.0%), infusion related reaction (2.0%), abnormal hepatic function, acute kidney injury, and pneumonitis (1.7%, each). Whilst for chemotherapy, were anaemia (2.1%), febrile neutropenia (1.1%), and pancytopenia (1.1%).

A higher proportion of subjects in the nivolumab plus ipilimumab arm than in the chemotherapy arm presented any-grade all-causality AEs leading to discontinuation (29.3% vs. 20.4%), grade 3-4 all-causality AEs leading to discontinuation (19.7% vs. 9.9%), any-grade drug-related AEs leading to discontinuation (23.0% vs 15.8%) and grade 3-4 drug-related AEs leading to discontinuation (15.0% vs. 7.4%).

The most frequently reported any-grade all-causality AEs leading to discontinuation in the nivolumab plus ipilimumab arm were colitis (2.3%), diarrhoea (2.3%), infusion related reaction (1.7%), and pneumonitis

(1.7%). Whilst in the chemotherapy arm were anaemia (3.9%), asthenia (2.1%), nausea, fatigue, neutropenia, and thrombocytopenia (1.8%, each). Most of these events were considered drug-related by the investigator.

In the dataset of ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in MPM (n = 300), with a minimum follow up of 22.1 months, the most frequent adverse reactions (≥ 10%) were fatigue (43%), diarrhoea (31%), rash (30%), musculoskeletal pain (27%), nausea (24%), decreased appetite (24%), pruritus (21%), constipation (19%), and hypothyroidism (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2) (SmPC section 4.8).

Select AEs, IMAEs and OESIs occurred more frequently with nivolumab plus ipilimumab compared to chemotherapy.

The majority of select AEs were Grade 1-2 and most were considered drug-related by the investigator. The most frequently reported drug-related select AE categories in the nivolumab plus ipilimumab arm were skin (36.0%), gastrointestinal (22.0%), hepatic and hypersensitivity/infusion reaction (12.0% each). Whilst in the chemotherapy arm were skin (9.9%), gastrointestinal (8.1%), renal (6.7%). The median time to resolution ranged from 0.14 to 12.14 weeks for select AEs.

Occurrence of IMAEs in the nivolumab plus ipilimumab arm was as follows (% of subjects with any grade IMAE | % of those subjects with grade 3-4 IMAE): rash (13.0% | 61.5%), hypothyroidism/thyroiditis (11.7% | 25.7%), diarrhoea/colitis (8.7% | 92.3%), and pneumonitis (6.7% | 65.0%). The majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. The proportion of patients with resolution of the above-mentioned IMAEs were 61.5%, 25.7%, 92.3%, and 65.0%, for rash, hypothyroidism/thyroiditis, diarrhoea/colitis, and pneumonitis, respectively. The median time to resolution ranged from 0.14 to 17.14 weeks for IMAEs.

OESIs were reported in 14 (4.7%) subjects in the nivolumab plus ipilimumab arm and 1 (0.4%) subject in the chemotherapy arm. 8/14 OESIs in the nivolumab plus ipilimumab arm were grade 3-4 including events of pancreatitis, encephalitis, myositis, myasthenic syndrome, uveitis and myocarditis.

With regards to laboratory findings, there was a higher frequency of elevated AST/ALT and abnormal increases or decreases in TSH with nivolumab plus ipilimumab treatment, and a higher frequency of hematologic abnormalities with chemotherapy. The proportions of subjects with amylase and lipase worsened to grade 3-4 relative to baseline were higher in the nivolumab plus ipilimumab arm than in the chemotherapy arm, as well as the proportions of subjects with laboratory and electrolyte abnormalities worsened to grade 3-4 relative to baseline.

Three (1.0%) subjects in the nivolumab plus ipilimumab arm, and 1 (0.4%) in the chemotherapy arm died due to study drug toxicity. Deaths in the nivolumab + ipilimumab arm included one patient with pneumonitis, one patient with toxicity of immunotherapy and development of neurological complications, and one with acute heart failure.

