EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 September 2020
EMA/CHMP/603938/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/WS1783

Worksharing applicant (WSA) Bristol-Myers Squibb Pharma EEIG

Yervoy	ipilimumab
OPDIVO	nivolumab

Procedure No. EMEA/H/C/xxxx/WS/1783

Note

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

Table of contents

List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AUC	area under the plasma drug concentration-time curve
ASBI	average symptom burden index
AST	aspartate aminotransferase
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BOR	best overall response
BSR	bioanalytical study report
CFR	Code of Federal Regulations
CGP	comprehensive genomic profile
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CSP	clinical safety program
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
DBL	database lock
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EQ-5D-3L	EuroQol 5 dimensional 3 level
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FMI	Foundation Medicine, Inc.
FPFV	first patient first visit
GCP	Good Clinical Practice
GI	gastrointestinal
HCRU	healthcare resource utilization
HLA	human leukocyte antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IWRS	Interactive Web Response System
KM	Kaplan-Meier
KRI	key risk indicators
KRAS	Kirsten rat sarcoma
LCSS	Lung Cancer Symptom Scale
LPLV	last patient last visit
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference

miRNA	micro RNA
mut/Mb	mutations per megabase
MSI	microsatellite instability
Nab	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NSQ	non-squamous
OESI	other events of special interest
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PFS2	progression-free survival after next line of treatment
PK	pharmacokinetics
PP	persistent positive
PR	partial response
PRO	patient reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
RSDV	reduced source data verification
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SMP	site monitoring plan
SmPC	summary of product characteristics
SNP	single-nucleotide polymorphisms
SOP	standard operating procedure
SQ	squamous
STK11	serine threonine kinase 11
TMB	tumour mutational burden
TTR	time to response
UI	utility index
UK	United Kingdom
ULN	upper limit normal
UTD	unable to determine
VAS	visual analogue score
WHO	World Health Organization

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 10 March 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 metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations for combination of OPDIVO and Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.0 of the RMP for OPDIVO and version 27.0 for Yervoy have 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 (an) EMA Decision(s) P/0003/2017 for Yervoy and P/0026/2020 for OPDIVO on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0003/2017 for Yervoy was completed and the P/0026/2020 for OPDIVO was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0003/2017.

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	10 March 2020
Start of procedure	28 March 2020
CHMP Rapporteur's preliminary assessment report circulated on	27 May 2020
PRAC Rapporteur's preliminary assessment report circulated on	29 May 2020
PRAC RMP advice and assessment overview adopted by PRAC on	11 June 2020
CHMP Rapporteur's updated assessment report circulated on	20 June 2020
Request for supplementary information and extension of timetable adopted by the CHMP on	25 June 2020
WSA's responses submitted to the CHMP on	16 July 2020
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on	19 August 2020
PRAC Rapporteur's preliminary assessment report on the WSA's responses circulated on	20 August 2020
PRAC RMP advice and assessment overview adopted by PRAC on	3 September 2020
CHMP Rapporteur's updated assessment report on the WSA's responses circulated on	11 September 2020
CHMP opinion adopted on	17 September 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Lung cancer is the most common cancer worldwide, with 1.8 million new cases diagnosed yearly, and an estimated 1.6 million deaths worldwide (Brambilla et al, 2014). NSCLC represents approximately 85% of all lung cancers and includes SQ and NSQ cell carcinoma, which encompasses a variety of histological subtypes including adenocarcinoma, large cell carcinoma, and less common subtypes (Brambilla et al, 2014; Brambilla et al, 2001; Beasley et al, 2005; Schrump et al, 2011 chapter 75).

State the claimed therapeutic indication

The proposed indication is:

- *OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults with no EGFR or ALK positive tumour mutations.*

- *YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults with no EGFR or ALK positive tumour mutations.*

Management

Until recently, platinum-doublet chemotherapy alone was the recommended standard of care for first-line treatment of metastatic NSCLC, with the exception of small subgroups of patients with NSCLC tumours harbouring known driver mutations (eg, EGFR and ALK) (National Comprehensive Cancer Network guidelines and European Society for Medical Oncology [ESMO] guidelines).

Most patients experience disease progression during the first year of treatment, with only 10% to 20% of patients who are progression free at 18 months and less than one-fourth to one-fifth of patients alive at 2 years.

Platinum-based chemotherapy alone remains a treatment option in certain cases of advanced NSCLC, such as when patients are not considered candidates to receive immunotherapy. Platinum doublets are used interchangeably and selected based on physician and patient preferences and comorbidities, with the exception of pemetrexed- and gemcitabine-based doublets, which are reserved for NSQ and SQ histology, respectively. Efforts to improve the efficacy of platinum-based doublet therapies for advanced and metastatic NSCLC have focused on the addition of targeted agents (eg, bevacizumab in NSQ and necitumumab in SQ) or anti-PD-(L)1 immunotherapies and on the use of maintenance therapy (eg, erlotinib or pemetrexed in NSQ) for subjects who did not progress on platinum-based first-line therapy.

Despite the recent approvals of anti-PD-(L)1 immunotherapies (either as monotherapy or in combination with chemotherapy), outcomes in 1L NSCLC remain poor, with potential improvement in long-term OS likely limited to the subjects with tumours responding to the anti-PD-(L)1 component of the regimens. Incremental responses observed with the addition of chemotherapy to PD-(L)1 inhibitors improve initial disease control, but appear to be rapidly lost, and unlikely to contribute to improved long-term outcomes.

Table 1 shows the European Union (EU)-approved first-line treatments for metastatic NSCLC other than those only approved for subgroups defined by genetic driver mutations. To date, no regimens with 2 immunotherapy agents (anti-PD-(L)1 + anti-CTLA-4) with or without chemotherapy are approved for treatment of first-line NSCLC.

Table 1 Agents Approved in the EU for First-line Treatment of Metastatic NSCLC - All Histologies (Excluding Approvals for Subgroups Defined by Genetic Driver Mutations)

Agent	Mechanism	First-line Indication
Pembrolizu-mab	Programmed death receptor-1 (PD-1)-blocking antibody	1) In combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic NSQ NSCLC in adults whose tumors have no EGFR or ALK positive mutations; 2) In combination of carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic SQ NSCLC in adults; 3) As monotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumors express PD-L1 with a ≥ 50% TPS with no EGFR or ALK positive tumor mutations
Atezolizumab	Programmed death-ligand-1 (PD-L1)-blocking antibody	1) In combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic NSQ NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies; 2) As monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab; 3) In combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC
Bevacizumab	VEGF-specific angiogenesis inhibitor	1) In addition to platinum-based chemotherapy, for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC other than predominantly SQ cell histology; 2) In combination with erlotinib, for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSQ NSCLC with EGFR activating mutations
Docetaxel	Microtubule inhibitor	With cisplatin for unresectable, locally advanced or metastatic NSCLC, in patients who have not previously received chemotherapy
Gemcitabine	Nucleoside metabolic inhibitor	In combination with cisplatin for first line treatment of locally advanced or metastatic NSCLC (monotherapy can be considered in elderly patients or those with performance status 2)
Necitumumab	EGFR antagonist	In combination with gemcitabine and cisplatin chemotherapy for the treatment of adult patients with locally advanced or metastatic EGFR expressing SQ NSCLC who have not received prior chemotherapy
Paclitaxel	Microtubule inhibitor	In combination with cisplatin, is indicated for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy
Paclitaxel (albumin-bound)	Microtubule inhibitor	In combination with carboplatin is indicated for the first-line treatment of NSCLC in adult patients who are not candidates for potentially curative surgery and/or radiation therapy
Pemetrexed	Folate analog metabolic inhibitor	In combination with cisplatin for the first line treatment of patients with locally advanced or metastatic NSCLC other than predominantly SQ cell histology
Vinorelbine	Vinca alkaloid	As a single agent or in combination for the first line treatment of stage 3 or 4 NSCLC

Abbreviations: ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; EU: European Union; NSCLC: non-small cell lung cancer; NSQ: non-squamous; PD-L1: programmed death receptor ligand 1; SQ: squamous; TPS: Tumor Proportion Score

Source: current approved product labels

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 (Figure 1 **Mechanisms of action of ipilimumab and nivolumab**).

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

Ipilimumab (ipi) 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.

Adding limited doses of chemotherapy (2 cycles) to the nivo+ipi regimen could further enhance the immunogenic effect of nivo+ipi by releasing neoantigens from apoptosing tumour cells, increasing antigen presentation to dendritic cells, decreasing the myeloid-derived suppressive cells and increasing the ratio of cytotoxic lymphocytes to regulatory T-cells.

Figure 1 Mechanisms of action of ipilimumab and nivolumab
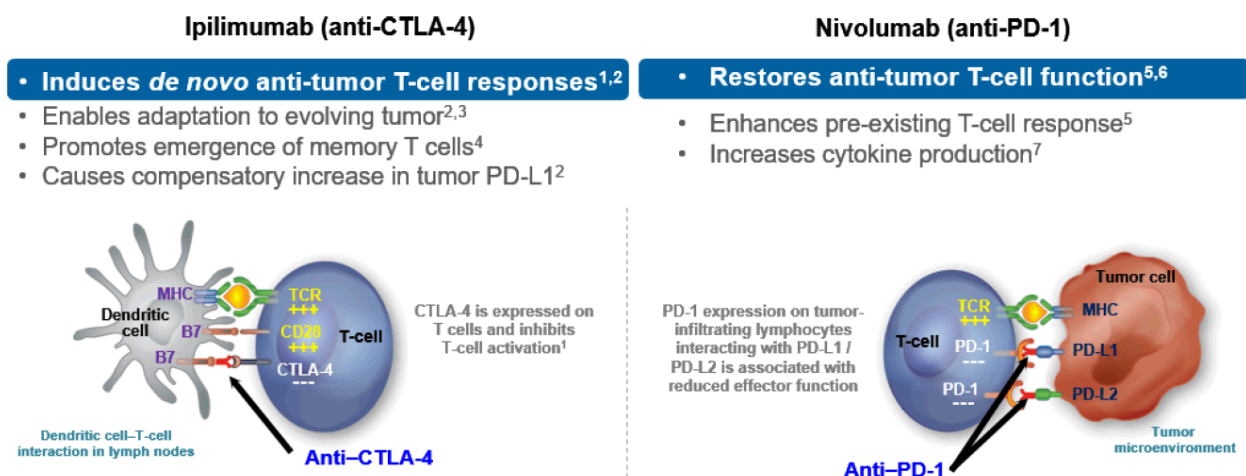
Sources: 1. Pardoll DM. Nat Rev Cancer 2012[53] 2. Wei SC, et al. Cancer Discov 2018[54] 3. Wei SC, et al. Immunity 2019[55] 4. Das R, et al. J Immunol 2015[56] 5. Wang C, et al. Cancer Immunol Res 2014[57] 6. Brahmer JR, et al. J Clin Oncol 2010[58] 7. Hamanishi J, et al. Proc Natl Acad Sci USA 2007[59]

The authorised indications are:

For OPDIVO:

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.

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.

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

<u>Renal cell carcinoma (RCC)</u>
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.

<u>Classical Hodgkin lymphoma (cHL)</u>
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.

<u>Squamous cell cancer of the head and neck (SCCHN)</u>
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.

<u>Urothelial carcinoma</u>
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.

For Yervoy:

<u>Melanoma</u>
YERVOY as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older.

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.

<u>Renal Cell Carcinoma (RCC)</u>
YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

The new proposed indication is the combination of nivolumab with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in adults with no EGFR or ALK positive tumour mutations.

The recommended dose of nivolumab in combination with ipilimumab and chemotherapy is 360 mg nivolumab administered intravenously (IV) Q3W in combination with 1 mg/kg ipilimumab administered IV Q6W, and platinum chemotherapy administered Q3W. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered IV Q3W in combination with 1 mg/kg ipilimumab Q6W. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No Scientific Advice have been requested to CHMP in regard to this development.

2.1.4. General comments on compliance with GCP

As claimed by the applicant, the studies were conducted in accordance with Good Clinical Practice (GCP), as defined by the International Council on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

However, for study CA 209227 a triggered GCP inspection conducted in Q2 2019 revealed system-related deficiencies at the sponsor site and at the CRO, related to a lack of solid measures to prevent dissemination of information to authorised/non authorised personnel within a non-robust and immature risk management system. In these regards the company has provided during assessment reassuring data that indicate that the pivotal study supporting this extension of indication is acceptable on the GCP aspect (see 2.4.3 Discussion on clinical efficacy).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

The clinical studies to support the combination of nivolumab + ipilimumab were Phase I study CA209012 (Cohorts G-J, N-Q). Phase II study CA209568, Phase III study CA209227 and Supportive Phase III study CA209026. However, study CA209227 was amended several times. A triggered GCP inspection revealed system-related deficiencies at the sponsor site and at the CRO related to a lack of solid measures to prevent dissemination of information to authorised/non authorised personnel within a non-robust and immature risk management system. It could not be excluded that the protocol amendments were data-driven, and trial integrity could not be ascertained. Therefore, reliable conclusions could not be drawn, and clinical efficacy was not considered established in any particular target population.

In parallel, mainly due to the crossing of the curves during the first months of treatment with immunotherapy vs. chemotherapy, the development also focussed on the use of the combination of nivolumab and ipilimumab with 2 cycles of chemotherapy. The current application applies for an indication for this treatment combination.

The clinical studies to support this application are:

- Phase II study CA209568 Part 2 (nivo/ipi/chemo)

- Phase III study CA2099LA (nivo/ipi/chemo vs chemo)

- Phase III study CA209227 (nivo/ipi, nivo/chemo, chemo, nivo)

Table 2   An overview for the phase II-III studies to support the application of first line nivolumab + ipilimumab + 2 cycles of chemotherapy for NSCLC.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Treatment Cohorts (Test Product(s): Dosage Regimen, Rte of Administration)	Number of Subjects (treated)	Diagnosis of Patients (Study Population)	Duration of Treatment	Study Status, Type of Report
Pivotal Study: Nivo + Ipi + Chemo									
Efficacy Safety	CA209-9LA (NCT032 15706)	Module 5.3.5.1	For nivo + ipi+ chemo vs chemo: **Primary:** OS **Secondary:** PFS and ORR by BICR; efficacy (OS, PFS and ORR by BICR) by PD-L1; efficacy (OS, PFS and ORR by BICR) by TMB (not included in the CSR)	Phase 3, randomized, open label, study of nivo + ipi + chemo vs chemo	**Nivo + ipi + chemo:** nivo 360 mg IV over 30 min Q3W + ipi 1 mg/kg IV over 30 min Q6W + 2 cycles of histology-based platinum-doublet chemo **Chemo:** 4 cycles of histolog- based platinum-doublet chemo (Subjects with NSQ histology: pemetrexed maintenance allowed)	**Nivo + ipi + chemo:** 358 **Chemo:** 349	Previously untreated NSCLC. Patients with EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	**Nivo + ipi + chemo:** 2 cycles of histology based platinum-doublet chemo; nivo + ipi until PD, unacceptable toxicity, or up to 24 months. Treatment beyond initial investigator-assessed PD permitted if clinical benefit and tolerating nivo + ipi. **Chemo:** Until PD, unacceptable toxicity or completed 4 cycles of platinum-doublet histology based chemo (Subjects with NSQ histology: pemetrexed maintenance allowed until PD or unacceptable toxicity)	Complete Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Treatment Cohorts (Test Product(s): Dosage Regimen, Rte of Administration)	Number of Subjects (treated)	Diagnosis of Patients (Study Population)	Duration of Treatment	Study Status, Type of Report
Supportive Studies									
Efficacy Safety	CA209-568 Part 2 (NCT026 59059)	Module 5.3.5.2	For nivo + ipi + chemo **Primary:** incidence of DLT (within 9 weeks after first dose); safety and tolerability **Secondary:** ORR, PFS by investigator assessment and OS	Phase 2 study to assess the safety of nivo + ipi + chemo	**Nivo + ipi + chemo:** nivo 360 mg IV over 30 min Q3W + ipi 1 mg/kg IV over 30 min Q6W + 2 cycles of histology-based platinum-doublet chemo	**Nivo + ipi + chemo:** 36	Previously untreated NSCLC. Patients treated with prior EGFR or ALK inhibitors were excluded	**Nivo + ipi + chemo:** 2 cycles of histology-based platinum-doublet chemo; nivo + ipi until PD, unacceptable toxicity, or up to 24 months. Treatment beyond initial investigator-assessed PD permitted if clinical benefit and tolerating nivo + ipi.	Complete Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Treatment Cohorts (Test Product(s): Dosage Regimen, Rte of Administration)	Number of Subjects (treated)	Diagnosis of Patients (Study Population)	Duration of Treatment	Study Status, Type of Report
Supportive Studies (continued)									
Efficacy Safety	CA209-227 Part 1 (NCT02477826)	Module 5.3.5.1	**Co-primary**: In PD-L1≥ 1% subjects: OS of nivo + ipi (Arm B) vs Chemo (Arm C) **Co-primary**: In TMB ≥ 10 mut/Mb subjects: PFS (per BICR) of nivo + ipi (Arms B + D) vs Chemo (Arms C + F) **Secondary Objectives:** **PD-L1 Hierarchy** 1. PFS (per BICR) of nivo + chemo (Arm G) vs chemo (Arm F) in PD-L1 < 1% subjects 2. OS of nivo + chemo (Arm G) vs chemo (Arm F) in PD-L1 < 1% subjects 3. OS of nivo (Arm A) vs chemo (Arm C) in PD-L1 ≥ 50% subjects **TMB Hierarchy** 1. PFS (per BICR) of nivo (Arm A) vs chemo (Arm C) in subjects with PD-L1 ≥ 1% and TMB ≥ 13 mut/Mb 2. OS of nivo + ipi (Arms B + D) vs chemo (Arms C + F) in subjects with TMB ≥ 10 mut/Mb regardless of PD-L1 expression level 3. OS of nivo (Arm A) vs chemo (Arm C) in subjects with PD-L1 ≥ 1% and TMB ≥ 13 mut/Mb	Phase 3, randomized, open label, study of nivo, nivo + ipi, or nivo + chemo vs chemo **Part 1a (PD-L1 ≥ 1%):** nivo, nivo+ipi, or chemo (randomized 1:1:1; stratified by SQ vs NSQ) **Part 1b (PD-L1 <1%):** nivo+ipi, nivo+chemo or chemo (randomized 1:1:1; stratified SQ vs NSQ)	**Part 1** **Arm A**: nivo 240 mg IV over 30 min Q2W **Arms B and D:** nivo 3 mg/kg IV over 30 min Q2W + ipi 1 mg/kg IV over 30 min Q6W **Arms C and F:** histology based platinum-doublet chemo in 3-week cycles, up to 4 cycles. **Arm G:** nivo 360 mg over 30 min + chemo IV Q3W up to 4 cycles. Subjects without PD to receive nivo 360 mg Q3W. **Chemo (Arms C, F, and G)** Pemetrexed maintenance allowed for subjects with NSQ histology	**Part 1** **Arm A** (nivo): 391 **Arm B** (nivo + ipi): 391 **Arm C** (chemo): 387 **Arm D** (nivo + ipi): 185 **Arm F** (chemo): 183 **Arm G** (nivo + chemo): 172 **Total:** 1709	Previously untreated NSCLC. Patients with EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	**Nivo + ipi or nivo:** Until PD, unacceptable toxicity, or up to 24 months, whichever was first. Treatment beyond initial investigator assessed PD permitted if clinical benefit and tolerating nivo + ipi or nivo. **Chemo:** Until PD, unacceptable toxicity or completed 4 cycles. (Subjects with NSQ histology: pemetrexed maintenance allowed until PD or unacceptable toxicity)	Complete Part 1 Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Treatment Cohorts (Test Product(s): Dosage Regimen, Rte of Administration)	Number of Subjects (treated)	Diagnosis of Patients (Study Population)	Duration of Treatment	Study Status, Type of Report
Supportive Studies (continued)									
Efficacy Safety	CA209-227 Part 2 (NCT02477826)	Module 5.3.5.1	For nivo + chemo vs chemo: **Primary**: OS in subjects with NSQ histology **Secondary**: *In all randomized subjects*: OS, OS in subjects with TMB ≥ 10 mut/Mb, PFS and ORR using BICR, OS, PFS, and ORR by PD-L1 levels, OS, PFS, and ORR by TMB levels *In subjects with NSQ histology*: OS in subjects with TMB ≥ 10 mut/Mb, PFS and ORR using BICR, OS, PFS, and ORR by PD-L1 levels, OS, PFS, and ORR by TMB levels	Phase 3, randomized, open-label, nivo + chemo vs chemo Stratified by histology (NSQ, SQ), gender (male, female), PD-L1 (≥1%, < 1%)	**Nivo + chemo:** nivo 360 mg IV over 30 min + histology-based platinum-doublet chemo IV Q3W up to 4 (3-week) cycles. Subjects without PD to receive nivo 360 mg IV Q3W. Pemetrexed maintenance allowed for subjects with NSQ histology **Chemo:** histology-based chemo platinum-doublet in 3-week cycles, up to 4 cycles. Pemetrexed maintenance allowed for subjects with NSQ histology	**Nivo + chemo:** 375 **Chemo:** 371	Previously untreated NSCLC. Patients with EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	**Chemo:** Chemo until PD, unacceptable toxicity or 4 cycles. (NSQ: pemetrexed maintenance allowed until PD or unacceptable toxicity) **Nivo + chemo:** see chemo above Subjects with SD, PR, or CR after chemo cycle 4 to continue nivo as maintenance therapy Q3W until PD, unacceptable toxicity or up to 24 months. Nivo treatment beyond initial investigator-assessed PD permitted if clinical benefit and tolerating nivo	Complete Part 2 Final CSR

Abbreviations: ALK - anaplastic lymphoma kinase, BICR - blinded independent central review, chemo - chemotherapy, CSR - clinical study report, DLT - dose-limiting toxicity, EGFR - epidermal growth factor receptor, ipi - ipilimumab, IV - intravenous, nivo - nivolumab, NSCLC - non-small cell lung cancer, NSQ - non-squamous, ORR - objective response rate, OS - overall survival, PD - progressive disease, PD-L1 - programmed cell death ligand 1, PFS - progression-free survival, QXW: every X weeks, SD - stable disease, SQ - squamous, TMB - tumor mutational burden

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.

2.3.2. Pharmacokinetics

Analytical methods

PK bioanalytical Methods

Validated bioanalytical methods were used to support the clinical pharmacology programs of nivolumab and ipilimumab. A total of four analytical methods were used;

  − Serum concentrations of nivolumab were analysed at Syngene International Ltd. (Bangalore, India) using a validated ECL assay (Method BAL-II/MOA/061).

  − Serum concentrations of nivolumab for China subjects were analysed at WuXi AppTec (Shanghai, P. R. China) using a validated ECL assay (Method 14BASM122).

  − Serum concentrations of ipilimumab were analysed at PPD Inc. (Richmond, VA) using a validated ELISA assay (Method ICD 267).

  − Serum concentrations of ipilimumab for China subjects were analysed at WuXi AppTec (Shanghai, P. R. China) using a validated ELISA assay (Method 13BASM127).

In general, all the analytical methods were validated successfully with respect to matrix selectivity, sensitivity, calibration curve fitting, accuracy, precision (total error), MRD, dilution linearity and hook effect, haemolysis and lipemic effect and carryover. Analytes stability was demonstrated for freeze/thaw, room temperature, processed stability and refrigerated stability. Long-term matrix and solution stability was also established.

Since all the four bioanalytical methods to determine the concentration of nivolumab and ipilimumab in study CA2099LA, cross-validations were performed between assay Methods BAL II/MOA/061 and 14BASM122 for nivolumab and Methods ICD 267 and 13BASM127 for ipilimumab (using QCs and incurred patient samples). The results of both cross-validation show that concentrations generated by the two testing labs at PPD and WuXi produced equivalent results for both analytes.

In-study validation

Since additional sample analysis was performed, the data generated was reported in several addenda to the bioanalytical study report. Previous analyses for this study are presented in the RFEA bioanalytical study report issued on January 20th, 2017, in the RFEA2 bioanalytical study report issued on May 22nd, 2017, in the RFEA3 bioanalytical study report addendum 2 issued on February 06th, 2018 and the RFEA3 bioanalytical study report addendum 3 issued on November 07th, 2018.

The in-study validations have been submitted for both clinical studies CA2099LA and CA209227. The in-study validation shows acceptable calibration standards and QCs.

Study samples analysed and reported for nivolumab and ipilimumab in support of studies CA2099LA and CA209227 were covered by the long-term stability demonstrated at nominal at -70 ºC.

The reasons for the samples re-assayed for both analytes in each study are considered acceptable.

The incurred sample re-analysis was performed in study CA2099LA for both analytes. The results show that the ISR measurements were within ±30% deviations.

Table 3.1-1:   Summary of Clinical Studies Included in the Pharmacometric Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule	Analysis
CA184004: A randomized Phase 2 study to determine potential predictive markers of response to MDX-010 (BMS-734016) in patients with unresectable stage III or IV malignant melanoma *Advanced Stage III or Stage IV melanoma who were administered a tetanus booster and influenza or pneumococcal vaccine within 10 days prior to receiving ipilimumab*	Ipi 3 or 10 mg/kg Q3W during induction period (Week 1, 4, 7, and 10), followed by Q12W during maintenance period (starting on Week 24)	90 (randomized 1:1 to 3 and 10 mg/kg ipi)	On D1 and D43, pre-infusion and after 90-min infusion. Three additional samples were taken between D3-7 (post-dose) after week 7 dose, D10-15 (post-dose) after week 7 dose and the pre-dose sample on D64.	Ipi PPK
CA184007: A randomized, double-blind, placebo-controlled, Phase 2 study comparing the safety of ipilimumab administered with or without prophylactic oral budesonide (Entocort™ EC) in patients with unresectable stage III or IV malignant melanoma *Histologic or cytologic diagnosis of unresectable Stage III or IV malignant melanoma*	Ipi 10 mg/kg (given with placebo or budesonide; 90 min infusion) Q3W during induction period (Week 1, 4, 7, and 10), followed by Q12W during maintenance period (starting on Week 24) Note: budesonide was administrated at 9 mg QD until Week 12, tapered to 6 mg QD until Week 14, and finally to 3 mg QD until Week 16	110	<u>Schedule A:</u> On D1 and D43, pre-infusion and 90-min post-infusion. 3 additional samples were taken between D45-49, D52-57, and the pre-dose sample on D64. <u>Schedule B:</u> On D1 and D43, pre-dose and 90-min postinfusion, 24, 72 hr post-infusion, D8 (± 27 hrs), D15 (± 48 hrs); 2 additional pre-dose samples were taken on D22 and D64.	Ipi PPK
CA184008: A multi-center, single arm Phase 2 study of MDX-010 (BMS-734016) monotherapy in patients with previously treated unresectable stage III or IV melanoma *Previously treated unresectable Stage III or IV melanoma*	Ipi 10 mg/kg (90 min infusion) Q3W during induction period (Week 1, 4, 7, and 10), followed by Q12W during maintenance period (starting on Week 24)	144	<u>Schedule A:</u> On D1 and D43, pre-infusion and 90-min post-infusion. 3 additional samples were taken between D3-7 after Week 7 dose, D10-15 after Week 7 dose and the pre-dose sample on D64. <u>Schedule B:</u> On D1 and D43, pre-dose and 90-min post-infusion, 24, 72 hr post-infusion, D8 (± 27 hrs), D15 (± 48 hrs); 2 additional pre-dose samples were taken on D22 and D64.	Ipi PPK
CA184022: A randomized, double-blind, multi-center, Phase 2 fixed dose study of multiple doses of Ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable Stage III or IV melanoma *Advanced Stage III or Stage IV melanoma, who were previously treated with any regimen except a CD-137 agonist or a CTLA4 inhibitor or agonist.*	Ipi 0.3, 3, and 10 mg/kg (90 min infusion) Q3W during induction period (Week 1, 4, 7, and 10), followed by Q12W during maintenance period (starting on Week 24)	210	On D1 and D43 pre-infusion and 90-min post-infusion. 3 additional samples were taken between D3-7 (post-dose) after Week 7 dose, D10-15 (post-dose) after Week 7 dose and the pre-dose sample on D64.	Ipi PPK
CA184396: Phase 2 Study of ipilimumab in Japanese subjects with unresectable or metastatic melanoma *Japanese subjects with unresectable or metastatic melanoma*	Ipi 3 mg/kg, 90 min infusion, Q3W in Japanese subjects	18	On D1 pre and post (1.5 hours) infusion, D22 (Week 4) predose, D43 (Week 7) pre and post infusion, a sample between D46-50 and D53-58 and D64 (Week 10) pre-infusion.	Ipi PPK
MDX1106-01 (CA209001): Phase I, open-label, multicenter, dose-escalation, study to evaluate the safety and pharmacokinetic of BMS-936558 in subjects with selected refractory or relapsed malignancies *Multiple tumor types including melanoma, RCC, and NSCLC*	<u>Single-dose Phase (Cycle 1):</u> Nivo 0.3, 1, 3, or 10 mg/kg (60 min infusion) <u>Re-treatment Phase (Cycle 2):</u> Nivo 0.3, 1, 3, or 10 mg/kg (60 min infusion) on D1 and D29; eligible subjects were treated with the same dose level as in the single-dose phase and could receive additional re-treatment cycles	39	<u>Single-dose Phase:</u> Pre-dose, 30 mins into dosing, immediately post-infusion, and 30 mins, 1, 2, 4, 6, 8, 24, 48, and 72 hrs post-infusion end time; on D8, D15, D22, D29, D43, D57, D71, and D85 <u>Re-treatment Phase:</u> Pre-dose and peak on treatment D1 and D29; single samples on D8, D15, D22, D36, D43, D57, D85, and D113	Nivo PPK

Table 3.1-1: Summary of Clinical Studies Included in the Pharmacometric Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule	Analysis
MDX1106-03 (CA209003): Phase I, open-label, multicenter, multidose, dose-escalation study to evaluate the safety and tolerability of BMS-936558 in subjects with selected advanced or recurrent malignancies *Pathologically verified and advanced or recurrent and progressing colorectal adenocarcinoma, melanoma, NSCLC, castrate resistant prostate adenocarcinoma, and RCC*	Nivo 0.1, 0.3, 1, 3, or 10 mg/kg depending upon tumor type (60 min infusion) Q2W for up to twelve 8-week cycles	338 (290 + 48 from amendment)	<u>Pre-Amendment</u>: C1: EOI and pre-infusion levels on infusion days: D1, D15, D29, and D43 and C2: Single samples were collected <u>Post-Amendment:</u> Serial PK samples were collected from all subjects enrolled in 0.1, 0.3 and 1 mg/kg melanoma cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts. C1: D1 (after 60-min infusion, 4, 8hr), D2, D3, D5, D8, D15), C2: D1 (pre-infusion), C3: D1 (pre-infusion, after 60-min infusion), and D2, D3, D5, D8, D15) Limited PK samples were collected from subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC. C1: D1 (after 60-min infusion), D3, D8, D15), C2D1 (pre-infusion), C3D1 (pre-infusion, after 60-min infusion), and D3, D8, D15 Each treatment cycle is comprised of 4 doses administered on D1, D15, D29, and D43 of the cycle	Nivo PPK
MDX1106-04 (CA209004): A Phase 1b, open-label, multicenter, multidose, dose-escalation study of MDX-1106 (BMS-936558) in combination with ipilimumab (BMS-734016) in subjects with unresectable stage III or stage IV malignant melanoma *Unresectable stage III or stage IV malignant melanoma*	**Cohort 1:** nivo 0.3 mg/kg Q3W for up to 8 doses + ipi 3 mg/kg Q3W for up to 4 doses **Cohort 2:** nivo 1 mg/kg Q3W for up to 8 doses + ipi 3 mg/kg Q3W for up to 4 doses **Cohort 2a:** nivo 3 mg/kg Q3W for up to 8 doses + ipi 1 mg/kg Q3W for up to 4 doses **Cohort 3:** nivo 3 mg/kg Q3W for up to 8 doses + ipi 3 mg/kg Q3W for up to 4 doses **Cohort 6:** nivo 1 mg/kg Q2W for up to 48 doses, following ipi monotherapy administered prior to enrollment **Cohort 7:** nivo 3 mg/kg Q2W for up to 48 doses, following ipi monotherapy administered prior to enrollment **Cohort 8:** 1 mg/kg nivo + 3 mg/kg of ipi, both Q3W for 4 doses, followed by 3 mg/kg nivo alone Q2W for up to 48 doses **Nivo:** 60 min infusion **Ipi:** 90 min infusion	127	Blood samples were collected to estimate peak and trough levels of nivolumab and ipilimumab during the induction and maintenance periods and at follow-up Visit 2.	Ipi PPK
ONO-4538-01 (CA209005): Phase 1 single dose study to evaluate of safety, tolerability, and pharmacokinetics in subjects with progressive or recurrent solid tumors *Melanoma and NSCLC*	Nivo 1, 3, 10, and 20 mg/kg Q3W for 1st dose then Q2W (60 min infusion)	24 (up to 6 subjects are each dose level)	<u>Single-dose phase:</u> D1: 1hr after the start and 2 and 8 hours after EOI, Pre-D2, pre-D3; pre-D4; D8, D15, and D22 or study discontinuation <u>Multiple-dose phase:</u> Before administration on D1; before administration and immediately after the end of administration on D15; and D29 or study discontinuation <u>Extended-treatment phase:</u> Before administration on D1; before administration on D15 and D29; before administration and immediately after the end of administration on D43 and D57	Nivo PPK

Table 3.1-1: Summary of Clinical Studies Included in the Pharmacometric Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule	Analysis
CA209012: A multi-arm phase I safety study of nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab or as monotherapy in first-line or in switch maintenance in subjects with stage IIIB/IV non-small cell lung cancer (NSCLC) *First-line or in switch maintenance in subjects with Stage IIIB/IV NSCLC*	Arm A: nivo 10 mg/kg + Chemo Q3W for 4 cycles then nivo 10 mg/kg Q3W Arm B: nivo 10 mg/kg + Chemo Q3W for 4 cycles then nivo 10 mg/kg Q3W Arm C10: nivo 10 mg/kg + Chemo Q3W for 4 cycles then nivo 10 mg/kg Q3W Arm C5: nivo 5 mg/kg + Chemo Q3W for 4 cycles then nivo 5 mg/kg Q3W Arm D: nivo 5 mg/kg Q3W + bevacizumab 15 mg/kg Q3W Arm E: nivo 3 mg/kg Q2W + erlotinib 150 mg QD Arm F: nivo 3 mg/kg Q2W Arm G/H: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 cycles then nivo 3 mg/kg Q2W Arm I/J: nivo 3 mg/kg + ipi 1 mg/kg Q3W for 4 cycles followed by nivo 3 mg/kg Q2W Arm K/L: nivo 3 mg/kg Q2W as switch maintenance Arm M: nivo 3 mg/kg Q2W Arm N: nivo 1 mg/kg + ipi 1 mg/kg Q3W for 4 cycles then nivo 3 mg/kg Q2W Arm O: nivo 1 mg/kg Q2W + ipi 1 mg/kg Q6W Arm P: nivo 3 mg/kg Q2W + ipi 1 mg/kg Q12W Arm Q: nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W Arm R: nivo 3 mg/kg Q2W + ipi 0.3 mg/kg Q6W Arm S: nivo 3 mg/kg Q4W + ipi 1 mg/kg Q12W One cycle = 2 weeks for arms O, P, Q	369 subjects dosed from arms showing on the left	Arms A to N: Nivo PK samples: C1D1 (predose and EOI), C1D8, C2D1 (predose), C4D1 (predose and EOI), C4D8, C7D1 (predose and EOI), C7D8 First 2 follow-up visits Arms O, Q, and R Ipi PK samples: Predose: Dose number of ipi 1, 2, 3, 5 and every alternative ipi dose (dose 7, 9, 11 etc) EOI: Dose number of ipi 1, 3, 5 First two follow up visits Arm P and S Ipi PK samples: Predose: Dose number of ipi 1, 2, 3, 5 and every ipi dose (dose 6, 7, 8 etc) EOI: Dose number of ipi 1, 3, 5 First two follow up visits	Nivo and Ipi PPK
	One cycle = 3 weeks for the first 4 cycles and 2 weeks for Cycle 5+ for Arms G/H, I/J, NF (nivo monotherapy)			
CA209017: An open-label, randomized phase 3 trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non small cell lung cancer (NSCLC) *SQ NSCLC*	Nivo 3 mg/kg (60 min infusion) Q2W	132	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion and pre-infusion at C2 and C3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	Nivo PPK
CA209026: An open-label, randomized, phase 3 trial of nivolumab versus investigator's choice chemotherapy as first-line therapy for stage IV or recurrent PD-L1+ non-small cell lung cancer (NSCLC) *PD-L1+ SQ and non-SQ NSCLC*	Nivo 3 mg/kg (60 min infusion) Q2W	330	Arm A: D1 at C1, C3, C8 and D1 every 8 cycle, and 2 follow samples Arm B: (crossover subjects for nivo treatment): D1 at C1, C3, C8 and D1 every 8 cycle, and 2 follow samples	Nivo PPK
CA209057: An open-label, randomized phase 3 trial of BMS-936558 (Nivolumab) versus docetaxel in previously treated advanced or metastatic non-squamous cell non-small cell lung cancer (NSCLC) *NSQ NSCLC*	Nivo 3 mg/kg (60 min infusion) Q2W	287	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion and pre-infusion at C2 and C3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	Nivo PPK
CA209063: A single-arm phase 2 study of BMS-936558 in subjects with advanced or metastatic squamous cell non-small cell lung cancer who have received at least two prior systemic regimens *SQ NSCLC*	Nivo 3 mg/kg (60 min infusion) Q2W	100	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion, and pre-infusion at C2 and C3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle.	Nivo PPK

Table 3.1-1: Summary of Clinical Studies Included in the Pharmacometric Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule	Analysis
CA209067: Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. *Previously untreated, unresectable or metastatic melanoma*	A: nivo 3 mg/kg Q2W B: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses then nivo 3 mg/kg Q2W C: ipi 3 mg/kg Q3W for a total of 4 doses + nivo-placebo on Weeks 1, 3, 4, and 5 for Cycles 1 and 2 then Q2W Nivo: 60 min infusion Ipi: 90 min infusion	915 (randomized to 1:1:1 ratio)	Pre-dose sample at D1, Wk 3 and 4 C1D1, C2D1, C3, and C4, and first 2 follow-up visits (approximately up to 100 days from discontinuation study drug); EOI samples at D1 C1, C2, and C4	Ipi PPK
CA209069: Phase 2, randomized, double blinded, study of nivolumab (BMS-936558) in combination with Ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma *Previously untreated, unresectable or metastatic melanoma*	A: Part I: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses; Part II: nivo 3 mg/kg Q2W B: Part I: nivo-placebo + ipi 3 mg/kg Q3W for 4 doses; Part II: nivo-placebo Q2W Nivo: 60 min infusion Ipi: 90 min infusion	150	Pre- dose sample at C1D1 (Part I), C3 (Part I), C5 (Part II), and C11 (Part II) and first 2 follow-up visits (approximately up to 100 days from the discontinuation study drug)	Ipi PPK
CA209227: An open-label, randomized phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent non-small cell lung cancer (NSCLC) (CheckMate 227, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 227) *Chemotherapy-naïve stage IV or recurrent NSCLC*	**Arm A:** nivo 240 mg (30 min infusion) Q2W **Arm B/D:** nivo 3 mg/kg (30 min infusion) Q2W + ipi 1 mg/kg (60 min infusion) Q6W **Arm G:** nivo 360 mg (30 min infusion) Q3W in combination with chemotherapy **Arm H:** nivo 360 mg (30 min infusion) Q3W in combination with chemotherapy	1514	Arms B/D for ipi: Blood samples were collected at C1D1 (ipi dose 1), C2D1 (ipi dose 2), C4D1 (ipi dose 2), C10D1 (ipi dose 4), D1 of every 9th cycle after C10D1 until end of study treatment (or ipi Dose 7, 10, 13...etc). First 2 follow-up visits (approximately up to 100 days from discontinuation of study drug	Nivo and Ipi PPK
CA209511: Phase IIIb/IV, randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in subjects with previously untreated, unresectable or metastatic melanoma *Unresectable or metastatic melanoma*	**Arm A:** nivo 3 mg/kg + ipi 1 mg/kg (N3I1) Q3W for 4 doses then nivo 480 mg Q4W **Arm B:** nivo 1 mg/kg + ipi 3 mg/kg (N1I3) IV Q3W for 4 doses then nivo 480 mg Q4W Part 1 (first 4 cycles): nivo + ipi for 4 doses Part 2 (starting from cycle 5): nivo monotherapy period Nivo: 30 min IV infusion Ipi: 30 min IV infusion	173 subjects per arm	<u>Part 1 (1 cycle = 3wks):</u> Nivo and ipi predose and EOI samples were collected at C1D1, C2D1, C3D1. <u>Part 2 (1 cycle = 4wks):</u> Nivo predose samples were collected at C5D1, C9D1, and D1 of every 4th cycle after C9D1 until discontinuation of study treatment, and 2 follow-up visits. Nivo EOI samples were collected at C5D1. Ipi predose samples were collected at C5D1	Ipi PPK
CA209568: A study of nivolumab in combination with ipilimumab (part 1); and nivolumab plus ipilimumab in combination with chemotherapy vs chemotherapy alone (part 2) as first line therapy in stage IV non-small cell lung cancer (NSCLC) *Stage IV NSCLC*	Part 1: Nivo 3 mg/kg Q2W (30 min infusion) + ipi 1 mg/kg Q6W (30 min infusion) until disease progression or unaccepted toxicity, or maximum 2 years. nivo and ipi can be reinitiated for progression for up to 1 additional year Part 2: Induction: Nivo 360 mg Q3W (30 min infusion) + ipi 1 mg/kg Q6W (30 min infusion) + histology-based platinum-oublet chemotherapy (2 cycles) Post Induction: Continued treatment with nivo 360 mg Q3W + ipi 1 mg/kg Q6W until progression or unacceptable toxicity, and up to 24 months	Part 1: 277 subjects Part 2: 51 subjects	Part 1: C1D1, C2D1, C4D1, C10D1, and D1 of every 9th cycle after C10D1 Each 3-weeks is a cycle Part 2: Predose and EOI time points on C1D1, and at predose only on C2D1, C4D1, C10D1 and at D1 of every 6th cycle (18 weeks) until discontinuation or up to a maximum of 24 months of treatment	Nivo and Ipi PPK
CA209817: A Phase IIIb/IV Safety Trial of Flat Dose Nivolumab in Combination with Ipilimumab in Participants with Non-Small Cell Lung Cancer. *Stage IV NSCLC*	Cohort A: 1L NSCLC Cohort B: 2L NSCLC Cohort C:1L NSCLC High TMB Cohort A1: Special Population All cohorts received nivo flat dose 240 mg IV Q2W + ipi 1 mg/kg IV Q6W	1100 subjects	Blood samples were collected from all cohorts at predose and EOI time points on C1D1, and at predose only on C1D15, C2D15, C4D15 and at D15 of every 4th cycle (24 weeks) until discontinuation or up to a maximum of 24 months of treatment	Nivo and Ipi PPK

Table 3.1-1:   Summary of Clinical Studies Included in the Pharmacometric Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule	Analysis
CA2099LA: A Phase 3, Randomized Study of Nivolumab plus Ipilimumab in Combination with Chemotherapy vs Chemotherapy alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC) (CheckMate 9LA, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9LA) *Stage IV NSCLC previously untreated advanced disease*	Treatment Arm Induction: Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + histology-based platinum-doublet chemotherapy (2 cycles) Post Induction: Continued treatment with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W until progression or unacceptable toxicity, and up to 24 months. Control Arm Histology-based platinum-doublet chemotherapy (4 cycles). Chemotherapy administered on day 1 of each 3-week cycle.	~ 700	Blood samples were collected from the Treatment Arm at predose and EOI time points on C1D1, and at predose only on C2D1, C4D1, C10D1 and at D1 of every 6th cycle (18 weeks) until discontinuation or up to a maximum of 24 months of treatment	Nivo and Ipi PPK

[a] as per protocol.
Abbreviations: C = Cycle; D = Day; EOI = end of infusion; ipi = ipilimumab; nivo = nivolumab; NSCLC = non-small cell carcinoma; NSQ = non-squamous; PD-L1 = programmed death-ligand 1; PK = pharmacokinetics; PPK = population pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks; QD = daily; RCC = renal cell carcinoma; SQ = squamous.

Pharmacokinetics in the target population

Nivolumab dataset

Table 3.3.1.1-1: Subjects Included in the Nivolumab Population Pharmacokinetic Analysis Dataset

| Study | No. of Subjects | | | |
	Nivolumab Treated	PK Database[a]	Flagged	Included (% of subjects in PK Database)
MDX1106-01 (CA209001)	39	39	0	39 (100.0)
MDX1106-03 (CA209003)	306	310	6	304 (98.1)
ONO-4538-01 (CA209005)	17	17	0	17 (100.0)
CA209012[b]	287	281	2	279 (99.3)
CA209017	132	127	2	125 (98.4)
CA209026	393	393	52	341 (86.8)
CA209057	287	282	2	280 (99.3)
CA209063	117	118	3	115 (97.5)
CA209227	1514	1418	114	1304 (92)
CA209568[c]	324	323	20	303 (93.8)
CA209817	962	839	19	820 (97.7)
CA2099LA	358	360	7	353 (98.1)
Total	4736	4507	227	4280 (95)

[a] eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS) included subjects with at least 1 PK sample collected, including baseline pre-dose samples (before nivolumab treatment) and samples collected after nivolumab treatment.

[b] Subjects treated with nivo 10 mg/kg + Chemo Q3W for 4 cycles then nivo 10 mg/kg Q3W (Arms A, B, and C10), nivo 5 mg/kg + Chemo Q3W for 4 cycles then nivo 5 mg/kg Q3W (Arm C5), or nivo 5 mg/kg Q3W + bevacizumab 15 mg/kg Q3W (Arm D) were excluded from the PK database as the number of subjects treated with these dosing regimens is too small for analysis.

[c] 36 subjects from Study CA209568 Part 2 were treated with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-based chemotherapy; of which, 36 were included in the PK database.

Table 3.3.1.2-1:   Samples Included in the Nivolumab Population Pharmacokinetic Analysis Dataset

Study	PK DB[a]	Missing dose or sample information	Duplicate samples at same time (set up for NCA)	Day 1 Pre-Dose[d]	LLOQ[b]	Other[c]	Outliers	Samples included in analysis (%)[f]
MDX1106-01 (CA209001)	915	33	0	40	42	0	1	799 (91.3)
MDX1106-03 (CA209003)	3733	32	76	331	74	2	8	3210 (94.4)
ONO-4538-01 (CA209005)	285	0	0	17	0	0	0	268 (100.0)
CA209012	1881	17	0	259	36	0	3	1566 (96.5)
CA209017	585	0	0	122	9	0	1	453 (97.8)
CA209026	1172	17	0	369	8	1	0	777 (96.8)
CA209057	1355	13	0	267	15	0	3	1057 (97.2)
CA209063	549	4	0	113	2	0	1	429 (98.4)
CA209227	4828	76	0	1170	30	6	6	3540 (96.8)
CA209568[e]	1392	13	0	274	17	5	0	1083 (96.9)
CA209817	2913	45	0	793	19	0	1	2055 (96.9)
CA2099LA	1143	21	0	0	5	0	6	1111 (97.2)
Total	20751	271	76	3755	257	14	30	16348 (96.2)

Abbreviations: DB = database; LLOQ = lower limit of quantification; NCA = non-compartmental analysis; PK = pharmacokinetic.

[a] Samples in eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS). All which are included in the analysis dataset with flag as noted

[b] LLOQ: Post-dose nivolumab serum concentration values below the lower limited of quantification.

[c] Hepatocellular carcinoma subjects in CA209227, subjects with increasing concentration for ATAPD > 10000 hours, subjects without valid samples, samples with nivolumab serum concentration > 2000 ug/mL, or samples collected using incorrect kit.

[d] Day 1 Pre-dose samples are excluded from the calculation of the percentage of samples included in analysis.

[e] A total of 138 PK samples from subjects in Study CA209568 Part 2 treated with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-based chemotherapy were included in the PK database; of which, 127 samples were included in the analysis.

f Samples included in analysis / (PK DB - Day 1 Pre-Dose) = %

Nivolumab serum concentration values below the LLOQ were flagged in the PPK analysis dataset and excluded from the analysis. Dataset records of missing nivolumab serum concentrations corresponding to PK samples that were collected were retained in the analysis dataset but were flagged and excluded from the analysis.

Missing dose data (infusion duration, dosing time, dosing amount) were imputed as described below to enable inclusion of PK samples associated with subsequent doses. However, nivolumab serum concentrations in the PPK analysis dataset were flagged and excluded from the analysis if the PK sample date/time was missing. Dose data with missing date were not included in the analysis.

