EMA/CHMP/193977/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

OPDIVO	nivolumab
Yervoy	ipilimumab

Procedure No. EMEA/H/C/xxxx/WS/1372

Note

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

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List of abbreviations

1L	first line
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AE-DC/D	adverse events leading to death or discontinuation
ALB	albumin
ALK	anaplastic lymphoma kinase
BALB	baseline albumin
BBWT	baseline body weight
BICR	blinded independent central review
BLDH	baseline lactate dehydrogenase
BMS	Bristol-Myers Squibb
BMS-936558	nivolumab
BMS-734016	ipilimumab
BTSIZE	baseline tumor size
Cavg0-12wk	average drug concentration over the first 12 weeks
CDx	companion diagnostic
chemo	chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CL	clearance
CNA	copy number alterations
CRC	colorectal cancer
CSR	clinical study report
CTLA-4	cytotoxic T-lymphocyte antigen 4
DC	discontinuation
DMC	Data Monitoring Committee
DoR	duration of response
E-R	exposure response
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
F1CDx	FoundationOne CDx
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FMI	Foundation Medicine, Inc.
HCC	hepatocellular carcinoma
HLGT	High-level Group Term
HR	hazard ratio
ipi	ipilimumab
IRRC	Independent Radiology Review Committee
IV	intravenous(ly)
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
mut/Mb	mutations per megabase (1 million bases) of exome sequence
NA	not available
NAb	neutralizing antibodies
nivo	nivolumab
nivo + ipi	nivolumab plus ipilimumab combination therapy
NSCLC	non-small cell lung cancer
NSQ	non-squamous
OESI	other event of special interest
ORR	objective response rate
OS	overall survival
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics

PL	Package Leaflet
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
RCC	renal cell carcinoma
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SQ	squamous
TGD	tumor growth dynamics
TMB	tumor mutational burden
TPS	tumor proportion score
TTR	time to response
UC	urothelial carcinoma
US	United States
VC	volume of distribution of central compartment
VEGF	vascular endothelial growth factor
WES	whole-exome sequencing

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 April 2018 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

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

Extension of Indication to include first-line treatment of adult patients with metastatic Non-Small Cell Lung Carcinoma (NSCLC) for OPDIVO and Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information from the pivotal study CA209227 (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-naïve stage IV or recurrent NSCLC). The Package Leaflet and RMP (version 14.0 for Opdivo and version 21.0 for Yervoy) are updated in accordance. In addition, the MAH has taken the opportunity to introduce minor editorial and formatting revisions in the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/1/2007 on the granting of a class waiver.

Information relating to orphan market exclusivity

NA

Similarity

NA

Derogation(s) of market exclusivity

NA

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Jorge Camarero Jiménez

Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	10 April 2018
Start of procedure:	28 April 2018
CHMP Co-Rapporteur Assessment Report	25 June 2018
CHMP Rapporteur Assessment Report	06 July 2018
PRAC Rapporteur Assessment Report	29 June 2018
PRAC members comments	05 July 2018
Updated PRAC Rapporteur Assessment Report	05 July 2018
PRAC Outcome	12 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 July 2018
Request for Supplementary information	26 July 2018
Submission of MAHs responses	11 October 2018
Restart of the procedure	15 October 2018
Rapporteur's preliminary assessment report circulated on:	20 November 2018
PRAC Rapporteur's preliminary assessment report circulated on:	19 November 2018
Updated PRAC Rapporteur Assessment Report	29 November 2018
CHMP members comments	3 December 2018
CHMP opinion:	13 December 2018
Summary report of the inspection carried out at CROs between April and May 2019 was issued on	14 June 2019
WSA's responses submitted to the CHMP on:	11 September 2019
Rapporteur's preliminary assessment report on the WSA's responses circulated on:	5 November 2019
Updated assessment report on the WSA's responses circulated on:>	9 November 2019
Request for Supplementary information	14 November 2019

2. Scientific discussion

2.1. Introduction

This application concerns an extension of indication to include the first-line combination treatment with nivolumab and ipilimumab of adult patients with metastatic non-small cell lung cancer (NSCLC) in adults who have tumour mutational burden ≥ 10 mutations per megabase with no known EGFR or ALK positive tumour mutations. However, with the full and final data of CA209227 Part 1, an updated indication has been now proposed. The initially proposed indication in the population of tumor mutational burden (TMB) ≥ 10 mut/Mb, is no longer pursued due to lack of OS predictiveness in the high (≥ 10 mut/Mb) versus low (< 10 mut/Mb) TMB populations, as assessed by the FoundationOne® CDx assay. In line with the totality of the data, the applicant proposes a revised indication in the

Product Information section 4.1, which reads: "OPDIVO in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations (see sections 4.4 and 5.1)."