For subgroups based on age, the frequency of drug-related AEs was 71.8%, 83.4%, 80.0%, and 100.0% in subjects aged < 65, ≥ 65 and < 75, ≥ 75 and < 85, and ≥ 85 years, respectively. The rate of discontinuation due to AEs (excluding progression terms) was higher in subjects aged 75 years or older, relative to all patients who received nivolumab plus ipilimumab (34.6% vs. 27.7%).

In addition, numerically higher frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs. the overall population for SAEs (65.3% vs. 54.7%) and SAEs requiring hospitalization/prolongation (62.7% vs 50.7).

With regards to immunogenicity, 17/269 (6.3%) subjects were nivolumab ADA positive at baseline and 25.7% were nivolumab ADA positive after the start of treatment. 1.9 % were persistent positive and 0.7% were positive for neutralizing ADA. 12/271 (4.4%) subjects were ipilimumab ADA positive at baseline and 13.7% were ipilimumab ADA positive after start of treatment. 1.1% were persistent positive and 0.4% were positive for neutralizing ADA. No differences were found in the frequency of hypersensitivity/infusion reactions between ADA positive and ADA negative subjects for both, nivolumab and ipilimumab.

In the IFCT-1501 MAPS2 study, subjects were treated with nivolumab 3 mg/kg Q2W or nivolumab plus ipilimumab at the same schedule, regimen, and treatment duration as that in CA209743. The study included subjects diagnosed with unresectable MPM and previously treated by at least one line of pemetrexed-based chemotherapy. The safety profiles of nivolumab and nivolumab plus ipilimumab arms seemed consistent with other trials.

A cross-study comparison was also provided by the MAH with other tumour types in which the combination nivolumab 3 mg/kg plus ipilimumab 1 mg/kg was studied: Study CA209227 Part 1 in NSCLC (nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W), study CA209214 in RCC (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W), and CA209142 in CRC (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W).

This comparison showed that all-causality and drug-related AEs, all-causality and drug-related SAEs, and all-causality and drug-related AEs leading to discontinuation were reported at similar frequencies with nivolumab plus ipilimumab in CA209743 MPM relative to CA209227 NSCLC, CA209214 RCC, and CA209142 CRC. IMAEs were reported at similar or lower frequencies with nivolumab plus ipilimumab in CA209743 MPM relative to nivolumab plus ipilimumab in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC in most IMAE categories. Most drug-related select AEs were reported at lower or similar frequencies with nivolumab plus ipilimumab in CA209743 MPM relative to nivolumab plus ipilimumab in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC in most select AE categories. OESIs (regardless of causality or immune-modulating medication) within 100 days after the last dose were reported at lower or similar frequencies with nivolumab plus ipilimumab in CA209743 MPM relative to nivolumab plus ipilimumab in CA209227 NSCLC, CA209214 RCC, and CA209142 CRC. Death attributed to study drug toxicity was rare with nivolumab plus ipilimumab across tumour types.

The most remarkable difference was related to the hypersensitivity/infusion reactions select AEs which occurred at a higher frequency in CA209743 MPM (12%) than in CA209227 NSCLC (4.0%), CA209214 RCC (4.0%), and CA209142 CRC (3.4%).

2.5.2. Conclusions on clinical safety

The safety profile of the combination of nivolumab 360 mg administered every 3 weeks in combination with 1 mg/kg ipilimumab administered every 6 weeks is mainly based on the pivotal study CA209743, a Phase 3, randomized, open label study of nivolumab plus ipilimumab versus chemotherapy in subjects with previously untreated unresectable MPM in which subjects were randomized to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (N = 300) or pemetrexed in combination with cisplatin or carboplatin (N = 284). Therefore, the combination regimen assessed through the study was different to the one proposed for the SmPC. See PK/PD section.

The combination treatment appears to be less well tolerated than chemotherapy as grade 3-4 all-causality AEs, all-causality and drug-related SAE (any-grade and grade 3-4), and all-causality and drug-related AEs leading to discontinuation (any-grade and grade 3-4) were reported more frequently with the nivolumab plus ipilimumab compared to chemotherapy. As expected, select AEs, IMAEs and OESIs also occurred more frequently with nivolumab plus ipilimumab compared to chemotherapy. The

safety profile of the combination is characterised by the immunological effects, compared to chemotherapy that is characterised by bone marrow suppression.