Figure 3.3.1.5-3: Distribution Plots of Baseline Demographic and Laboratory Covariates
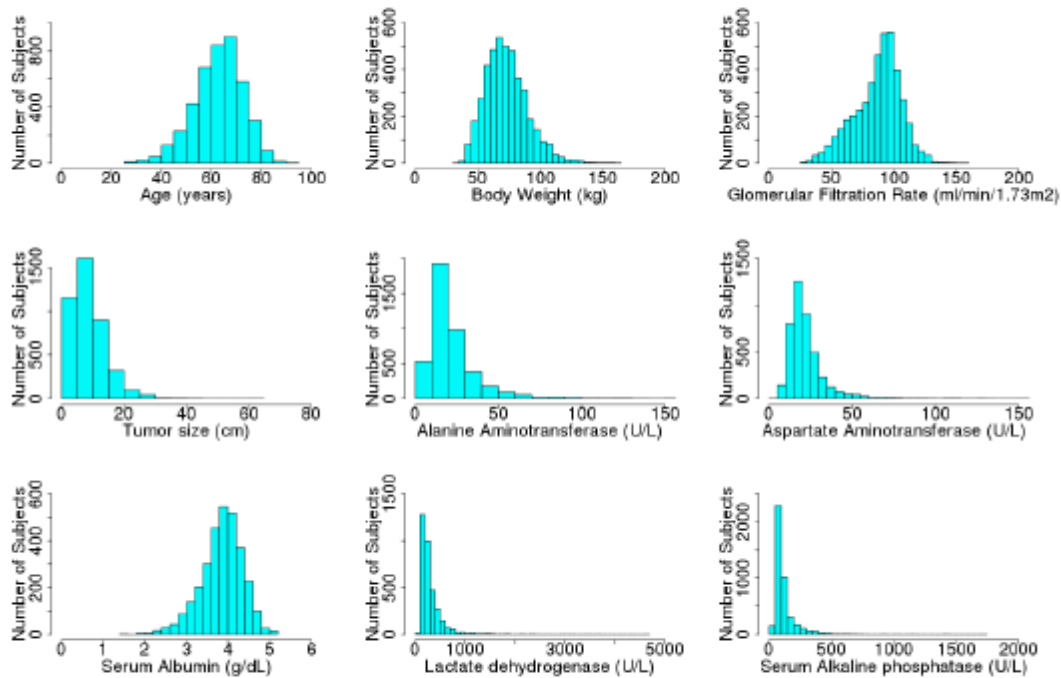
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final/R

R-Program Source: Analysis-Directory/scripts/plot_data.R

Source: Analysis-Directory/plots/Figure3.3.1.5-3.png

Table 3.3.1.5-1: Summary of Variables in the Nivolumab Population Pharmacokinetic Analysis Dataset

Covariate	Summary N= 4280
Sex N (%)	
Male	2732 (63.8)
Female	1548 (36.2)
Race N (%)	
Missing	3 (0.1)
White	3659 (85.5)
Black/African American	120 (2.8)
Asian	420 (9.8)
American Indian/Alaska Native	10 (0.2)
Native Hawaiian/Other Pacific Islander	1 (0.0)
Others	45 (1.1)
Unknown	22 (0.5)
Baseline Performance Status N (%)	
Missing	2 (0.0)
0	1474 (34.4)
1	2714 (63.4)
2	88 (2.1)
3	2 (0.0)
Tumor Type N (%)	
Missing	1 (0.0)
NSCLC	4058 (94.8)
MEL	120 (2.8)
Others	101 (2.4)
Liver Dysfunction Groups N (%)	
Missing	45 (1.1)
GROUP A: Normal	3886 (90.8)
GROUP B: Mild	344 (8.0)
GROUP C: Moderate	5 (0.1)
Nominal Dose of Nivolumab	
0.1 mg/kg	17 (0.4)
0.3 mg/kg	24 (0.6)
1.0 mg/kg	189 (4.4)
3.0 mg/kg	1860 (43.5)
10.0 mg/kg	157 (3.7)
20.0 mg/kg	3 (0.1)
240.0 mg	1148 (26.8)
360.0 mg	882 (20.6)
Nominal First Dose for Ipilimumab (mg/kg)	
0 (not treated with Ipilimumab)	2131 (49.8)
1	2125 (49.6)
3	24 (0.6)
Nominal Frequency for Ipilimumab (week)	
Not treated with Ipilimumab	2131 (49.8)
3	80 (1.9)
6	2033 (47.5)
12	36 (0.8)
Treatment	
nivo	1638 (38.3)
nivo+ipi	1760 (41.1)
nivo+chemo	493 (11.5)
nivo+ipi+chemo	389 (9.1)
Line of therapy	
1	2963 (69.2)
>1	1317 (30.8)

Table 3.3.1.5-1: **Summary of Variables in the Nivolumab Population Pharmacokinetic Analysis Dataset**

```
-------------------------------------------------------------------------------
Covariate                                          Summary
                                                   N= 4280
-------------------------------------------------------------------------------
Best overall response
Missing                                            102 (2.4)
CR                                                 101 (2.4)
PR                                                 1202 (28.1)
SD                                                 1583 (37.0)
PD                                                 1029 (24.0)
NE                                                 230 (5.4)
NA                                                 33 (0.8)

BOR Criteria
Missing                                            67 (1.6)
RECIST v1.0                                         304 (7.1)
RECIST v1.1                                         3909 (91.3)

Age (years)
Mean (SD)                                          63.3 (9.84)
Median (Min, Max)                                  64 (26, 91)

Baseline Body Weight (kg)
Mean (SD)                                          73.5 (17)
Median (Min, Max)                                  71.6 (34.9, 162)
Missing N (%)                                      4 (0.0935)

Baseline eGFR (ml/min/1.73m2)
Mean (SD)                                          87 (18.8)
Median (Min, Max)                                  90.2 (25.1, 158)
Missing N (%)                                      30 (0.701)

Baseline Lactate Dehydrogenase (U/L)
Mean (SD)                                          309 (264)
Median (Min, Max)                                  228 (74, 4619)
Missing N (%)                                      869 (20.3)

Baseline Serum Albumin (g/dL)
Mean (SD)                                          3.9 (0.498)
Median (Min, Max)                                  3.9 (1.5, 5.2)
Missing N (%)                                      1206 (28.2)

Baseline Alanine Aminotransferase (U/L)
Mean (SD)                                          22.9 (16.1)
Median (Min, Max)                                  18 (1, 157)
Missing N (%)                                      50 (1.17)

Baseline Aspartate Aminotransferase (U/L)
Mean (SD)                                          22.9 (12.2)
Median (Min, Max)                                  20 (2, 164)
Missing N (%)                                      53 (1.24)

Baseline Serum Alkaline Phosphatase (U/L)
Mean (SD)                                          120 (95.2)
Median (Min, Max)                                  93 (23, 1746)
Missing N (%)                                      69 (1.61)

Baseline Tumor Size (cm)
Mean (SD)                                          8.73 (5.46)
Median (Min, Max)                                  7.6 (0.6, 61.5)
Missing N (%)                                      142 (3.32)
-------------------------------------------------------------------------------
```

Source: Appendix 3.3.1.5-3.
Abbreviations: BOR = best overall response; CR = complete response; eGFR = estimated glomerular filtration rate; ipi = ipilimumab; MEL = melanoma; NA = missing or not reported; NE = unevaluable; nivo = nivolumab; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; SD = standard deviation or stable disease (for BOR values).

Ipilimumab dataset

Table 3.3.2.1-1: Subjects Included in the Ipilimumab Population Pharmacokinetic Analysis Dataset

Study	No. of Subjects			
	Ipilimumab Treated	PK Database[a]	Flagged	Included (% of subjects in PK Database)
CA184004	82	81	1	80 (98.8)
CA184007	115	115	1	114 (99.1)
CA184008	155	154	6	148 (96.1)
CA184022	214	194	15	179 (92.3)
CA184396	20	20	0	20 (100.0)
CA209004	94	94	1	93 (98.9)
CA209012	197	189	3	186 (98.4)
CA209067	624	629	8	621 (98.7)
CA209069	140	138	20	118 (85.5)
CA209227	576	561	44	517 (92.2)
CA209511	358	354	8	346 (97.7)
CA209568[b]	324	324	22	302 (93.2)
CA209817	962	840	35	805 (95.8)
CA2099LA	358	361	12	349 (96.7)
Total	4219	4054	176	3878 (95.7)

[a] eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS) included subjects with at least 1 PK sample collected, including baseline pre-dose samples (before ipilimumab treatment) and samples collected after ipilimumab treatment

[b] 36 subjects from Study CA209568 Part 2 were treated with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-based chemotherapy; of which, 36 were included in the PK database.

Table 3.3.2.2-1: Samples Included in the Ipilimumab Population Pharmacokinetic Analysis Dataset

Study	PK DB[a]	Missing dose or sample information	Duplicate samples at same time (set up for NCA)	Day 1 Pre-Dose	LLOQ[b]	Other[c]	|CWRES| >6	Sample included in analysis (%)[d]
CA184004	469	0	0	78	1	51	2	337 (86.2)
CA184007	737	0	0	107	7	43	1	579 (91.9)
CA184008	862	0	0	131	2	88	0	641 (87.7)
CA184022	967	0	0	174	0	80	2	711 (89.7)
CA184396	146	0	0	0	21	0	0	125 (85.6)
CA209004	1311	4	31	143	79	7	10	1037 (88.8)
CA209012	740	8	0	106	114	5	5	502 (79.2)
CA209067	3497	20	0	609	42	0	7	2819 (97.6)
CA209069	440	6	0	130	43	0	0	261 (84.2)
CA209227	2225	36	0	512	425	3	0	1249 (72.9)
CA209511	1980	83	0	353	17	134	9	1384 (85.1)
CA209568[e]	1364	12	0	277	240	0	0	835 (76.8)
CA209817	2900	106	0	798	51	3	2	1940 (92.3)
CA2099LA	1101	62	0	0	39	0	2	998 (90.6)
Total	18739	337	31	3418	1081	414	40	13418 (87.6)

Abbreviations: CWRES = conditional weighted residuals; DB = database; LLOQ = lower limit of quantification; NCA = non-compartmental analysis; PK = pharmacokinetic.

[a] Samples in eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS). All which are included in the analysis dataset with flag as noted

[b] LLOQ: Post-dose Ipilimumab serum concentration values below the lower limited of quantification.

[c] Hepatocellular carcinoma subjects in CA209227, samples with duplicate sample ID, duplicate samples with different concentration, samples with suspect concentration value, mismatch samples, and EOI samples with ATAPD > 5 hours.

[d] Day 1 Pre-dose samples are excluded from the calculation of the percentage of samples included in analysis

[e] 138 PK samples from subjects in Study CA209568 Part 2 treated with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-based chemotherapy were included in the PK database; of which, 114 samples were included in the analysis.

Ipilimumab serum concentration values below the LLOQ were flagged in the PPK analysis dataset and excluded from the analysis.

Dataset records of missing ipilimumab serum concentrations corresponding to PK samples that were collected were retained in the analysis dataset but were flagged and excluded from the analysis.

Missing dose data (infusion duration, dosing time, dosing amount) were imputed as described below to enable inclusion of PK samples associated with subsequent doses. However, ipilimumab serum concentrations in the PPK analysis dataset were flagged and excluded from the analysis if the PK sample date/time was missing. Dose data with missing date were not included in the analysis.

Figure 3.3.2.5-3: Distribution Plots of Baseline Demographic and Laboratory Covariates
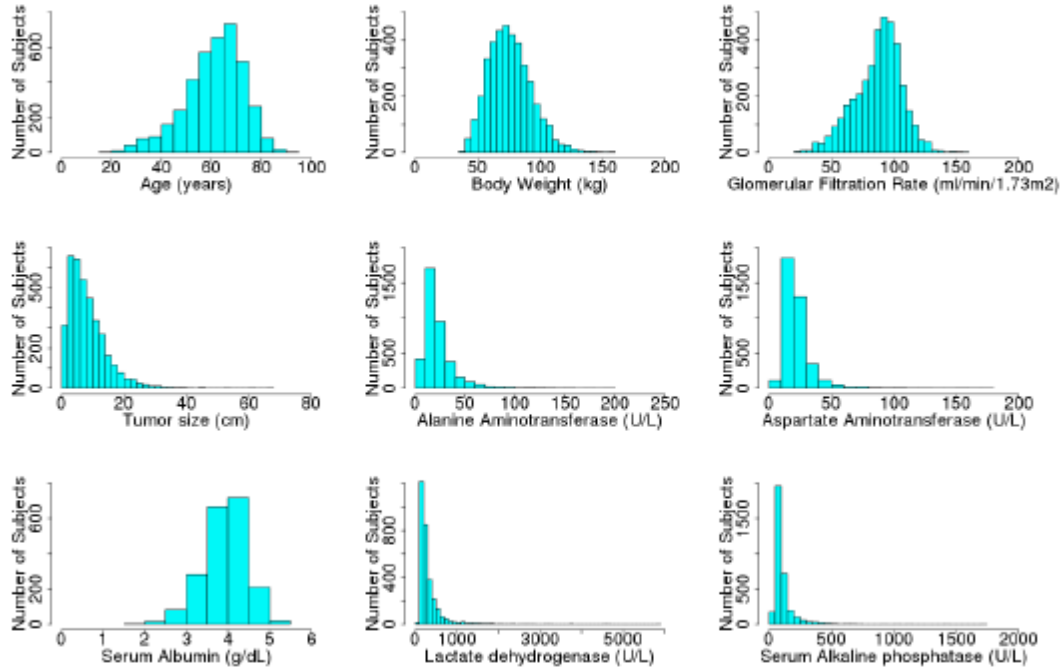
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final/R

R-Program Source: Analysis-Directory/scripts/plot_data.R

Source: Analysis-Directory/plots/Figure3.3.2.5-3.png

Table 3.3.2.5-1: Summary of Variables in the Ipilimumab Population Pharmacokinetic Analysis Dataset

Covariate	Summary N= 3878
Sex N (%)	
Missing	1 (0.0)
Male	2414 (62.2)
Female	1463 (37.7)
Race N (%)	
Missing	2 (0.1)
White	3555 (91.7)
Black/African American	55 (1.4)
Asian	204 (5.3)
American Indian/Alaska Native	6 (0.2)
Others	26 (0.7)
Unknown	30 (0.8)
Baseline Performance Status N (%)	
Missing	4 (0.1)
0	1987 (51.2)
1	1808 (46.6)
2	76 (2.0)
3	3 (0.1)
Tumor Type N (%)	
Missing	1 (0.0)
Melanoma	1719 (44.3)
SQ Non-small cell lung cancer	604 (15.6)
NSQ Non-small cell lung cancer	1554 (40.1)
Liver Dysfunction Groups N (%)	
Missing	560 (14.4)
GROUP A: Normal	3021 (77.9)
GROUP B: Mild	283 (7.3)
GROUP C: Moderate	13 (0.3)
GROUP D: Severe	1 (0.0)
Nominal Dosing of Nivolumab N (%)	
0 (not treated with Nivolumab)	893 (23.0)
0.3 mg/kg	14 (0.4)
1 mg/kg	707 (18.2)
3 mg/kg	1074 (27.7)
240 mg	805 (20.8)
360 mg	385 (9.9)
Nominal Dosing of Ipilimumab in mg/kg N (%)	
0.3	58 (1.5)
1.0	2326 (60.0)
3.0	1134 (29.2)
10.0	360 (9.3)
Line of therapy (%)	
1	3003 (77.4)
>1	875 (22.6)
Best overall response	
Missing	479 (12.4)
CR	173 (4.5)
PR	959 (24.7)
SD	1124 (29.0)
PD	884 (22.8)
NE	242 (6.2)
NA	17 (0.4)
BOR Criteria	
Missing	441 (11.4)
mWHO	193 (5.0)
RECIST v1.1	3244 (83.7)

Table 3.3.2.5-1: Summary of Variables in the Ipilimumab Population Pharmacokinetic Analysis Dataset

Covariate	Summary N= 3878
Age (years)	
Mean (SD)	61.6 (11.7)
Median (Min, Max)	63 (18, 91)
Missing N (%)	1 (0.0258)
Baseline Body Weight (kg)	
Mean (SD)	76.4 (17.3)
Median (Min, Max)	75 (36.8, 160)
Missing N (%)	2 (0.0516)
Baseline eGFR (ml/min/1.73m2)	
Mean (SD)	87.5 (18.9)
Median (Min, Max)	90 (21, 158)
Missing N (%)	27 (0.696)
Baseline Lactate Dehydrogenase (U/L)	
Mean (SD)	320 (324)
Median (Min, Max)	222 (74, 5868)
Missing N (%)	828 (21.4)
Baseline Serum Albumin (g/dL)	
Mean (SD)	3.97 (0.505)
Median (Min, Max)	4 (1.9, 5.3)
Missing N (%)	1887 (48.7)
Baseline Alanine Aminotransferase (U/L)	
Mean (SD)	23.8 (17.2)
Median (Min, Max)	19 (1, 195)
Missing N (%)	27 (0.696)
Baseline Aspartate Aminotransferase (U/L)	
Mean (SD)	23.3 (12.7)
Median (Min, Max)	20 (2, 179)
Missing N (%)	32 (0.825)
Baseline Serum Alkaline Phosphatase (U/L)	
Mean (SD)	110 (87.4)
Median (Min, Max)	87 (23, 1746)
Missing N (%)	563 (14.5)
Tumor Size (cm)	
Mean (SD)	8.42 (6.22)
Median (Min, Max)	7 (0.9, 67.2)
Missing N (%)	121 (3.12)

Source: Appendix 3.3.2.5-3.
Abbreviations: BOR = best overall response; CR = complete response; eGFR = estimated glomerular filtration rate; ipi = ipilimumab; MEL = melanoma; NA = missing or not reported; NE = unevaluable; nivo = nivolumab; NSCLC = non-small cell lung cancer; NSQ = non-squamous; PD = progressive disease; PR = partial response; SD = standard deviation or stable disease (for BOR values); SQ = squamous.

Nivolumab Base model

Base model development consisted of re-estimating parameters of the previously developed full model (with ipilimumab combination effect removed), which had been developed to characterise PK for nivolumab combination therapy in subjects with previously untreated NSCLC.

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, and line of therapy, tumour type on CL, BBWT and sex on VC, BBWT on Q, BBWT on VP, and PS on EMAX. Parameter estimates for this model are presented in Table 5.1.1.1-1. Baseline albumin was not included as a covariate as more than 20% of subjects have missing values. The stability of the base model was assessed by the condition number calculated from eigenvalues in the NONMEM output. The condition number of the base model was found to be 141, indicating the base model was stable (as the value is < 1000).

Table 5.1.1.1-1: Parameter Estimates of the Base Nivolumab Population Pharmacokinetic Model

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	12.1	0.314 (2.59)	11.5 - 12.8
VC_{REF} [L]	θ_2	4.20	0.0319 (0.758)	4.14 - 4.27
Q_{REF} [mL/h]	θ_3	34.8	2.34 (6.72)	30.2 - 39.4
VP_{REF} [L]	θ_4	2.81	0.0933 (3.32)	2.63 - 2.99
CL_{BBWT}	θ_7	0.452	0.0329 (7.27)	0.388 - 0.517
CL_{GFR}	θ_9	0.148	0.0260 (17.5)	0.0974 - 0.199
CL_{FEMALE}	θ_{12}	-0.206	0.0147 (7.13)	-0.235 - -0.177
CL_PS_1	θ_{13}	0.115	0.0162 (14.2)	0.0829 - 0.147
CL_{RAAA}	θ_{14}	0.0606	0.0339 (55.9)	-0.00575 - 0.127
CL_{RAAS}	θ_{15}	-0.114	0.0199 (17.5)	-0.153 - -0.0750
VI_{BBWT}	θ_{16}	0.567	0.0283 (4.99)	0.512 - 0.623
VI_{FEMALE}	θ_{17}	-0.143	0.0138 (9.66)	-0.170 - -0.116
$EMAX_{REF}$	θ_{18}	-0.363	0.0308 (8.48)	-0.423 - -0.302
CL_{T50}	θ_{19}	1.61E+03	67.5 (4.19)	1.48E+03 - 1.75E+03
CL_{HILL}	θ_{20}	2.48	0.342 (13.8)	1.81 - 3.15
CL_{MEL}	θ_{21}	0.0916	0.0439 (47.9)	0.00551 - 0.178
CL_{OTH}	θ_{22}	-0.0135	0.0283 (209)	-0.0690 - 0.0419
CL_{LINE}	θ_{31}	0.0281	0.0145 (51.7)	-3.76E-04 - 0.0565
$EMAX\_PS_1$	θ_{34}	-0.0717	0.0224 (31.2)	-0.116 - -0.0278
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.118 (0.344)	0.00602 (5.09)	0.106 - 0.130
ZVI [-]	$\omega_{2,2}$	0.0690 (0.263)	0.00594 (8.61)	0.0573 - 0.0806
$ZEMAX$ [h]	$\omega_{4,4}$	0.0491 (0.222)	0.00831 (16.9)	0.0328 - 0.0654
$ZCL{:}ZVI$	$\omega_{1,2}$	0.0464 (0.514)	0.00383 (8.26)	0.0389 - 0.0539
Residual Error				
$PERR$ [-]	θ_6	0.229	0.00375 (1.64)	0.222 - 0.236

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

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

Source: Analysis Directory/nm/base/reports/base_RTF1.rtf

Note: CL_{REF} is the typical value in a reference subject weighing 80 kg, white male with PS=0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg.

Note: Eta shrinkage (%): ETA_CL: 13.6; ETA_VC: 36.5; ETA_EMAX: 54.9; EPS shrinkage (%): 17.1

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

[b] 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 $\sigma_{i,j}$)

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

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

Figure 5.1.1.1-1: Observed versus Predicted Population and Individual Concentration in Nivolumab Monotherapy and Combination Therapy (Base Nivolumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd

Source: Analysis Directory/nm/base/plots/obs-pred/obs-pred-regimen.png

Source: Analysis Directory/nm/base/plots/obs-pred/obs-ipred-regimentry.png

Note: Solid red line represents linear regression line; Solid black line represents line of identity.

Figure 5.1.1.1-2: CWRES versus Time after First Dose in Nivolumab Monotherapy and Combination Therapy (Base Nivolumab Population Pharmacokinetic Model)
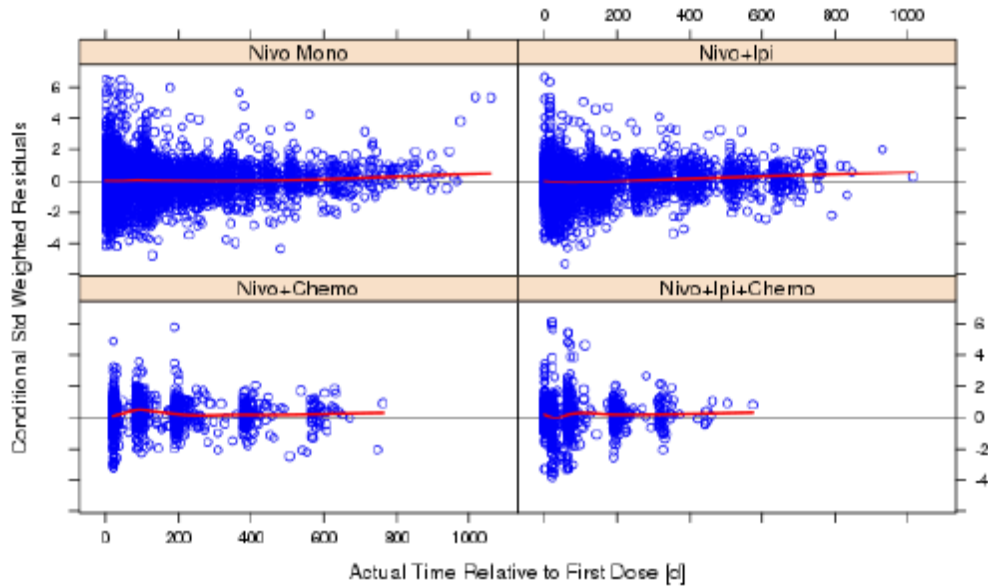
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd

Source: Analysis Directory/nm/base/plots/resid/cwres-time-group.png

Note: Solid red line represents locally weighted smooth line.

Figure 5.1.1.1-3: CWRES versus Time after Previous Dose in Nivolumab Monotherapy and Combination Therapy (Base Nivolumab Population Pharmacokinetic Model)
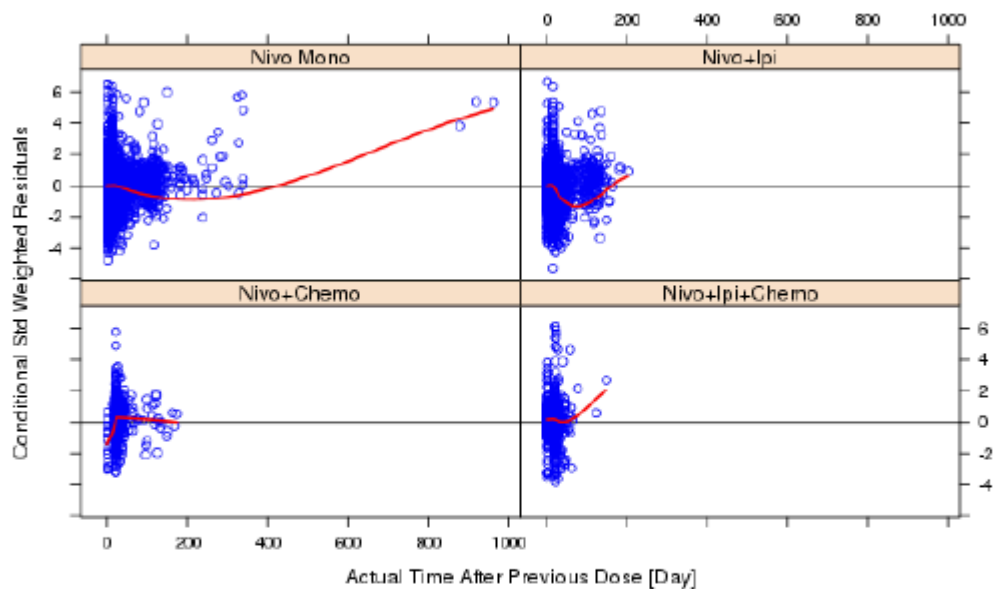
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd

Source: Analysis Directory/nm/base/plots/resid/cwres-timeprev-group.png

Note: Solid red line represents locally weighted smooth line.

Figure 5.1.1.1-4: CWRES versus Population Predicted Serum Concentration in Nivolumab Monotherapy and Combination Therapy (Base Nivolumab Population Pharmacokinetic Model)
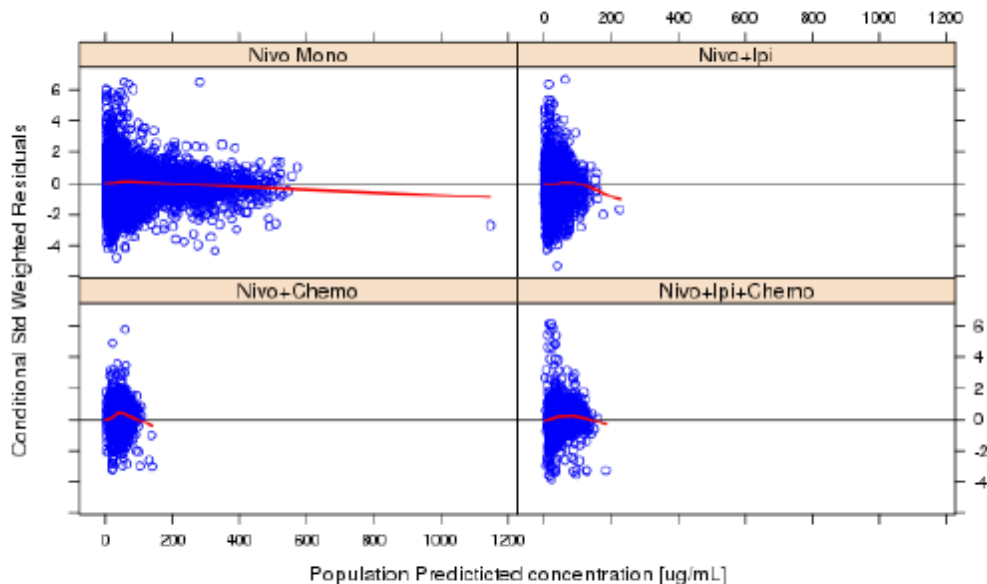
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final
R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd
Source: Analysis Directory/nm/base/plots/resid/cwres-pred-group.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Nivolumab final model

The full model was developed from the base model by incorporating additional covariates representing the effect of regimens of ipilimumab and/or chemotherapy coadministration on the CL of nivolumab. Similar to the previous analysis, the effect of ipilimumab coadministration on baseline CL is constant and remains present even after ipilimumab dosing is stopped. Serum albumin has previously been shown to be a significant covariate for nivolumab CL, but it was not included in the full model as data were not available for all the studies in the prior analysis.

$$CL0_i = CL0_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{CL_{BBWT}} \cdot \left(\frac{eGFR_i}{eGFR_{REF}} \right)^{CL_{GFR}} \cdot e^{CL_{IPI1Q3W} \cdot I_{IPI1Q3W}}$$
$$\cdot e^{CL_{IPI1Q6W} \cdot I_{IPI1Q6W}} \cdot e^{CL_{IPI1Q12W} \cdot I_{IPI1Q12W}} \cdot e^{CL_{IPI3Q3W} \cdot I_{IPI3Q3W}} \cdot e^{CL_{CHEMO} \cdot I_{CHEMO}}$$
$$\cdot e^{CL_{IPICHEMO} \cdot I_{IPICHEMO}} \cdot e^{CL_{MEL} \cdot I_{MEL}} \cdot e^{CL_{OTHER} \cdot I_{OTHER}} \cdot e^{CL_{LINE} \cdot I_{LINE}}$$
$$\cdot e^{CL_{FEMALE} \cdot I_{FEMALE}} \cdot e^{CL_{PS} \cdot I_{PS}} \cdot e^{CL_{RAAA} \cdot I_{RAAA}} \cdot e^{CL_{RAAS} \cdot I_{RAAS}} \cdot e^{\eta CLi}$$

$$EMAX_i = EMAX_{REF} + EMAX_{PS} \cdot I_{PS} + EMAX_{IPICO} \cdot I_{IPICO} + EMAX_{IPICHEMO} \cdot I_{IPICHEMO} + \eta EMAX_i$$

$$CL_{i,t} = CL0_i \cdot exp \left(\frac{(EMAX_i) \cdot t^{CL_{HILL}}}{T50_i{}^{CL_{HILL}} + t^{CL_{HILL}}} \right), CL_{SS,i} = CL0_i \cdot exp(EMAX_i)$$

$$VC_i = VC_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{VC_{BBWT}} \cdot e^{VC_{FEMALE} \cdot I_{FEMALE}} \cdot e^{\eta VCi}$$

$$Q_i = Q_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{CL_{BBWT}} \cdot e^{\eta_{Qi}}$$

$$VP_i = VP_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{VC_{BBWT}} \cdot e^{\eta_{VP_i}}$$

Coadministration with ipilimumab 1 mg/kg Q6W and 2 cycles of chemotherapy resulted in a 9.6% decrease in nivolumab CL compared with nivolumab monotherapy. Coadministration with ipilimumab 1 mg/kg Q6W resulted in an 8% increase in nivolumab CL compared with nivolumab monotherapy. Coadministration with ipilimumab 1 mg/kg Q3W or 3 mg/kg Q3W resulted in a 23% and 25% increase in nivolumab CL, respectively. Coadministration with chemotherapy resulted in a 13.1% decrease in nivolumab CL. Coadministration with ipilimumab 1 mg/kg Q12W did not have a statistically significant effect on nivolumab CL (95% CI included null value). Nivolumab CL was 12% higher in melanoma subjects than in NSCLC subjects. The conditional number of the base model was found to be 192, indicating the base model was stable (as the value is < 1000).

Table 5.1.1.2-1: Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	11.9	0.321 (2.69)	11.4 - 12.6
VC_{REF} [L]	θ_2	4.22	0.0322 (0.763)	4.15 - 4.28
Q_{REF} [mL/h]	θ_3	34.6	2.72 (7.88)	29.6 - 40.9
VP_{REF} [L]	θ_4	2.77	0.0954 (3.44)	2.57 - 2.95
CL_{BBWT}	θ_7	0.439	0.0324 (7.39)	0.365 - 0.502
CL_{GFR}	θ_9	0.155	0.0255 (16.5)	0.105 - 0.209
CL_{FEMALE}	θ_{12}	-0.218	0.0144 (6.61)	-0.248 - -0.189
CL_PS_1	θ_{13}	0.117	0.0163 (13.9)	0.0875 - 0.151
CL_{RAAA}	θ_{14}	0.0501	0.0344 (68.7)	-0.0153 - 0.121
CL_{RAAS}	θ_{15}	-0.0888	0.0192 (21.6)	-0.127 - -0.0540
VI_{BBWT}	θ_{16}	0.569	0.0286 (5.03)	0.512 - 0.627
VI_{FEMALE}	θ_{17}	-0.144	0.0139 (9.65)	-0.171 - -0.116
$EMAX_{REF}$	θ_{18}	-0.366	0.0332 (9.07)	-0.430 - -0.307
CL_{T50}	θ_{19}	1.64E+03	75.5 (4.61)	1.50E+03 - 1.79E+03
CL_{HILL}	θ_{20}	2.35	0.284 (12.1)	1.89 - 3.08
CL_{MEL}	θ_{21}	0.114	0.0446 (39.0)	0.0294 - 0.206
CL_{OTH}	θ_{22}	0.00968	0.0359 (371)	-0.0576 - 0.0774
CL_IPII_{3W}	θ_{27}	0.207	0.0483 (23.4)	0.110 - 0.311
CL_IPII_{6W}	θ_{28}	0.0770	0.0159 (20.7)	0.0445 - 0.111

Table 5.1.1.2-1: **Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model**

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
CL_IPI1_{12W}	θ_{29}	-0.00364	0.0529 (1.45E+03)	-0.127 - 0.110
CL_IPI3_{3W}	θ_{30}	0.223	0.0631 (28.3)	0.0910 - 0.352
CL_{LINE}	θ_{31}	0.0346	0.0172 (49.6)	0.00276 - 0.0673
CL_{CHEMO}	θ_{32}	-0.140	0.0250 (17.8)	-0.187 - -0.0936
$EMAX_{IPICO}$	θ_{33}	-0.0116	0.0288 (248)	-0.0677 - 0.0441
$EMAX\_PS_1$	θ_{34}	-0.0713	0.0232 (32.5)	-0.121 - -0.0270
$CL_{IPICHEMO}$	θ_{35}	-0.101	0.0314 (31.2)	-0.161 - -0.0385
$EMAX_{IPICHEMO}$	θ_{36}	-0.0366	0.0361 (98.4)	-0.104 - 0.0368
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.111 (0.334)	0.00537 (4.82)	0.101 - 0.126
ZV1 [-]	$\omega_{2,2}$	0.0689 (0.263)	0.00595 (8.63)	0.0572 - 0.0806
ZEMAX [h]	$\omega_{4,4}$	0.0503 (0.224)	0.00854 (17.0)	0.0340 - 0.0684
ZCL:ZV1	$\omega_{1,2}$	0.0454 (0.517)	0.00373 (8.22)	0.0380 - 0.0525
Residual Error				
PERR [-]	θ_6	0.229	0.00365 (1.59)	0.221 - 0.236

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

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

Source: Analysis Directory/nm/full/reports/full_RTF1.rtf

Note 1: CL_{REF} is the typical value in a reference subject weighing 80 kg, white male with PS=0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg.

Note 2: Eta shrinkage (%): ETA_CL: 14.1; ETA_VC: 36.5; ETA_EMAX: 54.7; EPS shrinkage (%): 16.9

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

[b] 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 $\sigma_{i,j}$)

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

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

Figure 5.1.1.2-2: Observed versus Predicted Population Average and Individual Concentration in Nivolumab Monotherapy and Combination Therapy (Full Nivolumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd

Source: Analysis Directory/nm/full/plots/obs-pred/obs-pred-regimen.png

Source: Analysis Directory/nm/full/plots/obs-pred/obs-ipred-regimentry.png

Note: Solid red line represents linear regression line; Solid black line represents line of identity.

Figure 5.1.1.2-3: CWRES versus Time after First Dose in Nivolumab Monotherapy and Combination Therapy (Full Nivolumab Population Pharmacokinetic Model)
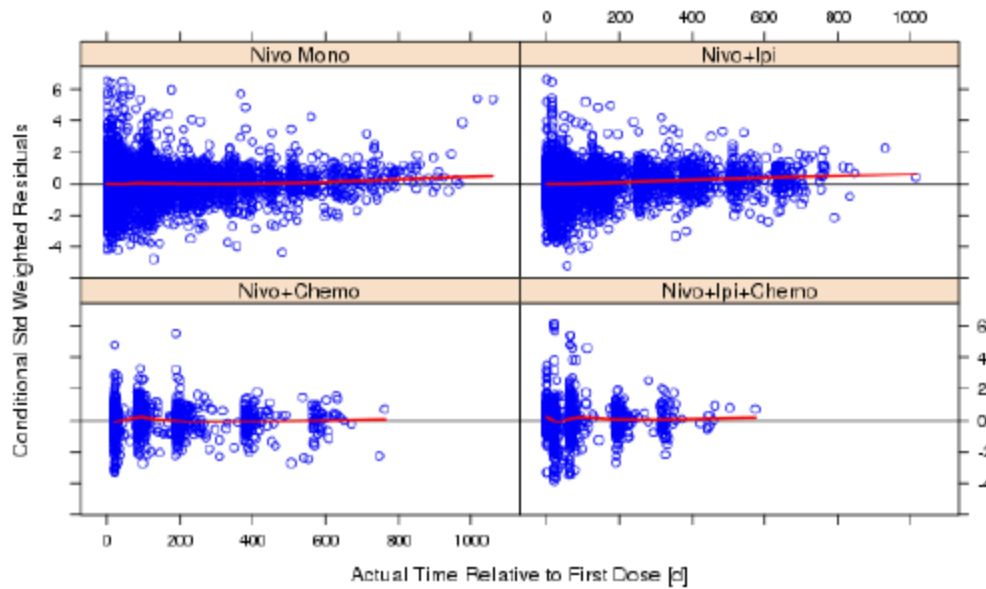
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final
R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd
Source: Analysis Directory/nm/full/plots/resid/cwres-time-group.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Figure 5.1.1.2-4: CWRES versus Time after Previous Dose in Nivolumab Monotherapy and Combination Therapy (Full Nivolumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final
R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd
Source: Analysis Directory/nm/full/plots/resid/cwres-timeprev-group.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Figure 5.1.1.2-5: CWRES versus Predicted (typical) Serum Concentration in Nivolumab Monotherapy and Combination Therapy (Full Nivolumab Population Pharmacokinetic Model)
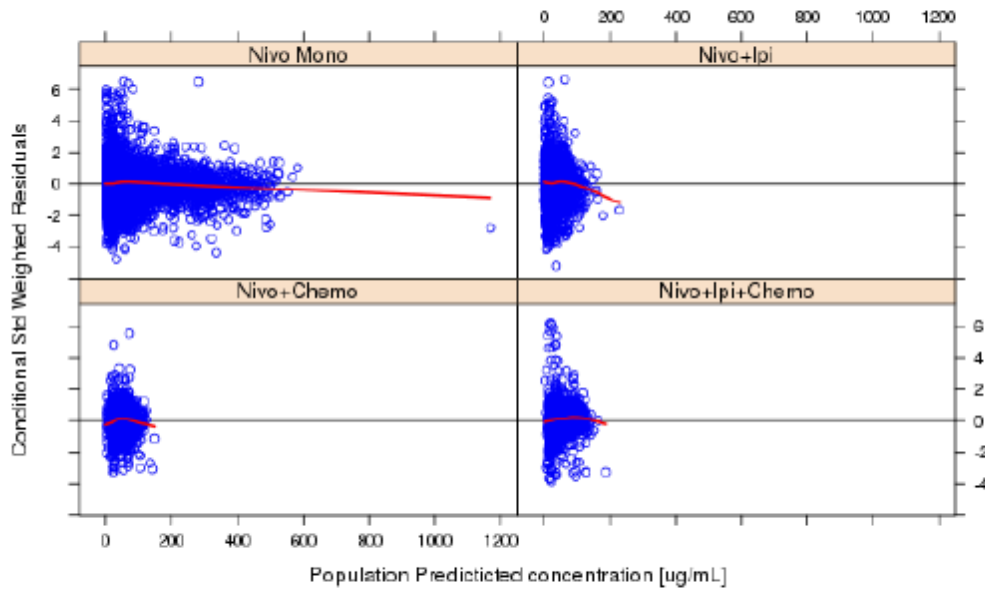
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd

Source: Analysis Directory/nm/full/plots/resid/cwres-pred-group.png

Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Figure 5.1.2-1: Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose in Nivolumab Monotherapy and Combination Therapies (Full Nivolumab Population Pharmacokinetic Model)
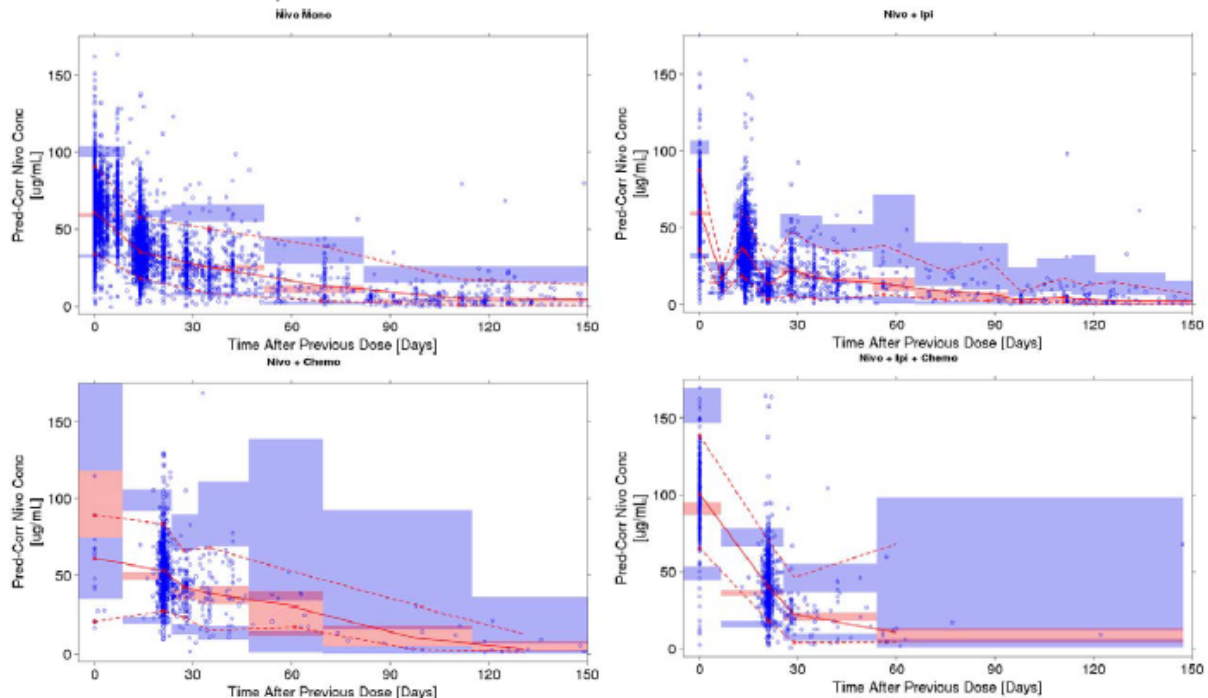
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd

Source: Analysis Directory/psn/vpc_full-dir11/VPC-plots 1.png

Source: Analysis Directory/psn/vpc_full-dir11/VPC-plots 2.png

Source: Analysis Directory/psn/vpc_full-dir11/VPC-plots 3.png

Source: Analysis Directory/psn/vpc_full-dir11/VPC-plots 4.png

Figure 5.1.2-2: Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose in Nivolumab Monotherapy and Combination Therapies (Full Nivolumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final
R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd
Source: Analysis Directory/psn/vpc_full_dir12/VPC-plots 1.png
Source: Analysis Directory/psn/vpc_full_dir12/VPC-plots 2.png
Source: Analysis Directory/psn/vpc_full_dir12/VPC-plots 3.png
Source: Analysis Directory/psn/vpc_full_dir12/VPC-plots 4.png

Figure 5.1.1.2-1: Covariate Effects on Nivolumab Pharmacokinetic Model Parameters (Full Nivolumab Population Pharmacokinetic Model)
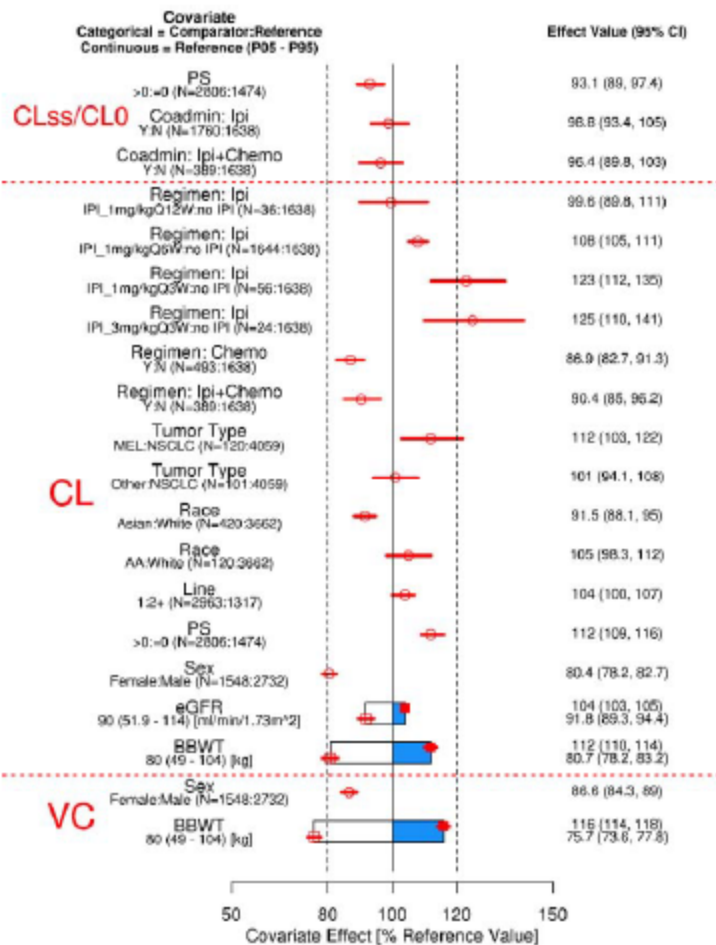
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk.Rmd

Source: Analysis Directory/R/plots/full-ppk-cov-eff-plot.png

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

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

Note 3: Reference subject is male, white/other race, BW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m², and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.

Note 5: PS appeared twice in the figure. Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 12%, whereas the reduction of nivolumab CL over time was more significant in subjects with PS > 0 than subjects with PS = 0 by 6.9%.

The distribution of nivolumab CL0 by different nivolumab dosing regimens (nivolumab 240 mg or 3 mg/kg Q2W monotherapy, nivolumab 240 mg or 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W, nivolumab 360 mg Q3W + up to 4 cycles of chemotherapy, nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy) is presented in Figure 5.1.3.1-1A. The difference in CL0 across the groups is not significant (< 20%). The distribution of the ratio of CLss/CL0 by different nivolumab dosing regimens is presented in Figure 5.1.3.1-1B. CLss/CL0 was similar across the regimens. For a closer look the ratio was 2% in nivolumab plus ipilimumab and nivolumab plus chemotherapy relative to nivolumab monotherapy, and the ratio was 5% lower in nivolumab co-administrated with ipilimumab and chemotherapy, relative to nivolumab monotherapy.

Figure 5.1.3.1-1: Distribution of Nivolumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance by Select Dosing Regimens in 1L NSCLC Subjects
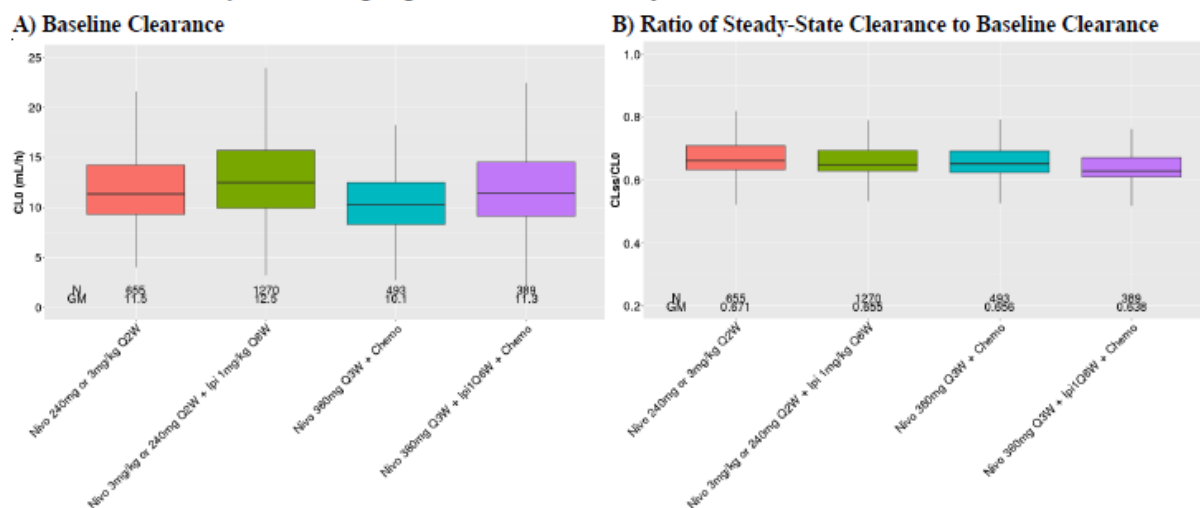
A) Baseline Clearance

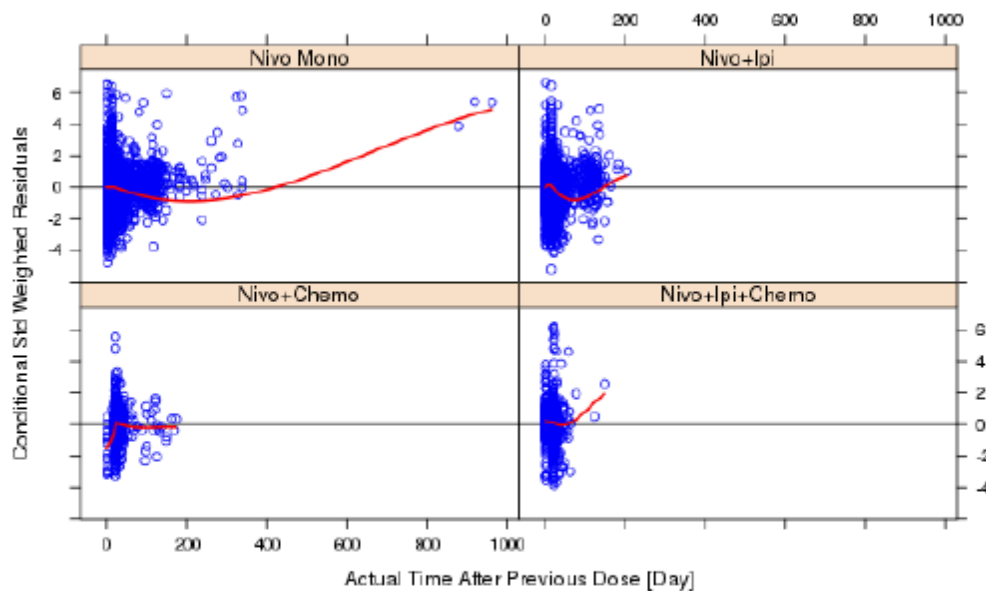B) Ratio of Steady-State Clearance to Baseline Clearance

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

R-Program Source: Analysis Directory/R/scripts/nivoppk2.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 1L NSCLC subjects from Studies CSA209012, CA209026, and CA209227. Nivo 240 mg or 3 mg/kg Q2W + Ipi 1 mg/kg Q6W includes data from 1L NSCLC subjects from Studies CA209012, 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.

The exposures for nivolumab 240 mg Q2W, nivolumab 240 mg or 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W, and nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy are summarised in Table 5.1.3.1-1. Compared to the reference group of nivolumab 240 mg Q2W monotherapy, the Cavgss was 12% lower in nivolumab + ipilimumab 1 mg/kg Q6W, while 8% higher in the nivolumab + ipilimumab + chemotherapy group.

Table 5.1.3.1-1: Predicted Exposure Measures by Dosing Regimen in 1L NSCLC Subjects

| Exposure	Nivo monotherapy Geo. Mean (CV%) N= 328	Nivo + Ipi Geo. Mean (CV%) N=1270	Nivo + Ipi + CT Geo. Mean (CV%) N=389
CMIN1	18.4(24.8)	16.2(27)	21(42.2)
CMAX1	64.4(19.1)	59.2(22.5)	98.7(27.2)
CAVG1	29.2(19.4)	26.3(20.9)	37.8(28.9)
CMINSS	70.6(39.1)	61.6(44.6)	69.3(64.5)
CMAXSS	137(27.7)	122(30.8)	171(41.1)
CAVGSS	91.6(33.5)	80.8(37.6)	98.8(52.6)

Analysis -Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final

Program Source: Analysis Directory/R/scripts/nivoppk2.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 1L NSCLC subjects from Study CA209227. Nivo + Ipi = Nivo 240 mg or 3 mg/kg Q2W + Ipi 1 mg/kg Q6W and includes data from 1L NSCLC subjects from Studies CA209012, CA209227, CA209568 Part 1, and CA209817. Nivo + Ipi + CT = Nivo 360 mg Q3W + Ipi 1 mg/kg Q6W + chemo and includes data from 1L NSCLC subjects from Studies CA209568 Part 2 and CA2099LA.