OPDIVO (nivolumab)

Nivolumab, a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), binds to the programmed death-1 (PD-1) receptor and blocks the interaction with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Interaction between the PD-1 receptor and PD-L1/ PD-L2 results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab blocks the binding of the PD-1 receptor to PD-L1/PD-L2 and potentiates T-cell responses, including anti-tumour responses. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth. Initial and subsequent Opdivo approvals have resulted in indications for advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, classical Hodgkin's lymphoma (cHL).

YERVOY (ipilimumab)

Ipilimumab, a fully human monoclonal antibody (IgG1κ), is a cytotoxic T-lymphocyte antigen 4 CTLA-4 immune checkpoint inhibitor. CTLA-4 is a regulator of T-cell activity. Ipilimumab blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoural T-effector/ T-regulatory cell ratio which drives tumour cell death. YERVOY is indicated for the treatment of unresectable or metastatic melanoma and.

Combination therapy with nivolumab + ipilimumab

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity. The combination of nivolumab + ipilimumab is approved for the treatment of unresectable or metastatic melanoma.

NSCLC

Lung cancer is the most common cancer worldwide, with 1.8 million new cases diagnosed yearly, and an estimated 1.6 million deaths worldwide.5 NSCLC represents approximately 85% of all lung cancers and includes SQ cell carcinoma and NSQ cell carcinoma, which encompasses a variety of histological subtypes including adenocarcinoma, large cell carcinoma, and less common subtypes.5,6,7,8 Lung cancer has been associated with a high prevalence of somatic mutations, primarily as a result of chronic exposure to tobacco, a known mutagen.9

Approved First-line Treatments in NSCLC

The table below shows EU-approved first-line treatments for metastatic NSCLC other than those only approved for subgroups defined by genetic driver mutations. The immunotherapy pembrolizumab, is approved in the EU for first-line treatment of subjects whose tumors have high PD-L1 expression (tumour proportion score [TPS] ≥50%).

Table 1: Medicinal products authorized in the EU for first-line treatment of metastatic NSCLC - All Histologies (excluding authorisations for subgroups defined by genetic driver mutations) (source: EPARs)

Agent	Mechanism	First-line indication
Bevacizumab	VEGF-specific angiogenesis inhibitor	In addition to platinum-based chemotherapy, for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSQ NSCLC 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 (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
Pembrolizumab	Programmed death receptor-1 (PD-1)-blocking antibody	As monotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumors express PD-L1 with a ≥50% tumor proportion score (TPS) with no EGFR or ALK positive tumor mutations

Gefitinib, afatinib, erlotinib, and crizotinib are excluded from this table because their approval is limited to subjects with molecularly-defined tumors (eg, with EGFR deletions/mutations or ALK-positive).
Abbreviations: ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; EU: European Union; NSCLC: non-small cell lung cancer; NSQ: non-squamous; PD-1: programmed death receptor 1; SQ: squamous; TPS: Tumor Proportion Score; VEGF: vascular endothelial growth factor.

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.

2.2.2. Discussion on non-clinical aspects

NA

2.2.3. Conclusion on the non-clinical aspects

NA

2.3. Clinical aspects

2.3.1. Introduction

OPDIVO (nivolumab) in combination with Yervoy (ipilimumab) is currently being developed for the treatment of patients with non-small cell lung cancer (NSCLC) as well as other tumor types. The clinical pharmacology data in this application support the use of the combination of nivolumab 3 mg/kg Q2W with ipilimumab 1 mg/kg Q6W intravenously (IV) for the treatment of patients with previously untreated metastatic NSCLC.

GCP

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

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

A triggered GCP inspection (GCP/2018/040) was carried out. The inspection was adopted by the CHMP on 28th February 2019 on an amended IREQ.