It is relevant to mention that the rate of discontinuation as well as the frequency of SAE and SAE requiring hospitalization/prolongation were higher in subjects aged 75 years and older compared to the overall population.

A cross-study analysis compared the safety profile of nivolumab plus ipilimumab in the MPM study with previous studies of the combination. Overall, the safety profile of the combination of nivolumab 3mg/kg (Q2W) plus ipilimumab 1 mg/kg (Q6W) in the first line treatment of subjects with unresectable MPM is in line with the known safety profile of the combination in other tumour types. The main difference found across them was related to hypersensitivity/infusion reactions which occurred at a higher frequency in CA209743 MPM compared to the rest of the studies which has been reflected by the MAH on the SmPC.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The WSA submitted updated RMP versions with this application.

Opdivo

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

The PRAC considered that the risk management plan version 20.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 20.1 with the following content:

Summary of the safety concerns

Table: Summary of the Safety Concerns

Category	Safety Concern
Important Identified Risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis and renal dysfunction
	Immune-related endocrinopathies
	Immune-related skin ARs
	Other Immune-related ARs
	Severe infusion reactions
Important Potential Risks	Embryofetal toxicity
	Immunogenicity
	Complications of allogeneic HSCT following nivolumab therapy in cHL
	Risk of GVHD with nivolumab after allogeneic HSCT
Missing Information	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Table: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Table: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report	Interim results provided annually
			2. Final CSR submission	4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update	With PSUR starting at DLP 03-Jul-2017
			2. Interim CSR submission	06-2019
			3. Final CSR submission	4Q2022

Risk minimisation measures

Summary Table of Risk Minimization Measures

Table: Summary table of Risk Minimisation Measures

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance Activities (PhVA)
Important Identified Risks		
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune related skin ARs Other immune-related ARs	Routine RMM: SmPC Sections 4.2, 4.4 and 4.8 Additional RMM: • Patient Alert Card	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: • Postmarketing pharmaco-epidemiology study (CA209234)
Severe infusion reactions	Routine RMM: SmPC Sections 4.4 and 4.8 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: • Postmarketing pharmaco-epidemiology study (CA209234)
Important Potential Risks		
Embryofetal Toxicity	Routine RMM: SmPC Sections 4.6 and 5.3 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: None
Immunogenicity	Routine RMM: SmPC Section 4.8 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: None
Complications of allogeneic HSCT following nivolumab therapy	Routine RMM: SmPC Sections 4.4 and 4.8 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: • Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine RMM: SmPC Sections 4.4 and 4.8 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: None
Missing Information		
Patients with severe hepatic and/or renal impairment	Routine RMM: SmPC Sections 4.2 and 5.2 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: None
Patients with autoimmune disease	Routine RMM: SmPC Section 4.4 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine RMM: SmPC Sections 4.4 and 4.5 Additional RMM: None	Routine PhVA beyond adverse reactions reporting and signal detection: None Additional PhVA: None

Yervoy

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

The PRAC considered that the risk management plan version 30.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 30.1 with the following content:

Safety concerns

Table: Summary of Safety Concerns

Important identified risks	• GI irARs (eg, diarrhoea, colitis, GI perforation) • Hepatic irARs (eg, hepatitis) • Skin irARs (eg, rash, pruritus, TEN, and DRESS) • Neurologic irARs (eg, neuropathy) • Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) • Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis) • Severe infusion reactions
Important potential risks	• Immunogenicity
Missing information	• Long-term safety in adolescent patients > 12 years of age • Potential PD interaction with systemic immunosuppressants • Patients with severe hepatic impairment • Patients with severe renal impairment • Patients with autoimmune disease