Ipilimumab base model

Base model development consisted of re-estimating parameters of the previously developed full model (with nivolumab combination effects removed), which was developed to characterize PK for ipilimumab combination therapy in subjects with previously untreated NSCLC.11

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, BLDH, tumour effect, and line of therapy on CL, BBWT on VC, Q and VP. In the present analysis, 40 outliers were identified using the CWRES criteria. These outliers were excluded from subsequent analyses. Parameter estimates for this model are presented in Table 5.2.1.1-1.

The stability of the base model was assessed by the condition number calculated from eigenvalues in the NONMEM output. The conditional number of the base model was found to be 54.67, indicting the base model was stable (as the value is well below 1000).

Table 5.2.1.1-1: Parameter Estimates of the Base Ipilimumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	14.5	0.277 (1.91)	14.0 - 15.1
VC_{REF} [L]	θ_2	4.05	0.0277 (0.684)	3.99 - 4.10
Q_{REF} [mL/h]	θ_3	26.1	1.77 (6.78)	22.6 - 29.6
VP_{REF} [L]	θ_4	3.30	0.0768 (2.42)	3.15 - 3.45
CL_{BBWT}	θ_7	0.649	0.0320 (4.93)	0.586 - 0.712
V_{BBWT}	θ_8	0.526	0.0323 (6.14)	0.462 - 0.589
CL_{BLDH}	θ_9	0.711	0.0762 (10.7)	0.561 - 0.860
$EMAX_{REF}$	θ_{10}	-0.238	0.0198 (8.31)	-0.276 - -0.199
T50	θ_{11}	2.41E+03	153 (6.34)	2.11E+03 - 2.71E+03
HILL	θ_{12}	3.15	0.570 (18.1)	2.03 - 4.27
CL_{NSCLC}	θ_{13}	0.135	0.0131 (9.74)	0.109 - 0.160
CL_{LINE}	θ_{25}	-0.0706	0.0168 (23.8)	-0.103 - -0.0377
Random Effects				
ZCL[-]	$\omega_{1,1}$	0.118 (0.343)	0.00499 (4.23)	0.108 - 0.128
ZVC [-]	$\omega_{2,2}$	0.131 (0.362)	0.0121 (9.19)	0.108 - 0.155
ZEMAX	$\omega_{3,3}$	0.0494 (0.222)	0.00921 (18.6)	0.0314 - 0.0675
ZCL[-]:ZVC	$\omega_{1,2}$	0.0502 (0.404)	0.00384 (7.64)	0.0427 - 0.0578
Residual Error				
Proportinal [-]	θ_5	0.221	0.00535 (2.42)	0.211 0.232
Additive [ug/mL]	θ_6	0.320	0.0329 (10.3)	0.256 0.385

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

Program Source: Analysis Directory/nm/base2/base2.lst

Source: Analysis Directory/nm/base2/reports/base2_RTF.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.

Figure 5.2.1.1-1: Observed versus Predicted Population Average and Individual Concentration in Ipilimumab Monotherapy and Combination Therapies (Base Ipilimumab Population Pharmacokinetic Model)
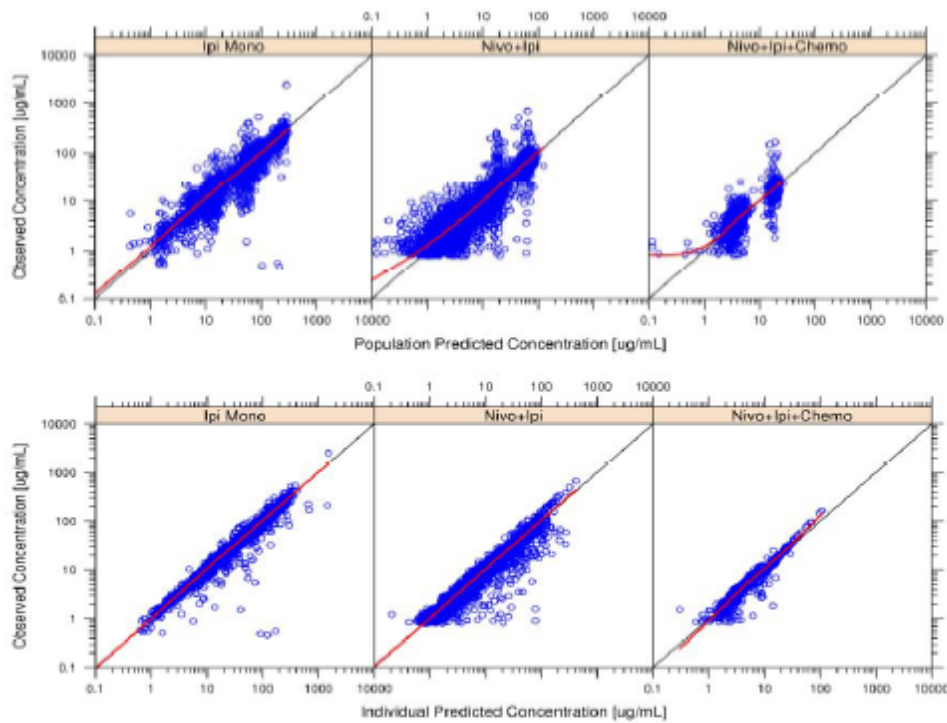
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
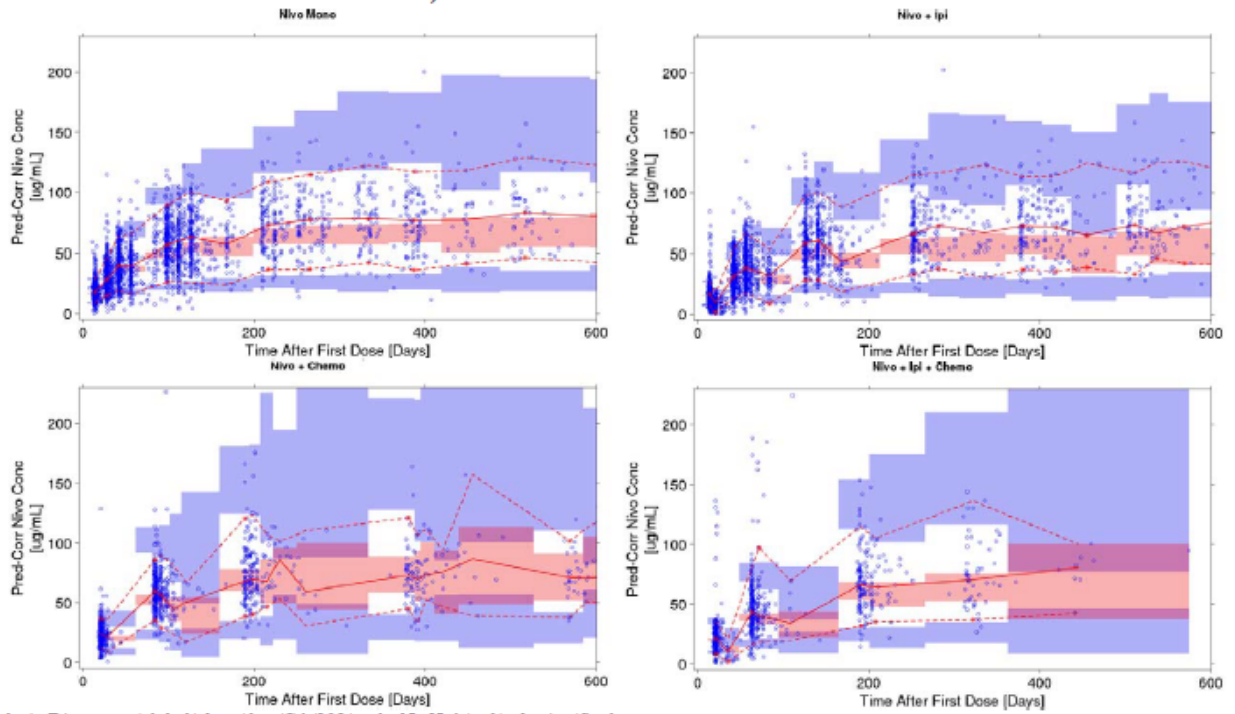Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents linear regression line; Solid black line represents line of identity

Figure 5.2.1.1-2: CWRES versus Time after First Dose in Ipilimumab Monotherapy and Combination Therapies (Base Ipilimumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents locally weighted smooth line.

Figure 5.2.1.1-3: CWRES versus Time after Previous Dose in Ipilimumab Monotherapy and Combination Therapies (Base Ipilimumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents locally weighted smooth line.

Figure 5.2.1.1-4: CWRES versus Predicted (typical) Serum Concentration in Ipilimumab Monotherapy and Combination Therapies (Base Ipilimumab Population Pharmacokinetic Model)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents locally weighted smooth line.

<u>Ipilimumab final model</u>

The full model was developed from the base model by incorporating additional covariates such as combination regimen effects on CL and on EMAX. The following combination regimen effects were

evaluated: nivolumab + ipilimumab + chemotherapy vs nivolumab + ipilimumab vs ipilimumab monotherapy.

$$CL0_i = CL0_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \cdot \left(\frac{\log(BLDH_i)}{\log(BLDH_{REF})}\right)^{CL_{BLDH}} \cdot e^{CL_{NSCLC} \cdot I_{NSCLC}}$$

$$\cdot\, e^{CL_{Nivo\ 0.3mg/kg\ Q3W} \cdot I_{Nivo\ 0.3mg/kg\ Q3W}} \cdot e^{CL_{Nivo 1mg/kgQ2W} \cdot I_{Nivo\ 1mg/kgQ2W}}$$

$$\cdot\, e^{CL_{Nivo 1mg/kgQ3W} \cdot I_{Nivo\ 1mg/kgQ3W}} \cdot e^{CL_{Nivo 3mg/kgQ2W} \cdot I_{Nivo 3mg/kgQ2W}}$$

$$\cdot\, e^{CL_{Nivo\ 3mg/kg\ Q3W} \cdot I_{Nivo\ 3mg/kg\ Q3W}}$$

$$\cdot\, e^{CL_{Nivo\ 360mg\ Q3W+Chemo} \cdot I_{Nivo\ 360mg\ Q3W+Chemo}} \cdot e^{CL_{Nivo\ 240mg\ Q2W} \cdot I_{Nivo\ 240mg\ Q2W}}$$

$$\cdot\, e^{CL_{LINE} \cdot I_{LINE}} \cdot e^{\eta CL_i}$$

$$EMAX_i = EMAX_{REF} + EMAX_{COMBO} \cdot I_{COMBO} + EMAX_{Triple} \cdot I_{Triple} + \eta EMAX_i$$

$$CL_{t,i} = CL0_i \cdot \left(\frac{EMAX_i \cdot t^{HILL}}{T50_i^{HILL} + t^{HILL}}\right)$$

$$CL_{SS,i} = CL0_i \cdot exp(EMAX_i)$$

$$VC_i = VC_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}} \cdot e^{\eta VC_i}$$

$$Q_i = Q_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}}$$

$$VP_i = VP_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}}$$

Parameter estimates for this model are presented in Table 5.2.1.2-1 and the covariate effects are shown in Figure 5.2.1.2-1.

Table 5.2.1.2-1: Parameter Estimates of the Full Ipilimumab Population Pharmacokinetic Model

| Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	13.7	0.293 (2.14)	13.1 - 14.2
VC_{REF} [L]	θ_2	4.05	0.0278 (0.685)	3.99 - 4.10
Q_{REF} [mL/h]	θ_3	26.2	1.86 (7.11)	22.6 - 30.8
VP_{REF} [L]	θ_4	3.34	0.0763 (2.28)	3.20 - 3.50
CL_{BBWT}	θ_7	0.648	0.0322 (4.97)	0.580 - 0.708
VC_{BBWT}	θ_8	0.543	0.0323 (5.94)	0.478 - 0.606
CL_{BLDH}	θ_9	0.779	0.0769 (9.88)	0.636 - 0.931
$EMAX_{REF}$	θ_{10}	0.0843	0.0450 (53.4)	0.00161 - 0.175
$T50$	θ_{11}	2.09E+03	160 (7.67)	1.79E+03 - 2.48E+03
$HILL$	θ_{12}	2.52	0.333 (13.2)	1.94 - 3.33
CL_{NSCLC}	θ_{13}	-0.0364	0.0319 (87.7)	-0.124 - 0.0403
CL Nivo0.3 mg/kg Q3W	θ_{18}	0.0655	0.116 (176)	-0.190 - 0.291
CL Nivo1mg/kg Q2W	θ_{19}	0.223	0.0575 (25.7)	0.0916 - 0.351
CL Nivo1mg/kg Q3W	θ_{20}	0.120	0.0253 (21.0)	0.0719 - 0.172
CL Nivo3 mg/kg Q2W	θ_{21}	0.254	0.0419 (16.5)	0.156 - 0.359
CL Nivo3mg/kg Q3W	θ_{22}	0.0186	0.0331 (178)	-0.0466 - 0.0865
CL Nivo360mg Q3W+Chemo	θ_{23}	0.196	0.0450 (23.0)	0.0923 - 0.307
CL Nivo240mg Q2W	θ_{24}	0.293	0.0410 (14.0)	0.198 - 0.400
CL_{LINE}	θ_{25}	-0.0686	0.0183 (26.7)	-0.106 - -0.0321
$EMAX_{COMBO}$	θ_{26}	-0.355	0.0499 (14.0)	-0.465 - -0.261
$EMAX_{Triple}$	θ_{27}	-0.367	0.0611 (16.7)	-0.489 - -0.254
Random Effects				
ZCL[-]	$\omega_{1,1}$	0.117 (0.342)	0.00497 (4.26)	0.107 - 0.126
ZVC [-]	$\omega_{2,2}$	0.132 (0.363)	0.0121 (9.15)	0.109 - 0.155
ZEMAX	$\omega_{3,3}$	0.0549 (0.234)	0.00958 (17.5)	0.0365 - 0.0765
ZCL[-]:ZVC	$\omega_{1,2}$	0.0495 (0.398)	0.00379 (7.68)	0.0422 - 0.0566
Residual Error				
Proportional [-]	θ_5	0.219	0.00534 (2.45)	0.208 - 0.229
Additive [ug/mL]	θ_6	0.319	0.0334 (10.5)	0.208 - 0.379

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

Program Source: Analysis Directory/nm/full3/full3.lst

Source: Analysis Directory/nm/full3/reports/full3_RTF1.rtf

Note 1: CL_{REF} is the typical value in a reference subject with melanoma tumor type, receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving ipilimumab monotherapy with a normal PS status. 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: The unit of CL_{REF} and Q_{REF} was converted to mL/h from L/h in the source.

Note 3: Eta shrinkage (%): ETA_CL: 13.3; ETA_VC: 24.5; ETA_EMAX: 61.3; EPS shrinkage (%): 20.7.

[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*

Figure 5.2.1.2-1: Covariate Effects on Ipilimumab Pharmacokinetic Model Parameters (Full Ipilimumab Population Pharmacokinetic Model)

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

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

Note 3: Reference subject with melanoma as tumor type, receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: Covariate effects on CL apply to both CL0 and CLss.

Note 5: Effects of BBWT on Q and VP are same as that of BBWT on CL and VC.

Figure 5.2.1.2-2: Observed versus Predicted Population and Individual Concentration in Ipilimumab Monotherapy and Combination Therapies (Full Ipilimumab Population Pharmacokinetic Model)
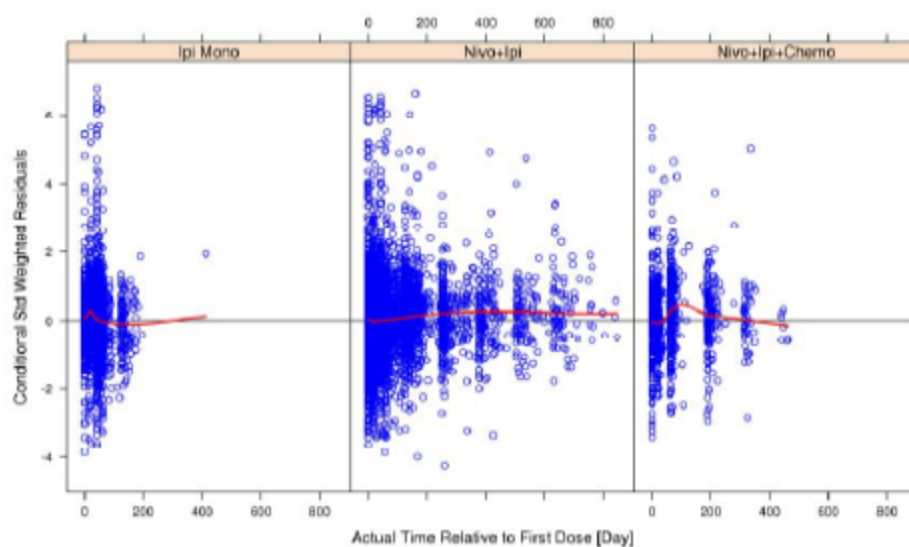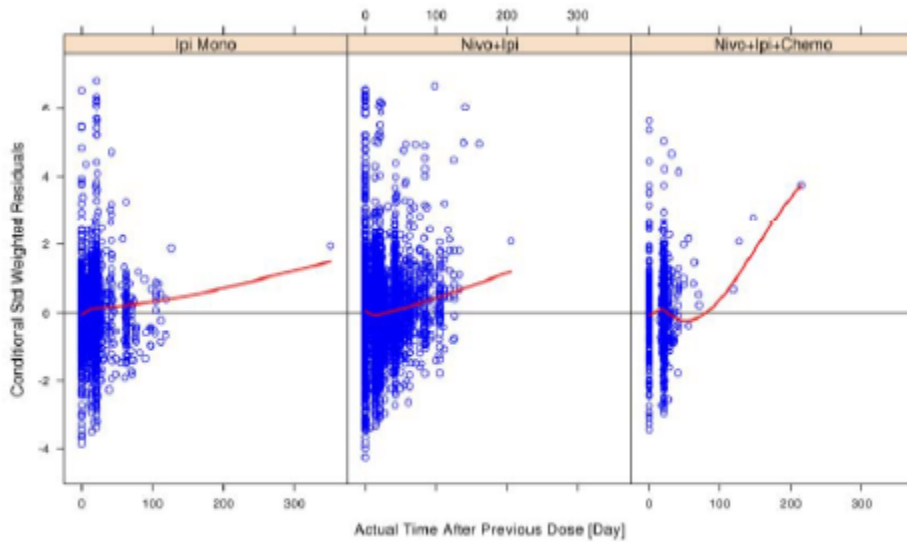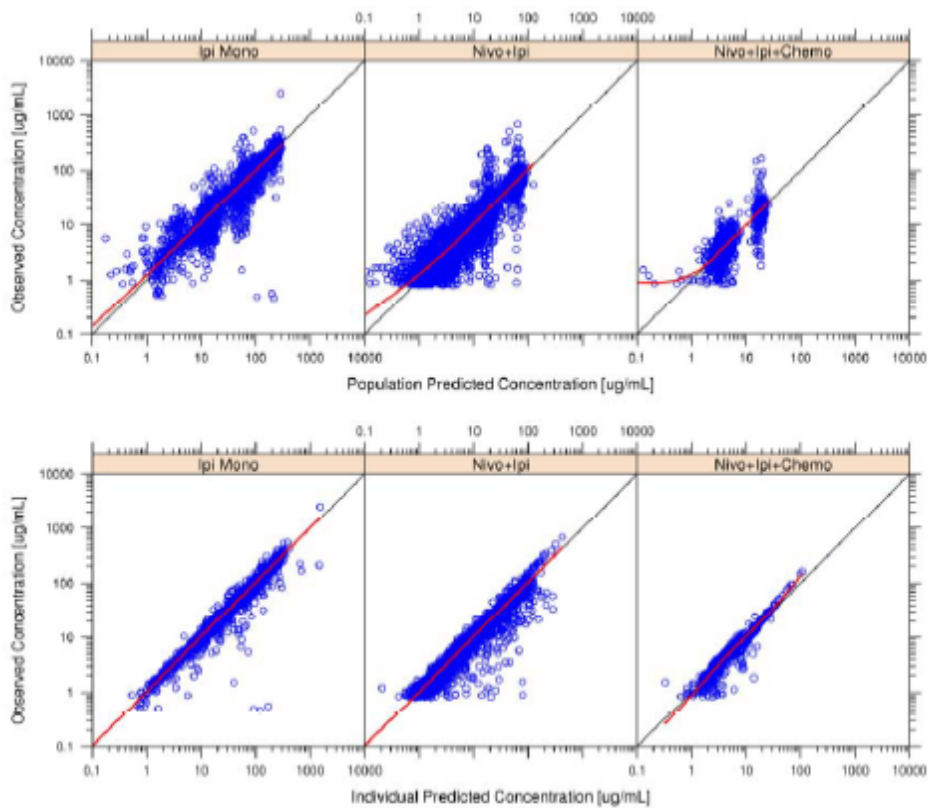

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd

Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx

Note: Solid red line represents linear regression line; Solid black line represents line of identity.

Figure 5.2.1.2-3: **CWRES versus Time after First Dose in Ipilimumab Monotherapy and Combination Therapies (Full Ipilimumab Population Pharmacokinetic Model)**

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
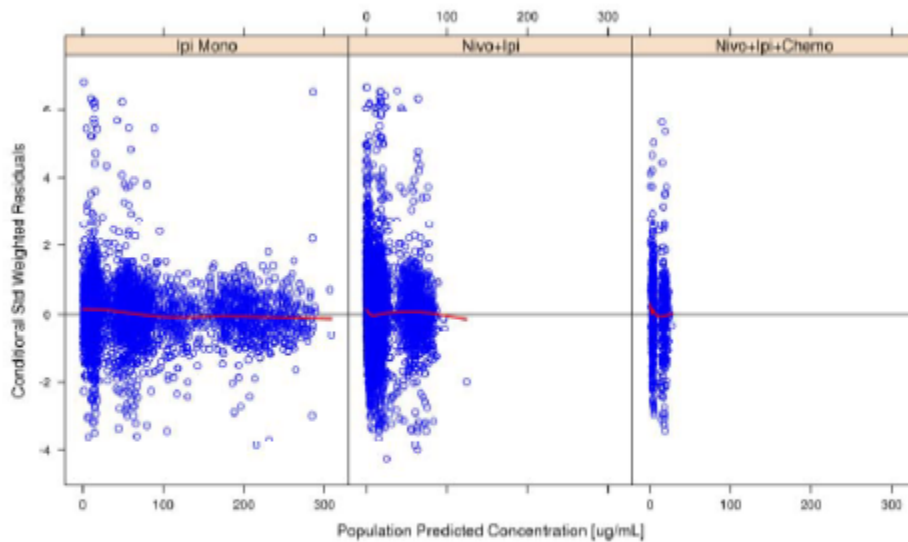Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents locally weighted smooth line.

Figure 5.2.1.2-4: **CWRES versus Time after Previous Dose in Ipilimumab Monotherapy and Combination Therapies (Full Ipilimumab Population Pharmacokinetic Model)**

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents locally weighted smooth line.

Figure 5.2.1.2-5: CWRES versus Predicted (typical) Serum Concentration in Ipilimumab Monotherapy and Combination Therapies (Full Ipilimumab Population Pharmacokinetic Model)
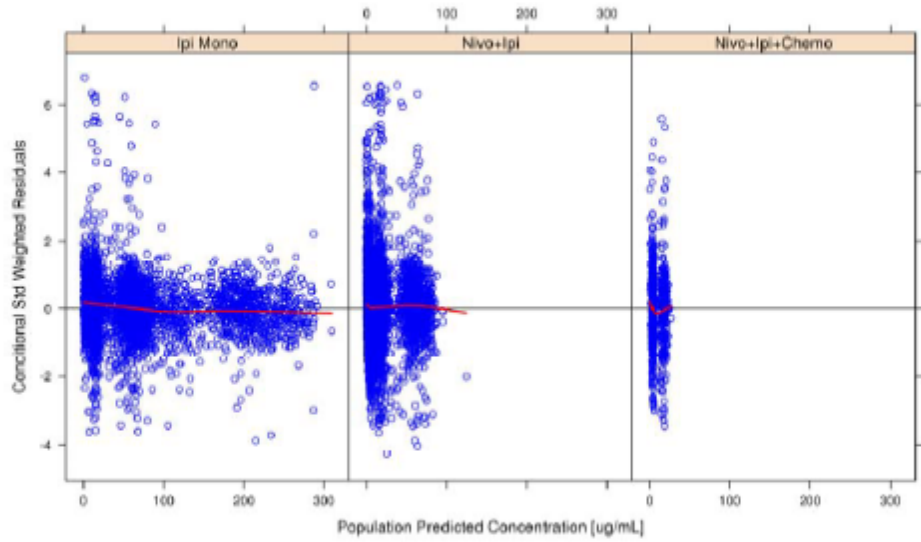
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx
Note: Solid red line represents locally weighted smooth line.

Figure 5.2.2-1: **Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose in Ipilimumab Monotherapy and Combination Therapies (Full Ipilimumab Population Pharmacokinetic Model)**
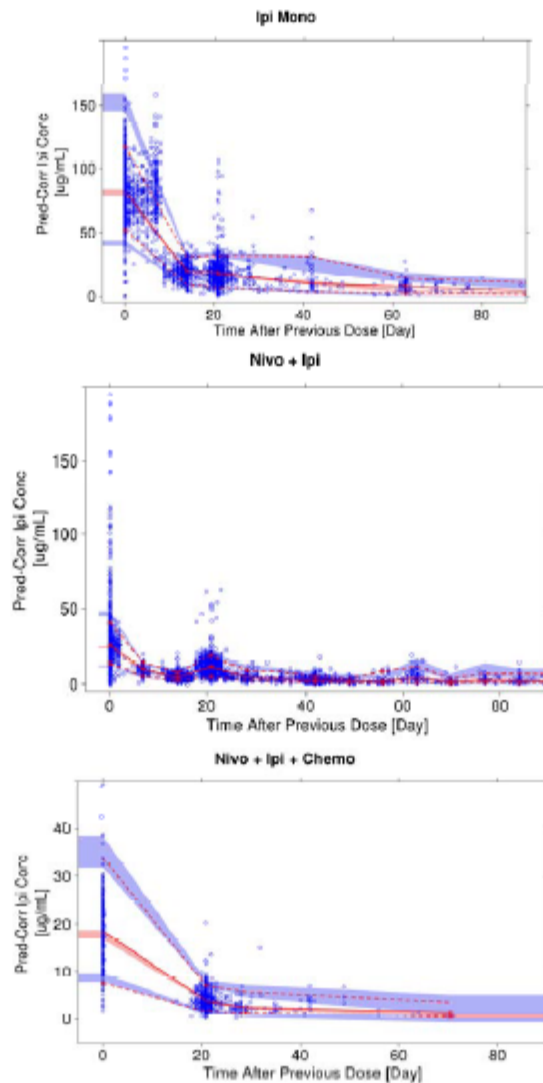
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd

Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx

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 5.2.1.2-1: Covariate Effects on Ipilimumab Pharmacokinetic Model Parameters (Full Ipilimumab Population Pharmacokinetic Model)
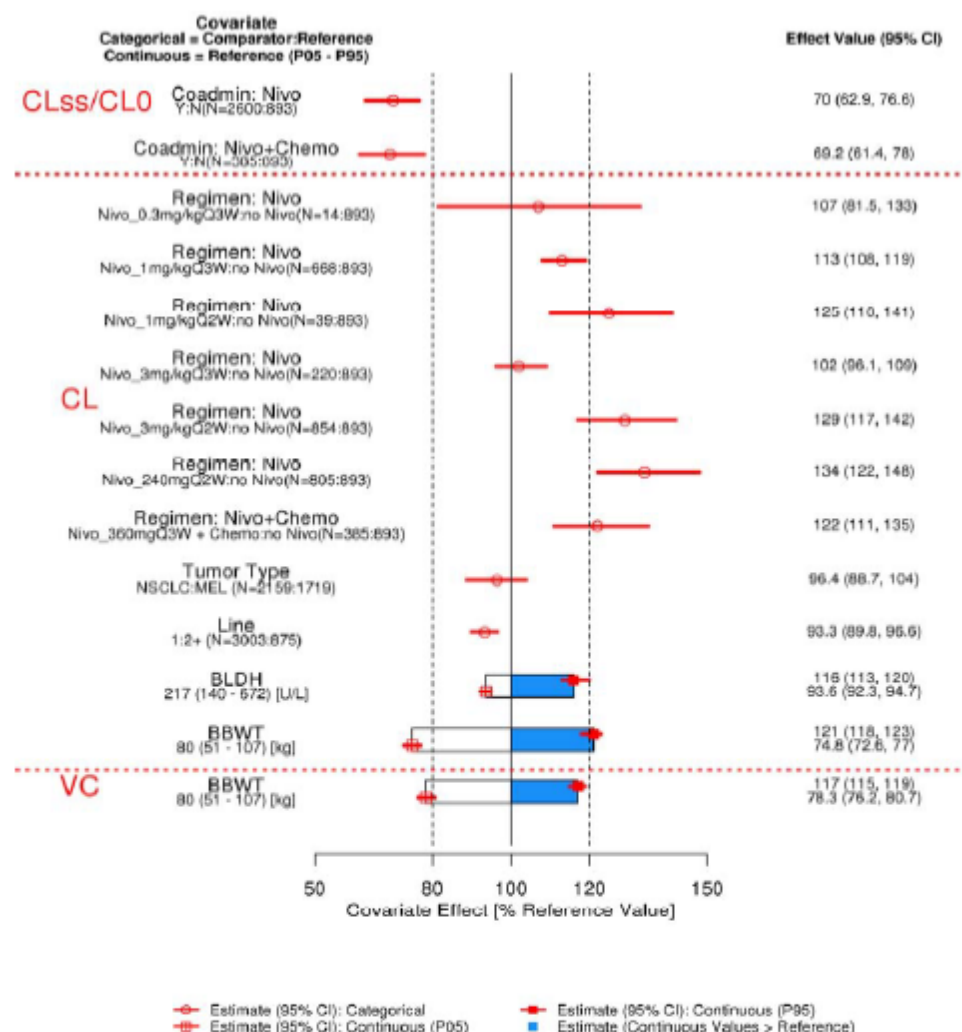
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd

Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx

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

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

Note 3: Reference subject with melanoma as tumor type, receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: Covariate effects on CL apply to both CL0 and CLss.

Note 5: Effects of BBWT on Q and VP are same as that of BBWT on CL and VC.

The distribution of ipilimumab CL0 by different nivolumab dosing regimens (nivolumab 240 mg or 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W and nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy) in 1L NSCLC subjects is presented in Figure 5.2.3.1-1A. The difference in CL0 between the two groups is not significant (< 20%). The distribution of the ratio of CLss/CL0 by different dosing regimens is presented in Figure 5.2.3.1-1B. CLss/CL0 was similar between the two dosing regimens (difference < 1.5%).

Figure 5.2.3.1-1: Distribution of Ipilimumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance by Dosing Regimens in 1L NSCLC Subjects
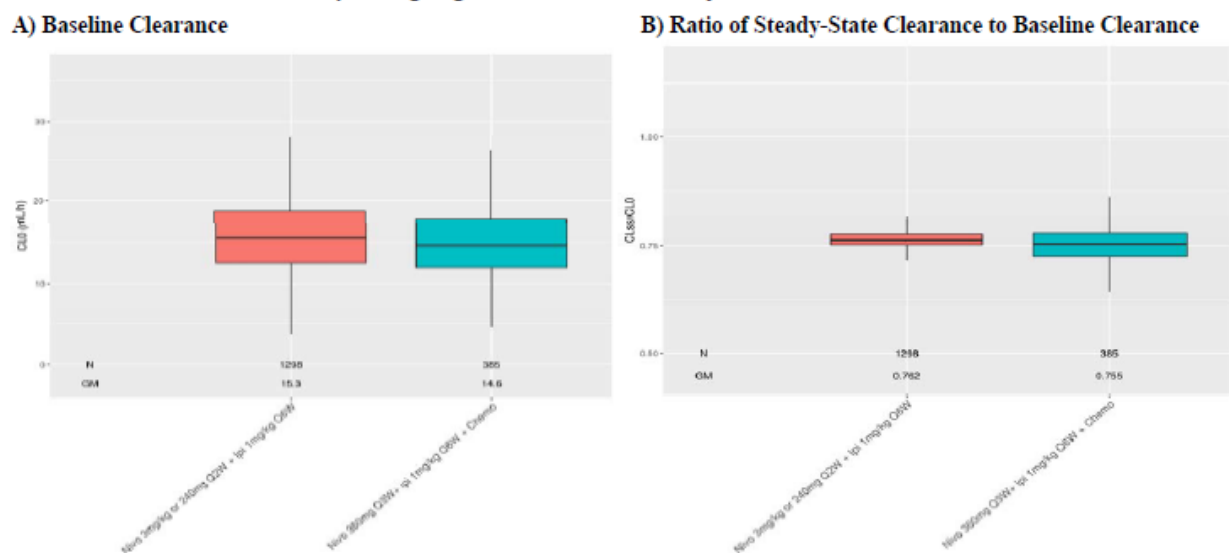
A) Baseline Clearance

B) Ratio of Steady-State Clearance to Baseline Clearance

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd

Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx

Note: Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W includes data from 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.

The exposures for nivolumab 240 mg or 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W versus nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy are summarized in Table 5.2.3.1-1. The Cavgss was similar (<10% difference) between the two dosing regimen groups.

Table 5.2.3.1-1: Predicted Exposure Metrics by Dosing Regimen in 1L NSCLC Subjects

Exposure	Nivo + Ipi Geo. Mean (CV%) N = 1298	Nivo + Ipi + CT Geo. Mean (CV%) N = 385
CMIN1	1.09(48.1)	1.24(50.3)
CMAX1	18.4(46.8)	18.6(48.7)
CAVG1	3.98(23.2)	4.18(25.3)
CMINSS	2.21(74.5)	2.54(69.2)
CMAXSS	20.8(43.1)	21.5(44.5)
CAVGSS	5.99(37.5)	6.48(39.2)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final

R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd

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

Note: Nivo + Ipi = Nivo 240 mg or 3 mg/kg Q2W + Ipi 1 mg/kg Q6W and includes data from 1L NSCLC subjects from Studies CA209012, CA209227, CA209568 Part 1, and CA209817. Nivo + Ipi + CT = Nivo 360 mg Q3W + Ipi 1 mg/kg Q6W + chemo and includes data from 1L NSCLC subjects from Studies CA209568 Part 2 and CA2099LA.

Special populations

Nivolumab

Ethnicity

The distribution of nivolumab CL0 in Japanese, non-Japanese Asian, and non-Asian subjects is presented in Figure 5.1.3.3-1A. The distribution of the ratios of CLss/CL0 is presented in Figure

5.1.3.3-1B. The lower baseline CL in all Asian subjects are related to their lower body weight. No clinically relevant difference in nivolumab CL was found in Japanese, non-Japanese Asian, and non-Asian subjects (< 20%).

Figure 5.1.3.3-1: Distribution of Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance in Japanese, Non-Japanese Asian, and Non-Asian Subjects with 1L NSCLC
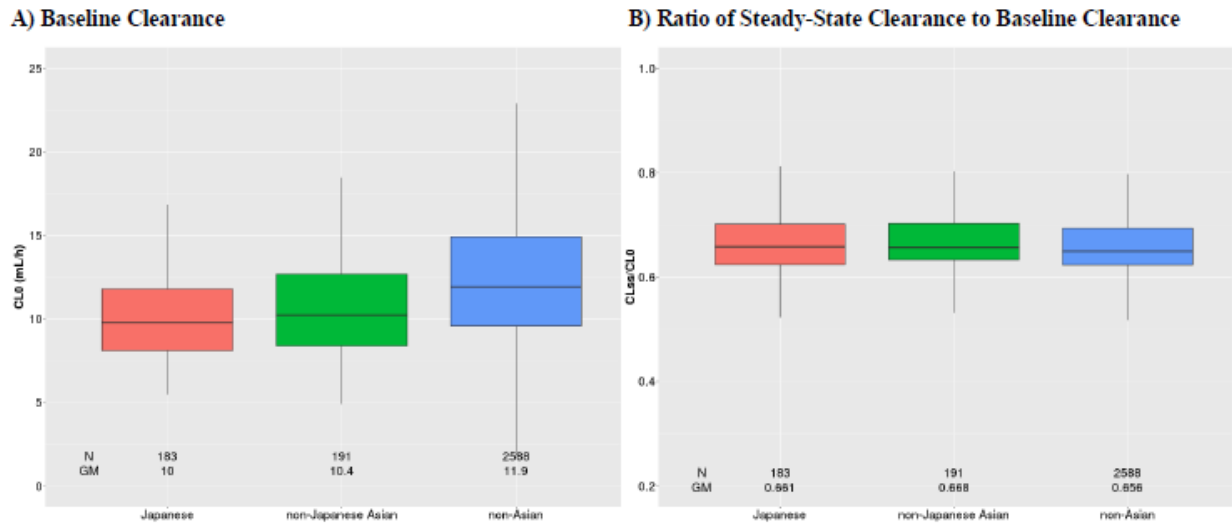
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final
R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd
Source: Analysis Directory/R/plots/CL0-JP.png
Source: Analysis Directory/R/plots/CL-ratio-JP.png
Note: Includes data from 1L NSCLC subjects from Studies CA209012, CA209026, CA209227, CA209568, CA209817, and CA2099LA.

Ipilimumab

Ethnicity

The distribution of ipilimumab CL0 in Japanese, non-Japanese Asian, and non-Asian subjects with 1L NSCLC is presented in Figure 5.2.3.2-1A. The distribution of the ratio of CLss/CL0 for subjects with 1L NSCLC is presented in Figure 5.2.3.2-1B. The baseline CL and the ratio of CLss/CL0 for Japanese, non-Japanese Asian, and non-Asian subjects were similar (< 15% difference).

Figure 5.2.3.2-1: Distribution of Ipilimumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance in Japanese, Non-Japanese Asian, and Non-Asian Subjects with 1L NSCLC
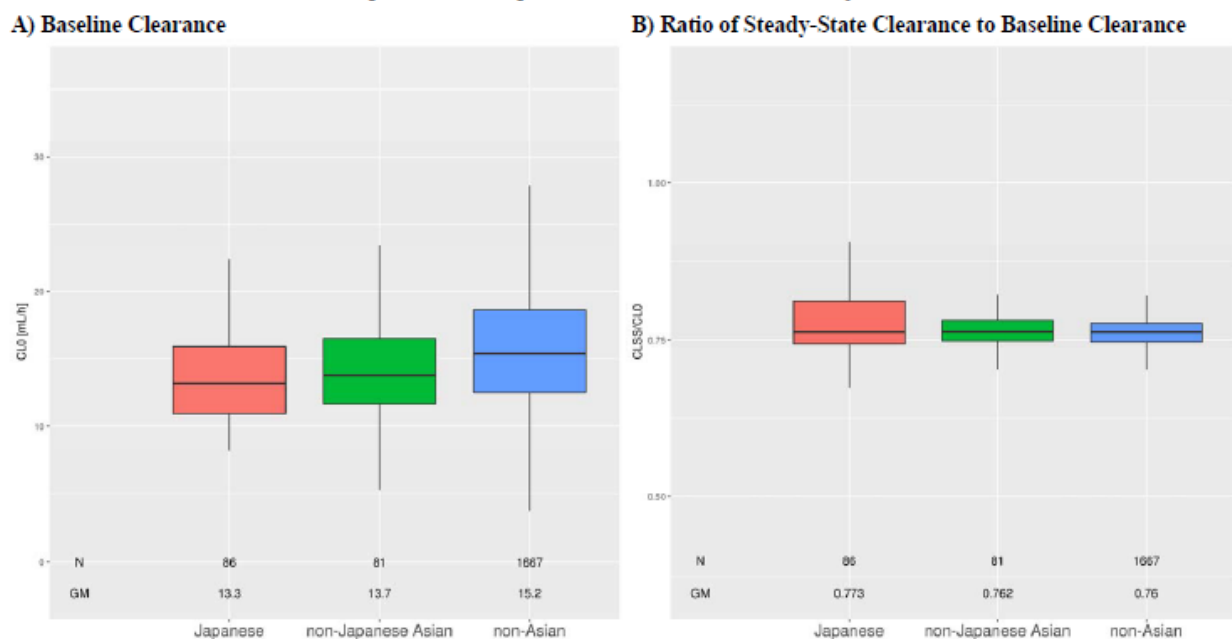
Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-ipi/final
R-Program Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.Rmd
Source: Analysis Directory/R/scripts/ ppk-ipi-9LA-nsclc-2.docx

Immunogenicity

Nivolumab

The distribution of nivolumab CL0 in ADA+ and ADA- subjects in Study CA2099LA (treated with nivolumab + ipilimumab + chemotherapy) is presented in Figure 5.1.3.2-1A; a subject was considered ADA+ if ADA was positive for any visit during the post-treatment. Baseline CL was higher in ADA+ subjects than ADA-subjects by ~29% (geometric mean). The distribution of the ratio of CLss/CL0 is presented in Figure 5.1.3.2-1B. The ratio CLss/CL0 was similar between ADA+ and ADA- subjects (difference 2%).

Figure 5.1.3.2-1: Distribution of Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance in ADA+ and ADA- Subjects in Study CA2099LA
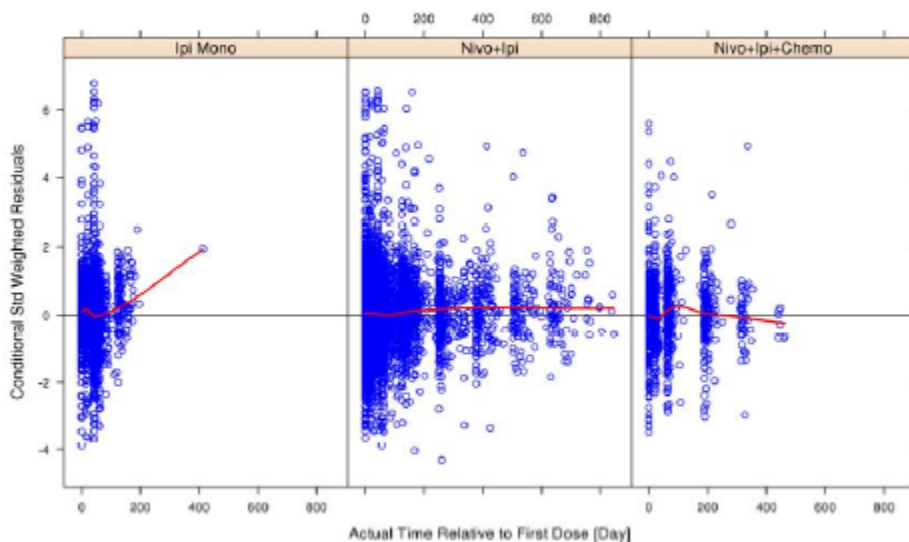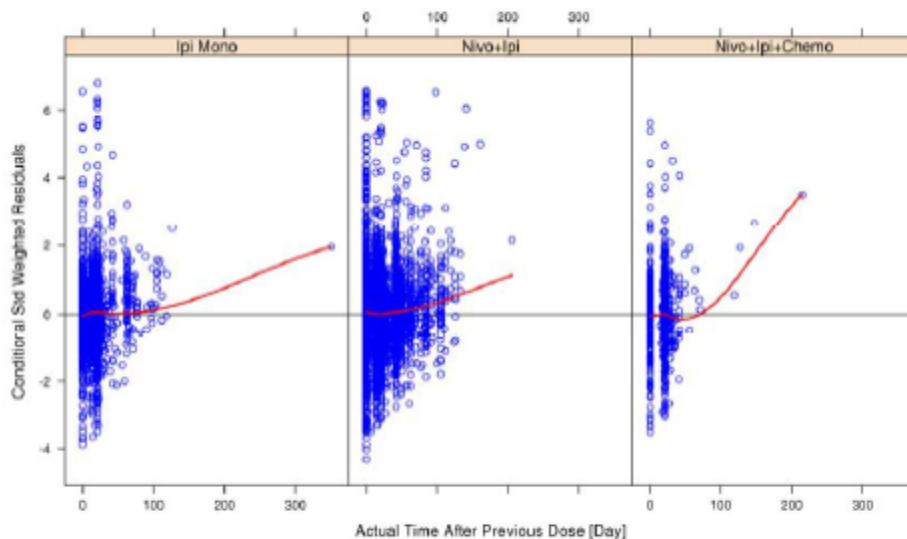

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/ppk-nivo/final
R-Program Source: Analysis Directory/R/scripts/nivoppk2.Rmd
Source: Analysis Directory/R/plots/CL0-ADA.png
Source: Analysis Directory/R/plots/CL-ratio-ADA.png

Ipilimumab

The effect of immunogenicity on ipilimumab CL was not evaluated because the ipilimumab ADA+ incidence rate was low.37

2.3.3. Pharmacodynamics

Mechanism of action

No mechanism of action studies have been submitted with this application.

Primary and secondary pharmacology

No primary or secondary pharmacology studies have been performed for this application.

2.3.4. PK/PD modelling

Exposure response of efficacy

The E-R analysis of efficacy included data from 697 subjects with NSCLC in Study CA2099LA, including 349 subjects who received 4 cycles of platinum-doublet chemotherapy and 348 subjects who received nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy treatment, and for whom estimates of both nivolumab and ipilimumab exposures (Cavg1) were available. Values of nivolumab and ipilimumab Cavg1 were imputed to be zero for subjects in the chemotherapy only arm of CA2099LA and were obtained from the PPK analysis for the remaining subjects. Additionally, in order to enable the assessment of log-transformed exposures, the values of Cavg1 of nivolumab and ipilimumab of subjects who received only chemotherapy was imputed to be a very low value (0.001 µg/mL), as log of zero is not defined.

Table 3.2.1.1-1 provides a summary of the subjects who were included in the analysis.

Table 3.2.1.1-1: Subjects Included in the Exposure-Response of OS Dataset

Study CA2099LA Treatment Regimen	Subjects		Included (%)
	Treated Subjects	Excluded due to Lack of Nivo or Ipi Exposure Estimates (%)	
Nivo 360 mg Q3W + ipi 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy	358	10 (2.8)	348 (97.2)
Chemotherapy	349	0 (0.0)	349 (100.0)
Total	707	10 (1.4)	697 (98.6)

Source: Appendix 3.2.1.1-1

Abbreviations: Ipi = ipilimumab; Nivo = nivolumab; Q3W = every 3 weeks; Q6W = every 6 weeks

Chemotherapy: 4 cycles of platinum-doublet chemotherapy plus optional pemetrexed maintenance therapy.

Note: Exposure of nivolumab or ipilimumab in chemotherapy arm is imputed as 0.

Table 3.2.1.2-1: Summary of Events in the Exposure-Response of OS Analysis Dataset

Study CA2099LA Treatment Regimen	Number of Subjects		
	Included in Analysis	Number of Events (%)	Number Censored (%)
Nivo 360 mg Q3W + ipi 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy	348	145 (41.7)	203 (58.3)
Chemotherapy	349	191 (54.7)	158 (45.3)
Total	697	336 (48.2)	361 (51.8)

Source: Appendix 3.2.1.1-1

Abbreviations: Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; Q3W = every 3 weeks; Q6W = every 6 weeks.

Chemotherapy: 4 cycles of platinum-doublet chemotherapy plus optional pemetrexed maintenance therapy.

The full model estimates are presented in Table 5.1.1.1-1. The parameter estimate between Cavg1 of nivolumab and ipilimumab is highly correlated (r > 0.9), suggesting these effects are not completely independent.

Figure 5.1.1.1-1 is a graphical presentation of all the estimated effects in the full model, showing the hazard ratios (HR) of OS across the predictor ranges and the associated 95% confidence intervals (CIs).

Table 5.1.1.1-1:   **Parameter Estimates of the Exposure-Response of OS (Full Model)**

| Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Cavg_nivo [μg/mL]	-0.0255	0.01074	42.12	0.9748 (0.9545, 0.9956)
Log_Cavg_ipi [μg/mL]	0.06408	0.05022	78.37	1.066 (0.9662, 1.176)
Age [yr]	0.00611	0.006282	102.8	1.006 (0.9938, 1.019)
Body Weight [kg]	-0.01076	0.004373	40.63	0.9893 (0.9808, 0.9978)
Log(LDH) [xULN]	0.3214	0.09879	30.73	1.379 (1.136, 1.674)
Albumin [g/L]	-0.5352	0.101	18.87	0.5855 (0.4804, 0.7137)
Tumor Size [cm]	0.03761	0.01124	29.9	1.038 (1.016, 1.061)
Disease Status [Stage IV:Recurrent]	0.0868	0.211	243	1.091 (0.7213, 1.649)
Performance Score [≥1:0]	0.4129	0.1321	32	1.511 (1.166, 1.958)
Smoking Status [Smoker:Non-smoker]	-0.1747	0.1812	103.7	0.8398 (0.5888, 1.198)
PD-L1 [≥ 1%:< 1%]	-0.1888	0.1147	60.76	0.8279 (0.6612, 1.037)
Histology [SQ:NSQ]	0.09301	0.1182	127.1	1.097 (0.8705, 1.384)
Sex [Male:Female]	0.3892	0.1421	36.51	1.476 (1.117, 1.95)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/er-os/final/

Program Source: Analysis Directory/R/scripts/os-model-cph-dev.r

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

Abbreviations: Cavg1 = average concenration after the first dose; CI = confidence interval; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; NSQ = nonsquamous; OS = overall survival; PD-L1 = programmed death-ligand 1; SQ = 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: Disease Stage recurrent, performance status = 0, NSQ NSCLC, non-smoker, and female subject.

Figure 5.1.1.1-1: **Estimated Covariate Effects of the Exposure-Response of OS (Full Model)**

Covariate Categorical = Comparator:Reference Continuous = Reference (P05 - P95)	Effect Value (95% CI)
PDL1 [>=1%:<1%] (N=441:256)	0.828 (0.661, 1.04)
Smoking Status [Smoker:Non-Smoker] (N=605:92)	0.84 (0.589, 1.2)
Histology [SQ:NSQ] (N=218:479)	1.1 (0.87, 1.38)
Disease Stage [Stage IV:Recurrent] (N=646:51)	1.09 (0.721, 1.65)
Performance Score [>=1:0] (N=477:220)	1.51 (1.17, 1.96)
Sex [Male:Female] (N=488:209)	1.48 (1.12, 1.95)
Baseline Tumor Size [cm] 8 (2.08 - 17.3)	1.42 (1.16, 1.73) 0.8 (0.704, 0.91)
Baseline Albumin [g/dL] 4 (2.88 - 4.7)	0.688 (0.599, 0.79) 1.82 (1.46, 2.27)
Baseline LDH [xULN] 1 (0.56 - 2.23)	1.29 (1.11, 1.51) 0.83 (0.742, 0.929)
Baseline Body Weight [kg] 70 (50.1 - 98.2)	0.738 (0.579, 0.94) 1.24 (1.04, 1.47)
Age [yr] 65 (46 - 77)	1.08 (0.928, 1.25) 0.89 (0.699, 1.13)
Ipi Cavg1 [ug/mL] 4.17 (2.72 - 6.34)	1.03 (0.986, 1.07) 0.973 (0.933, 1.01)
Nivo Cavg1 [ug/mL] 38.2 (25.7 - 54.8)	0.655 (0.462, 0.929) 1.38 (1.06, 1.79)

Hazard Ratio: 0.3 1.0 2.0 4.0

Legend:
- Estimate (95% CI): Categorical
- Estimate (95% CI): Continuous (P05)
- Estimate (95% CI): Continuous (P95)
- Estimate (Continuous Values > Reference)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/er-os/final/

Program Source: Analysis-Directory/R/scripts/os-plot-cov-eff-full.r

Source: Analysis-Directory/R/plots/coveff-full-os.png

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.