2.3.2. Pharmacokinetics

The nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics (PK) described by noncompartmental analysis, QT prolongation potential, and dose selection for Phase 2/3 studies has been previously described.

The clinical pharmacology profile of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg was characterized previously in subjects with advanced melanoma. The population PK (PPK) of nivolumab and ipilimumab in combination has been previously described and submitted in support of the advanced melanoma indication. For this submission, an update to the nivolumab and ipilimumab PPK analysis was performed as well as exposure-response of safety and efficacy.

Immunogenicity of nivolumab and ipilimumab in Studies CA209227, CA209012 and CA209568 is also summarized.

Analytical methods

Bioanalytical methods used for quantifying nivolumab serum concentrations in the development program were cross-validated, evaluated for interference with ipilimumab, and allowed merging of the exposure data for PPK analysis.

Special populations

Population Pharmacokinetics of Nivolumab

Monotherapy

Initially, nivolumab PK was described by a stationary (time-invariant) PK model; however, a comprehensive analysis of nivolumab PK with data from 3,458 subjects with advanced solid tumors and cHL found that nivolumab clearance (CL) decreases by a modest extent (~25%) over the course of treatment. The steady-state volume of distribution (Vss) and terminal half-life (T-HALF) of nivolumab were determined to be approximately 6.6 L and 25 days, respectively. Nivolumab CL and volume of distribution in the central compartment (VC) were higher in subjects with higher baseline body weight (BBWT), and nivolumab CL was ~26% lower in subjects with cHL relative to subjects with NSCLC. In

addition, the magnitude of the effects of the following covariates were not considered to be clinically relevant (< 20%): age, race, performance status (PS), baseline tumor burden, estimated glomerular filtration rate (eGFR), hepatic impairment status (by National Cancer Institute [NCI] Criteria), and PD-L1 expression.

Previous data on combination

The PK of nivolumab in combination with ipilimumab (at various dose levels) has been previously characterized.

In the initial analysis, nivolumab PK in subjects with previously untreated advanced melanoma was described by a time-invariant model.8 In that analysis, nivolumab CL was moderately higher (35%) when given in combination with 3 mg/kg ipilimumab, relative to the CL of nivolumab given as monotherapy (3 mg/kg every 2 weeks [Q2W]), and nivolumab CL was modestly higher (~24%) in the presence of nivolumab anti-drug antibodies (ADA) detected using a drug-tolerant assay. Additionally, nivolumab combined with ipilimumab 1 mg/kg did not have a significant effect on nivolumab CL. Effects of other covariates including BBWT, Eastern Cooperative Oncology Group (ECOG) PS, eGFR on CL; and sex and BBWT on VC were consistent with that of nivolumab monotherapy.

In a recent updated analysis, nivolumab PK was described by a time-varying model across multiple tumors types including NSCLC, SCLC, melanoma, and RCC. In that analysis, the CL of nivolumab combined with ipilimumab 1 mg/kg every 3 weeks (Q3W), 6 weeks (Q6W), or 12 weeks (Q12W) was similar to that of nivolumab monotherapy (< 20% difference), whereas the CL of nivolumab combined with ipilimumab 3 mg/kg Q3W was higher (~29%) than that of nivolumab monotherapy. The CL of nivolumab in subjects with melanoma, RCC, and SCLC was similar (< 20% difference) to that in subjects with NSCLC. Nivolumab CL was higher in subjects with higher BBWT and lower baseline albumin (BALB), and was higher (24%) in the presence of ADAs. Nivolumab VC was higher in subjects with higher BBWT. Sex, race, PS, eGFR, baseline lactate dehydrogenase (BLDH), and baseline tumor size (BTSIZE) did not have clinically relevant effects on nivolumab CL; sex did not have a clinically relevant effect on nivolumab VC. Nivolumab exposures were similar in Japanese and non-Japanese subjects for a given combination regimen.

Current data on combination

The same model was submitted for WS/1278 combination in RCC. It should be kept in mind that posology proposed is different.