Pharmacovigilance plan

Table: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
MAH to sponsor extension of the Dutch Melanoma Treatment Registry (DMTR) to include paediatric subjects and to collect their safety data (CA184557)[1]	To obtain additional safety information in paediatric patients	Long-term safety in adolescent patients > 12 years of age	1. Synopsis of the DMTR	16-Apr-2018
			2. Submission of protocol	02-Nov-2019
			3. Start of data collection	End of 2Q 2019
			4. Recruitment period[a]	2Q 2019 until 1Q 2029
			5. Progress Report	End of 2Q 2022
			6. Interim Study Report	End of 2Q 2024
			7. End of data collection	

Table: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
			6. Final report of study results	End of Q1 2029 End of 2Q 2029

[a] The recruitment period began in 2Q 2019, when the Princess Maxima Center officially confirmed its collaboration to the paediatric extension of the DMTR, but the data will include all paediatric patients entered in the DMTR who received ipilimumab prior to the start of data collection.

Risk minimisation measures

Table: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified Risks Immune-related Adverse Reactions (GI irARs, hepatic irARs, skin irARs, neurological irARs, endocrine irARs, and other irARs)	Routine risk minimisation measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list Additional risk minimisation measures: Patient Information Brochure and Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects Additional risk minimisation measures: • Patient Information Brochure and Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 5.1 Immunogenicity Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in adolescent patients > 12 years of age	Routine risk minimisation measures: SmPC Section 4.2, 4.4, 4.8, and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU. • Reporting of long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy (CA209070 and CA209908). • Monitoring of initial AEs and continued follow-up while on therapy and/or 100 days after the last dose by the treating physician. Follow-up information obtained by BMS using specified procedures (telephone interviews or

Table: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		mailing a questionnaire to the treating physician).
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: MAH to sponsor extension of the DMTR to include paediatric subjects and to collect their safety data.
Potential PD interaction with systemic immunosuppressants	Routine risk minimisation measures: SmPC Section 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

For final adopted wording please refer to the appended and agreed Product Information

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

The proposed indication for the combination of nivolumab + ipilimumab is for the *'first line treatment of adult patients with unresectable malignant pleural mesothelioma'.*

The recommended dose is nivolumab 360 mg Q3W in combination with ipilimumab 1 mg/kg Q6W up to 24 months in patients without disease progression.

3.1.1. Disease or condition

Malignant pleural mesothelioma (MPM) is a rare, locally invasive, and highly aggressive cancer of the pleural membrane. Patients with MPM usually have a very poor prognosis, and less than 10% of patients live beyond 5 years. Mesothelioma affects approximately 31,000 people around the world, with around 30,000 new cases diagnosed annually. Occupational exposure to asbestos is the most important risk factor associated with MPM.

MPM is usually diagnosed at an advanced stage due to late and non-specific symptoms. Thoracoscopy, or transparietal biopsies when thoracoscopy is contra-indicated, are the best methods for obtaining the diagnosis of MPM. Three major histological subtypes of MPM are well described: epithelioid (most common), sarcomatoid, and mixed-type (biphasic), with the poorest prognosis in non-epithelioid subtypes. Gender is also a known prognostic factor in MPM, with females typically having longer survival time than males. Measurement and evaluation of MPM based on imaging data is challenging given the lack of clearly demarcated margins of the lesions. The majority of newly diagnosed patients have unresectable MPM or are unsuitable candidates for surgery (i.e. age or medical comorbidities).

3.1.2. Available therapies and unmet medical need

For the past 15 years, standard of care (SOC) 1L chemotherapy for MPM has been a combination of pemetrexed and cisplatin, which has been shown to be more beneficial than cisplatin monotherapy. With this SOC, patients with MPM have a median overall survival (OS) of 12 months and a 5-year survival rate less than 10%. Pemetrexed-cisplatin chemotherapy also improves the quality of life and relieves some symptoms, such as dyspnoea. Although pemetrexed plus cisplatin is the SOC in 1L unresectable MPM, carboplatin is also recommended with pemetrexed, particularly in subjects who are unable to tolerate cisplatin. Based on published data in chemotherapy-naive subjects with MPM, clinical efficacy is similar between carboplatin and cisplatin-based regimens.

Improvement in 1L treatment has been observed by adding anti-angiogenic agents to platinum/pemetrexed chemotherapy as shown by the Phase 2 Intergroupe Francophone de Cancérologie Thoracique (IFCT)-Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) with bevacizumab in selected patients. However, this bevacizumab combination is not approved by health authorities.