Reference subjects: Subject had median value of nivolumab Cavg1 and ipilimumab Cavg1 who received nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy in Study CA2099LA, and median value of LDH, albumin, body weight, baseline clearance, baseline tumor size, NSQ, female, non-smoker, PS = 0, PD-L1 <1%, and recurrent disease stage.

Table 5.1.1.2-1: Parameter Estimates of the Exposure-Response of OS in the Sensitivity Analysis

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Cavg_nivo [μg/mL]	0.02775	0.02667	96.1	1.028 (0.9758, 1.083)
Log_Cavg_ipi [μg/mL]	-0.1375	0.4277	311.1	0.8716 (0.3769, 2.015)
Log(Baseline NIVO CL) [mL/h]	1.629	0.6883	42.25	5.1 (1.323, 19.65)
Age [yr]	0.01263	0.01142	90.44	1.013 (0.9903, 1.036)
Body Weight [kg]	-0.00986	0.007789	79	0.9902 (0.9752, 1.005)
Log(LDH) [xULN]	0.4242	0.1772	41.79	1.528 (1.08, 2.163)
Albumin [g/L]	-0.313	0.1645	52.56	0.7313 (0.5297, 1.01)
Tumor Size [cm]	0.004224	0.01882	445.6	1.004 (0.9679, 1.042)
Disease Status [Stage IV: Recurrent]	0.3486	0.3188	91.46	1.417 (0.7586, 2.647)
Performance Score [≥1:0]	0.5989	0.2136	35.67	1.82 (1.198, 2.766)
Smoking Status [Smoker:Non-smoker]	-0.5195	0.2678	51.54	0.5948 (0.3519, 1.005)
PD-L1 [≥ 1%:< 1%]	-0.1386	0.1791	129.2	0.8705 (0.6128, 1.237)
Histology [SQ:NSQ]	0.03851	0.1888	490.3	1.039 (0.7178, 1.505)
Sex [Male:Female]	0.25	0.2329	93.15	1.284 (0.8135, 2.027)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/er-os/final

Program Source: Analysis Directory/R/scripts/os-plot-cov-eff-sen.r

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

Abbreviations: Cavg1 = average concenration after the first dose; CI = confidence interval; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; NSQ = nonsquamous; OS = overall survival; PD-L1 = programmed death-ligand 1; SQ = 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: Disease Stage recurrent, performance status = 0, NSQ NSCLC, non-smoker, PDL1 positive (<1%) and female subject.

Figure 5.1.1.2-1: **Estimated Covariate Effects of the Exposure-Response of OS in the Sensitivity Analysis**

Covariate
Categorical = Comparator:Reference
Continuous = Reference (P05 - P95)

Effect Value (95% CI)

Covariate	Effect Value (95% CI)
PDL1 [>=1%:<1%] (N=441:256)	1.28 (0.814, 2.03)
Smoking Status [Smoker:Non-Smoker] (N=605:92)	1.04 (0.718, 1.5)
Histology [SQ:NSQ] (N=218:479)	0.871 (0.613, 1.24)
Disease Stage [Stage IV:Recurrent] (N=646:51)	0.595 (0.352, 1)
Performance Score [>=1:0] (N=477:220)	1.82 (1.2, 2.77)
Sex [Male:Female] (N=488:209)	1.42 (0.759, 2.65)
Baseline Tumor Size [cm] 8 (2.34 - 16)	1.03 (0.77, 1.39) / 0.976 (0.792, 1.2)
Baseline Albumin [g/dL] 4 (2.89 - 4.7)	0.803 (0.641, 1.01) / 1.42 (0.989, 2.02)
Baseline LDH [xULN] 1 (0.562 - 1.97)	1.33 (1.05, 1.69) / 0.783 (0.641, 0.957)
Baseline Body Weight [kg] 70 (49.4 - 99)	0.751 (0.483, 1.16) / 1.23 (0.902, 1.68)
Age [yr] 65 (49 - 76)	1.15 (0.898, 1.48) / 0.817 (0.568, 1.17)
Baseline Nivo Clearance [mL/hr] 11.4 (5.93 - 19.9)	2.49 (1.17, 5.3) / 0.347 (0.144, 0.834)
Ipi Cavg1 [ug/mL] 4.18 (2.72 - 6.36)	0.944 (0.664, 1.34) / 1.06 (0.739, 1.52)
Nivo Cavg1 [ug/mL] 38.2 (25.7 - 54.8)	1.59 (0.666, 3.76) / 0.707 (0.369, 1.36)

Hazard Ratio: 0.3 1.0 2.0 4.0

Estimate (95% CI): Categorical — Estimate (95% CI): Continuous (P95)
Estimate (95% CI): Continuous (P05) — Estimate (Continuous Values > Reference)

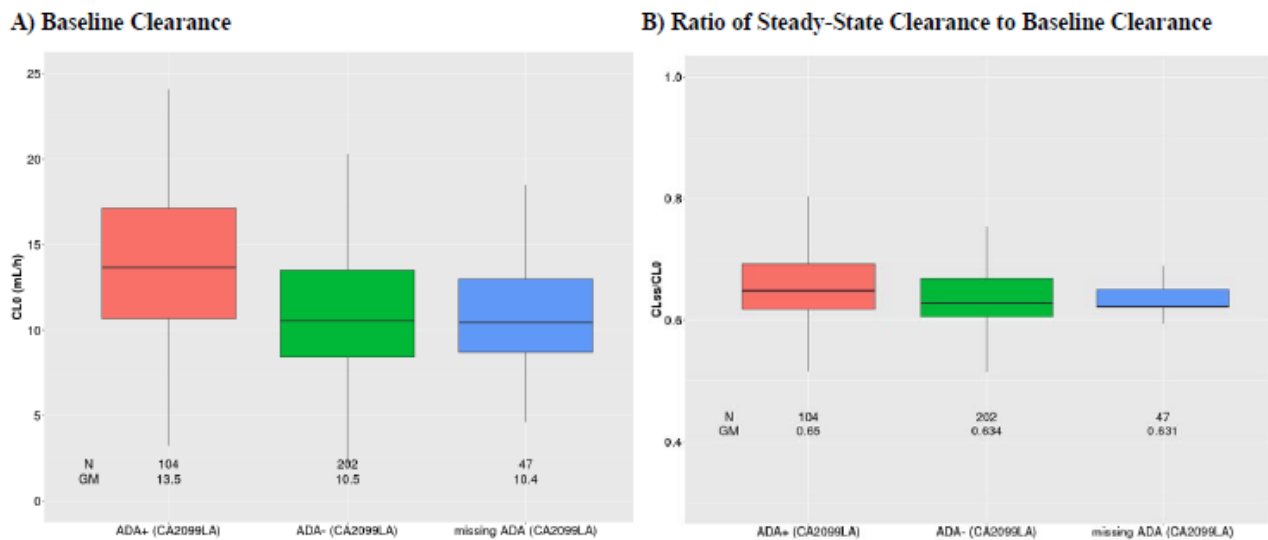Analysis-Directory: /global/pkms/data/CA/209/nsclc-1L-9LA/prd/er-os/final

Program Source: Analysis-Directory/R/scripts/os-plot-cov-eff-sen.r

Source: Analysis-Directory/R/plots/coveff-sen-os.png

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.

Reference subjects: Subject had median value of nivolumab Cavg1 and ipilimumab Cavg1 who received nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy in Study CA2099LA, and median value of LDH, albumin, body weight, baseline clearance, baseline tumor size, NSQ, female, non-smoker, PS = 0, PD-L1 < 1%, and recurrent disease stage.

Figure 5.1.2-1: Model Evaluation of the Exposure-Response of OS (Full Model), by Treatment Arm
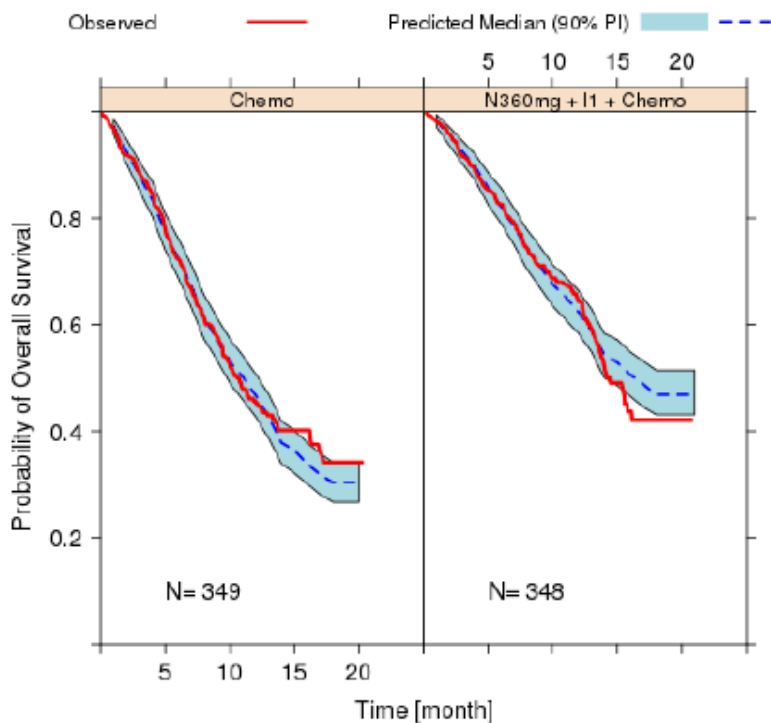
Analysis-Directory: /global/pkms/data/CA/209/ nsclc-1L-9LA/prd/er-os/final/

Program Source: Analysis-Directory/R/scripts/os-plot-vpc-full.r

Source: Analysis-Directory/R/plots/os-vpc-full-arm.png

Note: N360mg+I+Chemo: nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy; Chemo: 4 cycles of histology-based platinum-doublet chemotherapy

Exposure-response of safety

The initial analysis population for the E-R analysis of safety was identical to the analysis population for the E-R analysis of efficacy, and only included the 697 subjects in CA2099LA for whom nivolumab and ipilimumab exposures were available. Subsequently, data from 1525 subjects in CA209227 were added to the analysis, resulting in a pooled analysis data set of 2222 subjects.

The pooled analysis data set included data from all subjects in both CA2099LA and CA209227 for whom nivolumab and ipilimumab exposures were available. Nivolumab and ipilimumab exposures were imputed to zero for subjects who received only chemotherapy, and ipilimumab exposures were imputed to zero for subjects who received nivolumab monotherapy, or nivolumab in combination with chemotherapy.

Table 3.2.2.1-1:   Subjects Included in the Exposure-Response of Gr2+ IMAEs Analysis Dataset

Study	Subjects			
	Treated Subjects	Excluded due to Lack of Nivo or Ipi Exposure Estimates (%)	Excluded due to other tumor type	Included (%)
Study CA2099LA				
Nivo 360 mg Q3W + ipi 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy	358	10 (2.8)	0 (0.0)	348 (97.2)
Chemotherapy	349	0 (0.0)	0 (0.0)	349 (100.0)
Study CA209227				
Nivo 240 mg Q2W	391	63 (16.1)	0 (0.0)	328 (83.9)
Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	576	101 (17.5)	1 (0.2)	474 (82.3)
Nivo 360 mg Q3W + 4 cycles of platinum-doublet chemotherapy	172	19 (11.0)	0 (0.0)	153 (89.0)
Chemotherapy	570	0 (0.0)	0 (0.0)	570 (100.0)
Total	2416	193 (8.0)	1 (0.0)	2222 (92.0)

Source: Appendix 3.2.2.1-1

Abbreviations: Ipi = ipilimumab; Nivo = nivolumab; Q3W = every 3 weeks; Q6W = every 6 weeks

Chemotherapy: 4 cycles of platinum-doublet chemotherapy plus optional pemetrexed maintenance therapy

Table 3.2.2.2-1:   **Summary of Events in the Exposure-Response of Gr2+ IMAEs Analysis Dataset**

Study	Number of Subjects		
	Included in Analysis	Number of Events (%)	Number Censored (%)
CA2099LA Treatment Regimen			
Nivo 360 mg Q3W + ipi 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy	348	177 (50.9)	171 (49.1)
Chemotherapy	349	65 (18.6)	284 (81.4)
CA209227 Treatment Regimen			
Nivo 240 mg Q2W	328	125 (38.1)	203 (61.9)
Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	474	243 (51.3)	231 (48.7)
Nivo 360 mg Q3W + 4 cycles of platinum-doublet chemotherapy	153	58 (37.9)	95 (62.1)
Chemotherapy	570	95 (16.7)	475 (83.3)
Total	**2222**	**763 (34.3)**	**1459 (65.7)**

Source: Appendix 3.2.2.1-1

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

Chemotherapy: 4 cycles of platinum-doublet chemotherapy plus optional pemetrexed maintenance therapy.

The parameter estimates of the model are presented in Table 5.2.1.1-1, and the effects of exposure and covariates on the hazard ratio (95% CI) of Gr2+ IMAEs is shown in Figure 5.2.1.1-1.

Table 5.2.1.1-1: Parameter Estimates of the Exposure-Response of Gr2+ IMAEs (Initial Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Cavg_nivo [µg/mL]	-0.027	0.009629	35.67	0.9734 (0.9552, 0.9919)
Log_Cavg_ipi [µg/mL]	0.2583	0.04794	18.56	1.295 (1.179, 1.422)
Sex [Female:Male]	0.4548	0.1518	33.38	1.576 (1.17, 2.122)
Age [yr]	-0.003713	0.007649	206	0.9963 (0.9815, 1.011)
Histology [SQ:NSQ]	0.1797	0.1492	82.98	1.197 (0.8935, 1.603)
Disease Status [Recurrent:Stage IV]	-0.3776	0.275	72.84	0.6855 (0.3999, 1.175)
Smoking Status [Smoker:Non-smoker]	-0.1983	0.2084	105.1	0.8201 (0.5451, 1.234)
PDL1 status [≥ 1%:< 1]	-0.02342	0.1371	585.3	0.9768 (0.7467, 1.278)
Performance Status [≥ 1:0]	-0.1313	0.1398	106.5	0.877 (0.6667, 1.153)
Body Weight [kg]	0.001312	0.00516	393.3	1.001 (0.9912, 1.011)
Log(LDH) [xULN]	-0.4259	0.1801	42.3	0.6532 (0.4589, 0.9298)
Albumin	-0.1974	0.1292	65.44	0.8208 (0.6372, 1.057)
Tumor size [cm]	-0.01272	0.01558	122.5	0.9874 (0.9577, 1.018)

Analysis-Directory: /global/pkms/data/CA/209/ nsclc-1L-9LA/prd/er-imae/final/

Program Source: Analysis Directory/R/scripts/er-imae-gr2-9la.Rmd

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

Abbreviations: Cavg1 = average concentration after the first dose; CI = confidence interval; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; NSQ = nonsquamous; PD-L1 = programmed death-ligand 1; SQ = 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 5.2.1.1-1: Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Initial Full Model)

Covariate
Categorical = Comparator:Reference
Continuous = Reference (P05 - P95)

Effect Value (95% CI)

Covariate	Effect Value (95% CI)
Performance Score [>=1:0] (N=477:220)	0.877 (0.667, 1.15)
PD-L1 Status [>=1%:<1%] (N=441:256)	0.977 (0.747, 1.28)
Smoking Status [Non-smoker:Smoker] (N=92:605)	0.82 (0.545, 1.23)
Disease Stage [Recurrent/Metastatic:Stage IV] (N=51:646)	0.686 (0.4, 1.18)
Histology [SQ:NSQ] (N=218:479)	1.2 (0.894, 1.6)
Sex [Female:Male] (N=209:488)	1.58 (1.17, 2.12)
Baseline Tumor Size [cm] 8 (2.08 - 17.3)	0.888 (0.668, 1.18) / 1.08 (0.9, 1.29)
Baseline Albumin [g/dL] 4 (2.88 - 4.7)	0.871 (0.729, 1.04) / 1.25 (0.94, 1.66)
Baseline LDH [xULN] 1 (0.56 - 2.23)	0.711 (0.536, 0.943) / 1.28 (1.04, 1.57)
Baseline Body Weight [kg] 70 (50.1 - 98.2)	1.04 (0.78, 1.36) / 0.974 (0.804, 1.19)
Age [yr] 65 (46 - 77)	0.956 (0.799, 1.14) / 1.07 (0.812, 1.43)
Ipi Cavg1 [ug/mL] 0 (2.72 - 6.34)	9.6 (4.23, 21.8) / 7.71 (3.68, 16.2)
Nivo Cavg1 [ug/mL] 0 (25.7 - 54.8)	0.228 (0.0812, 0.641) / 0.5 (0.308, 0.812)

Hazard Ratio: 0.25 1.00 4.00 16.00

⊖ Estimate (95% CI): Categorical   ■ Estimate (95% CI): Continuous (P95)
⊞ Estimate (95% CI): Continuous (P05) | Estimate (Continuous Values > Median)

Analysis-Directory: /global/pkms/data/CA/209/ nsclc-1L-9LA/prd/er-imae/final/

Program Source: Analysis Directory/R/scripts/er-imae-gr2-9la.Rmd

Source: Analysis Directory/R/export/fullmodel -corr.csv

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: The reference value of ipilimumab Cavg1 utilized to calculate the HR is 0.001 µg/mL, as log-transformed value of Cavg1 = 0 is not defined.

The revised full model was developed with data from both CA2099LA and CA209227 using the same procedure as the initial full model. The relationship of Gr2+ IMAEs and exposure was best described by a log-linear with nivolumab Cavg1, and linear with ipilimumab Cavg1 (lowest BIC).

The parameter estimates of the model are presented in Table 5.2.1.2-1, and the effects of exposure and covariates on the hazard ratio (95% CI) of Gr2+ IMAEs is shown in Figure 5.2.1.2-1. The parameters of the model were well estimated given the modest correlation between effects of

nivolumab and ipilimumab exposure (r < |0.6|), and low correlation between all the other estimated parameters (r < |0.3|).

Table 5.2.1.2-1:   Parameter Estimates of the Exposure-Response of Gr2+ IMAEs (Revised Full Model)

Predictor	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Log Cavg_nivo [μg/mL]	0.06038	0.01025	16.97	1.062 (1.041, 1.084)
Cavg_ipi [μg/mL]	0.1151	0.01909	16.59	1.122 (1.081, 1.165)
Sex [Female:Male]	0.3139	0.08497	27.07	1.369 (1.159, 1.617)
Age [yr]	-0.001791	0.003993	223	0.9982 (0.9904, 1.006)
Histology [SQ:NSQ]	0.05156	0.08504	165	1.053 (0.8913, 1.244)
Disease Status [Recurrent:Stage IV]	0.04855	0.108	222.4	1.05 (0.8495, 1.297)
Smoking Status [Smoker:Non-smoker]	-0.258	0.1161	44.99	0.7726 (0.6154, 0.97)
PDL1 status [≥ 1%:< 1]	0.01903	0.07788	409.3	1.019 (0.8749, 1.187)
Performance Status [≥ 1:0]	-0.125	0.0758	60.63	0.8825 (0.7606, 1.024)
Body Weight [kg]	0.0007715	0.002563	332.3	1.001 (0.9958, 1.006)
Log(LDH) [xULN]	-0.07093	0.09288	130.9	0.9315 (0.7765, 1.117)
Albumin	-0.148	0.07671	51.82	0.8624 (0.742, 1.002)
Tumor size [cm]	-0.0051	0.008267	162.1	0.9949 (0.9789, 1.011)

Analysis-Directory: /global/pkms/data/CA/209/ nsclc-1L-9LA/prd/er-imae/final/

Program Source: Analysis Directory/R/scripts/er-imae-gr2-9la.Rmd

Source: Source: Analysis Directory/R/export/rev-fullmodel -corr.csv

Abbreviations: Cavg1 = average concentration after the first dose; CI = confidence interval; Gr2+ IMAE = Grade ≥ 2 immune-mediated adverse event; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; NSQ = nonsquamous; PD-L1 = programmed death-ligand 1; SQ = 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 5.2.1.2-1: Estimated Covariate Effects of the Exposure-Response of Gr.2+ IMAEs (Revised Full Model)

Covariate Categorical = Comparator:Reference Continuous = Reference (P05 - P95)	Effect Value (95% CI)
Performance Score [>=1:0] (N=1460:762)	0.882 (0.761, 1.02)
PD-L1 Status [>=1%:<1%] (N=1482:740)	1.02 (0.875, 1.19)
Smoking Status [Non-smoker:Smoker] (N=300:1922)	0.773 (0.615, 0.97)
Disease Stage [Recurrent/Metastatic:Stage IV] (N=280:1942)	1.05 (0.85, 1.3)
Histology [SQ:NSQ] (N=647:1575)	1.05 (0.891, 1.24)
Sex [Female:Male] (N=706:1516)	1.37 (1.16, 1.62)
Baseline Tumor Burden [cm] 8 (2.2 - 18.3)	0.949 (0.803, 1.12) 1.03 (0.939, 1.13)
Baseline Albumin [g/dL] 4 (2.9 - 4.6)	0.915 (0.836, 1) 1.18 (0.998, 1.39)
Baseline LDH [xULN] 1 (0.56 - 2.1)	0.949 (0.828, 1.09) 1.04 (0.937, 1.16)
Baseline Body Weight [kg] 80 (48.7 - 98)	1.01 (0.927, 1.11) 0.976 (0.829, 1.14)
Age [yr] 65 (46 - 77)	0.979 (0.891, 1.07) 1.03 (0.893, 1.2)
Ipi Cavg1 [ug/mL] 0 (2.73 - 6.12)	2.02 (1.61, 2.55) 1.37 (1.24, 1.52)
Nivo Cavg1 [ug/mL] 0 (19.6 - 48.5)	1.92 (1.54, 2.39) 1.82 (1.49, 2.22)

Hazard Ratio — 0.3 0.5 1.0 2.0 4.0

Estimate (95% CI): Categorical
Estimate (95% CI): Continuous (P05)
Estimate (95% CI): Continuous (P95)
Estimate (Continuous Values > Median)

Analysis-Directory: /global/pkms/data/CA/209/ nsclc-1L-9LA/prd/er-imae/final/
Program Source: Analysis Directory/R/scripts/er-imae-gr2-9la.Rmd
Source: Analysis Directory/R/export/rev-model-dev-smr.csv
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: The reference value of ipilimumab Cavg1 utilized to calculate the HR is 0.001 μg/mL, as log-transformed value of Cavg1 = 0 is not defined.

The estimated effects of nivolumab and ipilimumab Cavg1 indicate that the risk of Gr2+ IMAEs is higher in subjects who receive these agents compared to chemotherapy alone. Additionally, the log-linear functional form of nivolumab Cavg1, and the magnitude of the estimated effect indicates the effect of nivolumab reaches a plateau at the exposures produced by the 3 mg/kg Q2W, 240 mg Q2W, and 360 mg Q3W doses. On the other hand, the risk of Gr2+ IMAEs is higher for subjects at the 95th percentile of exposure produced by an ipilimumab dose of 1 mg/kg Q6W, relative to the 5th percentile exposure at the same dose level.

Importantly, the interaction between nivolumab and ipilimumab Cavg1 was not significant (the model without any interaction had the lowest BIC) indicating that the risk of Gr2+ IMAEs due to exposure of these agents was additive, and not synergistic. In addition, the potential interaction of the effect of chemotherapy was assessed and found to also not be significant (the model without any interaction had the lowest BIC). This indicates that chemotherapy does not change the risk of Gr2+ IMAE due to nivolumab and ipilimumab exposure.

The only covariates that had significant effects on the risk of Gr2+ IMAEs were sex and smoking status (95% CI excluded null effect). The risk was higher in females relative to males, and lower in non-smokers compared with current/former smokers.

Figure 5.2.2-1: Model Evaluation of the Exposure-Response of Gr2+ IMAE (Full Model), by Treatment Regimen
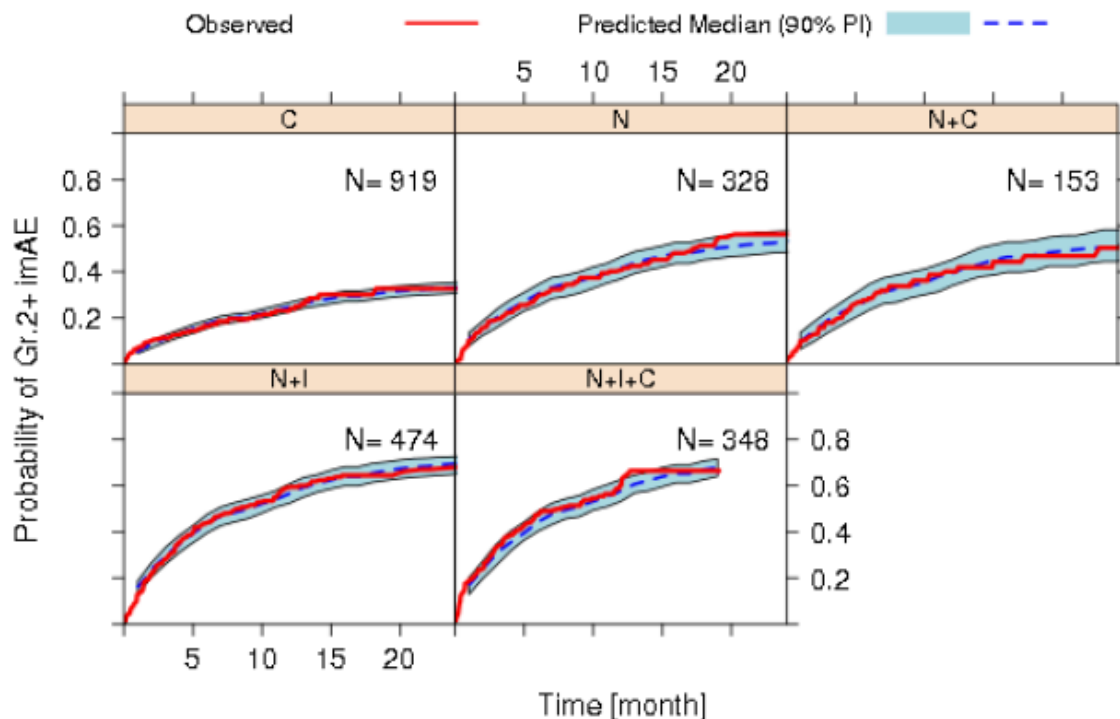
Analysis-Directory: /global/pkms/data/CA/209/ nsclc-1L-9LA/prd/er-imae/final/

Program Source: Analysis-Directory/R/scripts/er-imae-gr2-9la.rmd
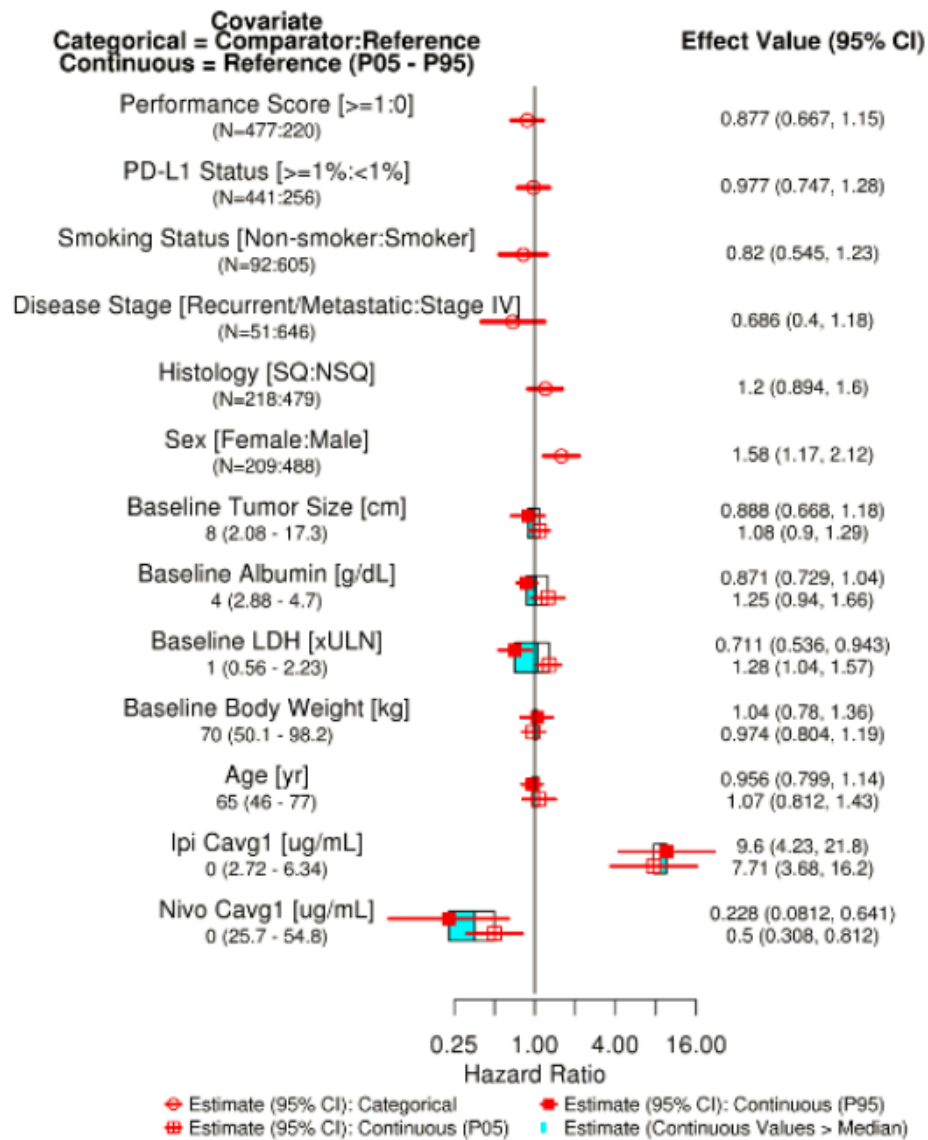
Source: Analysis-Directory/R/plots/vpc-imgr2-rfull-trt.png

Note: C: histology-based platinum-doublet chemotherapy; N: nivolumab 240 mg or 3 mg/kg Q2W monotherapy; N+C: nivolumab 360 mg Q3W + 4 cycles of histology-based platinum-doublet chemotherapy; N+I: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; N+I+C: nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy

2.3.5. Discussion on clinical pharmacology

Analytical methods

Validated bioanalytical methods were used to support the clinical pharmacology programs of nivolumab and ipilimumab. The Method BAL-II/MOA/061 for nivolumab and Method ICD 267 for ipilimumab were previously validated. In addition, updated cross-validated bioanalytical methods for nivolumab and ipilimumab concentrations used in CA2099LA between PPD and WuXi. The results show that concentrations generated by the two testing labs at PPD and WuXi produced equivalent results

In general, the analytical methods were validated successfully with respect to selectivity, sensitivity, calibration curve fitting, accuracy, precision, recovery, matrix effect and dilution. Analyte stability was demonstrated for freeze/thaw, whole blood stability room temperature and extract storage conditions and long-term matrix stability.

The in-study validations have been submitted for both clinical studies CA2099LA and CA209227. The calibration standards and the QCs were acceptable for both studies. For both studies, the reason for the re-analysis of samples are considered acceptable. Study samples analysed and reported for nivolumab and ipilimumab in support of studies CA299LA and CA209227 were covered by the long-term stability demonstrated at nominal at -70 ºC.

The incurred sample re-analysis was performed in study CA2099LA for both analytes. The results show that the ISR measurements were within ±30% deviations

Pharmacokinetics

A model-based analysis has been implemented to describe the pharmacokinetics of both nivolumab and ipilimumab based on previous population PK models of nivolumab and ipilimumab developed in monotherapy and combination in multiple tumour types, including patients with NSCLC.

The number of included clinical trials, patients, and observations seems adequate. The proportion of data below the limit of quantification is low (<10%), so its exclusion should not be relevant in the estimation of PK parameters.

Base population PK model of nivolumab

The PK structural model used has been maintained from the previous population models, allowing the re-estimation of the PK structural parameters and the previously identified covariates. Despite the fact that the condition number is adequate, the effect of several covariates (OTH, LINE and RAA) on CL were not statistically significant, since 95% CI includes 0. Furthermore, some of these parameters presented RSE values higher than 35%, which indicates high uncertainty in its estimation. A model refinement has been implemented, showing a more parsimonious model with similar parameter estimates compared to the full model. The current developed model should be used for further model evaluation exercises.

Final population PK model of nivolumab

The final model incorporates as covariates, the effects on CL and Vc of the schemes combined with ipilimumab or nivolumab and/or chemotherapy. This strategy evaluates the effect of the combination (nivolumab or ipilimumab and/or chemotherapy) as a categorical effect, without taking into account other mechanistic approaches that would justify the changes in CL or Vc with a continuous function based on nivolumab or ipilimumab plasma levels.

According to the pc-VPC (time after last dose), the bias in Vc and an over-estimation of the inter-individual variability of Vc are confirmed. On the other hand, based on the pc-VPC (time after last dose), there is an underestimation of the plasma levels of nivolumab around 24 hours, which indicates that the effect of the co-administration of ipilimumab and/or chemotherapy may be biased. The influence of patient's drop-out was suggested to explain the slight bias observed in pc-VPC. Responder patients tend to show a greater decrease on CL over time, which may influence model predictions observed in pc-VPC.

Intensive dosage regimens with ipilimumab (Q3W) cause clinically relevant increases in CL, which would lead to lower nivolumab plasma levels. However, according to the pc-VPC, this effect is over-estimated, since the experimental values are not adequately captured by the 95% PI of the 50th

percentile. Therefore, the clinical evaluation of the PK parameters and the exposure endpoints should be carried out once the model is updated.

<u>Final population PK model of ipilimumab</u>

The statistical significance of several covariates (NSCL, NIVO 0.3 Q3W, and NIVO 3 Q3W) are questioned, since their 95% CI includes 0. A clinically relevant effect was observed on patients with low body weight (20-30% change in exposure) which may influence the exposure metrics.

The co-administration of nivolumab modifies the ratio of steady-state clearance to baseline clearance in a clinically relevant way. Similarly, co-administration of nivolumab produces a clinically relevant increase in CL, which could lead to relevant decrease in ipilimumab exposure. Therefore, it is highly relevant to evaluate the impact of co-administration of nivolumab or ipilimumab using a continuous function that relates the plasma levels of both analytes. Currently, the effect that the administration of nivolumab clearly causes on the PK parameters of ipilimumab have been described empirically, allowing inconsistent results (i.e. 3 mg/kg Q3W vs 0.3 and 1 mg/kg Q3W)

<u>Special populations</u>

The impact of ethnicity on both nivolumab and ipilimumab CL0 and nivolumab and ipilimumab CLss/CL0 seems negligible and within the inter-individual variability observed. However, this analysis should be updated once the results from the structural joint population PK model become available.

<u>Exposure-response of efficacy</u>

The exposure-response model seems able to characterize the time-course of the cumulative probability of death in 1L NSCLC patients for both treatment arms: nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy, and 4 cycles of platinum-doublet chemotherapy. Due to the absence of nivolumab CL in the chemotherapy arm, nivolumab Cavg was initially included in the model. No statistical relationship was found when ipilimumab exposure was considered. However, the sensitive analysis revealed nivolumab exposure was not a significant predictor of OS, and baseline CL was included. This leads to observe that higher nivolumab Cavg and, at the same time, higher baseline nivolumab CL are associated with a high risk of death. The Applicant justified the inverse relationship as a consequence of having used data from only 1 dose level and the high correlation among both variables.

<u>Exposure-response of safety:</u>

The logistic regression model of Gr2+ IMAEs seems capable to describe the cumulative probability of the 1st occurrence of a Gr2+ IMAE in 1L NSCLC patients. An additive effect of higher risk of Gr2+ IMAEs was linked with nivolumab and ipilimumab exposure compared to the chemotherapy arm. The risk of occurrence of Gr2+ IMAEs were similar across the exposure of ipilimumab, suggesting that no exposure-safety relationship was established. The influence of concomitant administration of 2 cycles of platinum-based chemotherapy is unknown. From a clinical pharmacology perspective, it is impossible to link the higher risk of Gr2+ IMAEs to the observed exposure of nivolumab and ipilimumab.

The estimated effects of nivolumab and ipilimumab Cavg1 suggest that the risk of IMAEs is lower in subjects with higher nivolumab Cavg1, and higher in subjects with higher ipilimumab Cavg1. However, these estimated effects are highly and negatively correlated (r = -0.93) and should be interpreted in this context. The high negative correlation in the estimated effects of nivolumab and ipilimumab Cavg1 is not unexpected given the high correlation between these measures of exposure (r = 0.89). The high negative correlation indicates that the effect of ipilimumab Cavg1 may be overestimated, whereas the

effect of nivolumab Cavg1 may be underestimated, especially as it is unlikely that the risk of IMAEs decreases with higher nivolumab Cavg1.

Notably, all models that included nivolumab and ipilimumab exposure provided a better fit to the data than the null model (which included only covariates and no exposure predictors). Given the high negative correlation between the parameter estimates of nivolumab and ipilimumab Cavg1 (r = -93), the full model was revised by inclusion of data from CA209227.

2.3.6. Conclusions on clinical pharmacology

The Clinical Pharmacology evaluation of nivolumab and ipilimumab in monotherapy and combination regimens with and without chemotherapy in subjects with NSCLC has been characterized using population PK models previously developed. A model refinement has been implemented to account for significant parameter-covariates relationships, which increased the stability of the model.

2.4. Clinical efficacy

A total of 3 studies are submitted to support the application:
- Study CA209568 phase II Part 2(dose finding study)
- Study CA209229LA (main study)
- Study CA209227 (supportive study)

2.4.1. Dose response study

Phase II Study CA209568 Part 2 ("dose finding")

Study CA209568 is a Phase 2 study designed to evaluate the efficacy and safety of nivo+ipi±chemo in subjects with stage IV NSCLC previously untreated for advanced diseases. The study includes 2 independent sub-studies or parts.
In Part 1 of the study, all patients were treated with nivo+ipi. Part 1 of this study has been assessed in EMEA/H/C/WS/1372/0053 (nivo+ipi (TMB) procedure - withdrawn).
In Part 2, patients are treated with nivo + ipi + chemo in combination with histology-based platinum doublet chemotherapy for 2 cycles followed by nivo + ipi until progression or a max for 2 years. This Part 2 will be the focus in the current application.

Title: **A study of nivolumab in combination with ipilimumab (part 1); and nivolumab + ipilimumab in combination with chemotherapy (part 2) as first line therapy in stage IV Non-Small Cell Lung Cancer (NSCLC).**

Method: Ongoing phase II trial (**Figure 1**). Part 2 of the trial was designed as a safety lead-in phase to evaluate safe dose levels for the combination of nivo+ipi+chemo.

Figure 1 Study design schematic of study CA 209568 (part 2)

Histology-based chemotherapy
SQ: Carboplatin AUC6 +Paclitaxel 200mg/m²
NSQ: Carboplatin AUC 5 or 6 + Pemetrexed 500mg/m²
or Cisplatin 75mg/m² + Pemetrexed 500mg/m²
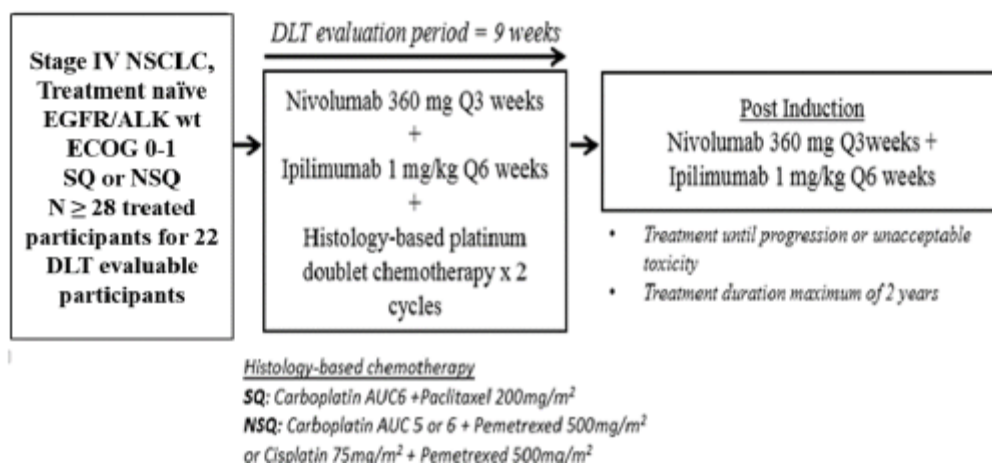
Primary objective

- To determine the incidence of the dose limiting toxicity (DLT) during DLT evaluation period (within 9 weeks after first dose)

- To determine the safety and tolerability of nivo+ ipi combined with chemotherapy

Secondary objective

- To evaluate the ORR, PFS by investigator assessment per RECIST 1.1 and OS

Main in-and exclusion criteria:

- Adult patients aged ≥ 18 years, with measurable, treatment naive advanced stage IV NSCLC

- Tumour tissue should be available for PD-L1 immunohistochemical (IHC) testing by central screening

- Patients with an EGFR mutation or ALK translocation were not allowed to participate

Treatments Part 2

Nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W in combination with 2 cycles of histology-based platinum doublet chemotherapy (Q3W):

- Squamous cell (SQ): carboplatin area under the concentration time curve (AUC) 6 + paclitaxel 200 mg/m²

- Non-squamous cell (NSQ) carboplatin (AUC 5 or 6) + pemetrexed 500 mg/m² or cisplatin 75m² + pemetrexed 500 mg/m²

Nivolumab + ipilimumab could be administered up to 2 years.

Results

A total of 60 patients were enrolled and a total of 36 treated. The median age was 70 years (min, max 35-90) and most patients (n=16) were aged between 65-75 years. Most patients were male n=23 (64%) and the majority was white n=32 (89%). The most included histology was NSQ n=24 (65%). Most patients n=18 (50%) had PD-L1 <1%.

The median duration of treatment was 6.36 months. A total of n=32 (89%) discontinued treatment

during the treatment period. Most frequently reported reason for discontinuation was disease progression n=16 (44%), followed by drug toxicity n=9 (25%).

Efficacy

After a minimum of 14.9 months of follow up[1]:

- The investigator's assessed ORR was 44.4% with a median DoR of 10.71 months

- The investigator's assessed median PFS after 35/36 (69%) of events was 8.74 months (95% CI 5.26, 13.83)

- The median overall survival after 16/36 (44.4%) of events was 21.09 months (95% CI 6.54, NA)

Safety

One patient met the predefined criteria for drug limiting safety during the first 9 weeks of treatment. The DLT was a Grade 3 increased AST and ALT. The overall incidence of DLT was less than the predefined incidence of ≤ 25%.

No deaths were related to drug toxicity. Drug related Serious Adverse Events (SAEs) and drug related AEs leading to discontinuation were reported in 36.1% and 22.2% of patients.

2.4.2. Main study

Title of Study

The main study to support this application is study CA2099LA:
A phase 3, randomised study of nivolumab plus ipilimumab in combination with chemotherapy vs chemotherapy alone as first line therapy in stage IV Non-Small Cell Lung Cancer (NSCLC). *Eudra-CT: 2017-001195-35.*

Methods

Study CA2099LA is an international 2-arm, 1:1 randomised, open label parallel group study to compare the efficacy and safety of nivolumab+ ipilimumab + chemotherapy vs chemotherapy in the first line treatment of stage IV NSCLC. Patients are stratified according to tumour histology (non-squamous vs squamous), gender, and PD-L1 –Level (<1% vs ≥1%). Patients with non-quantifiable PD-L1 expression were stratified as PD-L1 <1% (see **Figure 2**).

Figure 2 Schematic Study Design Study CA2099LA

---

[1]The results based on database lock of 22 Mar 2019 with clinical cut-off date 22 Jan 2019.
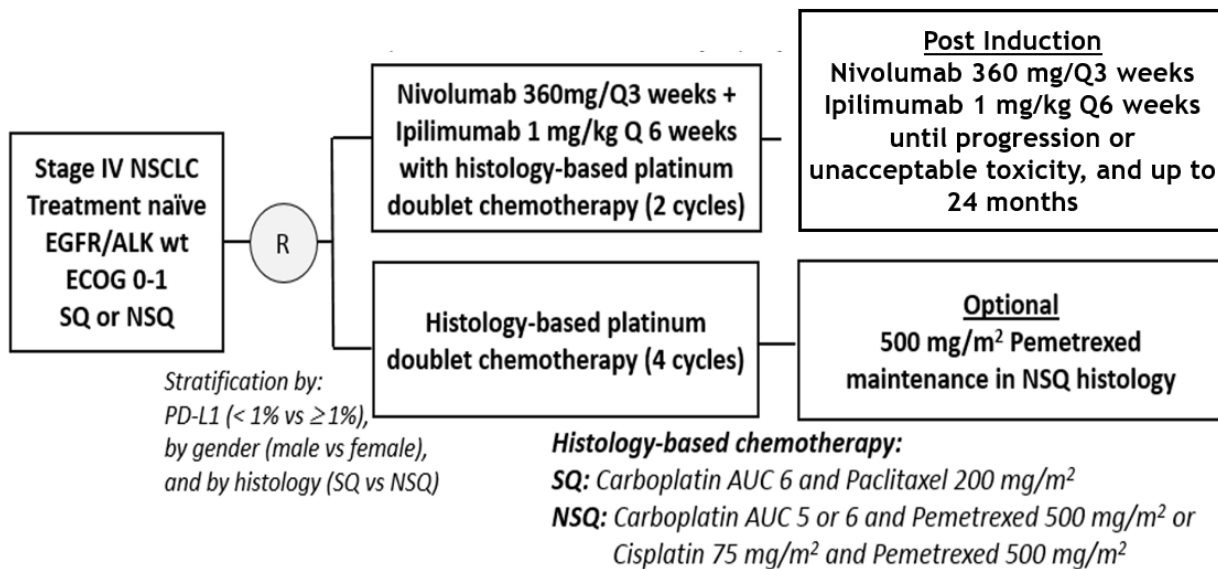
Abbreviations: ALK - anaplastic lymphoma kinase, AUC - area under the plasma drug concentration-time curve, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, NSQ - non-squamous, PD-L1 - programmed death ligand 1, Q3 - every 3, Q6 - every 6, R - randomization, SQ - squamous

Study participants

Main inclusion criteria:

- Adult (> 18 years) male and female subjects with histologically confirmed stage IV or recurrent NSCLC per the 7th International Association for the Study of Lung Cancer classification (IASLC)

- SQ or NSQ histology

- No prior systemic anti-cancer therapy (including epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] inhibitors) given as primary therapy for advanced or metastatic disease

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, with a life expectancy of at least 3 months

- Available tumour tissue sample with an available central laboratory PD-L1 immunohistochemistry (IHC) test before randomisation

Exclusion criteria:

- With known EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy

- Untreated central nervous system (CNS) metastases

Treatments

Prior to randomisation, the investigator decided if a subject with NSQ disease would receive cisplatin therapy, based on cisplatin eligibility criteria.

- **Treatment: nivolumab + ipilimumab + chemotherapy**

Nivolumab (360 mg Q3W) was administered with ipilimumab (1 mg/kg Q6W), plus 2 cycles of histology-based chemotherapy as follows:

SQ histology: carboplatin area under the concentration time curve (AUC) 6 + paclitaxel 200 mg/m^2 (or 175 mg/m^2 as per local institutional practice)

NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

After 2 cycles, nivolumab and ipilimumab treatment could continue for up to 24 months, or until Response Evaluation Criteria in Solid Tumours (RECIST) 1.1-defined disease progression or unacceptable toxicity.

Patients might continue treatment beyond initial RECIST 1.1 defined progressive disease, as long as they experience an investigator assessed clinical benefit without rapid disease progression, tolerated treatment, had a stable performance status, the continuation of treatment would not delay an imminent intervention to prevent serious disease complication, and had provided a written informed consent for continuation of the immunotherapy.

- **Treatment Chemotherapy**

Histology dependent, platinum-based doublet chemotherapy was selected by the investigator and administered on Day 1 Q3W for 4 cycles. Histology-based platinum-based doublet chemotherapy was one of the following:

- SQ histology: carboplatin AUC 6 + paclitaxel 200 mg/m^2 (or 175 mg/m^2 as per local institutional practice)

- NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2;
  After 4 cycles, subjects with NSQ histology could continue to receive optional maintenance therapy with 500 mg/m2 pemetrexed alone on Day 1 of each 3 weeks until disease progression or unacceptable toxicity.

The investigator had to decide before randomisation if the patients should be treated with cisplatin or with carboplatin.

Objectives

The primary and secondary objectives and endpoints are listed in Table 1.

Table 1: **Study Objectives and Endpoints**

Objectives	Endpoints
Primary	
To compare the efficacy of nivolumab + ipilimumab+chemotherapy (nivo+ipi+chemo) vs chemotherapy in participants with histologically confirmed stage IV NSCLC	Overall survival (OS)
Secondary	
To compare the efficacy of nivo+ipi+chemo vs chemotherapy in participants with histologically confirmed stage IV NSCLC	Progression-free survival (PFS) and objective response rate (ORR) by blinded independent central review (BICR)
To evaluate efficacy outcomes in participants with histologically confirmed stage IV NSCLC treated with nivo+ipi+chemo vs chemotherapy with different PD-L1 expression levels	ORR and PFS by BICR and OS in participants with different programmed death ligand 1 (PD-L1) levels

Outcomes/endpoints

OS was defined as the time from randomisation to the date of death from any cause. OS was censored on the last date a subject was known to be alive. Survival follow-up was to be conducted every 3 months after subject's off-treatment date.

PFS (primary definition) was defined as the time from the randomisation date to the date of the first documented tumour progression based on BICR assessment (per RECIST 1.1), or death from any cause, whichever occurred first.

- Subjects who died without a reported prior progression were considered to have progressed on the date of their death.

- Subjects who had not progressed or died were censored on the date of their last evaluable tumour assessment.

- Subjects who did not have any on-study tumour assessments and did not die were censored on the randomization date.

- Subjects who started any palliative local therapy or subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumour assessment prior to initiation of the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first.

PFS (**PFS2,** secondary definition) is defined as the time from randomisation to objectively documented progression after the next line of therapy, per investigator assessment, or to death from any cause, whichever occurred first. Subjects who were alive and without progression after the next line of therapy were censored at their last known alive date.

ORR was defined as the number of randomised subjects with a best overall response (BOR) of confirmed CR or PR based on BICR assessments (using RECIST v1.1 criteria), divided by the number of all randomised subjects. As part of the evaluation of ORR, duration of response (**DoR**) and time to response (**TTR**) were evaluated for subjects who achieved confirmed PR or CR. **DoR** was defined as the time between the date of first confirmed documented response (CR or PR) to the date of the first documented BICR-assessed tumour progression (per RECIST 1.1), or death from any cause, whichever

occurred first. **TTR** was defined as the time from randomisation 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.