After the first line, no treatment is approved for the second line treatment. The standard of care in the second line treatment consists of treatment with vinorelbine or gemcitabine or retreatment with pemetrexed.

Currently various immunotherapy products (combinations) are under investigation in malignant pleural mesothelioma. A recent phase 2b study failed to show the superiority of an anti-CTLA4 monoclonal antibody (tremelimumab) over placebo.

3.1.3. Main clinical studies

This application is based on data from study CA209743 which is a Phase 3, randomized (1:1), open-label, study evaluating nivo+ipi vs. chemotherapy as a 1L treatment in adults (18 years and older) with untreated, unresectable MPM. Randomization was stratified according to tumour histology: epithelioid vs. non-epithelioid (sarcomatoid or mixed histology subtypes), and gender (male vs. female). A tumour sample was required to be sent to the central laboratory for PD L1 status testing prior to randomization, but the results were not needed for randomization.

Nivolumab 3 mg/kg Q2W was administered with ipilimumab 1 mg/kg Q6W until disease progression, unacceptable toxicity, or a maximum treatment duration of 2 years. For the control arm, pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin (AUC of 5 mg per millilitre per minute) were administered on Day 1 of a 21-days cycle for 6 cycles or until disease progression or unacceptable toxicity.

OS was the primary endpoint. PFS, ORR (according to mRECIST or RECIST 1.1 criteria), DOR, DCR and PD-L1, as a predictive biomarker for efficacy, were assessed as secondary endpoints. They were not formally tested.

At database lock (DBL) (03-Apr-2020), the actual number of OS events was 419 (89% of total events planned). This corresponds to the first planned interim analysis for OS that was performed and the boundary for statistical significance for OS (p = 0.0345) was crossed (p = 0.0020). The study was then stopped for superiority of OS and the interim analysis considered the final primary analysis result.

3.2. Favourable effects

The efficacy results of nivolumab in combination with ipilimumab presented below are based on the database lock of 03 Apr 2020, with a median follow-up of 29.7 months.

- Nivo+ipi demonstrated a statistically and clinically significant improvement in **OS** compared with chemotherapy: HR = 0.74 (Stratified Cox proportional hazard model 96.6% CI HR: (0.60, 0.91); stratified log-rank test p value = 0.0020. Median OS was 18.1 (95% CI: 16.8, 21.5) months and 14.1 (95% CI: 12.5, 16.2) months for nivo+ipi and chemotherapy, respectively. Nivo+ipi demonstrated an improvement in OS regardless of histology and the observed treatment effect was larger in subjects with non-epithelioid MPM, traditionally associated with poor responses to standard chemotherapy. In relation to PD-L1 expression, which was not a stratification factor, the improvement was larger in subjects with PD-L1 ≥1%.
- The median **PFS** per BICR was 6.8 (95% CI: 5.6, 7.4) months in the nivo+ipi arm and 7.20 (95% CI: 6.9, 8.1) months in the chemotherapy arm (HR = 1.00 [95% CI: 0.82, 1.21]).
- BICR assessed **ORR** was 40% (95% CI: 34.1, 45.4) in the nivo+ipi arm and 43% (95% CI: 37.1, 48.5) in the chemotherapy arm.

- The median **DoR** was longer for confirmed responders in the nivo+ipi arm relative to confirmed responders in the chemotherapy arm (11.0 [95% CI: 8.1, 16.5] vs. 6.7 [95% CI: 5.3, 7.1] months, respectively).

3.3. Uncertainties and limitations about favourable effects

Since study CA209743 did not include a comparator arm with nivolumab or ipilimumab monotherapy, the additive efficacy of ipilimumab to nivolumab is substantiated primarily on an improvement in ORR, with support from PFS and OS, observed for the combination over nivolumab in a phase 2 study in patients with 2L+ MPM, and on available evidence that anti CTLA4 monoclonal antibodies might not be effective as monotherapy in the treatment of MPM, i.e. based on cross-study comparisons (only).