In both arms, on-study tumour assessments began at Week 6 post first dose date (~ 7 days) and were performed every 6 weeks (~ 7 days) until Week 48. After Week 48, tumour assessments were performed every 12 weeks (~ 7 days) until BICR assessed progression.

Sample size

Randomisation

Subjects were randomised 1:1 to treatment with nivo+ipi+chemo or chemotherapy. The stratification factors for randomisation were: PD-L1 level (≥1% vs < 1% or not quantifiable), histology (SQ vs NSQ), and gender (male vs female).

Blinding (masking)

The treatments in this study were open-label.

- – The personnel who conducted the PD-L1 and TMB testing were blinded to treatment group assignment of individual subjects during the conduct of the study

- – The whole BMS clinical study team were blinded to the aggregate treatment group information up to database lock

Select members of the BMS clinical team were unblinded to the treatment group assignment of individual subjects during the study in order to monitor the safety of individual subjects.

Statistical methods

- • **Sample size**

The sample size was based on the comparison of the primary endpoint of OS between nivo+ipi+chemo and chemotherapy with a 2-sided overall alpha of 0.05. The number of events was estimated assuming an exponential distribution of OS for the chemotherapy arm and a piecewise exponential distribution with a 3-month delayed treatment effect for the nivo+ipi+chemo arm.

Approximately 700 subjects were to be randomised to the nivo+ipi+chemo and chemotherapy arms in a 1:1 ratio. Approximately 402 events (i.e., deaths), observed among the 700 randomized subjects, would provide 81% power to detect an average hazard ratio (HR) of 0.75 with a type 1 error of 0.05 (2-sided). The average HR of 0.75 resulted from an assumed targeted HR of 1 for the initial 3 months and a targeted HR of 0.68 for the time beyond 3 months and corresponded to a 33% increase in the median OS (assuming a median OS of 13.93 months for chemotherapy alone and 18.57 months for nivo+ipi+chemo, respectively).

- • **Primary outcome: OS analyses**

The analysis of OS to compare nivo+ipi+chemo and chemotherapy was based on a 2-sided stratified log-rank test stratified by histology (SQ vs NSQ), sex (male vs female), and PD-L1 level (≥ 1% vs < 1% or not quantifiable). A Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary was employed to determine the nominal significance level for the interim analysis (nominal

significance level p < 0.033 is based on the actual number of OS events of 351). The stratified HR of OS between the treatment groups (nivo+ipi+chemo vs chemotherapy) and corresponding 2-sided 96.71% confidence interval (CI) was estimated using a stratified Cox proportional hazard model, with treatment arm as a single covariate. In addition, a 2-sided p-value was reported for the analysis of OS. For descriptive purposes, a 2-sided 95% CI for the HR was also presented.

There was 1 planned interim analysis of OS for superiority to be performed at approximately 80% of total events, i.e. 322. The stopping boundaries at the interim and final analyses were to be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis was performed exactly at 322 events, the boundary in terms of statistical significance for declaring OS superiority would be 0.024 (HR boundary of 0.78). The boundary for declaring superiority in terms of statistical significance for the final analysis of OS after 402 events would then be 0.042 (HR boundary of 0.82).

- **Planned interim analyses**

At the time of the 03-Oct-2019 Data Base lock (DBL) the actual number of OS events was 351. The planned interim analysis was performed and the primary analysis of OS for nivo+ipi+chemo vs chemotherapy crossed the pre-specified boundary for statistical significance (nominal significance level p < 0.033). Therefore, a final CSR was prepared based on the 03-Oct-2019 DBL.

- **Secondary outcome: PFS**

Comparison of PFS per BICR was a key secondary objective. 596 events would provide approximately 94% power to detect a HR of 0.75 with a type 1 error of 0.05 (2-sided).

The secondary objectives of this study (PFS and ORR by BICR assessment) were assessed using a hierarchical testing procedure[i] with an overall experiment-wise 2-sided Type I error rate of 0.05.

PFS (primary definition adjusting for subsequent therapy) was compared between the treatment groups via a stratified log-rank test among all randomised subjects. The stratification factors were histology (SQ vs NSQ), sex (male vs female), and PD-L1 level ($\geq$ 1% vs < 1% or not quantifiable). At the time of the database lock, the actual number of PFS per BICR events was 481; therefore, the O'Brien and Fleming adjusted alpha = 0.0252 was applied. The 2-sided log-rank p-value was reported.

- **Secondary outcome: ORR and DOR**

The number and percentage of subjects in each category of BOR per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) were presented, by treatment group. Estimates of response rate, along with its exact 2-sided 95% CI by Clopper and Pearson[ii] were presented, by treatment group. An estimate of the difference in response rates between the treatment groups along with the corresponding 2-sided 97.5% CI were computed using the Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for stratification factors[iii].

The DoR for each treatment group was estimated using KM product limit method for subjects who achieved PR or CR, including median values, 2-sided 95% CIs, and range.

Defined Populations

During the trial, the following patient populations were defined:

- **Enrolled:** Enrolled subjects who signed an ICF and were registered in IRT (used for pre-treatment disposition).

- **Randomised**: Subjects randomised to any treatment arm (used for demography, protocol deviations, baseline characteristics, efficacy)
- **Treated**: Treated subjects, who received at least 1 dose of study drug (used for drug exposure and safety)

Immunogenicity subjects: treated subjects with baseline and at least 1 post-baseline assessment for ADA (used for immunogenicity).

Amendment No 02

In amendment No02, the study sample size was expanded from 420 to 700 participants to maintain the power of the study to account for the adjusted HR from 0.65 to 0.70 assumption for the primary objective and to allow for subgroup analyses. It removed 1-year re-treatment following progression after maximum 2 years treatment duration and updated study endpoints i.e. TMB will be assessed in both tissue and blood and the endpoint PFS2 was added.

Amendment No 04

Amendment No04 affected the statistical analyses, number of interim analyses and the endpoints**.**

- *Statistical model adjustments and interim analyses*

The study was amended because since the original design of the study, findings in other studies assessing PD-1(L1) inhibitor + chemotherapy in first-line NSCLC showed PD-(L)1 inhibitor + chemotherapy treatment was superior to chemotherapy alone, but showed a delayed effect in terms of OS with late separation of the OS. [2 3 4 5 6 7 8 9 10]

The study CA2099LA was revised to ensure a sufficient power to detect a survival benefit when a delayed effect (late separation of curves after 3 months) occurred and the HR was adjusted.

In addition, the number of planned interim analyses was limited from two to one.

- *Endpoint: blood TMB was moved from exploratory endpoints to secondary endpoint*

The blood TMB was moved from an exploratory to a secondary endpoint, because based on the result of external data (results from the study conducted with durvalumab (MYSTIC trial) and atezolizumab (OAK and POPLAR studies)). It was hypothesised that blood TMB may correlate with efficacy of immunotherapy with chemotherapy.

---

[2] Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378:2078-2092

[3] Gadgeel SM, Garassino MC, Esteban E, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. DOI: 10.1200/JCO.2019.37.15_suppl.9013 Journal of Clinical Oncology 37. Abstract 9013

[4] Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018; 379:2040-2051

[5] Paz-Ares L, Vicente D, Tafreshi A, et al. Pembrolizumab plus chemotherapy in metastatic squamous NSCLC: final analysis and progression after the next line of therapy (PFS2) in KEYNOTE-407. Poster presented at ESMO Sep 27-Oct 1, 2019, Barcelona, Spain

[6] Socinski MA, Jotte RM, Cappuzzo MDF, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018; 378:2288-2301

[7] Cappuzzo F, McCleod M, Hussein M, et al. IMpower130: Progression-free survival (PFS) and safety analysis from a randomised phase 3 study of carboplatin + nab-paclitaxel (CnP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC. ESMO 2018

[8] Socinski MA, Rittmeyer A, Shapovalov D, IMpower131: Progression-free survival (PFS) and overall survival (OS) analysis of a randomised Phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. ESMO 2018

[9] Barlesi F, Nishio M, Cobo M. IMpower 132: efficacy of atezolizumab + carboplatin/cisplatin + pemetrexed as 1L treatment in key subgroups with stage IV non-squamous NSCLC. ESMO 2018

[10] Papadimitrakopoulou VA, Cobo M, Bordoni R, et al. IMpower132: PFS and Safety Results with 1L Atezolizumab + Carboplatin/Cisplatin + Pemetrexed in Stage IV Non-Squamous NSCLC. Presentation at the International Association for the Study of Lung Cancer 19th World Conference on Lung Cancer. Toronto, Canada

Revision statistical analyses plan

In addition to the pre-planned analyses in the SAP, the following ad hoc analyses were conducted:

- Number of chemotherapy cycles received, all treated subjects

- Confirmed BOR per BICR, all randomised subjects with SQ histology per IRT

- Confirmed BOR per BICR, all randomised subjects with NSQ histology per IRT

- Confirmed BOR per BICR and disease control rate for all randomised subjects

- AEs leading to discontinuation by age category

- Summary of total number and exposure adjusted drug-related AEs

- Summary of total number and exposure adjusted SAEs

- Summary of total number and exposure adjusted drug-related SAEs

- Summary of total number and exposure adjusted AEs leading to discontinuation

- Summary of total number and exposure adjusted drug-related AEs leading to discontinuation

- Confirmed BOR and ORR by PD-L1 expression (1-49%, ≥ 50%)

- SAE listing Investigator assessment of suspected causal relationship for each agent in the study drug regimen for all treated subjects

Data monitoring committee

During the study, the Data Monitoring Committee (DMC) was established to provide oversight of the safety and efficacy considerations in study CA2099LA and to provide advice to BMS regarding actions deemed necessary of the continuing protection of enrolled subjects and those to be recruited, as well as for the continuing validity and scientific merit of the study results.

The DMC members had no conflict of interest that could bias their opinion.

Results

Recruitment and participant flow

A total of 719 patients were randomised in 103 sites in 19 countries. The first patient was randomised 03 Oct 2017; the last patient was randomised 30 Jan 2019.

From the 1150 patients that signed an informed consent a total of 431 subjects were not randomised (37.5%) with the most common reason that inclusion/exclusion criteria were no longer met (85.4%). Among the criteria not fulfilled, the most common were ECOG PS ≤1 not confirmed prior to randomisation, tumour tissue sample not available at a central laboratory for PD-L1 IHC testing, presence of untreated CNS metastases and presence of sensitising EGFR mutation or unknown or indeterminate EGFR status for patients with NSQ histology.

Figure 3 Patient flow study CA2099LA

Enrolment

Assessed for Eligibility (N=1150)

Randomised N=719

Allocation

Allocated to nivo+ipi + chemo n= 361
Received allocated intervention n= 358.
Did not receive Allocated intervention n=3

    Adverse event n=1

    Withdrew informed consent n=1

Allocated to chemo n= 358
Received allocated intervention n= 349
Did not receive Allocated intervention n=9

    Withdrew informed consent n=3

    No longer meets study criteria n=4

    Other n=2

Analysis

Randomised n=361

Treated n=358

Randomised n=358

Treated n=349

Follow – up Notntinuing treatment p

Not continuing during treatment period n=239

    Disease progression n=150 (42%)

    Study drug toxicity n= 53 (15%)

    Death n=2 (1%)

    Adverse event unrelated to study drug n= 24 (7%)

    Subject request to discontinue treatment n=1 (0%)

    Subject withdrew informed consent n=3 (1%)

Not continuing during treatment period n= 208

    Disease progression n=142 (41%)

    Study drug toxicity n= 21 (6%)

    Death n=1 (0%)

    Adverse event unrelated to study drug n= 23 (6%)

    Subject request to discontinue treatment n= 6(2%)

    Subject withdrew informed consent n=4 (1%)

    Lost to follow up n=1 (0%)

    Other n= 5 (1%)

Not continuing in the study N=57 (16%)

    Death n=54 (15%)

    Subject withdrew informed consent n= 3 (1%)

    Lost to follow up n=0 (0%)

    Other n=4 (1%)

Not continuing in the study n=40 (12%)

    Death n=40 (12%)

    Subject withdrew informed consent n= 4 (1%)

    Lost to follow up n=1 (0%)

    Other n=1 (0%)

Conduct of the study

The original study was dated 10 May 2017. Before the 03-Oct-2019 Data base lock 4 global revisions, 2 site specific amendments, and 4 administrative letters were conducted.

The summary of the major global protocol revision is provided in **Table 2**.

Protocol revision 02 and 04 included protocol adjustments that might have affected the primary endpoint analyses and target population.

Table 3 Summary of major global protocol revisions

Document	Date of issue	Summary of change
Revised protocol 04	08-Mar-2019	• Updated the two planned interim analyses to one single interim analysis

		• The interim and final analyses were updated with number of events, power, hazard ratios, and projected timing of events, • Blood TMB moved to secondary endpoint from exploratory endpoint
Revised protocol 03	24-Jan-2019	• Updated appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow up and reporting • Updated appendix 4: woman of childbearing potential definition and methods of contraception • Updated appendix 6 for management of algorithms for immuno-oncology use • Excluded vaccine use
Revised protocol 02	02-Jul-2018	• Removed 1-year re-treatment after progression • Provided updated safety data from CA 209568 safety lead in study • Expanded study sample size, updated study endpoints • Updated document with program standards and corrected internal inconsistencies
Administrative letter 01	09-Oct 2017	• Added neurological adverse event management in algorithm
Revised protocol 01	10-Aug 2017	• Confirmed dosing language in study • Provided updated safety data from CA 209568 safety lead in study • Biomarker objective was clarified • Typographical and formatting errors were corrected
Original protocol	10-May 2017	• Not applicable

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 by category and subcategory in Table 4.3.1-1

Table 4.3.1-1:   Summary of Significant Protocol Deviations

	Nivo+Ipi+Chemo	Chemo	Total
Failure to obtain written informed consent prior to each subject's participation in the study	8	3	11
Failure to obtain written informed consent on the correct approved version	7	3	10
Failure to consent on treatment beyond progression	1	0	1
Failure to report all SAEs in accordance with the time period required by GCP, the protocol, BMS and applicable regulations	10	17	27
Implementation of protocol changes prior to review by IRB/IEC (except when necessary to eliminate an immediate hazard(s) to trial subjects)	6	2	8
Use of prohibited concomitant medications	4	1	5
Inclusion or exclusion deviations	29	26	55
Safety Labs Not Performed	11	5	16
Baseline Tumor Assessment	11	12	23
Adequate Tumor Slides	2	1	3
Prior Therapy	0	4	4
EGFR Testing for Non Squamous NSCLC	1	3	4
Other	4	1	5
Incorrect dosing or study treatment assignment	9	0	9

Table 4.3.1-1:   Summary of Significant Protocol Deviations

	Nivo+Ipi+Chemo	Chemo	Total
Other	11	10	21
ECOG not done at screening and/or on D1 prior to dosing	1	2	3
D1 dose given >6 days post randomization	4	1	5
Misclassified PD-L1 stratification level [IRT vs. Clinical database]	2	1	3
No baseline disease as per Investigator assessment	1	2	3
PRO not collected per protocol	2	4	6
Baseline ECG not performed	1	0	1
Grand Total	77	59	136

Abbreviations: BMS - Bristol-Myers Squibb, Chemo - chemotherapy, D1 - day 1, ECG - electrocardiogram, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, GCP - Good Clinical Practice, ICF - informed consent form, IEC - independent ethics committee, Ipi - ipilimumab, IRB - institutional review board, IRT - interactive response technology, Nivo - nivolumab, NSCLC - non-small cell lung cancer, PD-L1 - programmed death ligand 1, PRO - patient reported outcome, SAEs - serious adverse events

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. Relevant protocol deviations are predefined in the SAP.

Subjects with relevant protocol deviations are summarised in Table 4.3.2-1. Overall, relevant protocol deviations (at study entry and on-treatment) were reported in a total of 11 (1.5%) randomised subjects: 7 (1.9%) in the nivo+ipi+chemo arm, 4 (1.1%) in the chemotherapy arm.

Table 4.3.2-1:   **Relevant Protocol Deviations Summary - All Randomized Subjects**

	Number of Subjects (%)		
	Nivo+Ipi+Chemo N = 361	Chemo N = 358	Total N = 719
SUBJECTS WITH AT LEAST ONE DEVIATION AT ENTRANCE	7 (1.9)	4 (1.1)	11 (1.5)
SUBJECT WITH MISCLASSIFIED PD-L1 STRATIFICATION LEVEL (IRT VS CLINICAL DATABASE)	2 (0.6)	1 (0.3)	3 (0.4)
SUBJECT WITH NO MEASURABLE DISEASE AT BASELINE PER INVESTIGATOR	1 (0.3)	2 (0.6)	3 (0.4)
ON-TREATMENT DEVIATIONS SUBJECT WHO RECEIVED ANTI-CANCER THERAPY	4 (1.1)	1 (0.3)	5 (0.7)
SUBJECT TREATED DIFFERENTLY AS RANDOMIZED	0	0	0

Baseline data

Overall the baseline key demographics and disease characteristics appeared to be comparable (Table 4).

Table 4 Key Baseline Characteristics in All Randomised Subjects

	Nivo+Ipi+Chemo (N = 361)	Chemo (N = 358)	Total (N = 719)
Age (years)			
Median	65.0	65.0	65.0
< 65 (n, %)	176 (48.8)	178 (49.7)	354 (49.2)
≥ 65 and < 75 (n, %)	148 (41.0)	147 (41.1)	295 (41.0)
≥ 75 (n, %)	37 (10.2)	33 (9.2)	70 (9.7)
≥ 85 (n, %)	0	2 (0.6)	2 (0.3)
Male (n, %)	252 (69.8)	252 (70.4)	504 (70.1)
Race (n, %)			
White	322 (89.2)	316 (88.3)	638 (88.7)
Black	5 (1.4)	4 (1.1)	9 (1.3)
Asian (including Chinese & Japanese)	30 (8.3)	30 (8.4)	60 (8.3)
All other	4 (1.1)	8 (2.2)	12 (1.7)
Tumor Histology (n, %)			
SQ Carcinoma	113 (31.3)	111 (31.0)	224 (31.2)
NSQ Carcinoma	248 (68.7)	247 (69.0)	495 (68.8)
Metastasis Site			
Liver	68 (18.8)	87 (24.3)	155 (21.6)
CNS	63 (17.5)	58 (16.2)	121 (16.8)
Bone	96 (26.6)	110 (30.7)	206 (28.7)
ECOG PS (n, %)			
0	113 (31.3)	112 (31.3)	225 (31.3)
1	247 (68.4)	245 (68.4)	492 (68.4)
Not Reported	1 (0.3)	1 (0.3)	2 (0.3)
Smoking Status (n, %)			
Current/Former	315 (87.3)	305 (85.2)	620 (86.2)
Never smoker	46 (12.7)	53 (14.8)	99 (13.8)
PD-L1 Level (n, %)			
Quantifiable			
< 1%	135 (37.4)	129 (36.0)	264 (36.7)
≥ 1%	203 (56.2)	203 (56.7)	406 (56.5)
1 - 49%	127 (35.2)	106 (29.6)	233 (32.4)
≥ 50%	76 (21.1)	97 (27.1)	173 (24.1)
Not Quantifiable	21 (5.8)	25 (7.0)	46 (6.4)
Not Reported	2 (0.6)	1 (0.3)	3 (0.4)

Abbreviations: CNS - central nervous system, ECOG PS - Eastern Cooperative Oncology Group performance status, NSQ - non-squamous, PD-L1 - programmed death ligand 1, SQ - squamous.

A total of 25 (6.9%) subjects in the nivo+ipi+chemo arm and 22 (6.1%) in the chemotherapy arm received prior systemic anticancer therapy (platinum-based agent or other chemotherapy) in the adjuvant, neo-adjuvant, or definitive chemoradiation setting.

108 (29.9%) of patients in the nivo+ipi+ chemo arm and 91 (25.4%) in the chemotherapy arm received prior surgery related to cancer. 105 (29.1%) in the nivo +ipi + chemo arm and 83 (23.2%) in the chemotherapy arm received prior radiotherapy.

Numbers analysed

Table 6 shows the defined patient population as included in the current trial.

Table 5 Defined patient populations – number of included patients

Population	Nivo+Ipi+Chemo	Chemo	Total
Enrolled: Enrolled subjects who signed an ICF and were registered in IRT (used for pre-treatment disposition).	--	--	1150
Randomised: Subjects randomised to any treatment arm	361	358	719
Treated: Treated subjects, who received at least 1 dose of study drug	358	349	707
Immunogenicity subjects: treated subjects with baseline and at least 1 post-baseline assessment for ADA.			
Nivolumab ADA Evaluable	308	--	308
Ipilimumab ADA Evaluable	305	--	305

Abbreviations: ADA - anti-drug antibody, ICF - informed consent form, IRT - Interactive Response Technologies -

Outcomes and estimation (data cut-off date 3 Oct 2019)

Primary Endpoint Overall Survival

After a total of N=351/719 (49%) events, Nivo+ipi+chemo showed a median overall survival of 14.13 (95% CI: 13.24, 16.16) months compared to 10.74 (95% CI: 9.46, 12.45) months in the chemotherapy arm. This resulted in an overall improvement of 4 months, resulting in an HR of 0.69 (96.71% CI: 0.55, 0.87); stratified log-rank test p-value = 0.0006 (Figure 5).

At database lock, 56.8% and 45.5% of randomised subjects in the nivo+ipi+chemo and chemotherapy arms, respectively, were censored for OS (Figure 5).

Figure 4 Kaplan-Meier Plot of Overall Survival - All Randomised Subjects
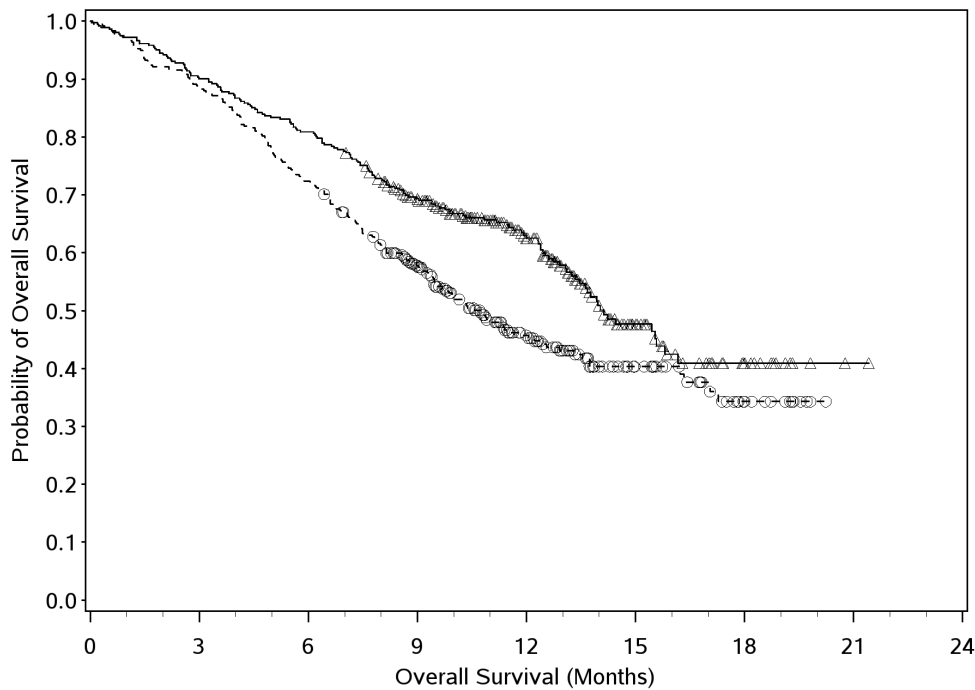
Number of Subjects at Risk

Nivo+Ipi+Chemo

| 361 | 325 | 292 | 230 | 129 | 46 | 16 | 1 | 0 |

Chemo

| 358 | 318 | 259 | 183 | 94 | 39 | 12 | 0 | 0 |

Nivo+Ipi+Chemo (events : 156/361), median and 95% CI : 14.13 (13.24, 16.16)

Chemo (events : 195/358), median and 95% CI : 10.74 (9.46, 12.45)

Nivo+Ipi+Chemo vs Chemo - hazard ratio (96.71% CI): 0.69 (0.55, 0.87)

Stratified log-rank test p-value : 0.0006

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

No crossing of curves occurred during the first months of treatment, although at 15 months the curves seem to touch, but interpretation is hampered by the large amount of censoring. Updated efficacy data (data cut-off date 09 Mar 2020) were submitted confirming the separation of the curves, see figure below.

Kaplan-Meier Plot of Overall Survival - All Randomised Subjects in CA2099LA - Final CSR (03-Oct-2019 Database Lock) [*left*] and Addendum 01 (09-Mar-2020 Database Lock) [*right*]

Number of Subjects at Risk
Nivo+Ipi+Chemo

361	325	292	230	129	46	16	1	

Chemo

358	318	259	183	94	39	12	0	

— △ — Nivo+Ipi+Chemo (events : 156/361), median and 95% CI : 14.13 (13.24, 16.16)
- - ○ - - Chemo (events : 195/358), median and 95% CI : 10.74 (9.46, 12.45)
Nivo+Ipi+Chemo vs Chemo - hazard ratio (96.71% CI): 0.69 (0.55, 0.87)
Stratified log-rank test p-value : 0.0006

Number of Subjects at Risk
Nivo+Ipi+Chemo

361	326	292	250	227	153	86	33	10	1	0

Chemo

358	319	260	208	166	116	67	26	11	0	0

— △ — Nivo+Ipi+Chemo (events : 190/361), median and 95% CI : 15.64 (13.93, 19.98)
- - ○ - - Chemo (events : 242/358), median and 95% CI : 10.91 (9.46, 12.55)
Nivo+Ipi+Chemo vs Chemo - hazard ratio (95% CI): 0.66 (0.55, 0.80)

Secondary endpoint, progression free survival

After a total of N=481 (67%) events, nivo+ipi+chemo showed a median progression free survival of 6.83 (95% CI: 5.55, 7.66) months compared to 4.96 (95% CI: 4.27, 5.55) months in the chemotherapy arm. This resulted in an overall median improvement of 1.9 months, resulting in a HR = 0.72 (95% CI: 0.60, 0.86); stratified log-rank test p value = 0.0001.

Figure 5 Kaplan-Meier Plot of Progression-Free Survival per BICR, Primary Definition - All Randomised Subjects
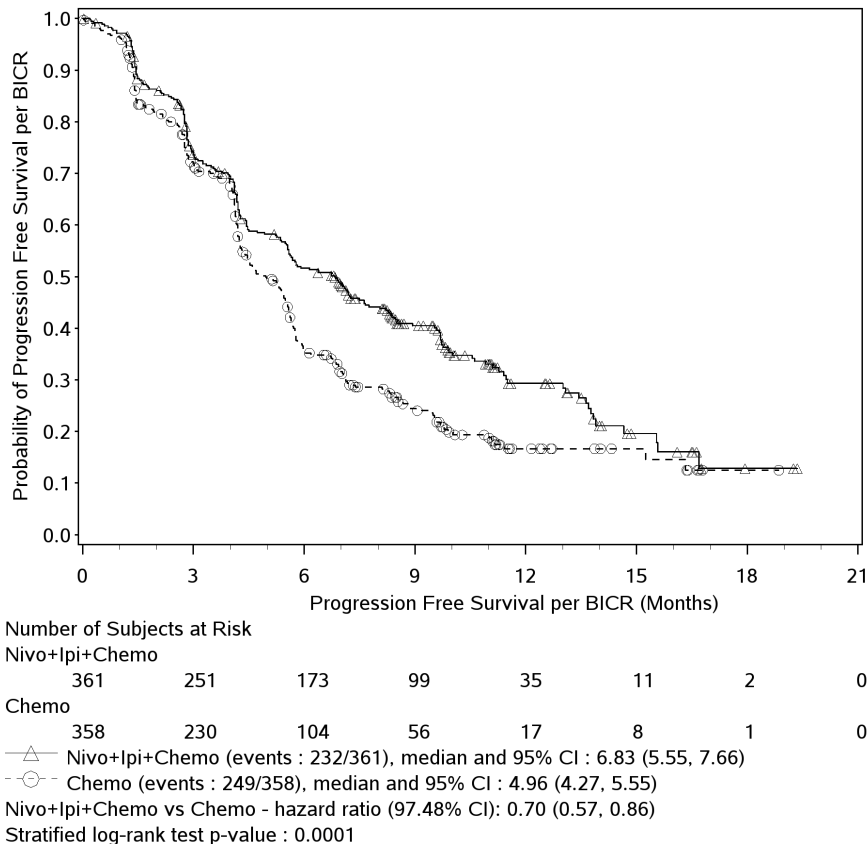
Number of Subjects at Risk
Nivo+Ipi+Chemo

361	251	173	99	35	11	2	0

Chemo

358	230	104	56	17	8	1	0

— △ — Nivo+Ipi+Chemo (events : 232/361), median and 95% CI : 6.83 (5.55, 7.66)
- - ○ - - Chemo (events : 249/358), median and 95% CI : 4.96 (4.27, 5.55)
Nivo+Ipi+Chemo vs Chemo - hazard ratio (97.48% CI): 0.70 (0.57, 0.86)
Stratified log-rank test p-value : 0.0001

Statistical model for hazard ratio and p-value: Stratified Cox proportional hazards model and stratified log-rank test.
Symbols represent censored observations.
The primary definition of PFS accounts for subsequent therapy by censoring at the last evaluable tumour assessment on or prior to the date of subsequent therapy.

Secondary endpoint, PFS2

Median PFS2 per investigator were 13.34 (95% CI: 11.86, 14.46) and 8.71 (95% CI: 7.43, 9.79) months for nivo+ipi+chemo vs chemotherapy, respectively. HR favoured the nivo+ipi+chemo arm over the chemotherapy arm: 0.62 (95% CI: 0.51, 0.76). A total of 175 (48.5%) subjects in the nivo+ipi+chemo arm and 226 (63.1%) subjects in the chemotherapy arm were censored (Figure 7).

Figure 6 Kaplan-Meier Plot of PFS2 - All Randomised Subjects
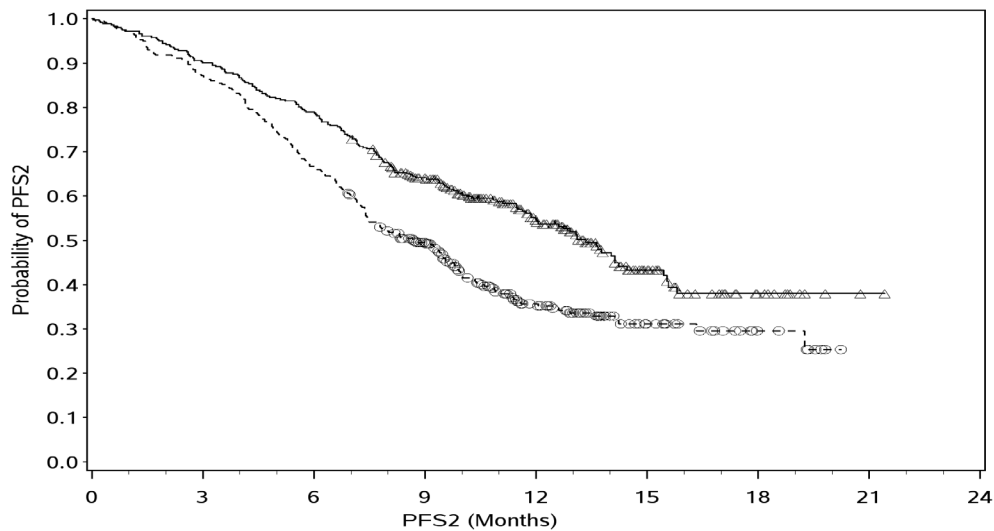
Number of Subjects at Risk
Nivo+Ipi+Chemo

| 361 | 325 | 285 | 213 | 111 | 42 | 14 | 1 | 0 |

Chemo

| 358 | 312 | 239 | 157 | 73 | 27 | 8 | 0 | 0 |

△ Nivo+Ipi+Chemo (events : 175/361), median and 95% CI : 13.34 (11.86, 14.46)
⊖ Chemo (events : 226/358), median and 95% CI : 8.71 (7.43, 9.79)
Nivo+Ipi+Chemo vs Chemo - hazard ratio (95% CI): 0.62 (0.51, 0.76)

Secondary endpoint: objective response rate

In all randomised subjects, BICR-assessed ORR was significantly higher with nivo+ipi+chemo than with chemotherapy: 37.7% (95% CI: 32.7, 42.9) vs 25.1% (95% CI: 20.7, 30.0); stratified CMH test p-value = 0.0003 (Table 9).

Table 6 Confirmed Best Overall Response per BICR - All Randomised Subjects

```
                                          Number of Subjects (%)
                                     -------------------------------------
                                     Nivo+Ipi+Chemo          Chemo
                                     N = 361                 N = 358
-------------------------------------------------------------------------
CONFIRMED BEST OVERALL RESPONSE

COMPLETE RESPONSE (CR)                  7 (  1.9)              3 (  0.8)
PARTIAL RESPONSE (PR)                 129 ( 35.7)             87 ( 24.3)
STABLE DISEASE (SD)                   166 ( 46.0)            184 ( 51.4)
PROGRESSIVE DISEASE (PD)               32 (  8.9)             45 ( 12.6)
UNABLE TO DETERMINE (UTD)              24 (  6.6)             30 (  8.4)
NOT REPORTED                            3 (  0.8)              9 (  2.5)

OBJECTIVE RESPONSE RATE (1)          136/361 ( 37.7%)       90/358 ( 25.1%)
  (95% CI)                             (32.7, 42.9)           (20.7, 30.0)

DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)  12.4%
  (97.5% CI)                            (4.8, 20.0)
  (95% CI)                             (5.7, 19.1)

ESTIMATE OF ODDS RATIO (3, 4)         1.81
  (97.5% CI)                           (1.25, 2.62)
  (95% CI)                             (1.31, 2.50)

P-VALUE (5)                           0.0003

DISEASE CONTROL RATE (6)             302/361 (83.7%)        274/358 (76.5%)
  (95% CI)                             (79.4, 87.3)           (71.8, 80.8)
-------------------------------------------------------------------------
```

Per RECIST 1.1, confirmation of response required.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivo+Ipi+Chemo - Chemo) based on CMH method of weighting.
(3) Stratified by Histology (squamous vs non-squamous), PD-L1(>= 1% vs < 1%/not quantifiable), Sex (male vs female) as entered into the IRT.
(4) Strata adjusted odds ratio (Nivo+Ipi+Chemo over Chemo) using CMH method.
(5) Two-sided p-value from stratified CMH Test.
(6) CR+PR+SD, confidence interval based on the Clopper and Pearson method.
Source: Table 5.5.2, Table 5.12.1 (Disease control rate)

Figure 7 Waterfall Plot of Best Percent Reduction from Baseline in Sum of Diameter of Target Lesions, per BICR - All Randomised Subjects
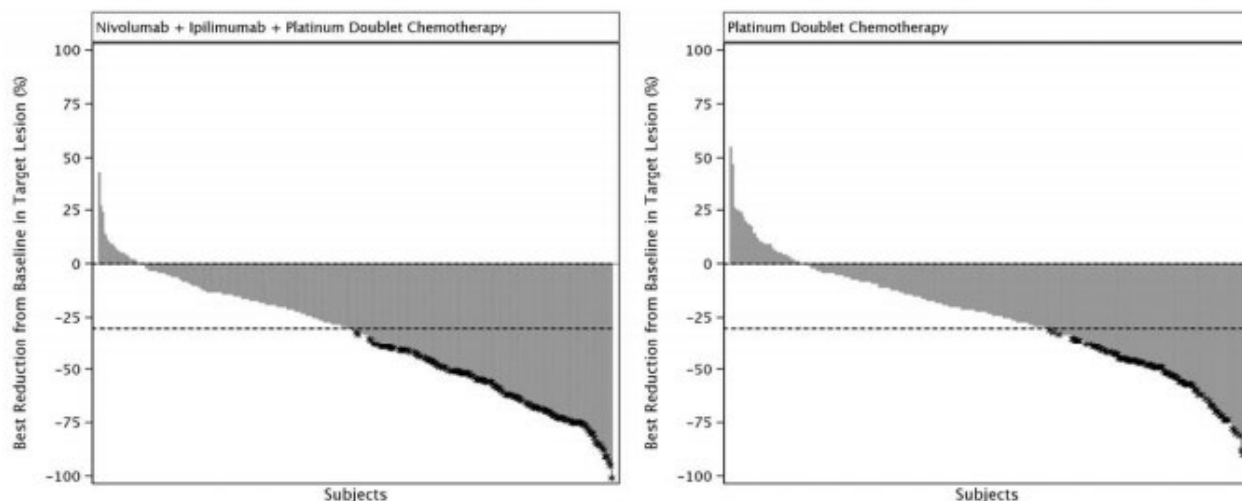
Subjects with target lesion at Baseline and at Least One On-Treatment Tumor Assessment.
Best reduction is maximum reduction in sum of diameters of target lesions (negative value means true reduction, positive value means increase only observed over time).
Horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response.
Asterisk symbol represents responders.
Square symbol represents % change truncated to 100%.

In all randomised subjects, the difference in unweighted ORRs favoured (ORR difference > 0%) the immuno-chemotherapy combination over chemotherapy. (ORR difference > 0%) (Table 9).

Time to response (TTR) and duration of response (DoR)

The nivo+ipi+chemo therapy group showed a prolonged median TTR per BICR of 2.51 months for all confirmed responses, compared to 1.56 months for the chemotherapy group.

The nivo+ipi+chemo therapy group showed median DoR of 10.2 (95% CI 8.21, 13.01) compared to 5.09 (4.34, 7.00) for the chemotherapy group.

Table 8 Time to Response and Duration of Response per BICR - All Confirmed Responders

```
---------------------------------------------------------------------------
                                    Nivo+Ipi+Chemo        Chemo
                                    N = 136               N = 90
===========================================================================
TIME TO OBJECTIVE RESPONSE (MONTHS)
    MEAN                            2.81                  2.55
    MEDIAN                          2.51                  1.56
    MIN, MAX                        1.1, 10.6             1.2, 8.3
    Q1, Q3                          1.41, 3.01            1.41, 2.86
    STANDARD DEVIATION              1.99                  1.72

DURATION OF RESPONSE (MONTHS)
    MIN, MAX (A)                    1.0+, 16.5+           1.4+, 15.2+
    MEDIAN (95% CI) (B)             10.02 (8.21, 13.01)   5.09 (4.34, 7.00)
    N EVENT/N RESP (%)              57/136 (41.9)         54/90 (60.0)

PROPORTION OF SUBJECTS WITH DURATION
OF RESPONSE OF AT LEAST (95% CI) (C)
    3 MONTHS                        0.88 (0.81, 0.92)     0.76 (0.66, 0.84)
    6 MONTHS                        0.74 (0.66, 0.81)     0.41 (0.30, 0.52)
---------------------------------------------------------------------------
```

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Based on Kaplan-Meier estimates of duration of response.

Ancillary analyses (data cut-off date 3 Oct 2019)

The subgroups analyses showed an overall outcome favouring the combination treatment compared to chemotherapy, including the subgroups according to the stratification factors gender, PD-L1 status and histology. The two subgroups according to PD-L1 expression and histology will be described in more detail below.

The subgroups that favoured the chemotherapy arm were the small subgroups of patients aged ≥75 years (n=70), the subgroups of never smokers (n=99) and the patients with unquantifiable PD-L1 expression (n=46).

Table 9 Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomised Subjects

	N	Nivo+Ipi+Chemo N of Events (N of Subjects)	Nivo+Ipi+Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo	
Overall	719	156 (361)	14.13 (13.24, 16.16)	195 (358)	10.74 (9.46, 12.45)	0.70	(0.57, 0.86)
Age Categorization							
<65	354	74 (176)	13.96 (12.62, N.A.)	100 (178)	10.25 (8.80, 13.73)	0.63	(0.46, 0.85)
>=65 and <75	295	56 (148)	15.80 (14.23, N.A.)	78 (147)	11.86 (9.03, 16.23)	0.64	(0.45, 0.90)
>=75 and <85	68	26 (37)	8.51 (5.59, 13.34)	16 (31)	10.91 (4.96, N.A.)	1.35	(0.72, 2.51)
>=85	2	0 (0)	N.A.	1 (2)	N.A. (5.75, N.A.)	N.A.	
>=75	70	26 (37)	8.51 (5.59, 13.34)	17 (33)	10.91 (5.75, N.A.)	1.36	(0.74, 2.52)
>=65	365	82 (185)	14.46 (13.11, N.A.)	95 (180)	11.50 (9.49, 13.54)	0.77	(0.58, 1.04)
Sex							
Male	504	119 (252)	13.77 (12.45, 15.44)	150 (252)	9.69 (8.15, 11.37)	0.69	(0.54, 0.88)
Female	215	37 (109)	15.80 (13.11, N.A.)	45 (106)	N.A. (10.87, N.A.)	0.73	(0.47, 1.13)
Race							
White	638	149 (322)	13.93 (12.91, 15.57)	174 (316)	10.58 (9.43, 12.55)	0.75	(0.61, 0.94)
Black or African American	9	1 (5)	N.A. (2.96, N.A.)	2 (4)	N.A. (6.21, N.A.)	0.42	(0.04, 4.66)
Asian	60	3 (30)	15.44 (11.93, N.A.)	13 (30)	12.22 (7.33, N.A.)	0.11	(0.03, 0.51)
Other	12	3 (4)	3.79 (3.58, N.A.)	6 (8)	4.96 (1.48, N.A.)	1.36	(0.33, 5.61)
Region							
Europe	425	101 (212)	13.93 (12.75, 16.16)	116 (213)	10.58 (9.26, 13.73)	0.76	(0.58, 1.00)
North America	64	19 (36)	13.24 (7.43, N.A.)	18 (28)	8.90 (4.96, N.A.)	0.70	(0.37, 1.34)
Rest of The World	172	33 (85)	N.A. (10.25, N.A.)	48 (87)	10.78 (8.77, 12.45)	0.68	(0.43, 1.05)
Asia	58	3 (28)	15.44 (11.93, 15.44)	13 (30)	12.22 (7.33, N.A.)	0.13	(0.03, 0.57)
Baseline ECOG PS							
0	225	32 (113)	N.A. (15.44, N.A.)	50 (112)	13.31 (10.78, N.A.)	0.53	(0.34, 0.83)
>=1	492	123 (247)	13.11 (11.93, 14.03)	144 (245)	9.46 (7.98, 11.01)	0.77	(0.60, 0.98)
Not Reported	2	1 (1)	9.03 (N.A., N.A.)	1 (1)	4.01 (N.A., N.A.)		
Smoking Status							
Current/Former	620	134 (315)	14.13 (13.34, 16.16)	173 (305)	10.02 (8.97, 12.06)	0.65	(0.52, 0.82)
Never Smoked	99	22 (46)	11.99 (8.02, N.A.)	22 (53)	12.55 (9.46, N.A.)	1.15	(0.64, 2.08)
Unknown	0	0 (0)	N.A.	0 (0)	N.A.		
Histology - per IRT							
Squamous	227	56 (115)	13.67 (12.39, 15.57)	69 (112)	8.97 (7.16, 12.22)	0.65	(0.46, 0.93)
Non-Squamous	492	100 (246)	15.80 (13.08, N.A.)	126 (246)	11.40 (9.69, 16.33)	0.72	(0.55, 0.93)

(Forest plot axis: 0.0625 0.125 0.25 0.5 1 2 — Nivo+Ipi+Chemo ← → Chemo)

Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects

	N	Nivo+Ipi+Chemo N of Events (N of Subjects)	Nivo+Ipi+Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo	
PD-L1 Status - per IRT							
<1%/Not Quantifiable	311	69 (157)	13.77 (12.32, 16.16)	84 (154)	11.01 (8.57, 16.23)	0.74	(0.54, 1.02)
>=1%	408	87 (204)	14.23 (13.08, N.A.)	111 (204)	10.58 (9.43, 12.91)	0.67	(0.51, 0.89)
PD-L1 Subgroups							
Not Quantifiable	46	14 (21)	10.84 (7.16, 15.57)	12 (25)	17.05 (8.64, N.A.)	1.64	(0.74, 3.63)
<1%	264	55 (135)	14.03 (13.24, N.A.)	72 (129)	9.95 (7.69, 13.73)	0.65	(0.46, 0.92)
>=1%	405	67 (203)	14.23 (13.08, N.A.)	111 (203)	10.58 (9.36, 12.55)	0.67	(0.51, 0.89)
1-49%	233	58 (127)	14.46 (12.45, N.A.)	61 (106)	10.25 (8.67, 12.22)	0.69	(0.48, 0.98)
>=50%	173	29 (76)	14.13 (12.39, N.A.)	50 (97)	11.86 (9.26, N.A.)	0.64	(0.41, 1.02)
Not Reported	3	0 (2)	N.A.	0 (1)	N.A.		
Disease Stage							
Stage IV	668	145 (330)	14.03 (13.11, 16.16)	181 (338)	10.87 (9.46, 13.31)	0.74	(0.59, 0.92)
Recurrent to Metastatic Disease	51	11 (31)	15.57 (12.45, N.A.)	14 (20)	9.05 (6.60, 12.91)	0.32	(0.15, 0.72)
CNS Metastasis							
Yes	121	25 (63)	13.63 (12.32, N.A.)	41 (58)	7.36 (4.99, 10.02)	0.42	(0.26, 0.69)
No	598	131 (298)	14.03 (13.24, 16.16)	154 (300)	11.37 (9.79, 13.73)	0.78	(0.62, 0.98)
Liver Metastasis							
Yes	155	40 (68)	9.89 (7.43, 13.77)	57 (87)	8.02 (6.60, 10.02)	0.80	(0.53, 1.20)
No	564	116 (293)	15.54 (13.67, N.A.)	138 (271)	11.86 (10.25, 16.23)	0.69	(0.54, 0.88)
Bone Metastasis							
Yes	206	51 (96)	11.93 (8.61, 15.80)	72 (110)	8.02 (6.60, 9.46)	0.67	(0.47, 0.97)
No	513	105 (265)	15.44 (13.34, N.A.)	123 (248)	12.06 (10.35, 17.05)	0.73	(0.56, 0.95)
Actual Investigator's Choice Therapy							
Carboplatin/Cisplatin/Pemetrexed	7	1 (1)	4.34 (N.A., N.A.)	4 (6)	10.02 (1.48, N.A.)		
Carboplatin/Paclitaxel	224	55 (114)	13.67 (12.39, 15.57)	67 (110)	8.97 (7.16, 12.22)	0.65	(0.45, 0.93)
Carboplatin/Paclitaxel/Pemetrexed	2	0 (1)	N.A.	1 (1)	10.25 (N.A., N.A.)		
Carboplatin/Pemetrexed	331	68 (168)	15.80 (13.24, N.A.)	86 (163)	10.74 (9.13, 16.33)	0.68	(0.50, 0.94)
Cisplatin/Pemetrexed	142	28 (73)	N.A. (12.32, N.A.)	33 (69)	12.55 (9.46, N.A.)	0.74	(0.45, 1.22)
Paclitaxel/Pemetrexed	1	1 (1)	6.24 (N.A., N.A.)	0 (0)	N.A.		
Not Reported	12	3 (3)	1.74 (0.03, 9.03)	4 (9)	N.A. (1.58, N.A.)		

(Forest plot axis: 0.0625 0.125 0.25 0.5 1 2 — Nivo+Ipi+Chemo ← → Chemo)

HR is not computed for subsets (except age, race, region, and sex) category with less than 10 subjects per treatment group.

In a subgroup analysis for all randomised subjects, PFS HRs by primary definition for most subgroups favoured (HR < 1) the nivo+ipi+chemo treatment, including the subgroups according to gender, histology and PD-L1 status. The subgroups according to histology and PD-L1 status will be described in more detail below.

Table 10 Forest Plot of Treatment Effect on PFS per BICR, Primary Definition in Predefined Subsets - All Randomised Subjects.

	N	Nivo+Ipi+Chemo N of Events (N of Subjects)	Nivo+Ipi+Chemo mPFS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo
Overall	719	232 (361)	6.83 (5.55, 7.66)	249 (358)	4.96 (4.27, 5.55)	0.72 (0.60, 0.86)
Age Categorization						
<65	354	114 (176)	6.37 (4.44, 7.49)	131 (178)	4.21 (4.11, 4.50)	0.61 (0.47, 0.78)
>=65 and <75	295	89 (148)	7.62 (5.59, 10.02)	96 (147)	5.59 (4.99, 6.93)	0.76 (0.57, 1.01)
>=75 and <85	68	29 (37)	5.08 (2.92, 8.51)	21 (31)	5.78 (4.14, 7.13)	1.05 (0.60, 1.88)
>=85	2	0 (0)	N.A.	1 (2)	N.A. (5.75, N.A.)	N.A.
>=75	70	29 (37)	5.08 (2.92, 8.51)	22 (33)	5.78 (4.21, 7.13)	1.12 (0.64, 1.96)
>=65	365	118 (185)	7.20 (5.39, 9.65)	118 (180)	5.62 (5.26, 6.05)	0.82 (0.64, 1.06)
Sex						
Male	504	165 (252)	5.75 (4.93, 7.62)	185 (252)	4.50 (4.21, 5.42)	0.65 (0.53, 0.80)
Female	215	67 (109)	7.20 (5.55, 9.89)	64 (106)	5.82 (4.24, 7.20)	0.89 (0.63, 1.25)
Race						
White	638	209 (322)	6.37 (5.49, 7.49)	216 (316)	4.99 (4.27, 5.59)	0.75 (0.62, 0.91)
Black or African American	9	4 (5)	6.97 (2.96, N.A.)	4 (4)	6.83 (1.25, 11.07)	1.59 (0.29, 8.72)
Asian	60	16 (30)	9.69 (4.24, 13.70)	21 (30)	5.39 (2.76, 6.93)	0.43 (0.22, 0.84)
Other	12	3 (4)	3.60 (1.31, N.A.)	8 (8)	4.53 (1.35, 5.45)	0.96 (0.25, 3.73)
Region						
Europe	425	143 (212)	5.91 (5.22, 7.26)	139 (213)	4.63 (4.17, 5.55)	0.77 (0.61, 0.97)
North America	64	23 (36)	5.85 (3.61, 9.72)	18 (28)	5.45 (2.66, 6.70)	0.79 (0.43, 1.48)
Rest of The World	172	52 (85)	6.97 (4.47, 9.53)	71 (87)	4.96 (4.21, 5.97)	0.68 (0.47, 0.97)
Asia	58	14 (28)	8.38 (4.21, 13.70)	21 (30)	5.39 (2.76, 6.93)	0.43 (0.21, 0.87)
Baseline ECOG PS						
0	225	65 (113)	8.48 (6.74, 9.92)	79 (112)	5.45 (4.21, 6.70)	0.59 (0.43, 0.82)
>=1	492	167 (247)	5.59 (4.40, 7.10)	170 (245)	4.70 (4.27, 5.55)	0.77 (0.62, 0.96)
Not Reported	2	0 (1)	N.A.	0 (1)	N.A.	
Smoking Status						
Current/Former	620	198 (315)	7.03 (5.59, 8.34)	221 (305)	4.53 (4.21, 5.39)	0.65 (0.54, 0.79)
Never Smoked	99	34 (46)	5.55 (4.21, 6.90)	28 (53)	7.13 (5.42, 9.59)	1.33 (0.86, 2.10)
Unknown	0	0 (0)	N.A.	0 (0)	N.A.	
Histology - per IRT						
Squamous	227	78 (115)	5.65 (4.44, 9.69)	82 (112)	4.30 (4.17, 4.99)	0.57 (0.42, 0.79)
Non-Squamous	492	154 (246)	6.97 (5.55, 8.05)	167 (246)	5.55 (4.47, 5.78)	0.78 (0.63, 0.97)

	N	Nivo+Ipi+Chemo N of Events (N of Subjects)	Nivo+Ipi+Chemo mPFS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo
PD-L1 Status - per IRT						
<1%/Not Quantifiable	311	101 (157)	6.14 (4.44, 7.62)	109 (154)	5.32 (4.21, 5.68)	0.77 (0.58, 1.01)
>=1%	408	131 (204)	7.13 (5.55, 8.51)	140 (204)	4.70 (4.24, 5.55)	0.68 (0.53, 0.86)
PD-L1 Subgroups						
Not Quantifiable	46	16 (21)	6.14 (3.61, 11.47)	17 (25)	5.78 (2.83, 8.84)	0.76 (0.36, 1.57)
<1%	264	85 (135)	5.82 (4.40, 7.26)	92 (129)	4.86 (4.17, 5.65)	0.77 (0.57, 1.03)
>=1%	408	130 (203)	7.03 (5.55, 8.51)	140 (203)	4.70 (4.24, 5.55)	0.67 (0.53, 0.85)
1-49%	233	87 (127)	6.74 (5.39, 8.51)	72 (106)	5.29 (4.24, 5.68)	0.71 (0.52, 0.97)
>=50%	173	43 (76)	8.28 (4.47, 11.50)	68 (97)	4.27 (4.14, 5.45)	0.59 (0.40, 0.86)
Not Reported	3	1 (2)	N.A. (8.05, N.A.)	0 (1)	N.A.	
Disease Stage						
Stage IV	668	212 (330)	6.74 (5.49, 7.49)	233 (338)	4.99 (4.30, 5.59)	0.74 (0.62, 0.90)
Recurrent to Metastatic Disease	51	20 (31)	10.55 (2.86, 13.90)	16 (20)	4.24 (2.89, 5.95)	0.43 (0.21, 0.88)
CNS Metastasis						
Yes	121	35 (63)	9.66 (5.68, 11.40)	45 (58)	4.11 (2.79, 4.99)	0.41 (0.26, 0.64)
No	598	197 (298)	5.78 (5.36, 7.20)	204 (300)	5.32 (4.47, 5.62)	0.80 (0.66, 0.97)
Liver Metastasis						
Yes	155	52 (68)	4.11 (2.83, 4.24)	66 (87)	4.24 (4.04, 5.42)	1.06 (0.73, 1.52)
No	564	180 (293)	7.62 (6.74, 9.59)	183 (271)	5.39 (4.47, 5.62)	0.66 (0.54, 0.82)
Bone Metastasis						
Yes	206	72 (96)	4.40 (4.11, 5.78)	78 (110)	4.21 (4.11, 5.16)	0.77 (0.56, 1.07)
No	513	160 (265)	8.05 (5.91, 9.69)	171 (248)	5.49 (4.40, 5.78)	0.70 (0.57, 0.87)
Actual Investigator's Choice Therapy						
Carboplatin/Cisplatin/Pemetrexed	7	1 (1)	2.46 (N.A., N.A.)	6 (6)	4.68 (0.03, 10.02)	
Carboplatin/Paclitaxel	224	78 (114)	5.65 (4.44, 9.69)	81 (110)	4.34 (4.17, 4.99)	0.58 (0.42, 0.80)
Carboplatin/Paclitaxel/Pemetrexed	2	0 (1)	N.A.	1 (1)	1.41 (N.A., N.A.)	
Carboplatin/Pemetrexed	331	102 (168)	7.13 (5.78, 8.51)	114 (163)	5.59 (4.47, 5.82)	0.74 (0.57, 0.97)
Cisplatin/Pemetrexed	142	51 (73)	5.36 (4.11, 7.75)	47 (69)	5.55 (4.04, 7.10)	0.92 (0.62, 1.37)
Paclitaxel/Pemetrexed	1	0 (1)	N.A.	0 (0)	N.A.	
Not Reported	12	0 (3)	N.A.	0 (9)	N.A.	

HR is not computed for subsets (except age, race, region, and sex) category with less than 10 subjects per treatment group.

The nivo+ipi+chemo treatment favoured response over chemotherapy in most subgroups, including the subgroups according to histology (SQ, NSQ) and PD-L1 expression (**Table 12**). The latter two subgroups will be described in more detail below.

Table 11 Forest Plot of Treatment Effect on ORR per BICR in Predefined Subsets - All Randomized Subjects

Forest Plot 1

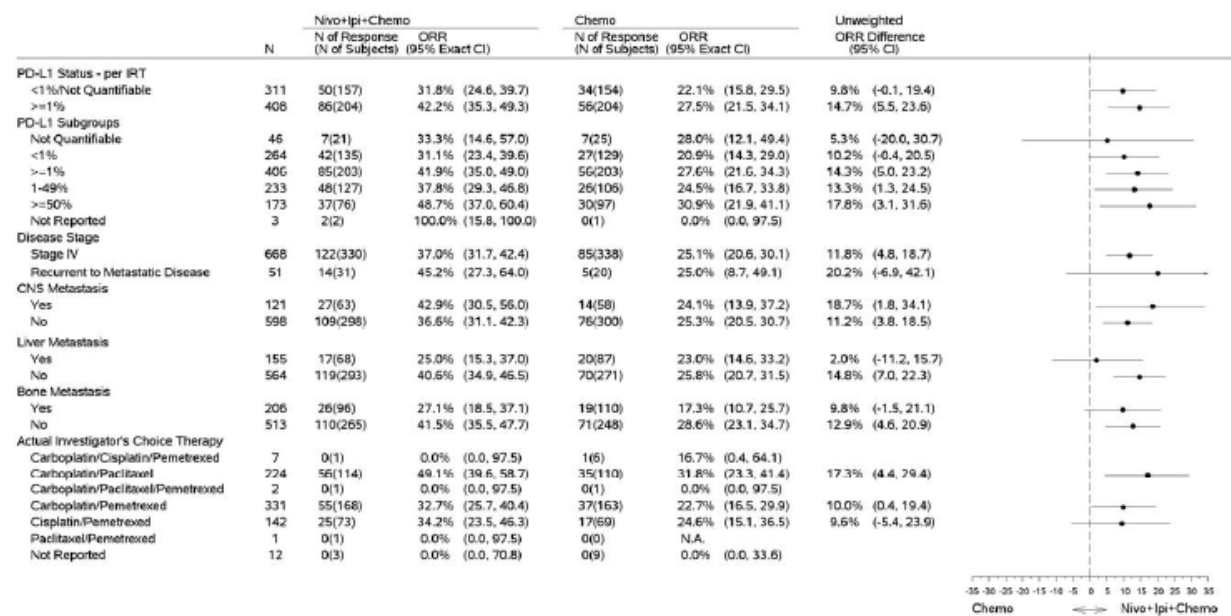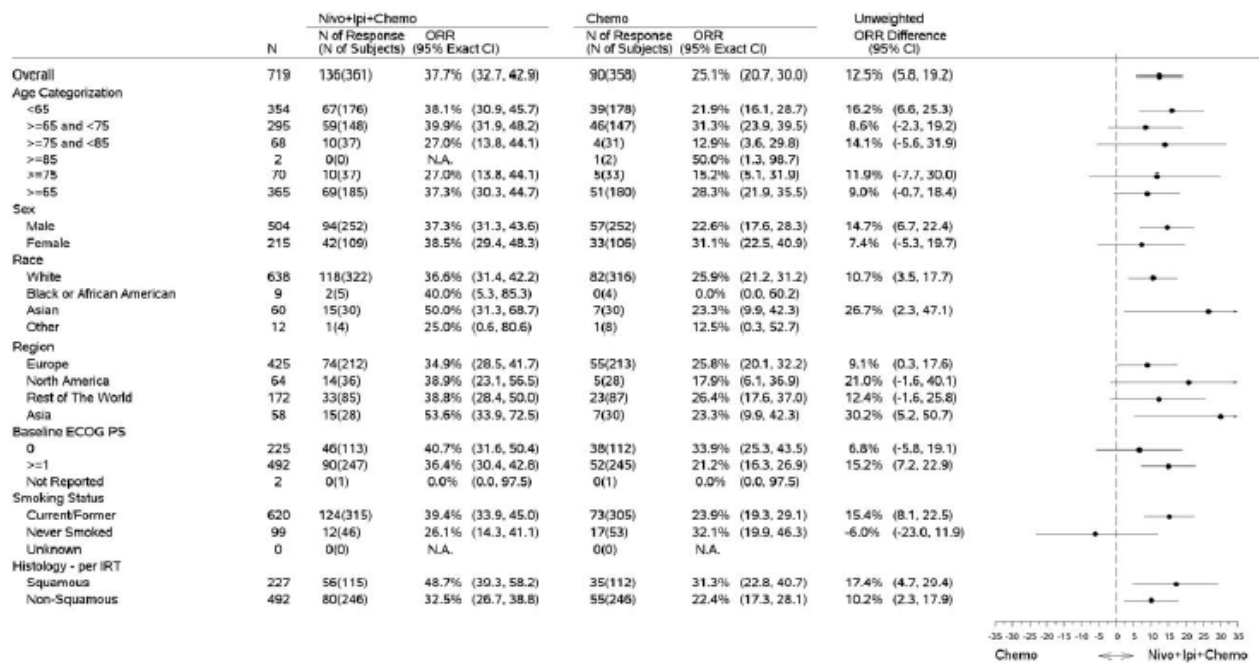|	N	Nivo+Ipi+Chemo N of Response (N of Subjects)	Nivo+Ipi+Chemo ORR (95% Exact CI)	Chemo N of Response (N of Subjects)	Chemo ORR (95% Exact CI)	Unweighted ORR Difference (95% CI)
Overall	719	136(361)	37.7% (32.7, 42.9)	90(358)	25.1% (20.7, 30.0)	12.5% (5.8, 19.2)
Age Categorization						
<65	354	67(176)	38.1% (30.9, 45.7)	39(178)	21.9% (16.1, 28.7)	16.2% (6.6, 25.3)
>=65 and <75	295	59(148)	39.9% (31.9, 48.2)	46(147)	31.3% (23.9, 39.5)	8.6% (-2.3, 19.2)
>=75 and <85	68	10(37)	27.0% (13.8, 44.1)	4(31)	12.9% (3.6, 29.8)	14.1% (-5.6, 31.9)
>=85	2	0(0)	N.A.	1(2)	50.0% (1.3, 98.7)	
>=75	70	10(37)	27.0% (13.8, 44.1)	5(33)	15.2% (5.1, 31.9)	11.9% (-7.7, 30.0)
>=65	365	69(185)	37.3% (30.3, 44.7)	51(180)	28.3% (21.9, 35.5)	9.0% (-0.7, 18.4)
Sex						
Male	504	94(252)	37.3% (31.3, 43.6)	57(252)	22.6% (17.6, 28.3)	14.7% (6.7, 22.4)
Female	215	42(109)	38.5% (29.4, 48.3)	33(106)	31.1% (22.5, 40.9)	7.4% (-5.3, 19.7)
Race						
White	638	118(322)	36.6% (31.4, 42.2)	82(316)	25.9% (21.2, 31.2)	10.7% (3.5, 17.7)
Black or African American	9	2(5)	40.0% (5.3, 85.3)	0(4)	0.0% (0.0, 60.2)	
Asian	60	15(30)	50.0% (31.3, 68.7)	7(30)	23.3% (9.9, 42.3)	26.7% (2.3, 47.1)
Other	12	1(4)	25.0% (0.6, 80.6)	1(8)	12.5% (0.3, 52.7)	
Region						
Europe	425	74(212)	34.9% (28.5, 41.7)	55(213)	25.8% (20.1, 32.2)	9.1% (0.3, 17.6)
North America	64	14(36)	38.9% (23.1, 56.5)	5(28)	17.9% (6.1, 36.9)	21.0% (-1.6, 40.1)
Rest of The World	172	33(85)	38.8% (28.4, 50.0)	23(87)	26.4% (17.6, 37.0)	12.4% (-1.6, 25.8)
Asia	58	15(28)	53.6% (33.9, 72.5)	7(30)	23.3% (9.9, 42.3)	30.2% (5.2, 50.7)
Baseline ECOG PS						
0	225	46(113)	40.7% (31.6, 50.4)	38(112)	33.9% (25.3, 43.5)	6.8% (-5.8, 19.1)
>=1	492	90(247)	36.4% (30.4, 42.8)	52(245)	21.2% (16.3, 26.9)	15.2% (7.2, 22.9)
Not Reported	2	0(1)	0.0% (0.0, 97.5)	0(1)	0.0% (0.0, 97.5)	
Smoking Status						
Current/Former	620	124(315)	39.4% (33.9, 45.0)	73(305)	23.9% (19.3, 29.1)	15.4% (8.1, 22.5)
Never Smoked	99	12(46)	26.1% (14.3, 41.1)	17(53)	32.1% (19.9, 46.3)	-6.0% (-23.0, 11.9)
Unknown	0	0(0)	N.A.	0(0)	N.A.	
Histology - per IRT						
Squamous	227	56(115)	48.7% (39.3, 58.2)	35(112)	31.3% (22.8, 40.7)	17.4% (4.7, 29.4)
Non-Squamous	492	80(246)	32.5% (26.7, 38.8)	55(246)	22.4% (17.3, 28.1)	10.2% (2.3, 17.9)

-35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35
Chemo ← → Nivo+Ipi+Chemo

Forest Plot 2

	N	Nivo+Ipi+Chemo N of Response (N of Subjects)	Nivo+Ipi+Chemo ORR (95% Exact CI)	Chemo N of Response (N of Subjects)	Chemo ORR (95% Exact CI)	Unweighted ORR Difference (95% CI)
PD-L1 Status - per IRT						
<1%/Not Quantifiable	311	50(157)	31.8% (24.6, 39.7)	34(154)	22.1% (15.8, 29.5)	9.8% (-0.1, 19.4)
>=1%	408	86(204)	42.2% (35.3, 49.3)	56(204)	27.5% (21.5, 34.1)	14.7% (5.5, 23.6)
PD-L1 Subgroups						
Not Quantifiable	46	7(21)	33.3% (14.6, 57.0)	7(25)	28.0% (12.1, 49.4)	5.3% (-20.0, 30.7)
<1%	264	42(135)	31.1% (23.4, 39.6)	27(129)	20.9% (14.3, 29.0)	10.2% (-0.4, 20.5)
>=1%	406	85(203)	41.9% (35.0, 49.0)	56(203)	27.6% (21.6, 34.3)	14.3% (5.0, 23.2)
1-49%	233	48(127)	37.8% (29.3, 46.8)	26(106)	24.5% (16.7, 33.8)	13.3% (1.3, 24.5)
>=50%	173	37(76)	48.7% (37.0, 60.4)	30(97)	30.9% (21.9, 41.1)	17.8% (3.1, 31.6)
Not Reported	3	2(2)	100.0% (15.8, 100.0)	0(1)	0.0% (0.0, 97.5)	
Disease Stage						
Stage IV	668	122(330)	37.0% (31.7, 42.4)	85(338)	25.1% (20.6, 30.1)	11.8% (4.8, 18.7)
Recurrent to Metastatic Disease	51	14(31)	45.2% (27.3, 64.0)	5(20)	25.0% (8.7, 49.1)	20.2% (-6.9, 42.1)
CNS Metastasis						
Yes	121	27(63)	42.9% (30.5, 56.0)	14(58)	24.1% (13.9, 37.2)	18.7% (1.8, 34.1)
No	598	109(298)	36.6% (31.1, 42.3)	76(300)	25.3% (20.5, 30.7)	11.2% (3.8, 18.5)
Liver Metastasis						
Yes	155	17(68)	25.0% (15.3, 37.0)	20(87)	23.0% (14.6, 33.2)	2.0% (-11.2, 15.7)
No	564	119(293)	40.6% (34.9, 46.5)	70(271)	25.8% (20.7, 31.5)	14.8% (7.0, 22.3)
Bone Metastasis						
Yes	206	26(96)	27.1% (18.5, 37.1)	19(110)	17.3% (10.7, 25.7)	9.8% (-1.5, 21.1)
No	513	110(265)	41.5% (35.5, 47.7)	71(248)	28.6% (23.1, 34.7)	12.9% (4.6, 20.9)
Actual Investigator's Choice Therapy						
Carboplatin/Cisplatin/Pemetrexed	7	0(1)	0.0% (0.0, 97.5)	1(6)	16.7% (0.4, 64.1)	
Carboplatin/Paclitaxel	224	56(114)	49.1% (39.6, 58.7)	35(110)	31.8% (23.3, 41.4)	17.3% (4.4, 29.4)
Carboplatin/Paclitaxel/Pemetrexed	2	0(1)	0.0% (0.0, 97.5)	0(1)	0.0% (0.0, 97.5)	
Carboplatin/Pemetrexed	331	55(168)	32.7% (25.7, 40.4)	37(163)	22.7% (16.5, 29.9)	10.0% (0.4, 19.4)
Cisplatin/Pemetrexed	142	25(73)	34.2% (23.5, 46.3)	17(69)	24.6% (15.1, 36.5)	9.6% (-5.4, 23.9)
Paclitaxel/Pemetrexed	1	0(1)	0.0% (0.0, 97.5)	0(0)	N.A.	
Not Reported	12	0(3)	0.0% (0.0, 70.8)	0(9)	0.0% (0.0, 33.6)	

-35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35
Chemo ← → Nivo+Ipi+Chemo

Two-sided 95% confidence interval for un-weighted difference was calculated using Newcombe method.
ORR difference is not computed for subsets with less than 10 subjects per treatment group.

I Analysis according to subgroup defined by baseline PD-L1 expression

The efficacy benefit of nivo+ipi+chemo vs chemotherapy was observed regardless of PD-L1 status (< 1%, ≥ 1%, 1 - 49%, and ≥ 50%) and across all efficacy endpoints (OS, PFS, ORR) (**Table 15, Figure 8**, **Figure 9**).

Table 15 Efficacy of Nivolumab + Ipilimumab + Chemotherapy vs Chemotherapy by Baseline PD-L1 Levels -All Randomised Subjects

	PD-L1 < 1%	PD-L1 ≥ 1%	PD-L1 1-49%	PD-L1 ≥ 50%

	Nivo+Ipi + Chemo N = 135	Chemo N = 129	Nivo+Ipi + Chemo N = 203	Chemo N = 203	Nivo+Ipi + Chemo N = 127	Chemo N = 106	Nivo+Ipi + Chemo N = 76	Chemo N = 97
OS								
HR (95% CI)[b]	0.65 (0.46, 0.92)		0.67 (0.51, 0.89)		0.69 (0.48, 0.98)		0.64 (0.41, 1.02)	
Events, n (%)	55 (40.7)	72 (55.8)	87 (42.9)	111 (54.7)	58 (45.7)	61 (57.5)	29 (38.2)	50 (51.5)
Median OS, mo.[a] (95% CI)	14.03 (13.24, NA)	9.95 (7.69, 13.73)	14.23 (13.08, NA)	10.58 (9.36, 12.55)	14.46 (12.45, NA)	10.25 (8.67, 12.22)	14.13 (12.39, NA)	11.86 (9.26, NA)
PFS per BICR (1 Definition)								
HR (95% CI)[b]	0.77 (0.57, 1.03)		0.67 (0.53, 0.85)		0.71 (0.52, 0.97)		0.59 (0.40, 0.86)	
Events, n (%)	85 (63.0)	92 (71.3)	130 (64.0)	140 (69.0)	87 (68.5)	72 (67.9)	43 (56.6)	68 (70.1)
Median PFS, mo.[a] (95% CI)	5.82 (4.40, 7.26)	4.86 (4.17, 5.65)	7.03 (5.55, 8.51)	4.70 (4.24, 5.55)	6.74 (5.39, 8.51)	5.29 (4.24, 5.68)	8.28 (4.47, 11.50)	4.27 (4.14, 5.45)
ORR per BICR (CR + PR)								
ORR (95% CI), %[c]	31.1 (23.4, 39.6)	20.9 (14.3, 29.0)	41.9 (35.0, 49.0)	27.6 (21.6, 34.3)	37.8 (29.3, 46.8)	24.5 (16.7, 33.8)	48.7 (37.0, 60.4)	30.9 (21.9, 41.1)
Unweighted ORR difference (95% CI), %	10.2 (-0.4, 20.5)		14.3 (5.0, 23.2)		13.3 (1.3, 24.5)		17.8 (3.1, 31.6)	

Minimum follow-up (date of the last subject randomised to date of the cutoff for OS) was 8.1 months for OS; median follow-up (date of randomisation to the last known date alive or death date) was 10.35 months for the nivo+ipi+chemo arm and 9.07 months for the chemo arm. The OS medians would likely be influenced by a high proportion of censored subjects.

Abbreviations: BICR - blinded independent central review; BOR - best overall response, chemo - chemotherapy; CI - confidence interval; CR - complete response; HR - hazard ratio; ipi - ipilimumab; nivo - nivolumab; ORR - objective response rate; OS - overall survival; PD - progressive disease, PD-L1 - programmed death-ligand 1; PFS - progression-free survival; PR - partial response, SD - stable disease, UTD - unable to determine

[a]   *Based on Kaplan-Meier estimates*

[b]   *Unstratified Cox proportional hazards model*

c   CR or PR; CI based on the Clopper and Pearson method

Figure 7 Kaplan-Meier Plot of Overall Survival by PD-L1 Expression Level - All Randomised Subjects

Statistical model for hazard ratio: unstratified Cox proportional hazards model
Subgroups defined based on baseline PD-L1 expression level in the clinical database.
Symbols represent censored observations.
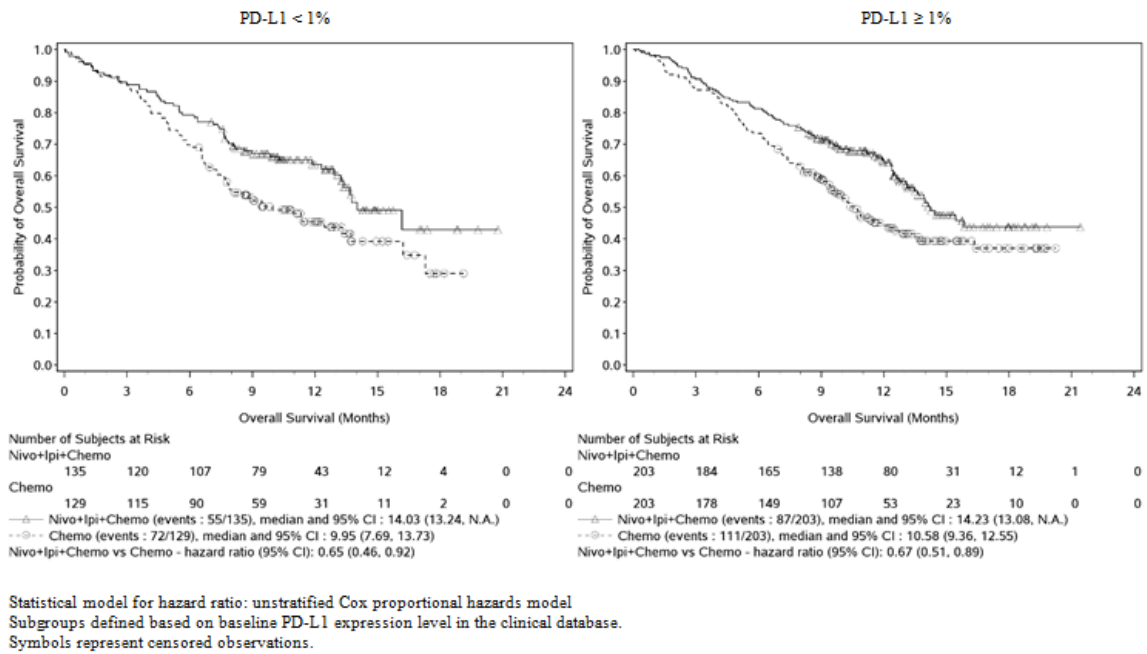
Figure 8 Kaplan-Meier Plot of Overall Survival by PD-L1 Expression Level - All Randomised Subjects

Statistical model for hazard ratio: unstratified Cox proportional hazards model
Subgroups defined based on baseline PD-L1 expression level in the clinical database.
Symbols represent censored observations.
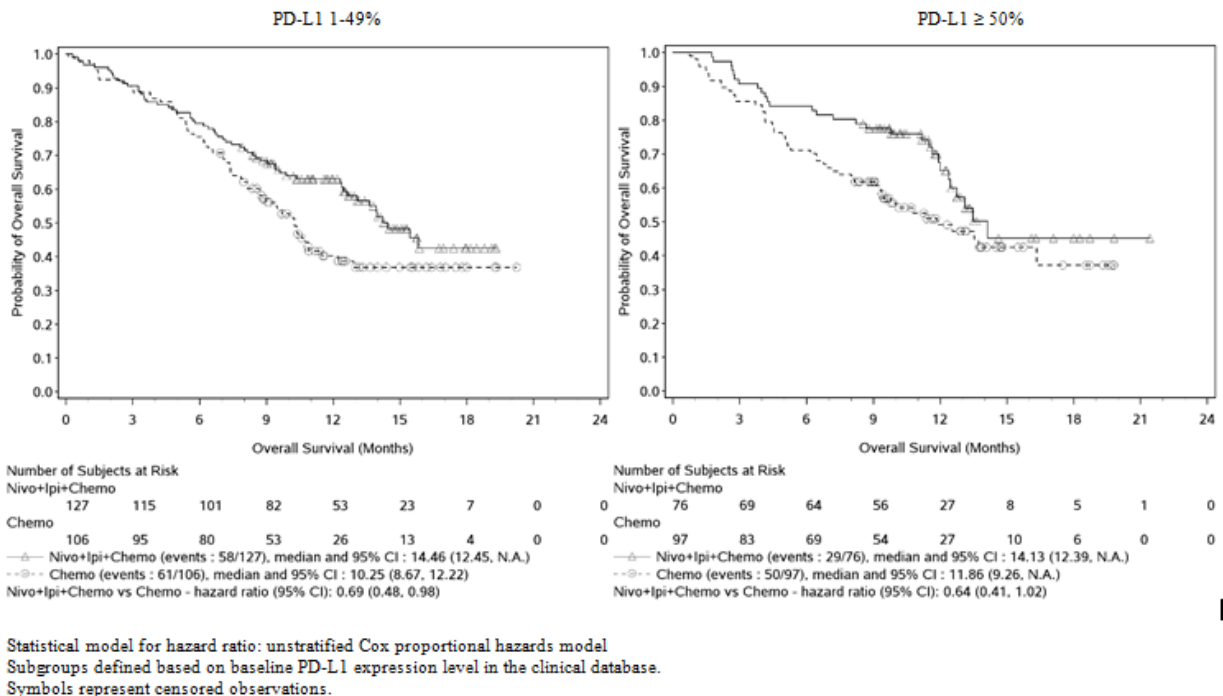
Table 12 Outcome in patients with unquantifiable PD-L1

	Nivo + ipi + chemo	chemo

Number	21	26
Events	14/21 (67%)	12/25 (48%)
HR	HR 1.64 (95% CI 0.74, 1.01)	
mOS (months)	10.84	17.05
95% CI	7.16, 15.57	8.64, NA
PFS HR	0.77 (0.88, 1.01)	
mPFS (months)	6.14	5.78
95% CI	(3.61, 11.47)	(2.83, 8.84)
ORR	7/21 (33%)	7/25 (28%)
95% CI	14.6, 57.0	12.1, 49.4

Table made by assessor, based on the data from Table 7 (OS), **Table 8** *(PFS)* **Table 12** *(ORR)*

Analysis of outcome per histology

The nivo+ ipi+ chemo groups showed in both the NSQ and SQ population a more favourable OS, PFS and ORR compared to the chemotherapy group. The largest differences with chemotherapy were observed in the SQ group (Table 15, Figure 10).

Table 13 Efficacy of Nivolumab + Ipilimumab + Chemotherapy vs Chemotherapy by Histology -All Randomised Subjects

	Squamous (N = 227)		Non-Squamous (N = 492)	
	Nivo +Ipi+Chemo N = 115	**Chemo N = 112**	**Nivo+Ipi+Chemo N = 246**	**Chemo N = 246**
Overall Survival (OS)				
HR (95% CI)[b]	0.65 (0.46, 0.93)		0.72 (0.55, 0.93)	
Events, n (%)	56 (48.7)	69 (61.6)	100 (40.7)	126 (51.2)
Median OS (95% CI), mo.[a]	13.67 (12.39, 15.57)	8.97 (7.16, 12.22)	15.80 (13.08, NA)	11.40 (9.69, 16.33)
PFS per BICR (1st Definition)				
HR (95% CI)[b]	0.57 (0.42, 0.79)		0.78 (0.63, 0.97)	
Events, n (%)	78 (67.8)	82 (73.2)	154 (62.6)	167 (67.9)
Median PFS (95% CI), mo.[a]	5.65 (4.44, 9.69)	4.30 (4.17, 4.99)	6.97 (5.55, 8.05)	5.55 (4.47, 5.78)

	Squamous (N = 227)		Non-Squamous (N = 492)	
	Nivo +Ipi+Chemo N = 115	Chemo N = 112	Nivo+Ipi+Chemo N = 246	Chemo N = 246
ORR per BICR (CR + PR)				
ORR (95% CI), %[c]	48.7 (39.3, 58.2)	31.3 (22.8, 40.7)	32.5 (26.7, 38.8)	22.4 (17.3, 28.1)
Unweighted ORR difference (95% CI), %	17.4 (4.7, 29.4)		10.2 (2.3, 17.9)	
BOR per BICR, n (%)				
CR	5 (4.3)	0	2 (0.8)	3 (1.2)
PR	51 (44.3)	35 (31.3)	78 (31.7)	52 (21.1)
SD	40 (34.8)	50 (44.6)	126 (51.2)	134 (54.5)
PD	9 (7.8)	14 (12.5)	23 (9.3)	31 (12.6)
UTD	9 (7.8)	12 (10.7)	15 (6.1)	18 (7.3)
Not Reported	1 (0.9)	1 (0.9)	2 (0.8)	8 (3.3)

[a]   *Based on Kaplan-Meier estimates*

[b]   *Unstratified Cox proportional hazards model*

[c]   *CR or PR; CI based on the Clopper and Pearson method*

Abbreviations: BICR - blinded independent central review, BOR - best overall response, CI - confidence interval, CR - complete response, HR - hazard ratio, NSCLC - non-small cell lung cancer, ORR - objective response rate, OS - overall survival, PD - progressive disease, PFS - progression-free survival, PR - partial response, SD - stable disease, UTD - unable to determine

Figure 9 Kaplan-Meier Plot of Overall Survival by Histology per IRT - All Randomised Subjects

Squamous | Non-Squamous

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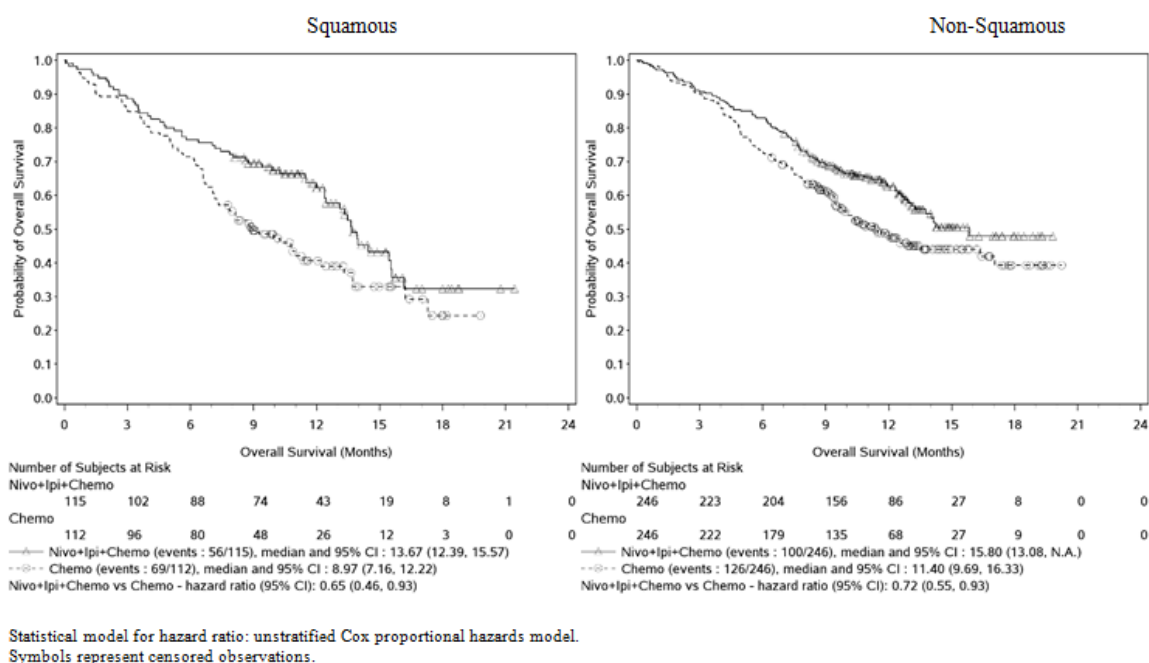
Subsequent therapy

More patients in the chemotherapy arm compared to the immunotherapy arm received subsequent therapy. A total of 28% of chemotherapy patients received subsequent immunotherapy (Table 5).

Table 14 Subsequent Cancer Therapy Summary - All Randomised Subjects

	Number of Subjects (%)	
	Nivo+ipi+Chemo n = 361	Chemo n = 358
Subsequent therapy (%)	104 (28.8)	147 (41.1)
Radiotherapy (%)	33 (9.1)	41 (11.5)
Surgery (%)	0	0
Systemic therapy (%)	90 (24.9)	131 (36.6)
immunotherapy	14 (3.9)	100 (27.9)
targeted therapy	8 (2.2)	8 (2.2)
chemotherapy	86 (23.8)	72 (20.1)
carboplatin	39 (10.8)	10 (2.8)
docetaxel	36 (10.0)	37 (10.3)
pemetrexed	20 (5.5)	5 (1.4)
gemcitabine	17 (4.7)	8 (2.2)
paclitaxel	16 (4.4)	10 (2.8)

Summary of main study(ies)

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 15 Summary of efficacy CA2099LA (database lock 3 Oct 2019)

> **Study CA2099LA: A phase 3, randomised study of nivolumab plus ipilimumab in combination with chemotherapy vs chemotherapy alone as first line therapy in stage IV Non-Small Cell Lung Cancer (NSCLC)**

Study identifier	Study CA2099LA, Checkmate 9LA		
	Eudra-CT: 2017-001195-35		
Design	Study CA2099LA is an international 1:1 randomised, open label parallel group study. Patients are stratified according to tumour histology (non-squamous vs squamous), gender and PD-L1 –Level (<1% vs ≥1%).		
	Duration of main phase		Nivolumab + ipilimumab + chemotherapy 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		not applicable
	Duration of Extension phase		not applicable
Hypothesis	Superiority		
Treatments groups	Nivolumab+ ipilimumab + chemotherapy (n=361)		Nivolumab (360 mg Q3W) + ipilimumab (1 mg/kg, Q6W) + histology-based chemotherapy (see below). Chemotherapy was given for two cycles.
	Chemotherapy (n=358)		Chemotherapy Q3W for 4 cycles -SQ histology: Carboplatin AUC 6 + paclitaxel 200 mg/m^2 (or 175mg/m^2 per local institutional practice) -NSQ histology: Carboplatin AUC 5 or AUC 6 + pemetrexed 500 mg/m² or Cisplatin 75 mg/m² + pemetrexed 500 mg/m²
Endpoints and definitions	Primary endpoint	OS	Time from randomisation to the date of death of any course
	Secondary endpoint	PFS	Time from the randomisation data to the date of first documented tumour progression (BICR/RECIST v1.1)
	Secondary endpoint	ORR	proportion of randomised patients who have confirmed CR or PR (BICR/RECIST v1.1)
	Secondary endpoint	TTR	For CR and PR patients only: Time from randomisation to data of the first confirmed documented response (CR or PR) as assessed by the BICR)
	Secondary endpoint	DoR	Time between first confirmed response to first documented tumour progression (BICR/ RECIST 1.1) or death from any cause.
Database lock	03-Oct 2019		
Results and Analysis			

Analysis description	Primary Analysis all randomised patients		
	Planned interim based on database lock 3 Oct 2019, by 80% of planned total events i.e. 322. The clinical cut of data of 16-Aug 2019. The minimum follow-up is 8.1 months		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Nivo + Ipi + chemo	Chemo
	Number of subjects	361	358

		Nivo + Ipi + chemo	Chemo
	median OS[a] (months) 95% CI	14.13 (13.14, 16.16)	10.74 (9.46, 12.45)
	median PFS[a] (months) (95% CI)	6.83 (5.55, 7.66)	4.96 (4.27, 5.55)
	ORR (n, %) (95% CI)	136 (37.7%) (32.7,42.9)	90 (25%) (20.7,30.0)
	TTR (months) Median (min, max)	2.51 (1.1, 0.6)	1.56 (1.2, 8.3)
	DOR N events/ N responders median (95% CI (months) Min, Max	57/136 (42.9% 10.02 (8.21, 13.01) 1.0+, 16.5+	54/90 5.09 (4.34, 7.00) 1.4+, 15.2+
Effect estimate per comparison	OS (primary endpoint)	Comparison group	Nivo+Ipi+Chemo vs Chemo
		HR	0.69
		96.71 CI	0.55, 0.87
		P-value [b]	0.0006
	PFS Secondary	Comparison group	Nivo+Ipi+Chemo vs Chemo
		HR	0.70
		97.5% CI	0.57, 0.86

	endpoint		
		P-value [b]	0.0001
	ORR (secondary endpoint)	Comparison groups	Nivo+Ipi+Chemo vs Chemo
		difference	12.4%
		97.5% CI	4.8, 20.0
		P-value	0.0003
	DOR, number with DOR (95% ≥ 6 months)	74 (66, 81)	41 (30, 52)
Notes	Patients with unidentifiable PD-L1 expression (n=46) are categorised as PD-L1<1%.		
Analysis description			

Symbol + indicates a censored value.

Minimum follow-up (date of the last subject randomized to date of the cut off for OS) was 8.1 months for OS; median follow-up (date of randomization to the last known date alive or death date) was 10.35 months for the nivo+ipi+chemo arm and 9.07 months for the chemo arm.

Abbreviations: BICR - blinded independent central review; chemo - chemotherapy; CI - confidence interval; DoR - duration of response; HR - hazard ratio; ipi - ipilimumab; nivo nivolumab; ORR - objective response rate; OS - overall survival; PFS - progression-free survival; TTR - time to objective response

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. Hazard Ratio is Nivo+Ipi+Chemo over Chemotherapy.

Updated confirmatory efficacy data were submitted as part of the responses to the RSI based on a database lock on 9 Mar 2020 and that are included in the updated table below:

Table 16bis - Summary of efficacy CA2099LA (database lock 9 Mar 2020)

Database lock	09-Mar 2020		
Results and Analysis			
Analysis description	**Primary Analysis all randomised patients** Updated data based on database lock 9 Mar 2020; minimum follow-up for OS: 12.7 months		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	**Treatment group**	**Nivo + Ipi + chemo**	**Chemo**

	Number of subject	361	358

	median OS [a] (months) 95% CI	15.64 (13.93, 19.98)	10.91 (9.46, 12.55)
	median PFS [a] (months) (95% CI)	6.74 (5.55, 7.75)	4.96 (4.27, 5.55)
	ORR (n, %) (95% CI)	138 (38.2%) (33.2, 43.5)	89 (24.9%) (20.5, 29.7)
	DoR N events/ N responders median (months) (95% CI) Min, Max	67/138 (48.6%) 11.30 (8.51, NA) 1.0+, 22.0+	64/89 (71.9%) 5.59 (4.37, 7.46) 1.6, 20.9+
Effect estimate per comparison	OS (primary endpoint)	Comparison group	Nivo+Ipi+Chemo vs Chemo
		HR[b]	0.66
		95% CI	0.55, 0.80
	PFS Secondary endpoint	Comparison group	Nivo+Ipi+Chemo vs Chemo
		HR[b]	0.68
		95% CI	0.57, 0.82
	ORR (secondary endpoint)	Comparison groups	Nivo+Ipi+Chemo vs Chemo
		difference	13.3%
		95% CI	6.6, 19.9
	DoR, % of subjects with DoR (95% CI) ≥ 6 months	73 (65, 80)	45 (34, 55)

Symbol + indicates a censored value.

Minimum follow-up (date of the last subject randomized to date of the cut off for OS) was 12.7 months for OS.

Abbreviations: BICR - blinded independent central review; chemo - chemotherapy; CI - confidence interval; DoR - duration of response; HR - hazard ratio; ipi - ipilimumab; nivo nivolumab; ORR - objective response rate; OS - overall survival; PFS - progression-free survival; TTR - time to objective response

a *Based on Kaplan-Meier estimates.*

b *Stratified Cox proportional hazards model. Hazard Ratio is Nivo+Ipi+Chemo over Chemotherapy.*

Clinical studies in special populations

The subgroup of elderly patients i.e. aged ≥ 75 was limited in study CA2099LA. A total of n=70 were included, a total of n=37 were randomised to nivo+ipi+chemo and a total of n=33 were randomised to chemotherapy.

Main results

Primary efficacy

The patient group aged ≥ 75 years shows a decreased overall survival compared with chemotherapy: HR 1.36 (95% CI 0.74, 2.52). The nivo+ipi+chemo group shows a mOS 8.51 (95% CI 5.59, 13.39) months and the chemotherapy group shows a mOS of 10.91 (95% CI 5.75, NA) months (Table 7).

PFS

The subgroup of elderly patients ≥ 75 years show a reduced PFS HR 1.12 (95% CI 0.61, 1.96). The nivo + ipi + chemo group shows a mPFS 5.08 (95% CI 2.92, 8.81) months; the chemotherapy group shows a mOS 5.78 (95% CI 4.21, 7.13) months (**Table 8**).

ORR

The response rate for the nivo + ipi + chemo group is 27.0% (13.8, 44) and for the chemotherapy group 15.1% (5.1, 31.9). This results in a difference of 11% (-7.7, 30.0) favouring the nivo+ipi+chemo group (**Table 12**).

Supportive study

Study CA209227 is a randomized, open-label Phase 3 trial of nivo+ipi vs chemotherapy (Part 1) and nivo+chemo vs chemotherapy (Part 2) in subjects with chemotherapy-naive stage IV or recurrent NSCLC with no known EGFR or ALK positive tumour mutations, who were previously untreated for advanced disease.

Study CA209227 has been previously assessed. Please also refer to:
- ipilimumab (EMEA/H/C/002213/WS1372/0057)

- nivolumab (EMEA/H/C/003985/WS1372/0053)

Title study

Study CA 209227

An open label, randomised phase 3 trial of Nivolumab, or Nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy naive stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC)

Study design

An open label, randomised controlled, parallel, phase III trial. The study consisted of two parts: 1A and 1B. The study was initially aimed to show the superiority of nivo+ ipi vs chemotherapy in patients with PD-L1 ≥1% (part 1A) and PD-L1 <1% (part 1B). The study was amended several times, which

resulted in that the original part 1B disappeared and was displaced by another target population characterized by a TMB ≥ 10 mut /MB. However, the results of <u>original</u> part 1B will be presented in the current application.
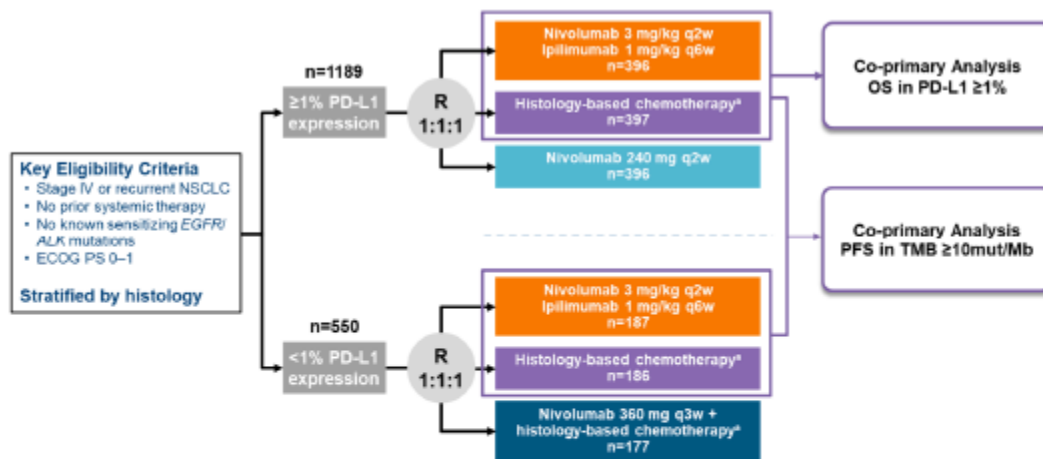
a Squamous (SQ) histology: gemcitabine with cisplatin or gemcitabine with carboplatin
  Non-squamous (NSQ) histology: pemetrexed with cisplatin or pemetrexed with carboplatin. Subjects with stable disease or response after cycle 4 could have continued pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity.

Abbreviations: ALK - anaplastic lymphoma kinase, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, IV - intravenous, mut/Mb - mutations per megabase, NSCLC - non-small cell lung cancer, OS - overall survival, PD-L1 - programmed cell death ligand 1, PFS - progression-free survival, PS - performance status, qXw - every X weeks, TMB - tumor mutational burden

Main inclusion- and exclusion criteria

Adult patients with ECOG PS ≤1 and histologically confirmed stage IV or recurrent NSCLC, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease. Patients must provide a tumour specimen for central PD-L1 IHC testing.

Patient with central nervous system metastases or known EGFR mutations or ALK translocation were excluded

Treatments

- Arm A: nivolumab 240 mg over 30 minutes every 2 weeks (Q2W) (PD-L1≥1% only)

- Treatment arm B and G: nivolumab 3 mg/kg over 30 minutes Q2W + ipilimumab 1 mg/kg over 30 minutes every 6 weeks (Q6W)

- Treatment C and F: histology-based platinum-doublet chemotherapy in 3-week cycles for a maximum of 4 cycles or until disease progression or unacceptable toxicity (whichever came first).

- Treatment arm G (PD-L1 <1% only): Nivolumab 360 mg over 30 minutes combined with platinum-doublet chemotherapy administered every 3 weeks (Q3W) for a maximum of 4 cycles. Subjects who have not experienced disease progression were to receive nivolumab 360 mg Q3W until disease progression, unacceptable toxicity, or up to 24 months (whichever comes first).

The choices for the platinum doublet therapy were

- SQ: gemcitabine (1000 or 1250 mg/m^2) with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

- NSQ: pemetrexed 500 mg/m^2 with cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6)

For subjects with NSQ histology, pemetrexed maintenance was allowed until disease progression or unacceptable toxicity after 4 cycles of chemotherapy. See the choices for platinum-doublet chemotherapy below.

Results

The study included a total of 1789 patients with a median age of 64.0 years. Most patients were white (75%) and male (69%). Most patients had an adenocarcinoma (69%) and were either current or former smokers (85%).

Overall survival

The median overall survival reported for nivo+ ipilimumab was 17.12 (95% CI 15.21, 19.94) months, compared to 13.86 (95% CI 12.16, 15.11) months with chemotherapy (HR 0.73, 95% CI 0.62, 0.86). The KM crossed at 3 months. The OS HR favoured chemotherapy for the first 3 month (HR 1.39, 95% CI 0.98, 1.97), after 3 months the OS HR favoured nivo + ipi over chemotherapy. The KM curves separated at approximately 7 months. (**Figure 11**)

The observed improvement in OS is supported with improvement in the ORR and DoR, but not with PFS. (Table 17).

Subgroup according to PD-L1 expression

- PD-L1 ≥ 1% (part 1A of trial)

For the PD-L1 ≥1% population, the survival showed an improvement of the nivo+ ipi combination therapy compared to chemotherapy (HR 0.79: 97.72% CI 0.65, 0.96). The median overall survival reported for nivo+ ipilimumab was 17.08 (95% CI 14.95, 20.07) months, compared to 14.88 (95% CI 12.71, 16.72) months with chemotherapy.

KM curves showed a crossing at 3 months. After 3 months the survival benefited the nivo+ ipi combination (Figure 12).

The observed improvement in OS was supported with improvements in the ORR and DoR, but not with PFS (Table 17).

- PD-L1 <1% (part 1B of trial)

Nivo + ipi vs chemo

In contrast to the PD-L1 ≥1% population, the PD-L1<1% showed an immediate survival benefit of the nivo+ ipi combination compared to chemotherapy. The median overall survival reported for nivo+ ipilimumab was 17.15 (95% CI 12.85, 22.05) months, compared to 12.19 (95% CI 9.17, 14.32) months with chemotherapy (0.62 97.5% CI 0.47, 0.81) (Figure 13).

The observed improvement in OS was supported with improvement in PFS, ORR and DoR (Table 17).

Nivo + chemo vs chemo

This part of the trial included also a comparison arm of nivolumab + chemotherapy vs chemotherapy. The nivo+ chemotherapy showed an immediate survival advantage over chemotherapy (HR 0.78, 97.5% CI 0.60, 1.02, p = 0.035) (Figure 13).

The median OS of nivo + chemo was 15.21 (95% CI 12.19, 19.78) months, compared to 12.19 (9/17, 14.32) months with chemo. The observed improvement in OS was supported with ORR and DOR, but not with PFS (Table 17).