Efficacy assessment was based on radiological response by mRECIST or RECIST 1.1 criteria but they were updated by a protocol amendment when 68% of subjects had already been randomized which could have influenced the consistency of the efficacy results. The primary endpoint was not affected when presenting results for subjects randomized before and after the amendment, median OS and HR were similar in both cases. Some differences were expected for secondary endpoints as the amendment included a re-definition of the radiology assessment of these endpoints. Median PFS for both groups was not significantly changed before and after the revised protocol although, for the nivo+ipi arm, it was reduced from 6.97 to 5.59 months. The reported HR (95% CI) was 0.91 (0.69, 1.19) and 1.09 (0.82, 1.45), respectively. It is noted that the reported HR for the overall population was 1.00 (0.82, 1.21) and, as said, it did not support the PFS benefit, in fact, numerically favoured the chemotherapy arm vs. the nivo+ipi arm. The same discordance/trend was shown in the new data provided. Although the ORR was not highly affected by the revision, there was a remarkable before/after difference for the DOR in the immunotherapy group: 14.59 vs. 8.18 months respectively. In the chemotherapy arm, the DOR was also reduced after the amendment (7.03 vs. 5.68 months) but the difference was not as worrying as in the nivo+ipi arm. The MAH clarified that the same criteria were applied during all the trial and that the amendment was only intended to adapt the protocol to the criteria already used by the BICR. Although some slight unbalances across arms before and after the amendment are observed that could have played a role (most likely differences in the distribution of patients by histology and PD-L1 expression), their contribution to the observed findings need to be very cautiously interpreted and no definitive conclusions can be drawn. Having said that, and although a level of uncertainty still remains, there appears to be no strong justification to question the reliability of radiologically assessed endpoints based on the differences found in the requested post-hoc analysis. In addition, it is considered that PFS, ORR and DOR results are of interest for prescribers and are therefore included in the PI, along with an explicit reference to their descriptive nature.

The primary endpoint was changed during the study, as originally OS and PFS were co-primary. Also, the hierarchical testing of the secondary endpoints was removed and all results for these endpoints became descriptive. Due to the extensive nature of MPM, tumour measurements have always been challenging and the progression-free survival (PFS) endpoint is considered imprecise to evaluate clinical benefit.

Benefit reported with this combination in OS does not match the results from PFS and ORR, where better results for chemotherapy arm were observed. Also, for OS, crossing of the KM curves is observed, probably due to early deaths of non-responder subjects. This is in line with results from other immunotherapy studies.

The observed median OS was comparable in the epithelioid and non-epithelioid group. The non-epithelioid group are known for its chemoresistancy, indicating that the immunotherapy combination might be of particular advantage for this tumour type. Indeed, in this subgroup, the observed OS benefit was larger than in the epithelioid group. These subgroup results are included in the PI.

Regarding OS results in predefined subsets, they generally concur with the overall results but some of them (≥75 y, stage I-II, prior radiotherapy, Asia region, PD-L1 expression <1%) seemed to favour the chemotherapy treatment. Once again, small sample size for these subsets and the lack of stratification factors among them precludes any firm conclusion. Benefit in elderly patients (≥75 years) is also unclear, as OS results did not evidently favour the combination and its toxicity should be included in the benefit/risk assessment for this population. This information is included in the PI. Further, efficacy results by tumour PD-L1 expression are also included in the PI to inform treating physicians.

3.4. Unfavourable effects

The safety profile of nivolumab 360 mg administered every 3 weeks in combination with 1 mg/kg ipilimumab administered every 6 weeks is based on the pivotal study CA209743 (N=584). However, the posology used in this study differed from the one proposed to be included in the SmPC for unresectable MPM as subjects received nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks.

The median (95% CI) duration of nivolumab plus ipilimumab administration was 5.55 (4.63, 6.70) with a median number of doses of 12 for nivolumab and 4 for ipilimumab. The proportion of subjects who received at least 90% of the planned dose intensity were 68.7% for nivolumab and 82.3% for ipilimumab.