Table 17 Overview of the point estimates of the primary and key secondary outcomes of study CA209227- all randomised patients

	PD-L1 <1%			PD-L1 ≥1%			Overall population	
	Nivo + Ipi	Nivo + Chemo	Chemo	Nivo + Ipi	Nivo	Chemo	Nivo+ Ipi	Chemo
N	187	177	186	396	396	397	583	583
mOS months	17.15	15.21	12.19	17.08	15.70	14.88	17.12	13.86
95% CI	12.85,22.05	12.29, 19.78	9.17, 14.32	14.95, 20.07	13.27, 18.14	12.71, 16.72	15.21-19.94	12.16, 15.11
mPFS (months)	5.06	5.55	4.70	5.06	4.17	5.55	5.06	5.49
95% CI	3.15, 6.37	4.63, 6.90	4.21, 5.59	4.07,6.31	3.02,5.32	4.63, 5.82	4.14, 5.68	4.60, 5.59
ORR	51 (23%)	67 (38%)	43 (23%)	142 (36%)	106 (28%)	119 (30%)	193 (33%)	162 (28%)
DoR	17.97	8.31	4.83	23.16	15.54	6,24	19.58	5.78
95%	12.42, 28.66	5.88, 9.43	3.71, 5.78	15.21, 32.16	12.71, 23.52	5.59, 7.39	16.07, 28.65	5.42, 6.93

Figure 10 Kaplan-Meier Plot of overall survival – Nivolumab + ipilimumab (Arm B+D), and Chemotherapy (Arm C+F) – all randomised patients
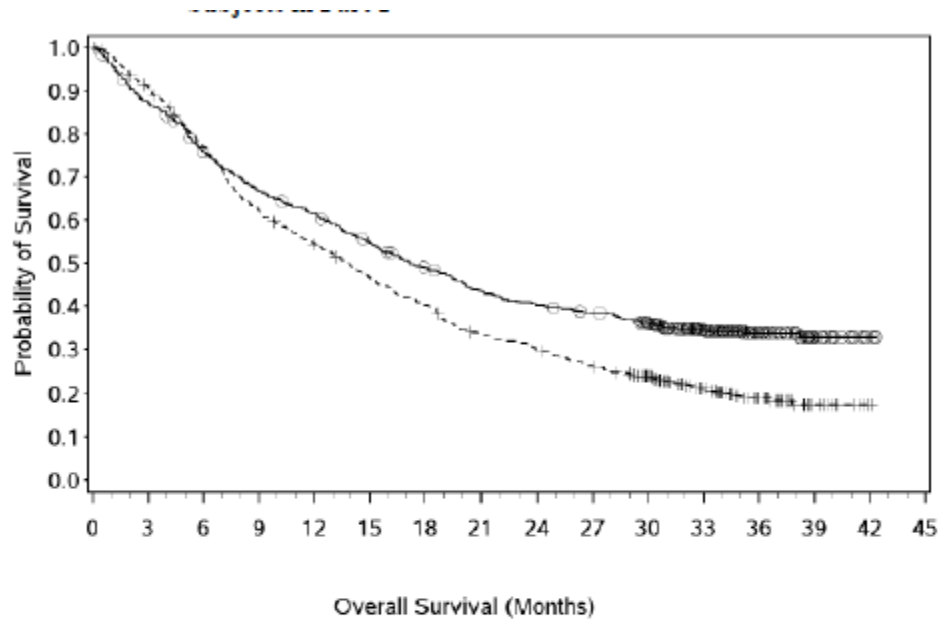
Number of Subjects at Risk

Nivo + Ipi (Arm B + D)
583 506 437 384 354 312 277 245 226 214 188 125 60 17 3 0

Chemo (Arm C + F)
583 522 441 357 310 264 228 190 167 147 122 76 34 11 1 0

——o—— Nivo + Ipi (Arm B + D) (events : 377/583), median and 95% CI : 17.12 (15.21, 19.94)
--+-- Chemo (Arm C + F) (events : 454/583), median and 95% CI : 13.86 (12.16, 15.11)
Nivo + Ipi (Arm B + D) vs. Chemo (Arm C + F) - hazard ratio (97.5%CI) : 0.73 (0.62, 0.86)

Stratified log-rank test p-value : <0.0001

Based on database lock: 02-Jul-2019. Symbols represent censored observations.
Hazard Ratio (Nivolumab + Ipilimumab over Chemotherapy) is based on a stratified Cox proportional hazard model.
Source: Figure S.5.120.1.2

*Figure 11 Kaplan-Meier Plot of overall survival – Nivolumab + ipilimumab (Arm B), Nivolumab (Arm A)
and Chemotherapy (Arm C) – all randomised patients with PD-L1 ≥1%*
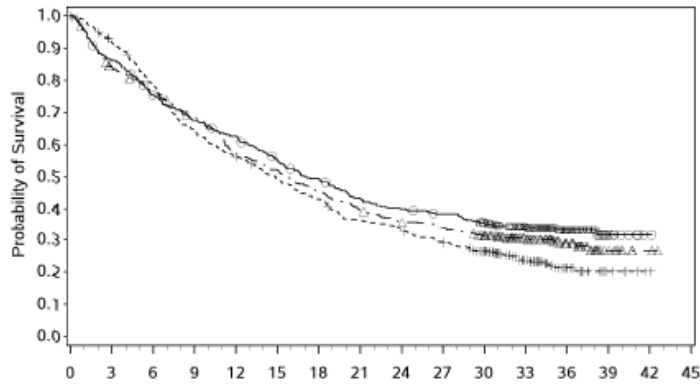
Number of Subjects at Risk

Arm B: Nivo + Ipi
  396 341 295 264 244 212 190 165 153 145 129 91 41 9 1 0
Arm A: Nivolumab
  396 330 299 265 220 201 176 153 139 129 115 70 36 10 2 0
Arm C: Chemo
  397 358 306 250 218 190 166 141 126 112 93 57 22 6 1 0
—◦— Arm B: Nivo + Ipi (events : 258/396), median and 95% CI : 17.08 (14.95, 20.07)
— △ - Arm A: Nivolumab (events : 274/396), median and 95% CI : 15.70 (13.27, 18.14)
- -+- - Arm C: Chemo (events : 298/397), median and 95% CI : 14.88 (12.71, 16.72)
Arm B: Nivo + Ipi vs. Arm C: Chemo - hazard ratio (97.5%CI) : 0.79 (0.66, 0.96)
Arm A: Nivolumab vs. Arm C: Chemo - hazard ratio (97.5%CI) : 0.88 (0.73, 1.06)
Arm B: Nivo + Ipi vs. Arm A: Nivolumab - hazard ratio (97.5%CI) : 0.90 (0.74, 1.10)

Symbols represent censored observations. .

Figure 12 Kaplan-Meier Plot of overall survival – Nivolumab + ipilimumab (Arm D), Nivolumab + Chemotherapy (Arm G), and chemotherapy (Arm F) – all randomised patients with PD-L1 <1%
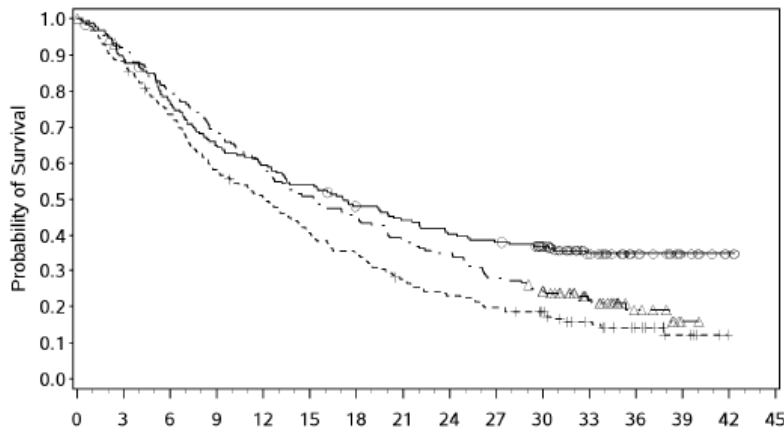
Number of Subjects at Risk

Arm D: Nivo + Ipi
  187 165 142 120 110 100 87 80 73 69 59 34 19 8 2 0
Arm G: Nivo + Chemo
  177 159 139 119 102 88 78 67 60 48 40 23 9 1 0 0
Arm F: Chemo
  186 164 135 107 92 74 62 49 41 35 29 19 12 5 0 0
—◦— Arm D: Nivo + Ipi (events : 119/187), median and 95% CI : 17.15 (12.85, 22.05)
— △ - Arm G: Nivo + Chemo (events : 137/177), median and 95% CI : 15.21 (12.29, 19.78)
- -+- - Arm F: Chemo (events : 156/186), median and 95% CI : 12.19 (9.17, 14.32)
Arm D: Nivo + Ipi vs. Arm F: Chemo - hazard ratio (97.5%CI) : 0.62 (0.47, 0.81)
Arm G: Nivo + Chemo vs. Arm F: Chemo - hazard ratio (97.5%CI) : 0.78 (0.60, 1.02)

Symbols represent censored observations.

Subgroup according to histology

The subgroup analyses according to histology showed that the nivo+ ipi treatment showed an improved OS compared to chemotherapy for both the SQ and the NSQ population. The largest benefit was observed in patients with squamous disease (Figure 14).

Figure 13 Forest plot of treatment effect of OS of nivo+ ipi vs chemotherapy in all randomised subjects.
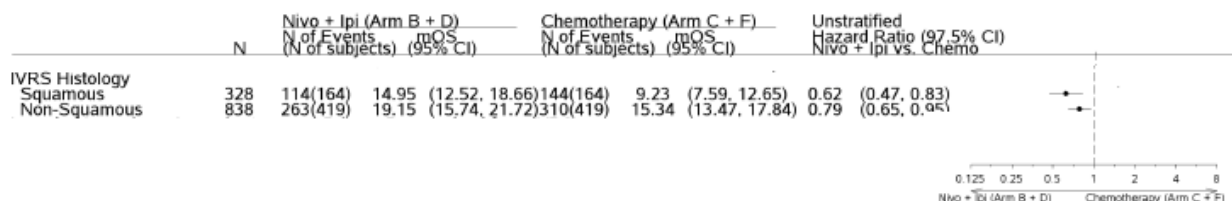
2.4.3. Discussion on clinical efficacy

With the current application the MAH applies for an extension of the indication of nivolumab+ ipilimumab + chemotherapy for treatment-naive stage IV or recurrent 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 cancers in adults with no EGFR or ALK positive tumour mutation.*

The combination of immunotherapy and chemotherapy combines two different treatment classes in the treatment of NSCLC. They both have a distinct mode of action, when combined may lead to an improved survival benefit, although an additive effect might be seen for the toxicity profile.

Design and conduct of the trial

The pivotal trial CA2099LA is not blinded. The open-label design might be accepted, because the blinding of the two-treatment arms would be severely hampered by the different treatment regimens and different associated toxicities of the traditional chemotherapy compared with immune chemotherapy treatment arm. The BMS clinical study team (with unblinding of a selected number to monitor safety) was blinded to the aggregate treatment group information up to database lock.

Study population

The study included patients with stage IV NSCLC. Patients with known sensitising EGFR mutations or ALK translocation or with CNS metastases were excluded. The exclusion of these patient groups is agreed. The patients with a sensitising EGFR mutation or ALK translocation are a distinct group of NSCLC which should be treated with targeted 1L and 2L therapies. Patients with known CNS metastases generally have a shortened life expectancy, which makes them unsuitable for participation in a clinical trial. Participants are eligible if CNS metastases are adequately treated and participants are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first treatment.

Endpoints

The choice of OS as primary endpoint enables a clinical benefit evaluation based on relevant efficacy outcomes in cancer therapy, and it is therefore deemed adequate. The key secondary endpoints were PFS per RECIST 1.1 by BICR, ORR per RECIST 1.1 and DOR. The key secondary endpoints are also adequate.

Treatment allocation

The treatment allocation/randomisation was stratified according to PD-L1 expression, histology and gender. This approach is deemed adequate because PD-L1 expression and histology are distinct tumour characteristics with a different response to immunotherapy. Regarding gender, lung cancer may have a more favourable prognosis in females and as such, the stratification/randomisation strategy can be regarded as adequate.

No stratification was made according to baseline platinum therapy (cisplatin vs. carboplatin) or smoking status. This is also considered adequate as cisplatin was only applied in the NSQ treated group and received by a limited number of patients (30%). The number of never smokers was small as anticipated. Both the baseline characteristics cisplatin/carboplatin and smoking history were evenly distributed over both treatment groups.

A computer-generated randomisation schedule was used in the assignment of subjects to treatment groups in the study. This was transferred to the Interactive Response Technologies (IRT) vendor for use in an interactive web response system (IWRS) from which sites obtained a subject identification number and randomised/assigned a subject to a treatment arm. This is acceptable.

Treatments

- Use of non-approved treatments

The applied chemotherapies are in line with the recommendations made by the European Society for Medical Oncology[11]. However, in this trial, various treatments used are not approved in the EU:

- Nivolumab: fixed dose Q3W dose regimen

- Carboplatin dose combination with pemetrexed (source SmPC pemetrexed)

- Carboplatin dose combination with paclitaxel (source SmPC paclitaxel)

The use of the fixed-dose combination of nivolumab (3qw) over the weight-based dosing (2wq) is justified because of the less frequent dosing, particularly if combined with chemotherapy.

The use of the carboplatin combinations is justified because they are recommended by the European Society for Medical Oncology[12]. As such, these treatments can be regarded as well established.

- Number of chemotherapy cycles

In the experimental arm, the number of chemotherapy cycles is limited to two. This limitation to two cycles is accepted because of the anticipated combined toxicity of the combination of immunotherapy and chemotherapy.

Patients randomised to the comparator chemotherapy arm could receive up to 4 cycles of platinum-based chemotherapy. Those patients who used pemetrexed could continue pemetrexed monotherapy if indicated. These treatment recommendations are adequate and in line with international guidelines. The limitation to 4 cycles of therapy is justified, as no OS benefit has been demonstrated for six versus fewer cycles of first-line platinum-based doublets, although a longer PFS was reported in patients receiving six cycles (Rossi A, Lancet Oncol 2014).

Conduct of the trial

As the study is open-label, the study might be more prone to bias. Concerns regarding the conduct of trial were raised in relation to GCP findings for study CA209227 that was performed in a similar target population and overlapping in time. The GCP inspection revealed a lack of solid Sponsor's systems to

---

[11]Ann Oncol (2018) 29 (suppl 4):iv 193-iv 237;. https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer
[12]Ann Oncol (2018) 29 (suppl 4):iv 193-iv 237;. https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer

prevent dissemination of information to unauthorised/non authorised personnel within a non-robust and immature risk management system.

The impact analyses provided revealed that study CA2099LA was conducted using improved systems and processes, i.e. in comparison to those used in study CA209227. In addition, a clinical quality self-assessment (CQA) was conducted for Study CA2099LA, while continuing the implementation of the GCP inspection CAPAs resulting from study CA209227 inspection. At this time, about 95% of CAPA are implemented.

The improved systems and processes, resulted in an enhanced data audit trail and transparency of the dataset traceability compared to study CA209227.

These measures limited the access to data and improved the transparency of dataset traceability and audit trail. As such, the risk of dissemination of trial data was reduced.

A specific concern was that select BMS staff members had access to unaggregated select safety data, including mortality data. The above-mentioned improved systems and procedures reduced the risk for preliminary clinical data to strategic members compared to study CA209227. Also, the preliminary dissemination of clinical trial data to strategic members is unlikely to occur because:

- o No interim analysis was conducted prior to the one pre-planned (this statement is supported with the Unix Audit trail). The lack of such an interim analysis provides a lower risk of dissemination of trial data, which could lead to protocol amendments.

- o BMS personnel reviewed the safety on a patient level. Only select safety listings with individual patient level treatment information were provided to select members to review safety toxicities according to protocol algorithms and allow query and data clarifications. This safety review is part of the Sponsor responsibility for a good conduct of the trial.

- o A third party prepared the safety listing for the blinded DMC meetings. No data or results were communicated from the DMC to BMS.

- o The MAH sufficiently substantiated that the amendments 02 (increasing of sample size) and 04 (another statistical method for analyses) were based on external data:

  - There was very limited knowledge available for the efficacy of the combination of immunotherapy + chemotherapy vs chemotherapy when the study was initiated. No OS data was available. The data was limited to phase I data and limited phase II data obtained from the pembrolizumab and chemotherapy combination showing a superior PFS data of the combination vs chemotherapy.

  - The sample size was increased (amendment 02) when n=287 patients (66% of the total population) were randomised. Only OS data of n=35 patients was available and (n=19) 6.6% and (n=106) 36.9% of subjects had >6 month and >3 month of follow-up, respectively.

  - At the end of 2018, when the enrolment of study CA2099LA was almost complete, more studies showed that the immuno-chemotherapy combination showed a delayed separation of the OS curves. The statistical analysis plan was adjusted (amendment 04) before database lock.

- o In addition, the supplemental requested analyses of study results before and after the implementation of amendment 02 (sample size) and amendment 04 aligned with the results before the implementation of the amendments.

- o Updated study results (database lock 09-Mar-2020) confirm the primary efficacy results.

Based on all these above considerations, it is considered unlikely that efficacy data has been preliminary disseminated to the strategic decision makers of the trial. Also, the data management is deemed adequate. The updated OS data with more mature data also confirm the primary analyses. Overall, the trial data is regarded valid and can be used to support the requested marketing authorisation.

Efficacy

The results of this trial are based on a planned interim analysis when >322 events (80% of planned events) had occurred.

The first patient included in Study CA2099LA was randomized on 03 Oct 2017.

Deaths occurring after treatment discontinuation or completion were not captured as part of the 'end-of-treatment period subject status' but were included in the overall survival summary for the primary analysis, i.e. total number of deaths among randomised subjects. This explains the discrepancies identified in the reported number of deaths. A total of 719 patients were randomised, 668 were reported with Stage IV and n=51 were reported as recurrent to metastatic disease of whom 31 were in the nivo+ipi+chemo arm (19 'recurrent to metastatic' and 12 'recurrent') and 20 were in the chemotherapy arm (17 'recurrent to metastatic' and 3 'recurrent').

- **Patient characteristics**

The study included mainly patients with metastatic NSCLC (93%) and as such, is reflective for the proposed target population. The patient population with unspecified PD-L1 expression were included in the patient group with PD-L1 <1%. The patients with unspecified PD-L1 expression appear to be somewhat under-represented, as they included about 6.4% of the target population, while in study CA209277, up to 12% patients were included. However, it is expected that over time this group will be smaller, as techniques and experience improved for the quantification of PD-L1 expression. The median age was 66 years, which is in line with earlier studies in metastatic NSCLC, but somewhat younger than the mean age of patients with NSCLC (72 years).

A total of ~ 7% of the patients had received (neo)adjuvant treatment before entering the study. It was confirmed that none of these 47 patients were reported to have received immunotherapy (e.g. durvalumab).

In the NSQ group, a total of 70% of patients used the combination of carboplatin and pemetrexed. This proportion appears to be high, considering that the ESMO recommends that this combination should only be used in patients who cannot tolerate cisplatin. Though, in a previous comparable application, also a similar high proportion of NSQ patients used carboplatin instead of cisplatin in combination with immunotherapy (Pembrolizumab - EMEA /H/C/003820/0043).
The safety profile of carboplatin is characterised by bone marrow toxicity, while cisplatin and immunotherapy have overlapping renal side effects. Therefore, the combination of carboplatin + immunotherapy will be easier to monitor clinically than the combination of cisplatin + immunotherapy.

The distribution of subsequent radiotherapy and surgery is overall comparable between treatment arms. More patients in the chemotherapy arm received subsequent systemic therapy. The most common second line treatment was immunotherapy. Immunotherapy has shown to improve the overall survival in second line NSCLC. Therefore, the reported OS for the chemotherapy arm might be larger than described historically, before the approval of second line immunotherapy

- **Outcome measures**

The study showed a clinically relevant improvement of the overall survival with nivo + ipi + chemo compared with chemotherapy alone. The KM curves showed an immediate improvement in overall survival, without a delayed treatment effect as would be observed for nivo + ipi alone.

No crossing of curves occurred during the first months of treatment, although at 15 months the curves seem to touch, but interpretation is hampered by the large amount of censoring. Updated efficacy data were submitted confirming the separation of the curves.

The overall benefit for the OS by nivo + ipi + chemo vs chemo is supported by the secondary outcome measures PFS, ORR, TTR and DoR. Besides, an overall treatment benefit was observed in almost all predefined subgroups favouring the combination treatment compared with chemotherapy, including the subgroups of patients according to gender, PD-L1 expression and baseline histology (i.e. the stratification factors). These data support the robustness of the observed survival benefit.

However, the outcomes for overall survival favoured chemotherapy in the subgroups of patients who were never smokers, patients ≥ 75 years and unquantifiable PD-L1 expression. Indeed, the elderly and non-smokers showed in previous studies also a smaller effect of immunotherapy.
The current results in the subgroup of patients with unquantifiable PD-L1 expression are hard to interpret, as the patient group with unquantifiable PD-L1 expression is small (n=46).

Supportive studies

The results of the pivotal phase III CA2099LA comparative trial are supported by two other trials:

- CA209568 (A Study of Nivolumab in Combination with Ipilimumab (Part 1); And Nivolumab Plus Ipilimumab In Combination With Chemotherapy (Part 2) As First Line Therapy In Stage IV Non-Small Cell Lung Cancer (NSCLC)): a single-arm phase II study conducted in n=36 showing an improved PFS of nivo+ipi + chemo compared to nivo+ ipi alone.

- CA209227 (An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus Platinum Doublet Chemotherapy versus Platinum Doublet Chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)): a large phase III trial comparing nivo + ipi vs. platinum-based chemotherapy in the same target population. However, several issues related to study conduct and methodology were identified (as discussed above). The MAH withdrew the application before opinion by the CHMP (EMEA/H/C/WS1372).

2.4.4. Conclusions on the clinical efficacy

The results of the Interim Analysis of the pivotal study CA2099LA showed a clinically relevant improvement in overall survival for nivo+ ipi+ chemo compared to chemotherapy as first-line treatment of metastatic NSCLC in patients without a sensitising EGFR mutation and who do not harbour an ALK translocation. The effect in overall survival is supported by the secondary outcome measures and in several predefined subgroups. These supportive outcomes show the robustness of the overall survival results. The updated efficacy data submitted during the procedure (09-Mar-2020 database lock; minimum duration of follow-up for OS of 12.7 months) confirm the initially reported efficacy results.

The data is limited for patients ≥ 75 years for whom the nivolumab + ipilimumab+ chemotherapy combination should be used with caution after careful consideration of the potential benefit/risk based on an individual basis (see section 5.1 of the SmPC).

Concerns were raised regarding the conduct of this open-label trial. Some BMS personnel were unblinded to individual patienttreatment information for the purpose of safety review and data review

and cleaning before database lock and it was unknown whether and which preventive measures had been taken to prevent the dissemination of critical data to the clinical and strategic decision-makers, especially as the Sponsor's system to protect against information dissemination was shown to be weak in a GCP inspection of study CA209227, and how this may have impacted the (quality of the) study results. Evidence was however provided by the MAH to support that study CA2099LA was conducted using improved systems and processes in comparison to those used in study CA209227. This allowed for the conclusion that even if there is an overlap in the timing of conduct with study CA209227, for which major GCP findings were reported, these do not impact the results of study CA2099LA. A clinical quality self-assessment (CQA) was conducted for study CA2099LA, while continuing the implementation of the GCP inspection CAPAs resulting from study CA209227 inspection. Based on the justifications/data provided it can be concluded that the integrity of study CA2099LA is not in question and the reported data can overall be considered reliable for benefit/risk assessment.

Additional supportive efficacy data has been provided from two additional trials (phase II CA209568 and phase III CA209227) where an improved PFS of nivo+ipi + chemo compared to nivo+ ipi alone and an overall improvement in OS of nivo + ipi vs. platinum-based chemotherapy were shown, respectively.

The wording of the indication has been refined to adequately reflect the included study population, i.e.:

OPDIVO:

"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".

Yervoy:

"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"

2.5. Clinical safety

Introduction

In this application, the immunotherapy is combined with chemotherapy. The main safety set for nivolumab/ipilimumab/chemotherapy (nivo+ipi+chemo) as first line treatment in NSCLC is based on 358 subjects from CA2099LA and 36 subjects from CA209568 Part 2 (chemotherapy is based on 349 subjects from CA2099LA). There was no pooling of safety data from CA2099LA and CA209568 Part 2 due to limited sample size in CA209568 Part 2. In study CA2099LA and CA209568, nivo+ipi+chemo treatment was continued until disease progression, unacceptable toxicity or up to 24 months.

Since chemotherapy is administered Q3W, a nivolumab 360 mg flat dose Q3W was chosen for study CA209568 part 2. Nivolumab 360 mg Q3W has similar steady-state average exposures relative to the 3 mg/kg Q2W dose (at a median body weight of ~ 80 kg). Based on the safety results of CA209568 part 2 the dose of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy Q3W was chosen for further development.

Patient exposure

At the time of the database lock of 03 Oct 2019, all patients are randomised (n=719) and have minimum follow up of 8.1 months for OS.

The proportion of subjects who received ≥ 90% of the planned dose intensity was as follows

- Nivo+ipi+chemo arm: 79.1% for nivolumab, 85.2% for ipilimumab, 78.4% for cisplatin, 72.1% for carboplatin, 70.7% for paclitaxel, and 78.7% for pemetrexed ((Table 18)

- Chemotherapy arm: 81.3% for cisplatin, 75.7% for carboplatin, 70.3% for paclitaxel, and 73.2% for pemetrexed (Table 19)

The median (95% CI) duration of therapy was 6.05 (4.93, 7.06) months for the nivo+ipi+chemo arm and 2.43 (2.30, 2.83) months in the chemotherapy arm.

The median number of doses received was as follows:

- Nivo+ipi+chemo arm: 9 doses for nivolumab, 4 doses for ipilimumab, and 2 doses for each of cisplatin, carboplatin, paclitaxel, and pemetrexed

- Chemotherapy arm: 4 doses for each of cisplatin, carboplatin, and paclitaxel, and 6 doses for pemetrexed.

In the nivo+ipi+chemo arm, most treated subjects (93.0%) received 2 cycles of chemotherapy. Per protocol, chemotherapy was to be given for 4 cycles (12 weeks) to subjects in the chemotherapy arm, followed by optional pemetrexed maintenance therapy in patients with NSQ histology.

Table 18: Cumulative Dose and Relative Dose Intensity - All Treated Subjects in the Nivolumab + Ipilimumab + Chemotherapy Arm - CA2099LA

	Nivo+Ipi+Chemo					
	Nivolumab N = 358	Ipilimumab N = 358	Cisplatin N = 74	Carboplatin N = 284	Paclitaxel N = 116	Pemetrexed N = 244
NUMBER OF DOSES RECEIVED						
MEAN	10.0	5.2	1.9	1.9	1.9	1.9
(SD)	(6.5)	(3.3)	(0.3)	(0.3)	(0.3)	(0.3)
MEDIAN	9.0	4.0	2.0	2.0	2.0	2.0
(MIN – MAX)	(1 – 28)	(1 – 14)	(1 – 2)	(1 – 2)	(1 – 2)	(1 – 2)
CUMULATIVE DOSE (A)						
MEAN	3587.35	5.15	156.03	10.37	374.39	943.79
(SD)	(2327.02)	(3.26)	(85.45)	(2.06)	(73.09)	(145.17)
MEDIAN	3240.00	4.24	149.07	10.07	396.17	995.02
(MIN – MAX)	(360.0 – 10080.0)	(0.1 – 14.1)	(74.6 – 697.9)	(1.2 – 17.6)	(74.9 – 766.0)	(145.9 – 1047.1)
RELATIVE DOSE INTENSITY (%)						
>= 110%	0	2 (0.6)	3 (4.1)	18 (6.3)	2 (1.7)	0
90% TO < 110%	283 (79.1)	303 (84.6)	55 (74.3)	187 (65.8)	80 (69.0)	192 (78.7)
70% TO < 90%	61 (17.0)	49 (13.7)	12 (16.2)	61 (21.5)	25 (21.6)	37 (15.2)
50% TO < 70%	13 (3.6)	3 (0.8)	3 (4.1)	14 (4.9)	8 (6.9)	9 (3.7)
< 50%	1 (0.3)	1 (0.3)	0	3 (1.1)	1 (0.9)	2 (0.8)
NOT REPORTED	0	0	1 (1.4)	1 (0.4)	0	4 (1.6)

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

Source: Refer to Table 6.1-1 of the CA2099LA Final CSR[1]

Table 19: Cumulative Dose and Relative Dose Intensity - All Treated Subjects in the Chemotherapy Arm-CA2099LA

	Chemotherapy			
	Cisplatin N = 75	Carboplatin N = 280	Paclitaxel N = 111	Pemetrexed N = 239
NUMBER OF DOSES RECEIVED				
MEAN	3.3	3.4	3.4	8.1
(SD)	(1.1)	(1.0)	(1.0)	(6.0)
MEDIAN	4.0	4.0	4.0	6.0
(MIN - MAX)	(1 - 4)	(1 - 4)	(1 - 4)	(1 - 29)
CUMULATIVE DOSE (A)				
MEAN	246.42	18.80	657.59	3938.77
(SD)	(90.56)	(5.95)	(211.61)	(2962.71)
MEDIAN	291.89	20.01	765.55	3017.25
(MIN - MAX)	(74.6 - 606.7)	(3.7 - 29.7)	(192.4 - 1150.1)	(486.8 - 14333.3)
RELATIVE DOSE INTENSITY (%)				
>= 110%	1 (1.3)	21 (7.5)	2 (1.8)	0
90% TO < 110%	60 (80.0)	191 (68.2)	76 (68.5)	175 (73.2)
70% TO < 90%	10 (13.3)	58 (20.7)	26 (23.4)	49 (20.5)
50% TO < 70%	2 (2.7)	10 (3.6)	5 (4.5)	5 (2.1)
< 50%	0	0	0	2 (0.8)
NOT REPORTED	2 (2.7)	0	2 (1.8)	8 (3.3)

(A) Dose units: Paclitaxel, Cisplatin and Pemetrexed in mg/m^2 and Carboplatin in AUC.
Source: Refer to Table 6.1-2 of the CA2099LA Final CSR[1]

Table 20 Number of chemotherapy cycles- all treated patients

	Nivo+Ipi+Chemo N = 358	Chemo N = 349
NUMBER OF CYCLES OF CHEMOTHERAPY RECEIVED PER SUBJECT (%)		
0	0	0
1	25 (7.0)	23 (6.6)
2	333 (93.0)	49 (14.0)
3	0	16 (4.6)
4	0	103 (29.5)
>= 5	0	158 (45.3)

The overall rates of **discontinuation** during the treatment period were 66.2% and 58.2% in the nivo+ipi+chemo and chemotherapy arm, respectively.

The primary reason for not completing the treatment period was disease progression (292 subjects, 41.3%): 150 (41.9%) nivo+ipi+chemo treated subjects and 142 (40.7%) chemotherapy-treated subjects (see also Figure 4).

In the nivo+ipi+chemo arm, 18 (5.0%) of the 358 treated subjects discontinued ipilimumab early. Note that ipilimumab could be discontinued and nivolumab continued; however, if nivolumab was discontinued, ipilimumab could not be continued alone as monotherapy. After ipilimumab was stopped in 18 subjects, the median number of nivolumab doses received was 3 (range: 1 - 13) and the median duration of treatment was 91 days (range: 20 - 304). Subjects who discontinued study therapy due to AEs are further described below.

Most treated subjects received all doses of study medication without infusion interruption or rate reduction; 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+chemo arm: 55.9% for nivolumab, 48.0% for ipilimumab, 13.5% for cisplatin, 16.2% for carboplatin, 17.2% for paclitaxel, and 14.8% for pemetrexed

- Chemotherapy arm: 26.7% for cisplatin, 29.3% for carboplatin, 33.3% for paclitaxel, and 47.3% for pemetrexed

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:

- Nivo+ipi+chemo arm: 10.8% for cisplatin, 25.4% for carboplatin, 16.4% for paclitaxel, and 9.0% for pemetrexed.

- Chemotherapy arm: 12.0% for cisplatin, 27.9% for carboplatin, 22.5% for paclitaxel, and 16.3% for pemetrexed.

AE related to dose delay or dose reduction

In both arms, the most common cause of dose delay for nivolumab, ipilimumab, and chemotherapy was an adverse event. The most frequently reported (≥ 2.5%) all causality AEs of any grade leading to dose delay or reduction were:

- Nivo+ipi+chemo arm: anaemia (7.3%), neutropenia (4.7%), diarrhoea (4.5%), pneumonitis (3.1%), asthenia (3.1%), rash (2.5%) and ALT increased (2.5%).

- Chemotherapy arm: anaemia (13.5%), neutropenia (10.3%), thrombocytopenia (4.9%), platelet count decreased (2.9%), and asthenia (2.6%).

The most frequently reported (≥ 2%) drug-related AEs of any grade leading to dose delay or reduction were:

- Nivo+ipi+chemo arm: anaemia (4.7%), neutropenia (4.7%), diarrhoea (3.6%), pneumonitis (2.8%), and ALT increased (2.5%).

- Chemotherapy arm: anaemia (12.0%), neutropenia (9.5%), thrombocytopenia (4.6%), platelet count decreased (2.9%), and neutrophil count decreased (2.3%).

Table 21: Dose Delay Summary - All Treated Subjects in the Nivolumab + Ipilimumab + Chemotherapy Arm - CA2099LA.

	Nivo+Ipi+Chemo					
	Nivolumab N = 358	Ipilimumab N = 358	Cisplatin N = 74	Carboplatin N = 284	Paclitaxel N = 116	Pemetrexed N = 244
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	200 (55.9)	172 (48.0)	10 (13.5)	46 (16.2)	20 (17.2)	36 (14.8)
NUMBER OF DOSES DELAYED PER SUBJECT (%)						
0	158 (44.1)	186 (52.0)	64 (86.5)	238 (83.8)	96 (82.8)	208 (85.2)
1	123 (34.4)	115 (32.1)	10 (13.5)	46 (16.2)	20 (17.2)	36 (14.8)
2	49 (13.7)	44 (12.3)	0	0	0	0
3	26 (7.3)	12 (3.4)	0	0	0	0
>= 4	2 (0.6)	1 (0.3)	0	0	0	0
TOTAL NUMBER OF DOSES DELAYED /TOTAL NUMBER OF DOSES RECEIVED (%) (A)	308/3226 (9.5)	243/1488 (16.3)	10/69 (14.5)	46/261 (17.6)	20/106 (18.9)	36/226 (15.9)
REASON FOR DOSE DELAY (%) (B)						
ADVERSE EVENT	232 (75.3)	104 (42.8)	9 (90.0)	40 (87.0)	16 (80.0)	33 (91.7)
OTHER	70 (22.7)	39 (16.0)	1 (10.0)	6 (13.0)	4 (20.0)	3 (8.3)
NOT REPORTED (C)	6 (1.9)	100 (41.2)	0	0	0	0
LENGTH OF DOSE DELAY (%) (B)						
4 - 7 DAYS	141 (45.8)	107 (44.0)	5 (50.0)	20 (43.5)	8 (40.0)	17 (47.2)
8 - 14 DAYS	78 (25.3)	66 (27.2)	2 (20.0)	17 (37.0)	8 (40.0)	12 (33.3)
15 - 42 DAYS	79 (25.6)	57 (23.5)	3 (30.0)	8 (17.4)	4 (20.0)	6 (16.7)
> 42 DAYS	10 (3.2)	13 (5.3)	0	1 (2.2)	0	1 (2.8)

A dose was considered as actually delayed if the delay is exceeding 3 days for any given study medication.

(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.

(B) Percentages are computed out of the total number of doses delayed.

(C) Ipilimumab dose delays falling in the NOT REPORTED category included adjustment of ipilimumab dosing schedule to be resynchronized with nivolumab dosing schedule, after prior cycle of nivolumab dose delay (as nivolumab was given every 3 weeks and ipilimumab was given every 6 weeks). This will be sub-categorized in the next database lock

Source: Refer to Table 6.3-1 of the CA2099LA Final CSR[1]

Table 22 Dose Delay Summary - All Treated Subjects in the Chemotherapy Arm - CA2099LA

	Chemo			
	Cisplatin N = 75	Carboplatin N = 280	Paclitaxel N = 111	Pemetrexed N = 239
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	20 (26.7)	82 (29.3)	37 (33.3)	113 (47.3)
NUMBER OF DOSES DELAYED PER SUBJECT (%)				
0	55 (73.3)	198 (70.7)	74 (66.7)	126 (52.7)
1	18 (24.0)	58 (20.7)	29 (26.1)	61 (25.5)
2	2 (2.7)	16 (5.7)	7 (6.3)	31 (13.0)
3	0	8 (2.9)	1 (0.9)	11 (4.6)
>= 4	0	0	0	10 (4.2)
TOTAL NUMBER OF DOSES DELAYED /TOTAL NUMBER OF DOSES RECEIVED (%) (A)	22/174 (12.6)	114/680 (16.8)	46/263 (17.5)	212/1707 (12.4)
REASON FOR DOSE DELAY (%) (B)				
ADVERSE EVENT	19 (86.4)	92 (80.7)	36 (78.3)	143 (67.5)
OTHER	3 (13.6)	22 (19.3)	9 (19.6)	68 (32.1)
NOT REPORTED	0	0	1 (2.2)	1 (0.5)
LENGTH OF DOSE DELAY (%) (B)				
4 - 7 DAYS	13 (59.1)	73 (64.0)	30 (65.2)	135 (63.7)
8 - 14 DAYS	8 (36.4)	33 (28.9)	11 (23.9)	61 (28.8)
15 - 42 DAYS	1 (4.5)	8 (7.0)	5 (10.9)	15 (7.1)
> 42 DAYS	0	0	0	1 (0.5)

A dose was considered as actually delayed if the delay is exceeding 3 days for any given study medication.

(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.

(B) Percentages are computed out of the total number of doses delayed.

Source: Refer to Table 6.3-2 of the CA2099LA Final CSR[1]

Infusion interruptions occurred during nivolumab administration in 21 subjects (5.9%) and ipilimumab administration in 3 subjects (0.8%). In both arms, for the chemotherapy treatment, infusion interruptions occurred most frequently during paclitaxel administration (nivo+ipi+chemo arm: 9 subjects, 7.8%; chemo arm, 7 subjects, 6.3%).

Infusion rate reductions occurred during nivolumab administration in 10 subjects (2.8%) and during ipilimumab administration in 4 subjects (1.1%). In the chemotherapy arm, infusion rate reductions

occurred most frequently during paclitaxel administration (nivo+ipi+chemo arm: 2 subjects, 1.7%; chemo arm, 6 subjects, 5.4%).

Adverse events

The overall frequencies of any-grade AEs and drug-related AEs were similar between the nivo+ipi+chemo and chemotherapy arms; however, the overall frequencies of Grade 3-4 AEs and drug-related AEs were higher with nivo+ipi+chemo compared with chemotherapy (Table 23).

Consistent with the limited cycles of chemotherapy, several toxicities typically related to chemotherapy were less frequently reported with nivo+ipi+chemo relative to chemo (Table 24)

Table 23 Overview of CA2099LA Safety - All Treated Subjects

Safety Parameters	No. of Subjects (%)			
	Nivo + Ipi + Chemo (N = 358)		Chemotherapy (N = 349)	
Deaths	153 (42.7)		191 (54.7)	
Primary Reason for Death				
Disease	124 (34.6)		163 (46.7)	
Study Drug Toxicity [a]	7 (2.0)		6 (1.7)	
Unknown	5 (1.4)		4 (1.1)	
Other [b]	17 (4.7)		17 (4.9)	
Not Reported	0		1 (0.3)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	203 (56.7)	157 (43.9)	144 (41.3)	111 (31.8)
Drug-related SAEs	104 (29.1)	90 (25.1)	61 (17.5)	51 (14.6)
All-causality AEs leading to DC	100 (27.9)	77 (21.5)	59 (16.9)	38 (10.9)
Drug-Related AEs leading to DC	68 (19.0)	54 (15.1)	26 (7.4)	14 (4.0)
All-causality AEs	355 (99.2)	228 (63.7)	341 (97.7)	184 (52.7)

Drug-related AEs	322 (89.9)	159 (44.4)	304 (87.1)	129 (37.0)
≥ 15% of Subjects in Any Treatment Group				
Nausea	94 (26.3)	5 (1.4)	126 (36.1)	3 (0.9)
Anemia	80 (22.3)	20 (5.6)	130 (37.2)	48 (13.8)
Asthenia	73 (20.4)	3 (0.8)	61 (17.5)	8 (2.3)
Diarrhea	73 (20.4)	14 (3.9)	42 (12.0)	4 (1.1)
Pruritus	66 (18.4)	3 (0.8)	4 (1.1)	0
Rash	64 (17.9)	5 (1.4)	10 (2.9)	0
Fatigue	59 (16.5)	8 (2.2)	37 (10.6)	2 (0.6)
Decreased Appetite	56 (15.6)	4 (1.1)	53 (15.2)	4 (1.1)
Neutropenia	35 (9.8)	22 (6.1)	58 (16.6)	31 (8.9)
All-causality Select AEs				
Endocrine	96 (26.8)	12 (3.4)	20 (5.7)	0
Gastrointestinal	111 (31.0)	20 (5.6)	64 (18.3)	6 (1.7)
Hepatic	66 (18.4)	17 (4.7)	38 (10.9)	6 (1.7)
Pulmonary	24 (6.7)	7 (2.0)	9 (2.6)	6 (1.7)
Renal	37 (10.3)	10 (2.8)	28 (8.0)	5 (1.4)
Skin	143 (39.9)	17 (4.7)	40 (11.5)	2 (0.6)
Hypersensitivity/Infusion Reactions	22 (6.1)	2 (0.6)	4 (1.1)	2 (0.6)
Drug-Related Select AEs				
Endocrine	86 (24.0)	10 (2.8)	1 (0.3)	0
Gastrointestinal	80 (22.3)	19 (5.3)	42 (12.0)	4 (1.1)
Hepatic	48 (13.4)	16 (4.5)	26 (7.4)	3 (0.9)
Pulmonary	19 (5.3)	6 (1.7)	4 (1.1)	1 (0.3)
Renal	25 (7.0)	8 (2.2)	20 (5.7)	4 (1.1)
Skin	135 (37.7)	16 (4.5)	24 (6.9)	1 (0.3)
Hypersensitivity/Infusion Reactions	17 (4.7)	2 (0.6)	4 (1.1)	2 (0.6)
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Diarrhea/Colitis	17 (4.7)	10 (2.8)	0	0
Hepatitis	18 (5.0)	15 (4.2)	0	0
Pneumonitis	18 (5.0)	9 (2.5)	0	0
Nephritis/Renal Dysfunction	5 (1.4)	2 (0.6)	0	0
Rash	50 (14.0)	13 (3.6)	1 (0.3)	1 (0.3)
Hypersensitivity/Infusion Reactions	2 (0.6)	0	0	0

Table 23 (Continued): Overview of CA2099LA Safety - All Treated Subjects

Safety Parameters	No. of Subjects (%)			
	Nivo + Ipi + Chemo (N = 358)		Chemotherapy (N = 349)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Adrenal Insufficiency	12 (3.4)	5 (1.4)	1 (0.3)	0
Hypophysitis	8 (2.2)	5 (1.4)	0	0
Hypothyroidism/Thyroiditis	53 (14.8)	2 (0.6)	3 (0.9)	0
Hyperthyroidism	27 (7.5)	0	0	0
Diabetes Mellitus	0	0	0	0
All-causality OESIs within 100 days of last dose				
With or Without Immune Modulating Medication				
Pancreatitis	5 (1.4)	3 (0.8)	0	0
Encephalitis	2 (0.6)	1 (0.3)	0	0
Myositis	0	0	1 (0.3)	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0
Uveitis	0	0	0	0
Myocarditis	0	0	0	0
Rhabdomyolysis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

[a] The causes of death per investigator were as follows: in the **nivo+ipi+chemo arm**: 2 deaths were due to nivolumab + ipilimumab (pneumonitis, hepatitis), 1 death was due to ipilimumab (diarrhea), 1 death was due to ipilimumab + chemotherapy (sepsis), 1 death was due to nivo+ipi+chemo (hepatic toxicity), and 2 deaths were due to chemotherapy (acute renal failure, thrombocytopenia) and in the **chemotherapy arm**: sepsis (2 subjects), anemia, pancytopenia, respiratory failure, and neutropenia.

[b] The verbatim terms reported for the 'other' reasons for death are provided in Sections 2.2.2, and were consistent with events expected in the population under study.

Abbreviations: AE - adverse event; DC: discontinuation; IMAE - immune-mediated adverse event; OESI - other event of special interest; SAE - serious adverse event

Source: Refer to Table 8.1-1. of the CA2099LA Final CSR[1]

Table 24 Select Chemotherapy-related Toxicities, All Nivolumab + Ipilimumab + Chemotherapy and Chemotherapy Treated Subjects in CA2099LA

Drug-Related Adverse Events	Nivo + Ipi + Chemo (N = 358)		Chemo (N = 349)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Anemia, n (%)	80 (22.3)	20 (5.6)	130 (37.2)	48 (13.8)
Neutropenia, n (%)	35 (9.8)	22 (6.1)	58 (16.6)	31 (8.9)
Alopecia, n (%)	32 (8.9)	3 (0.8)	31 (8.9)	2 (0.6)
Thrombocytopenia, n (%)	17 (4.7)	10 (2.8)	34 (9.7)	8 (2.3)
Mucosal inflammation, n (%)	15 (4.2)	2 (0.6)	8 (2.3)	1 (0.3)
Febrile Neutropenia, n (%)	14 (3.9)	14 (3.9)	11 (3.2)	10 (2.9)
Neuropathy peripheral, n (%)	9 (2.5)	0	13 (3.7)	1 (0.3)
Pancytopenia, n (%)	2 (0.6)	1 (0.3)	5 (1.4)	5 (1.4)

MedDRA Version: 22.0. CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.1-2 of the CA2099LA Final CSR[1]

Any-grade AEs (regardless of causality) were reported in 355 (99.2%) subjects in the nivo+ipi+chemo arm, and 341 (97.7%) subjects in the chemotherapy arms (Table 25).

When incidence rates were exposure-adjusted, AE incidence rates (per 100 person-years) were 1770.8 with nivo+ipi+chemo treatment and 1935.6 with chemotherapy treatment (Table 26).

Table 25: Adverse Events by Worst CTC Grade in ≥ 10% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo+Ipi+Chemo N = 358			Chemo N = 349		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	355 (99.2)	228 (63.7)	21 (5.9)	341 (97.7)	184 (52.7)	21 (6.0)
General disorders and administration site conditions	253 (70.7)	33 (9.2)	2 (0.6)	192 (55.0)	28 (8.0)	1 (0.3)
Asthenia	102 (28.5)	10 (2.8)	0	88 (25.2)	14 (4.0)	0
Fatigue	77 (21.5)	9 (2.5)	0	55 (15.8)	3 (0.9)	0
Pyrexia	49 (13.7)	2 (0.6)	0	35 (10.0)	2 (0.6)	0
Gastrointestinal disorders	246 (68.7)	38 (10.6)	1 (0.3)	218 (62.5)	25 (7.2)	0
Nausea	114 (31.8)	6 (1.7)	0	144 (41.3)	3 (0.9)	0
Diarrhoea	105 (29.3)	15 (4.2)	1 (0.3)	64 (18.3)	6 (1.7)	0
Constipation	76 (21.2)	2 (0.6)	0	79 (22.6)	2 (0.6)	0
Vomiting	64 (17.9)	7 (2.0)	0	60 (17.2)	5 (1.4)	0
Metabolism and nutrition disorders	184 (51.4)	47 (13.1)	0	137 (39.3)	26 (7.4)	0
Decreased appetite	101 (28.2)	7 (2.0)	0	76 (21.8)	6 (1.7)	0
Skin and subcutaneous tissue disorders	182 (50.8)	23 (6.4)	0	80 (22.9)	5 (1.4)	0
Pruritus	72 (20.1)	3 (0.8)	0	8 (2.3)	0	0
Rash	66 (18.4)	5 (1.4)	0	14 (4.0)	0	0
Alopecia	41 (11.5)	3 (0.8)	0	34 (9.7)	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	168 (46.9)	41 (11.5)	4 (1.1)	124 (35.5)	25 (7.2)	4 (1.1)
Dyspnoea	59 (16.5)	17 (4.7)	0	46 (13.2)	11 (3.2)	0
Cough	55 (15.4)	1 (0.3)	0	39 (11.2)	3 (0.9)	0
Blood and lymphatic system disorders	148 (41.3)	57 (15.9)	0	203 (58.2)	96 (27.5)	0
Anaemia	115 (32.1)	28 (7.8)	0	157 (45.0)	59 (16.9)	0

	Nivo+ipi+chemo			Chemotherapy		
Neutropenia	38 (10.6)	23 (6.4)	0	61 (17.5)	33 (9.5)	0
Thrombocytopenia	20 (5.6)	11 (3.1)	0	38 (10.9)	11 (3.2)	0
Musculoskeletal and connective tissue disorders	146 (40.8)	16 (4.5)	0	103 (29.5)	9 (2.6)	0
Arthralgia	47 (13.1)	1 (0.3)	0	25 (7.2)	1 (0.3)	0
Back pain	43 (12.0)	5 (1.4)	0	30 (8.6)	1 (0.3)	0
Nervous system disorders	120 (33.5)	11 (3.1)	0	113 (32.4)	9 (2.6)	0
Headache	39 (10.9)	2 (0.6)	0	25 (7.2)	0	0
Endocrine disorders	84 (23.5)	12 (3.4)	0	16 (4.6)	0	0
Hypothyroidism	55 (15.4)	1 (0.3)	0	11 (3.2)	0	0

MedDRA Version: 22.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 6.1.31.1

Any-grade drug-related AEs were reported in 322 (89.9%) subjects in the nivo+ipi+chemo arm, and 304 (87.1%) subjects in the chemotherapy arm.

The most frequently reported drug-related AEs (≥15%) were:

- Nivo+ipi+chemo: nausea (26.3%), anaemia (22.3%), asthenia (20.4%), diarrhoea (20.4%), pruritus (18.4%), rash (17.9%), and fatigue (16.5%).

- Chemotherapy: anaemia (37.2%), nausea (36.1%), asthenia (17.5%), neutropenia (16.6%), and decreased appetite (15.2%).

Grade 3-4 drug-related AEs were reported in 159 (44.4%) subjects in the nivo+ipi+chemo arm, and 129 (37.0%) subjects in the chemotherapy arm.

The most frequently reported Grade 3-4 drug-related AEs (≥2%) were:

- Nivo+ipi+chemo: neutropenia (6.1%), anaemia (5.6%), diarrhoea (3.9%), and lipase increased (3.6%).

- Chemotherapy: anaemia (13.8%), neutropenia (8.9%), asthenia (2.3%), and thrombocytopenia (2.3%).

When incidence rates were exposure-adjusted, drug-related AE incidence rates (per 100 person years) were 866.6 with nivo+ipi+chemo treatment and 1013.2 with chemotherapy treatment (Table 26).

Table 26 Exposure-adjusted Adverse Events Rates

	Exposure Adjusted Rates per 100 person-years	
Safety Parameters	Nivo+Ipi+Chemo (N = 358)	Chemotherapy (N = 349)
Serious Adverse Events (SAEs)	172.0	166.3
Drug-Related SAEs	73.5	63.2
Adverse Events (AEs) Leading to Discontinuation	62.6	53.6
Drug-Related AEs Leading to Discontinuation	41.7	24.1
All AEs	1770.8	1935.6
Drug-Related AEs	866.6	1013.2

Source: Table 6.142.2 (SAEs), Table 6.142.3 (drug-related SAEs), Table 6.142.4 (AEs leading to discontinuation), Table 6.142.5 (drug-related AEs leading to discontinuation), Table 6.26.1 (AEs), and Table 6.142.1 (drug-related AEs) of the CA2099LA Final CSR[1]

Serious adverse event/deaths/other significant events

The overall frequencies of SAEs (all causality, drug-related, Grade 3-4) were higher with nivo+ipi+chemo than with chemotherapy alone (Table 23 and Table 27).

A higher frequency of all causality SAEs with nivo+ipi+chemo relative to chemotherapy alone were reported in all SOCs (except for blood and lymphatic systems disorders, refer to Table 27)

A higher frequency of drug-related SAEs with nivo+ipi+chemo relative to chemotherapy alone were reported in the following SOCs (GI disorders (7.3% vs 2.6%), endocrine disorders (3.1% vs 0%), and hepatobiliary disorders (2.5% vs 0%)) (Table 27)

Table 27 Serious Adverse Events Reported in ≥ 2% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo+Ipi+Chemo N = 358			Chemo N = 349		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	203 (56.7)	157 (43.9)	21 (5.9)	144 (41.3)	111 (31.8)	21 (6.0)
Infections and infestations	47 (13.1)	35 (9.8)	0	39 (11.2)	28 (8.0)	3 (0.9)
Pneumonia	16 (4.5)	10 (2.8)	0	16 (4.6)	12 (3.4)	2 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38 (10.6)	24 (6.7)	12 (3.4)	31 (8.9)	20 (5.7)	9 (2.6)
Malignant neoplasm progression	28 (7.8)	17 (4.7)	10 (2.8)	29 (8.3)	19 (5.4)	9 (2.6)
Respiratory, thoracic and mediastinal disorders	38 (10.6)	28 (7.8)	4 (1.1)	26 (7.4)	16 (4.6)	4 (1.1)
Dyspnoea	8 (2.2)	8 (2.2)	0	7 (2.0)	5 (1.4)	0
Pneumonitis	7 (2.0)	4 (1.1)	0	4 (1.1)	2 (0.6)	0
Respiratory failure	7 (2.0)	5 (1.4)	2 (0.6)	1 (0.3)	0	1 (0.3)
Gastrointestinal disorders	35 (9.8)	24 (6.7)	1 (0.3)	19 (5.4)	15 (4.3)	0
Diarrhoea	13 (3.6)	7 (2.0)	1 (0.3)	2 (0.6)	2 (0.6)	0
Blood and lymphatic system disorders	28 (7.8)	26 (7.3)	0	34 (9.7)	31 (8.9)	0
Anaemia	11 (3.1)	9 (2.5)	0	14 (4.0)	13 (3.7)	0
Febrile neutropenia	11 (3.1)	11 (3.1)	0	9 (2.6)	8 (2.3)	0
Thrombocytopenia	3 (0.8)	3 (0.8)	0	7 (2.0)	5 (1.4)	0

MedDRA Version: 22.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 6.3.1.2.1

Any-grade drug-related SAEs were reported in 104 (29.1%) subjects in the nivo+ipi+chemo arm, and 61 (17.5%) subjects in the chemotherapy arm. **Grade 3-4 drug-related SAEs** were reported in 90 (25.1%) subjects in the nivo+ipi+chemo arm and 51 (14.6%) subjects in the chemotherapy arm (Table 23).

The most frequently reported drug-related SAEs were as follows:

- Nivo+ipi+chemo: diarrhea (3.1%), febrile neutropenia (3.1%), anemia (2.2%), acute kidney injury (1.7%), colitis (1.4%), and adrenal insufficiency (1.4%)

- Chemotherapy: anaemia (3.4%), febrile neutropenia (2.6%), thrombocytopenia (1.7%), and pancytopenia (1.4%)

Death

As of the 03-Oct-2019 database lock, 42.7% subjects in the nivo+ipi+chemo arm and 54.7% of subjects in the chemotherapy arm died (Table 28).

Table 28: Death Summary - All Treated Subjects

	Nivo+Ipi+Chemo N = 358	Chemo N = 349
NUMBER OF SUBJECTS WHO DIED (%)	153 (42.7)	191 (54.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	124 (34.6)	163 (46.7)
STUDY DRUG TOXICITY	7 (2.0)	6 (1.7)
UNKNOWN	5 (1.4)	4 (1.1)
OTHER	17 (4.7)	17 (4.9)
NOT REPORTED	0	1 (0.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	40 (11.2)	42 (12.0)
PRIMARY REASON FOR DEATH (%)		
DISEASE	30 (8.4)	28 (8.0)
STUDY DRUG TOXICITY	4 (1.1)	6 (1.7)
UNKNOWN	2 (0.6)	1 (0.3)
OTHER	4 (1.1)	7 (2.0)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	97 (27.1)	101 (28.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	73 (20.4)	80 (22.9)
STUDY DRUG TOXICITY	7 (2.0)	6 (1.7)
UNKNOWN	4 (1.1)	2 (0.6)
OTHER	13 (3.6)	12 (3.4)
NOT REPORTED	0	1 (0.3)

Of these deaths, a total of 13 were considered due to study drug toxicity.

- 7 subjects (2.0%) in the nivo+ipi+chemo group died due to acute kidney injury (chemo), thrombocytopenia (chemo), pneumonitis (nivo+ipi), hepatic toxicity (nivo+ipi+chemo), hepatitis (nivo+ipi), diarrhoea (ipi) and sepsis (ipi+chemo).

- 6 subjects (1.7%) in the chemotherapy group due to sepsis, anaemia, pancytopenia, respiratory failure, pulmonary sepsis and febrile neutropenia.

Death attributed to other reasons occurred in 17 subjects (4.7%) and 17 subjects (4.9%) in the nivo+ipi+chemo arm and chemotherapy arm, respectively.

Select adverse events

Select AEs are AEs of special clinical interest that are potentially associated with the use of nivolumab + ipilimumab and nivolumab. Adverse events including endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively. Hypersensitivity/infusion reactions were analysed along with the select AE categories.

Most of select AEs were Grade 1-2 and most were considered drug-related by the investigator.

Table 29 Overview of Select adverse event- all cause and drug related- Treated population study CA2099LA

Safety Parameters	No. of Subjects (%)			
	Nivo + Ipi + Chemo (N = 358)		Chemotherapy (N = 349)	
All-causality Select AEs				
Endocrine	96 (26.8)	12 (3.4)	20 (5.7)	0
Gastrointestinal	111 (31.0)	20 (5.6)	64 (18.3)	6 (1.7)
Hepatic	66 (18.4)	17 (4.7)	38 (10.9)	6 (1.7)
Pulmonary	24 (6.7)	7 (2.0)	9 (2.6)	6 (1.7)
Renal	37 (10.3)	10 (2.8)	28 (8.0)	5 (1.4)
Skin	143 (39.9)	17 (4.7)	40 (11.5)	2 (0.6)
Hypersensitivity/Infusion Reactions	22 (6.1)	2 (0.6)	4 (1.1)	2 (0.6)
Drug-Related Select AEs				
Endocrine	86 (24.0)	10 (2.8)	1 (0.3)	0
Gastrointestinal	80 (22.3)	19 (5.3)	42 (12.0)	4 (1.1)
Hepatic	48 (13.4)	16 (4.5)	26 (7.4)	3 (0.9)
Pulmonary	19 (5.3)	6 (1.7)	4 (1.1)	1 (0.3)
Renal	25 (7.0)	8 (2.2)	20 (5.7)	4 (1.1)
Skin	135 (37.7)	16 (4.5)	24 (6.9)	1 (0.3)
Hypersensitivity/Infusion Reactions	17 (4.7)	2 (0.6)	4 (1.1)	2 (0.6)

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

- Nivo+ipi+chemo: diarrhoea (3.1%), pneumonitis (2.0%), acute kidney injury (1.7%), and adrenal insufficiency (1.4%)

- Chemotherapy: acute kidney injury (1.1%).

The incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), and 0.6% (2/358) of patients, respectively. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9+).

The incidence of diarrhoea or colitis was 22.3% (80/358). Grade 2, Grade 3, Grade 4, and Grade 5 cases were reported in 7% (25/358), 5% (18/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.1-53.6). Resolution occurred in 70 patients (87.5%) with a median time to resolution of 1.4 weeks (range: 0.1-76.9+)

The incidence of liver function test abnormalities was 13.4% (48/358). Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. Median time to onset was 10.6 weeks (range: 1.1-68.3). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3+-45.0+).

The incidence of nephritis or renal dysfunction was 7% (25/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6 (2/358) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-51.3). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1+-82.9+).

The incidence of thyroid disorders was 24% (86/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. Median time to onset of these endocrinopathies was 12.1 weeks (range: 1.9-58.3). Resolution occurred in 30 patients (35.3%). Time to resolution ranged from 1.4 to 72.4+ weeks.

The incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 3.3 weeks (range: 0.1-83.1). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1+-84.1+).

The incidence of hypersensitivity/infusion reactions was 4.7% (17/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively (see section 4.8 of the SmPC).

Across the select AE categories, most events in the nivo+ipi+chemo arm were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic corticosteroids) were administered (Table 30).
Some endocrine select AEs, though well controlled with hormone replacement therapy, were not considered resolved due to the continuing need for hormone replacement therapy.

Table 30: Onset, Management, and Resolution of Drug-Related Select AEs - Nivolumab + Ipilimumab + Chemotherapy Treated Subjects (N = 358) - CA2099LA

Table 2.6-1:   Onset, Management, and Resolution of Drug-Related Select AEs - Nivolumab + Ipilimumab + Chemotherapy Treated Subjects (N = 358) - CA2099LA

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 Time[b] to Resolution of Drug-related Select AE (range), wks[c,d,e]	% Subj. with Drug-related Select AE that Resolved [d,e]
Endocrine	24.0 / 2.8	12.14 (1.9 - 58.3)	2.0	20.9 / 8.1	N.A. (1.4 - 72.4+)	35.3
Gastrointestinal	22.3 / 5.3	5.07 (0.1 - 53.9)	4.2	23.8 / 20.0	1.43 (0.1 - 76.9+)	87.5
Hepatic	13.4 / 4.5	10.64 (1.1 - 68.3)	3.4	33.3 / 29.2	5.0 (0.3+ - 45.0+)	80.4
Pulmonary	5.3 / 1.7	18.14 (0.6 - 52.4)	2.2	73.7 / 68.4	4.29 (0.7 - 27.9+)	73.7
Renal	7.0 / 2.2	10.57 (0.1 - 51.3)	1.4	24.0 / 24.0	6.29 (0.1+ - 82.9+)	56.0
Skin	37.7 / 4.5	3.29 (0.1 - 83.1)	1.1	45.2 / 10.4	9.43 (0.1+ - 84.1+)	71.6
Hypersensitivity/ Infusion Reaction	4.7 / 0.6	3.14 (0.1 - 10.9)	0.6	35.3 / 29.4	0.14 (0.1 - 8.9)	100

[a] Denominator is based on the number of subjects who experienced the event.
[b] From Kaplan-Meier estimation
[c] Symbol + 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
Source: Source: Refer to Table 8.7-1 of the CA2099LA Final CSR[1]

Other Events of Special Interest

Other events of special interest (OESIs) (regardless of causality or immune-modulating medication [IMM] treatment) include the following categories: Pancreatitis, Encephalitis, Myositis, Myasthenic Syndrome, Demyelination, Guillain-Barre Syndrome, Uveitis, Myocarditis, Rhabdomyolysis, Graft versus Host Disease.

OESIs were infrequent in both treatment arms. Overall, OESIs were reported in 7/358 (2.0%) subjects in the nivo+ipi+chemo arm and 1/349 (0.3%) subject in the chemotherapy arm:

- OESIs in the nivo+ipi+chemo arm were: pancreatitis (5 subjects, 4 drug-related, 4 resolved with IMM treatment) and encephalitis (2 subjects, 1 drug-related, 1 resolved with IMM treatment).

- OESI in the chemotherapy arm was: Myositis (1 subject, unrelated, resolved without treatment)

Laboratory findings

Laboratory measurements were recorded regardless of causality and some were correlated with reported laboratory-based AEs.

Laboratory results 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+chemo or chemotherapy in CA2099LA.

Haematology

Abnormalities in hematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2.

On-treatment worsening of haematology parameters to Grade 3-4 was generally similar between nivo+ipi+chemo and chemotherapy (Table 31).

Table 31 Summary of On-Treatment Worst CTC Grade Hematology Tests That Worsened Relative to Baseline (SI Units) - Treated Subjects - CA2099LA

| | Number of Subjects (%) | | | | | |
| | Nivo+ipi+chemo | | | Chemotherapy | | |
Lab Test Description	N(A)	Grade 1-4	Grade 3-4	N(A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	347	243 (70.0)	32 (9.2)	335	248 (74.0)	55 (16.4)
PLATELET COUNT	347	80 (23.1)	15 (4.3)	334	81 (24.3)	17 (5.1)
LEUKOCYTES	347	126 (36.3)	34 (9.8)	335	134 (40.0)	30 (9.0)
LYMPHOCYTES (ABSOLUTE),	257	105 (40.9)	15 (5.8)	240	95 (39.6)	26 (10.8)
ABSOLUTE NEUTROPHIL COUNT	346	140 (40.5)	51 (14.7)	332	139 (41.9)	49 (14.8)

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.
Source: Appendix L.7b.USPI.3 (SI)

Liver test

During the treatment period, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2. A total of 3/346 (0.9%) subjects in the nivo+ipi+chemo arm and no subjects in the chemotherapy arm had concurrent ALT or AST > 3 x upper limit of normal (ULN) with total bilirubin > 2 x 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

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.

- Nivo+ipi+chemo: increased ALT (4.3%), increased AST (3.5%), and increased alkaline phosphatase (ALP) (1.2%).

- Chemotherapy: increased ALT (1.2%).

Kidney test

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. 4 subjects in the nivo+ipi+chemo arm and 2 subjects 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 1.2% and 0.6% in the nivo+ipi+chemo and chemotherapy arms, respectively.

Thyroid function test

Table 32 On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - Treated Subjects - CA2099LA

	Number of Subjects (%)	
	Nivo+ipi+chemo	Chemotherapy
Abnormality (%)	N = 314	N = 276
TSH > ULN	105 (33.4)	32 (11.6)
TSH > ULN WITH TSH <= ULN AT BASELINE	82 (26.1)	13 (4.7)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	65 (20.7)	5 (1.8)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	28 (8.9)	23 (8.3)
WITH FT3/FT4 TEST MISSING (A) (B)	12 (3.8)	4 (1.4)
TSH < LLN	90 (28.7)	34 (12.3)
TSH < LLN WITH TSH >= LLN AT BASELINE	80 (25.5)	24 (8.7)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	48 (15.3)	4 (1.4)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	31 (9.9)	26 (9.4)
WITH FT3/FT4 TEST MISSING (A) (B)	11 (3.5)	4 (1.4)

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

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

(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.

Source: Refer to Table 8.10.2.3-1 of CA2099LA Final CSR[1]

Pancreas function test

Abnormalities in amylase and lipase during treatment were primarily Grade 1 to 2 in severity. The following Grade 3 abnormalities in amylase and lipase were observed in ≥ 5% of treated subjects with on-treatment laboratory results:

- Nivo+ipi+chemo: lipase (10.0% Grade 3) and amylase (7.2% Grade 3)

- Chemotherapy: none

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 as follows

- Nivo+ipi+chemo: lipase (11.9%) and amylase (6.7%)

- Chemotherapy: lipase (2.2%) and amylase (1.3%)

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+chemo: hyponatremia (12.1% Grade 3)

- Chemotherapy: hyponatremia (7.5% Grade 3)

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+chemo: hyponatremia (10.7%) and hypokalaemia (3.5%)

- Chemotherapy: hyponatremia (6.9%) and hyperkalaemia (2.7%)

Selected Laboratory Abnormalities that Worsened Relative to Baseline

In CA2099LA, laboratory abnormalities that worsened relative to baseline in ≥20% of nivo+ipi+chemo treated subjects are presented in Table 33.

Table 33 Selected Laboratory Abnormalities (US Units) Worsening from Baseline in more than or equal to 20% of Nivolumab + Ipilimumab + Chemotherapy treated Subjects - CA2099LA.

| Laboratory Abnormality | Percentage of Subjects with Worsening Laboratory Test from Baseline[a] | | | |
| | Niv+ipi+chemo | | Chemotherapy | |
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Anemia	70.0	9.2	74.0	16.4
Lymphopenia	40.9	5.8	39.6	10.8
Neutropenia	40.5	14.7	41.9	14.8
Leukopenia	36.3	9.8	40.0	9.0
Thrombocytopenia	23.1	4.3	24.3	5.1
Chemistry				
Hyperglycemia	45.2	7.1	42.4	2.6
Hyponatremia	37.4	10.4	26.9	6.9
Increased ALT	34.2	4.3	24.3	1.2
Increased lipase	31.2	11.9	10.3	2.2
Increased alkaline phosphatase	31.0	1.2	25.9	0.3
Increased amylase	30.4	6.7	18.8	1.3
Increased AST	29.6	3.5	22.1	0.3
Hypomagnesemia	29.3	1.2	32.8	0.6
Hypocalcemia	26.4	1.4	22.2	1.8
Increased creatinine	26.3	1.2	22.8	0.6
Hyperkalemia	22.0	1.7	21.3	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Niv+ipi+chemo (range: 197 to 347); Chemotherapy (range: 191 to 335).

Source: Appendix L.7b.USPI.1 (US)

Safety in special populations

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 in Table 34 for nivo+ipi+chemo and chemotherapy treated subjects.

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 a few exceptions:

- Nivo+ipi+chemo:
  - Numerically higher frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs the overall population for SAEs with fatal (death) outcome (29.7% vs 12.8%) and AEs leading to discontinuation (43.2% vs 27.9%).
  - Numerically lower frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs the overall population for psychiatric disorders (2.7% vs 16.5%), nervous system disorders (16.2% vs 33.5%), and anticholinergic syndrome (18.9% vs 31.0%).

- Chemotherapy:
  - A numerically higher frequency (≥10% difference) was reported in the 75 to 84 years of age subgroup vs the overall population for SAEs with fatal (death) outcome (26.7% vs 14.3%). A similar increase in SAEs with fatal (death) outcome in subjects 75 to 84 years of age over the overall population was observed, regardless of treatment.

Table 34   Summary of safety results by age groups – Treated Subjects - CA2099LA

	Age Groups					
	Nivo+ipi+chemo			**Chemotherapy**		
	<65 n=174	**65-74** n=147	**75-84** n=37	**<65** n=174	**65-74** n=143	**75-84** n=30
Patients with events	**172 (98.9)**	**146 (99.3)**	**37 (100.0)**	**170 (97.7)**	**139 (97.2)**	**30 (100.0)**
SAE	**103 (59.2)**	**77 (52.4)**	**23 (62.2)**	**68 (39.1)**	**60 (42.0)**	**15 (50.0)**
Fatal	21 (12.1)	14 (9.5)	11 (29.7)	24 (13.8)	18 (12.6)	8 (26.7)
Hospitalisation /prolongation	89 (51.1)	66 (44.9)	19 (51.4)	64 (36.8)	57 (39.9)	13 (43.3)
life threatening	18 (10.3)	18 (12.2)	5 (13.5)	8 (4.6)	15 (10.5)	3 (10.0)
Ae leading to discontinuation	**44 (25.3)**	**40 (27.2)**	**16 (43.2)**	**23 (13.2)**	**31 (21.7)**	**5 (16.7)**

From Patients aged > 85 not reported due to the low numbers included (N+I +C n=0; chemo n=2)
Source: table 5.1.1-1 from safety summary.

Discontinuation due to adverse events

AEs leading to discontinuation included events where 1 or more drugs of a multidrug regimen were discontinued, even if the subject remained on treatment. The overall frequencies of all causality AEs leading to discontinuation were higher in the nivo+ipi+chemo arm relative to the chemotherapy arm (Table 23).

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 100 (27.9%) subjects in the nivo+ipi+chemo arm and 59 (16.9%) subjects in the chemotherapy arm. Grade 3-4 AEs leading to discontinuation were reported in 77 (21.5%) subjects in the nivo+ipi+chemo arm and 38 (10.9%) subjects in the chemotherapy arm.

The most common AEs leading to discontinuation (regardless of causality) were as follows:

- Nivo+ipi+chemo: malignant neoplasm progression (3.6%), diarrhoea (2.5%), pneumonitis (2.0%), and colitis (1.4%)

- Chemotherapy: malignant neoplasm progression (3.4%), general physical health deterioration (1.4%), and anaemia (1.1%)

Any-grade drug-related AEs leading to discontinuation were reported in 68 (19.0%) subjects in the nivo+ipi+chemo arm and 26 (7.4%) subjects in the chemotherapy arm. Grade 3-4 AEs leading to discontinuation were reported in 54 (15.1%) subjects in the nivo+ipi+chemo arm and 14 (4.0%) subjects in the chemotherapy arm.

The most common drug-related AEs leading to discontinuation were as follows:

- Nivo+ipi+chemo: diarrhoea (2.5%), pneumonitis (2.0%), colitis (1.4%), hepatotoxicity (0.8%), adrenal insufficiency (0.8%), acute kidney injury (0.8%), and ALT increased (0.8%)

- Chemotherapy: anaemia (0.9%)

<u>Immunogenicity</u>

Of the 308 nivolumab ADA evaluable subjects in the nivo+ipi+chemo arm, 19 (6.2%) subjects were nivolumab ADA positive at baseline and 104 (33.8%) subjects were nivolumab ADA positive after the start of treatment (Table 35).

Of the 305 ipilimumab ADA evaluable subjects in the nivo+ipi+chemo arm, 9 (3.0%) subjects were ipilimumab ADA positive at baseline and 23 (7.5%) subjects were ipilimumab ADA positive after the start of treatment (Table 35).

Table 35 ADA Assessments Summary - All ADA Evaluable Subjects - CA2099LA

```
-------------------------------------------------------------------------
                                        Nivo+Ipi+Chemo
                            ---------------------------------------------
                              Nivolumab ADA            Ipilimmab ADA
Subject ADA Status (%)          N = 308                  N = 305
-------------------------------------------------------------------------
BASELINE ADA POSITIVE          19 (  6.2)                9 (  3.0)

ADA POSITIVE                  104 ( 33.8)               23 (  7.5)

  PERSISTENT POSITIVE (PP)      1 (  0.3)                0
  NOT PP - LAST SAMPLE POSITIVE 31 ( 10.1)               8 (  2.6)
  OTHER POSITIVE               72 ( 23.4)               15 (  4.9)

  NEUTRALIZING ADA POSITIVE     8 (  2.6)                5 (  1.6)

ADA NEGATIVE                  204 ( 66.2)              282 ( 92.5)
-------------------------------------------------------------------------
```

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: Refer to Table 11.1-1 of the CA2099LA Final CSR[1]

Of all the nivo+ipi+chemo treated subjects who were evaluable for ADA, hypersensitivity/infusion reaction select AEs were experienced by 16 (7.8%) nivolumab ADA-negative subjects, 5 (4.8%) nivolumab ADA-positive subjects, 20 (7.1%) ipilimumab ADA-negative subjects and 2 (8.7%) ipilimumab ADA-positive subjects.

Supportive Safety Data – study CA209568 Part 2

In Part 2 of CA209568, all subjects were treated with nivo+ipi+chemo, the same schedule and regimen as that used in CA2099LA. Median treatment duration was 6.36 months. The population in CA209568 Part 2 was the same as that in CA2099LA. Safety data from the CA209568 Part 2 Final CSR2 based on the DBL date of 22-Mar-2019, with a minimum follow-up of 14.9 months are summarized in Table 36.

Table 36 Overview of CA209568 (Part 2) Safety - All Treated Subjects

```
----------------------------------------------------------------------------
                                              All Treated
                                                 N = 36
----------------------------------------------------------------------------
DEATHS
NUMBER OF SUBJECTS WHO DIED (%)                  16 (44.4)
  PRIMARY REASON FOR DEATH (%)
    DISEASE                                       9 (25.0)
    STUDY DRUG TOXICITY                           0
    UNKNOWN                                        1 (2.8)
    OTHER                                          6 (16.7)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)    4 (11.1)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)  12 (33.3)
----------------------------------------------------------------------------
```

Preferred Term (%)	Any Grade	Grade 3-4	Grade 5 (A)
ALL CAUSALITY SAEs (%)	26 (72.2)	20 (55.6)	3 (8.3)
DRUG-RELATED SAEs (%)	13 (36.1)	12 (33.3)	0
ALL CAUSALITY AEs LEADING TO DISCONTINUATION (%)	11 (30.6)	8 (22.2)	2 (5.6)
DRUG-RELATED AEs LEADING TO DISCONTINUATION (%)	8 (22.2)	7 (19.4)	0
ALL CAUSALITY AEs	36 (100.0)	28 (77.8)	3 (8.3)
AEs (≥25% ANY GRADE)			
Pruritus	15 (41.7)	0	0
Rash	10 (27.8)	2 (5.6)	0
Nausea	16 (44.4)	0	0
Constipation	14 (38.9)	0	0
Diarrhoea	14 (38.9)	1 (2.8)	0
Fatigue	20 (55.6)	0	0
Cough	9 (25.0)	0	0
Arthralgia	12 (33.3)	2 (5.6)	0
Decreased appetite	9 (25.0)	0	0
Hypomagnesaemia	9 (25.0)	0	0
Anaemia	12 (33.3)	4 (11.1)	0
DRUG-RELATED AEs	33 (91.7)	21 (58.3)	0
Drug-related AEs (≥15% ANY GRADE)			
Pruritus	11 (30.6)	0	0
Rash	8 (22.2)	1 (2.8)	0
Rash maculo-papular	6 (16.7)	1 (2.8)	0
Diarrhoea	7 (19.4)	0	0
Nausea	7 (19.4)	0	0
Lipase increased	6 (16.7)	6 (16.7)	0
Fatigue	10 (27.8)	0	0
Hypothyroidism	6 (16.7)	1 (2.8)	0
Anaemia	7 (19.4)	2 (5.6)	0
ALL CAUSALITY IMAEs WITHIN 100 DAY OF LAST DOSE, BY CATEGORY, TREATED WITH IMMUNE MODULATING MEDICATION			
Pneumonitis	3 (8.3)	2 (5.6)	0
Diarrhea/Colitis	7 (19.4)	1 (2.8)	0
Hepatitis	0	0	0
Adrenal insufficiency	4 (11.1)	2 (5.6)	0
Hypothyroidism	0	0	0
Thyroiditis	0	0	0
Diabetes mellitus	0	0	0
Nephritis and Renal dysfunction	1 (2.8)	1 (2.8)	0
Rash	8 (22.2)	2 (5.6)	0
Hypersensitivity	0	0	0
Hyperthyroidism	0	0	0
Hypophysitis	0	0	0
ALL CAUSALITY ENDOCRINE IMAEs WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY, TREATED WITH OR WITHOUT IMMUNE MODULATING MEDICATION			
Adrenal insufficiency	6 (16.7)	3 (8.3)	0
Hypothyroidism	6 (16.7)	1 (2.8)	0
Thyroiditis	1 (2.8)	0	0
Diabetes mellitus	0	0	0
Hyperthyroidism	4 (11.1)	0	0
Hypophysitis	1 (2.8)	1 (2.8)	0
ALL CAUSALITY SELECT AEs, BY CATEGORY			
Gastrointestinal	16 (44.4)	3 (8.3)	0
Hepatic	10 (27.8)	1 (2.8)	0
Pulmonary	3 (8.3)	2 (5.6)	0
Renal	7 (19.4)	1 (2.8)	0
Skin	25 (69.4)	2 (5.6)	0
Hypersensitivity/Infusion reaction	2 (5.6)	0	0
DRUG-RELATED SELECT AEs, BY CATEGORY			
Endocrine	11 (30.6)	3 (8.3)	0
Gastrointestinal	11 (30.6)	2 (5.6)	0
Hepatic	4 (11.1)	1 (2.8)	0
Pulmonary	3 (8.3)	2 (5.6)	0
Renal	2 (5.6)	1 (2.8)	0
Skin	18 (50.0)	2 (5.6)	0
Hypersensitivity/Infusion reaction	2 (5.6)	0	0

MedDRA Version: 21.1, CTC Version 4.0

(A) Events that lead to death within 24 hours are documented as Grade 5. Events leading to death >24 hours after onset are reported with the worst grade before death.

Includes events reported between first dose and 30 days after last dose of study therapy, except as indicated.

Source: Refer to Table 8.1-1 of the CA209568 Part 2 Final CSR[2]

Post marketing experience

Not applicable

2.5.1. Discussion on clinical safety

The primary safety set for nivolumab/ipilimumab/chemotherapy (nivo+ipi+chemo) in the first line treatment in NSCLC is provided by study CA2099LA. Additional supportive data is provided by the n=36 patients from the single-arm phase II study CA209568. In general, study CA209568 Part 2 shows a similar profile for nivo+ipi+chemo as seen in study CA2099LA. These extra data are limited, and therefore no pooling occurred. In both studies, the immuno-chemotherapy combination was continued until disease progression, unacceptable toxicity or up to 24 months.

Study CA2099LA provides a comparative analysis of the combination immuno-chemotherapy (n=358) vs chemotherapy (n=349). The provided safety data is considered numerically appropriate for safety evaluation, also in consideration that the safety profile of nivo+ ipilimumab is described in various applications including second-line metastatic NSCLC (EMEA/H/C/3985/II/0001) and 1L metastatic NSCLC (EMEA/H/C/WS1372).

In study CA209227, most patients (≥70%) received ≥ 90% of the planned dose intensity. The proportion of subjects who received at least two cycles of chemotherapy in the chemotherapy arm was similar to the proportion of patients who received the maximum two cycles of chemotherapy in the combination treatment arm (93.4% vs. 93%) so that differences in the safety profile for the combination, particularly in relation to AEs reported during the first two first cycles of chemotherapy, is attributable to the addition of nivolumab and ipilimumab.

The nivo+ipi+chemo group showed a higher median treatment duration (6.05 (95% CI 4.93, 7.06) months) compared with the chemotherapy group (2.43 (2.50, 2.83) months). As such, adverse events/ SAE / AEs leading to discontinuation might be higher in the nivo+ipi+ chemo group. However, this more prolonged treatment is required to obtain the observed improvement in overall survival compared to chemotherapy. Therefore, the use of exposure-related adverse incidence rates will be of limited value and the overall, unadjusted data has to be taken into account.

Both treatment arms showed dose delays and dose reductions. Dose reductions were only allowed for the chemotherapy. Overall, 117 (32.7%) subjects from the nivo+ipi+chemo arm and 150 (43%) subjects from the chemo arm received treatment without any dose delay or dose reduction (if permitted). As expected this percentage is higher in the chemotherapy arm due to the increased/different toxicity profile of the combination treatment. The nivo+ ipi+ chemo group showed a lower number of dose delays and dose reductions for chemotherapy compared to the chemotherapy group. This reduction is most likely due to the reduced amount of cycles (n=2 vs n=4) but also due to the reduction of cumulative toxicity when less cycles of chemotherapy are used (nivo+ipi +chemo: 2 cycles, chemo 4 cycles).

Both treatments showed a high, similar amount of AE (> 97%). The reported number of toxic deaths (2% vs 1.7%) was also comparable.

However, the reported toxicity profile differed. The safety profile of the chemotherapy arm was characterised by the bone marrow suppression, while the safety profile of the combination therapy was characterised by the combination of bone marrow suppression and immune related adverse events. Consistent with the more limited cycles of chemotherapy, several toxicities typically related to chemotherapy (anemia, neutropenia, thrombocytopenia) were less frequently reported with nivo+ipi+chemo compared with chemo (Table 24). However, select immune-related adverse events

occurred more frequently in the nivo+ ipi+ chemotherapy group (Table 23). These observations show that the toxic profile of the treatments differ.

The nivo+ipi+chemo groups showed a higher frequency of Grade 3-4 AEs to the chemotherapy arm (63.7% vs 52.7%, respectively). The most frequently reported grade 3-4 AEs (≥3%) were mainly chemotherapy-related AEs in both treatment arms. nivo+ipi+chemo: neutropenia (6.1%), anaemia (5.6%); chemotherapy: anaemia (13.8%), neutropenia (8.9%). These observations suggest that immunotherapy related grade 3-4 AEs are more diverse compared with chemotherapy and therefore do not pop-up as the most frequently detected. It shows that the adverse event profile in the immune-chemotherapy group is more diverse than in the chemotherapy group.

Most patients discontinued treatment because of disease progression, with similar rates in both treatment arms (±40% both groups). However, more patients in the nivo+ipi+chemotherapy arm discontinued because of AEs compared with the chemotherapy arm (27.9% vs 16%). Also, the type of AEs leading to discontinuation differed between the two treatment arms. In the triple therapy arm, these events appeared to be immune-related (diarrhoea, pneumonitis, colitis) while in the chemotherapy arm, the reported events were general health deterioration and anaemia. These observations show again that the toxic profile differs between the two treatment regimens. The overall higher rate of discontinuation due to adverse events suggest that the nivo + ipi +chemotherapy is less well tolerated compared to chemotherapy despite the lower cycles of chemotherapy provided.

The presence of nivolumab or ipilimumab ADA did not appear to be associated with the occurrence of hypersensitivity/infusion reaction select AEs.

As expected, the nivo+ipi + chemo group reported a higher number of immune-related and other-events of specific interest compared to chemotherapy. The number of these events were generally in line with the nivo+ipi therapy reported in study CA 209227, including the number of resolved select adverse events. However, cross-study comparisons may show a higher number of unresolved select renal adverse events.

The cross-study comparison with study CA209227 show that frequency of reported select renal events is comparable between nivo+ipi +chemo (n=37 (10.3%) vs nivo+ ipi (n=56 9.7%) or nivo+ chemo (n=22, 12.8%)). The frequency of resolved AEs (56%) is lower with nivo+ipi+ chemo compared to nivo+ ipi (90%) or with nivo + chemo (86) though this percentage did increase with longer follow-up. Although the numbers are low, this raises concerns about the added renal toxicity when nivo+ ipi is added to chemotherapy.

The use of chemotherapy is associated with renal impairment. Cisplatin has more renal side effects than carboplatin which likely explains why more than 60% of patients with NSQ histology received carboplatin as part of their chemo regimen in both arms. Further data provided show that the proportions of subjects with renal select AEs (all and drug related) were similar across the treatment arms (nivo+ipi+chemo and chemotherapy arms), both in subjects treated with cisplatin and in subjects treated with carboplatin, but the numbers are too low to be conclusive.

Previous studies also showed added renal side effects when pembrolizumab was added to chemotherapy EMEA/H/C/003820/0043), but also in that case the number was too low to be conclusive.

Except for these unresolved select renal side effects, the provided data does not suggest that the addition of chemotherapy to the nivo+ ipi combination will induce new immune-related adverse events. No new indication specific, immune-mediated adverse event caused by nivolumab + ipilimumab was found.

In general, study CA209568 Part 2 shows a similar profile for nivo+ipi+chemo as seen in study CA2099LA. The frequency is slightly lower, but this is likely caused by the low sample size of only 36 subjects.

Safety in the Elderly

The overall safety profile indicates that more SAEs were experienced with nivo+ipi+chemo compared to chemotherapy, regardless of age. However, the number of patients aged ≥ 75 years that discontinued treatment in nivo+ ipi + chemo group is worrisome. Although the number of included patients is low, the number of patients aged ≥ 75 years that discontinued treatment is high (16/37 = 43.2%) and differs considerably compared to 5/33 (17%) in the chemotherapy arm. This difference in discontinuation is troublesome and it may provide a rationale for why in elderly patients, no OS benefit is shown with the nivo+ipi+chemo combination compared to chemotherapy. Information about the safety in this population, which represents a significant part of the proposed target population, is included in sections 4.4 and 5.1 of the SmPC.

2.5.2. Conclusions on clinical safety

The safety profiles of nivo+ipi+chemo in CA2099LA were reflective of the known safety profile of the immunotherapy and chemotherapy components in first-line NSCLC. No new safety signals or toxicities were identified with nivo+ipi+chemo, relative to each agent as monotherapy or the nivo+ipi combination. Also, no new safety signals or toxicities were identified relative to previous experience with each monotherapy, or the nivolumab + ipilimumab regimen in prior melanoma studies and renal cell carcinoma studies.

The nivo + ipi + chemo treatment appears to be less well tolerated compared to chemotherapy as shown by the higher number of (drug-related) AEs and SAEs, and AEs leading to discontinuation. This lesser tolerance is mainly due to the fact that the toxic safety profile of the nivo+ipi + chemo group is characterised by a combination of the immunologically induced adverse events and bone marrow suppression. In contrast, the toxic safety profile of the chemotherapy group is limited to bone marrow suppression.

The combination of nivo+ipi+ chemo may have an added negative effect on renal adverse events compared with the combination of nivo+ipi alone, but the reported numbers are too low to be conclusive.

The combination treatment appears less well tolerated in patients aged ≥75 years, but the provided data is limited. Of concern is the high discontinuation rate (about 43%) in that population. The combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis (see sections 4.4 and 5.1 of the SmPC).

2.5.3. PSUR cycle

OPDIVO (Nivolumab)

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.

YERVOY (Ipilimumab)

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 17.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 17.1 with the following content:

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

No changes to the list of safety concerns were made as a result of the newly added indication.

Pharmacovigilance plan

Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization

None

Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances

None

Category 3 - Required additional pharmacovigilance activities

CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06/2019 4Q2022

No changes to the pharmacovigilance plan.

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities

Immune-related nephritis and renal dysfunction
 	
Immune-related endocrinopathies
 	
Immune-related skin ARs
 	
Other immune-related ARs
	Additional risk minimization measures:
	   Patient Alert Card
		Additional pharmacovigilance activities:
		   Postmarketing pharmacoepidemiology study (CA209234)

Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

No changes to the risk minimisation measures were proposed as a result of the new indication.

The proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indications.

Yervoy

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

The PRAC considered that the risk management plan version 28.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 28.1 with the following content:

Safety concerns

Category	Safety Concern
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
	~~Severe skin drug reactions from concurrent or sequential (in any order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors~~
Missing Information	~~Reproductive and lactation data~~
	Long-term safety in adolescent patients > 12 years of age
	~~Data in ethnic groups~~
	Potential PD interaction with systemic immunosuppressants
	Patients with severe hepatic impairment
	Patients with severe renal impairment
	Patients with autoimmune disease
	~~Long-term safety~~

No changes to the list of safety concerns were made as a result of the newly added indication. Important potential risk and missing information were deleted as a result of the alignment with the revised version of GVP module V (rev.2).

Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing 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				

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
None				

Category 3 - Required additional pharmacovigilance activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
MAH to sponsor extension of the Dutch Melanoma Treatment Registry (DMTR) to include paediatric subjects and to collect their safety data (CA184557) Protocol CA184557: Long-term Follow-up of Ipilimumab-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR). Bristol Myers Squibb Company; 2019. Document Control No. 930139126.	To obtain additional safety information in paediatric patients	Long-term safety in adolescent patients > 12 years of age	Synopsis of the DMTR Submission of protocol Registration of paediatric patients in the DMTR register Interim safety reporting Final study report	16-Apr-2018 02-Nov-2019 2Q 2019 PSUR 2Q 2029

No changes to the pharmacovigilance plan.

Risk minimisation 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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: • Patient Information Brochure and Alert Card	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 5.1 Immunogenicity	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
~~Severe skin drug reactions from concurrent or sequential (in any order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors~~	~~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~~
~~Reproductive and lactation data~~	~~Routine risk minimisation measures: SmPC Sections 4.6 and 5.3~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None~~
	~~Additional risk minimisation measures: 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 mailing a questionnaire to the treating physician).

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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.
~~Data in ethnic groups~~	~~Routine risk minimisation measures:~~ ~~SmPC Section 5.2~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None~~
	~~Additional risk minimisation measures: None~~	~~Additional pharmacovigilance activities: None~~
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
~~Long term safety~~	~~Routine risk minimisation measures:~~ ~~N/A~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: N/A~~
	~~Additional risk minimisation measures: N/A~~	~~Additional pharmacovigilance activities: N/A~~

No changes to the risk minimisation measures were proposed as a result of the new indication.

The proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

All changes are reported in the highlighted full PI in attachment

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 for the following reasons:

- The new indication that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indications.

- Administration is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL remain unchanged.

- The general design and layout of the proposed PL have not changed.

- The modifications now proposed in the PL do not represent major changes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH is seeking an extension of indication for *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 cancers in adults whose tumours have no sensitising EGFR mutation or ALK translocation.*

3.1.1. Disease or condition

Lung cancer is the most common cancer worldwide, with 1.8 million new cases diagnosed yearly. NSCLC is mainly diagnosed at an advanced stage with overall poor prognosis. The overall survival (OS) for metastatic NSCLC is dismal with a 5-year survival of <5%, although recently approved immunotherapy has improved survival.

3.1.2. Available therapies and unmet medical need

At the time of study initiation (May 2017), the standard of care therapy for metastatic treatment-naive NSCLC without driver mutations included histology-based platinum-doublet chemotherapy. Pembrolizumab, an anti-PD-1 monotherapy, had recently received a positive opinion for first-line NSCLC with patients with high PD-L1 expression (≥ 50%) (27 Jan 2017; EMEA/H/C/003820/II/0011). However, this therapy was not generally established in clinical practice yet.

During the conduct of the trial, two immunotherapy (pembrolizumab and atezolizumab) + platinum-based chemotherapy combinations were approved for the treatment for the 1L NSCLC. These products showed an improvement in overall survival when the immunotherapy was added to chemotherapy (EMEA/H/C/003820/II/0043 and EMEA/H/C/004143/II/0019).

3.1.3. Main clinical studies

The current application is based on the results of the first planned interim analyses and updated efficacy data (with additional follow-up for OS) submitted during the procedure of the phase III study CA2099LA. Study CA2099LA is an international, randomised, open-label, parallel study comparing

nivolumab + ipilimumab + chemotherapy with chemotherapy in the first line treatment of metastatic NSCLC.

3.2. Favourable effects

The combination therapy of nivolumab + ipilimumab + chemotherapy (nivo+ipi+chemo) showed an improved overall survival compared with chemotherapy (HR 0.69, 96.71% CI 0.55, 0.87), p=0.0006. Nivo+ipi+chemo median OS: 14.13 months (95% CI 13.24, 16.16), chemotherapy median OS 10.74 months (95% CI 9.46, 12.45).
The Kaplan–Meier curves show an almost immediate separation of the curves for overall survival.

These results are supported with all secondary outcome measures like improvement in PFS, ORR and DoR favouring the nivolumab+ ipilimumab+ chemotherapy compared to chemotherapy.

These beneficial effects favouring the nivo+ipi+chemo groups are overall consistent across the predefined subgroups.

Updated efficacy data submitted during the procedure confirm the initially reported clinical benefit. With an additional 4.6 months of follow-up (09-Mar-2020 database lock; minimum duration of follow-up for OS of 12.7 months), the median OS (95% CI) increased to 15.64 months (13.93, 19.98) in the nivo+ipi+chemo arm and remained relatively unchanged in the chemotherapy arm: 10.91 months (9.46, 12.55). The results for median PFS and other secondary outcome measures also matured and overall slightly improved in the nivo+ipi+chemo arm while remained unchanged in the chemotherapy arm.

The number of drug related death is similar between the two treatment groups (nivo+ipi+chemo 2%, chemo 1.7%).

3.3. Uncertainties and limitations about favourable effects

The subgroup of patients aged ≥ 75 years is small (n=70). Although the nivo + ipi + chemo group show a better ORR compared to chemotherapy (11.9% (95% CI -7.7, 30.0), the nivo+ ipi + chemo combination shows a decreased overall survival (HR 1.36 (95% CI 0.74, 2.52) and reduction in PFS (HR 1.12 (95% CI 0.61, 1.96) in this population. Information in this respect is included in section 5.1 of the SmPC.

3.4. Unfavourable effects

The safety profile of the nivolumab + ipilimumab + chemotherapy combination is characterised by the combination of immunological adverse events and bone marrow suppression. This leads to a more variable adverse events profile compared to chemotherapy alone.

The number of Grade 3-4 AE are higher in the nivo+ipi+chemo therapy group compared with the chemotherapy group (all causality grade 3-4 (43.9% vs 31.8 %), drug related grade 3-4 (25.1% vs 14.6%).

The frequency of all-causality and drug related serious adverse events leading to discontinuation are higher with nivo+ipi+chemo vs chemotherapy (all causality (27.9% vs 16.9%); drug related (19.0% vs 7.4%).

As expected, select AEs, immune-mediated adverse events (IMAEs), and other events of special interest (OESIs) occurred more frequently with nivo+ipi+chemo relative to chemotherapy.

The age group ≥ 75 years treated with nivo+ipi + chemotherapy showed a higher number of AEs leading to discontinuation than in the younger age groups (43% vs 27%) and compared with the same age group treated with chemotherapy (43.2% vs 16.7%).

Although cross-study comparison with study CA 209227 show the same frequency of renal select adverse event (9.7%) for nivo+ipi+ chemo vs nivo + ipi, the reported frequency of resolved renal AE is lower with nivo+ipi + chemo (56%) vs nivo + ipi (90%). This percentage increased with longer follow-up.

3.5. Uncertainties and limitations about unfavourable effects

The median age in NSCLC is 71 years, while the median age in the investigated population is younger (64 years). This might indicate that the safety profile in clinical practice might be worse compared with the safety profile presented in the clinical study report, but the included number of patients is too small to be conclusive.

The number of patients with select renal adverse event is too small to conclude that the immune-chemotherapy combination leads to more unresolved select renal adverse event compared to the combination of nivolumab+ ipilimumab alone.

3.6. Effects Table

Table 37 Nivolumab 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 (data base lock 03-OCT-2019)

Effect	Short Description	Unit	Nivo + ipi + chemo	chemo	Uncertainties/ Strength of evidence	References
Favourable Effects						
median OS	Time from randomisation to the date of death of any course	months (95% CI	14.13 (13.24, 16.16)	10.74 (9.46,12.45)	HR 0.69 96.71 % CI 0.55, 0.87, p = 0.0006	CSR
median PFS	Time from the randomisation data to the date of first documented tumour progression or death (BICR per RECIST 1.1)	months (95% CI)	6.83 (5.55, 7.66)	4.96 (4.27, 5.55)	HR 0.70 97.5% CI (0.57, 0.86) p= 0.0001	CSR
ORR	confirmed CR + PR BICR per RECIST 1.1	n,% (95% CI)	136 (37.7%) (2.7,42.9)	90 (25%) (20.7,30.0)	difference 12.4% 97.5 CI (4.8, 2.0) p=0.003	CSR

Effect	Short Description	Unit	Nivo + ipi + chemo	chemo	Uncertainties/ Strength of evidence	References
median DoR	time between the date of first confirmed response to data to first documented BICR assessed tumour progression or death BICR per RECIST 1.1	months (95% CI)	10.02 (8.21,13.01)	5.09 (4.34, 7.00)		CSR
Unfavourable Effects						
Grade 3-4 AEs	All Causality Grade 3-4 AEs	%	99.2	97.7	open label study, collection of AEs (and attributability to the drug) might be biased.	
	Drug-related Grade 3-4 AEs	%	63.7	52.7		
SAEs	All Causality SAEs	%	56.7	41.3		
	Drug-related SAEs	%	29.1	17.5		
Grade 3-4 SAEs	All Causality Grade 3-4 SAEs	%	43.9	31.8		
	Drug-related Grade 3-4 SAEs	%	29.1	14.6		
AEs leading to DC	All causality AEs leading to DC	%	27.9	16.9		
	Drug-related AEs leading to DC	%	19.0	7.4		
Deaths	Deaths due to study drug toxicity	%	2.0	1.7		

Abbreviations: CSR: clinical study report, OS: overall survival, PFS: progression free survival, ORR: overall response rate, DoR: duration of response BICR per RECIST 1.1.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with metastatic NSCLC have a dismal prognosis despite treatment with chemotherapy. Additional treatments are needed to improve the overall survival. The combination of two different

classes of treatments (immuno therapy + chemotherapy) showed an improved survival, but it was also associated with more side effects.

In study CA2099LA, the addition of nivo+ipi to two platinum-based chemotherapy cycles was compared to four cycles of chemotherapy. The immuno-chemotherapy arm showed a clinically relevant improvement in OS > 3 months (HR 0.69, 96.71% CI 0.55, 0.87, p = 0.0006) compared with chemotherapy, with an almost immediate separation of the KM curves for overall survival. The overall survival was supported with improvements in the secondary outcome measures like the PFS, ORR, DOR and almost all predefined subgroups. This support for the OS shows the robustness of the observed improvement in OS. Additional updated efficacy results (with additional 4.6 months of follow-up for OS) confirm the initially reported efficacy results and with the curves remaining separated over time.

The overall safety profile of the immune-chemotherapy combination is characterised by the combination of immunological adverse events and bone marrow suppression. The combination of these side effects resulted in that more patients reported AEs grade 3-4, and that more patients discontinued treatment because of AE in the nivo+ipi+chemo group compared with chemotherapy. These observations indicate that the immune-chemotherapy treatment appeared to be less well tolerated compared to chemotherapy alone. However, despite the higher percentage of early discontinuation, still a clinically relevant improvement in OS is observed compared to chemotherapy.

This lower tolerability is of concern for patients aged ≥ 75 years. Although the included number is limited (n=70), the reported efficacy and safety raise concern about the B/R profile in this critical target population in the treatment of NSCLC cancer with a median age of 71 years. In the subgroup of patients aged ≥ 75 years, a high proportion of patients (43%) discontinued treatment. The high discontinuation rate may provide a rationale why the point estimate for the OS HR in elderly patients is close to 1 when the nivo+ipi+chemo combination is compared to chemotherapy. This information is reflected in section 4.4 and 5.1 of the SmPC.

During the conduct of the trial, members of the BMS team had access to the unblinded select safety toxicity data (including mortality data) for individual patients before database lock, and the open label study had several important protocol revisions. It was unknown whether and which preventive measures had been taken to avoid the dissemination of data to clinical and strategic decision makers for trial CA2099LA and whether there was an impact of the GCP findings related to study CA209227 (O/Y in 1L NSCLC) on the quality of the CA2099LA study results. The requested impact analyses of previous GCP findings related to study CA209227 revealed that study CA2099LA was conducted using improved systems and processes, while most CAPAs were implemented. These improved systems and processed limited the number of persons with access to the data based and resulted in improved dataset traceability and audit trail. In addition, it was sufficiently justified that the protocol amendments were based on external data. More importantly, the results of the requested supplemental analyses on the data before and after the implementation of the two main amendments of the study were aligned (e.g. HRs for OS in initially enrolled patients vs. those recruited following the revision of the sample size are consistent confirming that the results were not driven by the latter group). Further, updated study results (database lock 09-Mar-2020) confirmed the primary efficacy results. Based on these considerations, it can be concluded that the integrity of study CA2099LA is not questioned and the reported data can overall be considered reliable and used for benefit/risk assessment.

Finally, the wording of the indication has been refined to reflect the included study population, i.e.:

OPDIVO:

"*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*".

Yervoy:

"*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*"

3.7.2. Balance of benefits and risks

The trial shows a robust and clinically relevant improvement in overall survival that has been confirmed with updated efficacy data submitted (longer follow-up). It is considered that this OS benefit outweighs the observation that treatment appears to be less well tolerated compared to chemotherapy. The benefit/risk ratio is considered positive.

3.8. Conclusions

The overall benefit/risk ratio of nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W in combination with 2 cycles of platinum-based chemotherapy is considered positive in the intended indication.

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 metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation for combination of OPDIVO/Yervoy and chemotherapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.1 of the RMP for OPDIVO and version 28.1 for Yervoy have also been submitted.

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 8 "*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 & Yervoy-H-C-2213-WS-1783.

---

i Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine 2010;29:219-228.

iiClopper, C.; Pearson, E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26: 404–413.

iii Statistical Methodology in the Pharmaceutical Sciences edited by Berry DA, Chapter 13, Categorical Data Analysis, p 415 and 417 ff., Marcel Dekker, 1990.