The frequency of any-grade all-causality AEs was above 95%. The most frequently reported (≥ 25%) all-causality AEs were diarrhoea (31.3%), fatigue (28.7%), dyspnoea (26.0%). Grade 3-4 all-causality AEs were reported in 53% of subjects, being the most frequent (≥5%) increased lipase (5.3%).

The overall frequency of all-causality SAEs was 54.7%. The frequency of SAEs that were considered related to study treatment was 21.3%. The most frequently reported (≥5%) SAE was malignant neoplasm progression (10.7%).

The frequency of any-grade and grade 3-4 of AEs leading to discontinuation was 29.3% and 19.7%, respectively. Most of them were considered treatment-related. The main AEs that lead to treatment discontinuation were colitis, diarrhoea, infusion related reactions, and pneumonitis (<2.5% each).

The majority of select AEs were Grade 1-2 and most were considered drug-related by the investigator. The most frequently reported drug-related select AE categories in the nivolumab plus ipilimumab arm were skin (36.0%), gastrointestinal (22.0%), hepatic and hypersensitivity/infusion reaction (12.0% each). Compared to previous studies in different tumour types, a higher frequency of hypersensitivity/infusion reactions select AE was found in CA209743 (12% vs. ≤ 4%). In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM (n = 300), with a minimum follow-up of 22.1 months, the most frequent adverse reactions (≥ 10%) were fatigue (43%), diarrhoea (31%), rash (30%), musculoskeletal pain (27%), nausea (24%), decreased appetite (24%), pruritus (21%), constipation (19%), and hypothyroidism (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). This has been reflected in the SmPC.

The most frequent (≥ 10%) IMAEs were rash (13%) and hypothyroidism/thyroiditis (11.7%). The majority of the events were resolved with the administration immune-modulating medications (mostly systemic corticosteroids) with a median time to resolution between 0.14 to 17.14 weeks. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

OESIs were reported in 4.7% subjects which included grade 3-4 events of pancreatitis, encephalitis, myositis, myasthenic syndrome, uveitis and myocarditis.

Three (1.0%) subjects died due to study drug toxicity including one patient with pneumonitis, one patient with toxicity of immunotherapy and development of neurological complications, and one with acute heart failure.

With regards to laboratory findings, increased ALT and AST worsened to grade 3-4 relative to baseline occurred in 7.1% of subjects, each. In addition, abnormal increases or decreases in TSH were found with nivolumab plus ipilimumab treatment.

Finally, the rate of discontinuation due to AEs (excluding progression terms) was higher in subjects aged 75 years or older, relative to all patients who received nivolumab plus ipilimumab (34.6% vs. 27.7%). In the same way, higher frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs. the overall population for SAEs (65.3% vs 54.7%) and SAEs requiring hospitalization/prolongation (62.7% vs 50.7).

3.5. Uncertainties and limitations about unfavourable effects

The cross-study comparison found a higher frequency of hypersensitivity/infusion reactions in CA209743 compared to the studies CA209227 Part 1, CA209214, and CA209142. This has been reflected on the SmPC.

3.6. Effects Table

Effects table for Study CA209743 (clinical data cut-off: 15-Jan-2020; database lock: 03-Apr-2020) - Nivolumab in combination with ipilimumab for the first line treatment of adult patients with unresectable malignant pleural mesothelioma.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Median OS	Time from randomisation to the date of death of any course	months (95% CI)[a]	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)	HR 0.74 (96.6%CI[a]: 0.60, 0.91) p=0.002[b]	
Median PFS	Time from randomisation to the date of death of any course PFS measured by adapted mRECIST and/or RECIST 1 criteria	months (95% CI)[a]	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)	HR 1.00 (95% CI: 0.82, 1.21)	
ORR	Confirmed CR + PR Using adapted mRECIST and/or RECIST v.1. criteria	N, % (95% CI)	40 (34.1, 45.4)	43 (37.1, 48.5)		
Median DoR	Time between the date of first confirmed response to data to first documented BICR assessed tumour progression or death Using adapted mRECIST and/or RECIST v.1. criteria	months (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)	See ORR	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
AEs G3-4	All causality -Adverse events of grade 3 or 4	%	53	42.6	Open-label design	SCS
SAEs	All causality -Serious adverse events	%	54.7	25		SCS
AEs leading to discontinuations	All causality -Discontinuations due to adverse events	%	29.3	20.4		SCS
Diarrhoea	Common adverse event	%	AE: 31.3% G3/4:4.0%	NA		SCS
Fatigue	Common adverse event	%	AE: 28.7% G3/4:3.0%	NA		SCS
Dyspnoea	Common adverse event	%	AE: 26.0% G3/4:<3.0%	NA		SCS

Abbreviations: Abbreviations: CSR: clinical study report, OS: overall survival, PFS: progression free survival, ORR: overall response rate, DoR

ORR, PFS and DOR per adapted mRECIST or RECIST 1 criteria.

[a]: Stratified Cox proportional hazard model

[b]: Stratified log-rank p-value; p-value is compared with the allocated alpha of 0.0345 for this interim analysis

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, the reported results of nivolumab in combination with ipilimumab for the 1L treatment of MPM are considered relevant. Malignant pleural mesothelioma is a rare disease with poor prognosis and usually diagnosed in advanced stages. Standard treatment, platinum+pemetrexed chemotherapy, was authorized in 2004 showing a survival benefit of 12 months, but no other treatment combination has showed better results thus far.

This application is based on the results from a phase III randomized trial, in comparison with the SOC in this treatment line. Subjects were randomized by histology and gender, two widely known prognostic factors for this condition. Nivolumab + ipilimumab have showed a clinically relevant survival benefit of 4 months. This was also observed for most of the predefined subgroups. The median OS was comparable between both histologies (epithelioid and non-epithelioid), with a larger improvement in the non-epithelioid group which has been associated with poor responses to chemotherapy. In relation to PD-L1 expression, which was not a stratification factor, the improvement in OS with nivo+ipi treatment over chemotherapy was larger in subjects with PD-L1 positive tumours.

No improvement was shown for PFS and ORR with the nivolumab + ipilimumab combination, compared with chemotherapy, but quite durable responses were reported for responders. This phenomenon has been previously observed in other immunotherapy studies but the question about what subgroups of patients may not benefit from this kind of treatment remains unclear at this time.

Regarding the contribution of monocomponents, the additive efficacy of ipilimumab to nivolumab has sufficiently been shown in a qualitative manner based primarily on an improvement in ORR, with support from PFS and OS, observed for the combination over nivolumab, and on available evidence that anti CTLA4 monoclonal antibodies might not be effective as monotherapy in the treatment of MPM, even though based on cross-study comparisons (only). Further, the fact that an improvement in OS has been reported in study CA209743 with the proposed combination vs. current standard of care in the intended treatment setting substantially reduces the concerns (reference is made to EMEA/H/C/WS1278).

From a safety point of view, the safety profile of nivolumab in combination with ipilimumab in the intended indication appears consistent with that previously observed in other indications and is in line with the already known safety profile of each component. The combination of nivolumab + ipilimumab is characterised by a high incidence of adverse events, especially those considered immunomediated.

3.7.2. Balance of benefits and risks

Combination treatment with nivolumab and ipilimumab, in comparison with chemotherapy standard treatment, resulted in an OS benefit in the treatment of MPM which has a very poor prognosis.

The overall safety profile of the combination appears to be similar to that observed with the same combination in other indications and seems in line with the safety profile of both components

The benefit-risk balance is therefore considered positive in the target population as represented by the adopted indication.

3.7.3. Additional considerations on the benefit-risk balance

The final adopted indication is:

For OPDIVO:

OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable malignant pleural mesothelioma.

For YERVOY:

YERVOY in combination with nivolumab is indicated for the first line treatment of adult patients with unresectable malignant pleural mesothelioma.

3.8. Conclusions

The overall B/R of nivolumab + ipilimumab in the claimed indication is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) for combination treatment of Opdivo and Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 (for both products) and 6.6 (for Opdivo) of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.1 for Opdivo and version 30.1 for Yervoy of the RMP has also been adopted.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Opdivo-H-C- 3985-WS-1881" and 'Yervoy-H-C-2213-WS-1881'