For the current analysis, the nivolumab PPK analysis dataset included 32843 nivolumab concentration values from 6468 subjects with melanoma, NSCLC, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), colorectal cancer (CRC) or small-cell lung cancer (SCLC) who received nivolumab monotherapy or combination therapy (with ipilimumab or chemotherapy). The analysis dataset included data for nivolumab doses ranging from 0.1 to 10 mg/kg, and dosing frequency of once every 2 or 3 weeks (Q2W or Q3W). The covariates assessed included administration with ipilimumab 3 mg/kg (Q3W) or 1 mg/kg (Q3W, Q6W or Q12W), tumor type, sex, race, baseline body weight (BBWT), baseline eGFR, line of therapy, and baseline PS on nivolumab CL; and sex and BBWT on VC. The effect of ipilimumab coadministration and PS on EMAX was also assessed.

The final nivolumab model was a two-compartment, zero-order IV infusion and time-varying CL model (sigmoidal-Emax function) with a proportional residual error model, with random effects on CL, VC, VP, and EMAX; and correlation of random effect between CL and VC. The final nivolumab PPK model contained ipilimumab regimen, chemotherapy coadministration, BBWT, eGFR, PS, sex, and race on CL, ipilimumab coadministration and PS on change of CL over time, and BBWT and sex on VC.

The parameter estimates from the final PPK model are provided in Table 2

Table 2: Parameter Estimates for the Final Nivolumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	10.8	0.162 (1.50)	10.5 - 11.2
VC_{REF} [L]	θ_2	4.27	0.0311 (0.728)	4.21 - 4.34
Q_{REF} [mL/h]	θ_3	34.9	2.41 (6.91)	30.4 - 40.7
VP_{REF} [L]	θ_4	2.70	0.0668 (2.47)	2.58 - 2.83
CL_{BBWT}	θ_7	0.530	0.0286 (5.40)	0.470 - 0.589
CL_{GFR}	θ_9	0.202	0.0199 (9.85)	0.162 - 0.243
CL_{FEMALE}	θ_{12}	-0.181	0.0133 (7.35)	-0.206 - -0.155
CL_PS_1	θ_{13}	0.181	0.0130 (7.18)	0.156 - 0.208
CL_{RAAA}	θ_{14}	0.0374	0.0322 (86.1)	-0.0308 - 0.111
CL_{RAAS}	θ_{15}	-0.0354	0.0169 (47.7)	-0.0670 - -0.00215
VC_{BBWT}	θ_{16}	0.534	0.0240 (4.49)	0.489 - 0.579
VC_{FEMALE}	θ_{17}	-0.161	0.0141 (8.76)	-0.189 - -0.132
$EMAX_{REF}$	θ_{18}	-0.240	0.0210 (8.75)	-0.283 - -0.199
$T50\ [h]$	θ_{19}	2.20E+03	131 (5.95)	1.97E+03 - 2.50E+03
$HILL$	θ_{20}	2.77	0.263 (9.49)	2.30 - 3.34
CL_IPI1_{6W}	θ_{28}	0.159	0.0179 (11.3)	0.124 - 0.191
CL_IPI3_{3W}	θ_{30}	0.227	0.0213 (9.38)	0.185 - 0.269
CL_{CHEMO}	θ_{32}	-0.104	0.0255 (24.5)	-0.155 - -0.0525
$EMAX_{IPICO}$	θ_{33}	-0.0668	0.0234 (35.0)	-0.118 - -0.0249
$EMAX\_PS_1$	θ_{34}	-0.138	0.0200 (14.5)	-0.179 - -0.0987
Random Effects	θ_{34}			
ZCL [-]		0.157 (0.396)	0.00856 (5.45)	0.141 - 0.175
ZVC [-]	$\omega_{1,1}$	0.152 (0.390)	0.0149 (9.80)	0.123 - 0.185
$ZEMAX$	$\omega_{2,2}$	0.0874 (0.296)	0.0113 (12.9)	0.0662 - 0.114
$ZCL:ZVC$	$\omega_{5,5}$	0.0596 (0.386)	0.00894 (15.0)	0.0439 - 0.0792
Residual Error	$\omega_{1,2}$			
$PERR$ [-]		0.245	0.00405 (1.65)	0.237 - 0.253

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

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Source: Analysis Directory/nm/final.rtf

Bootstrap Source: Analysis Directory/psn/final.est_dir1/bootstrap_results_mod.csv

Note: *CL0REF* is the typical value in a reference subject with NSCLC, receiving nivolumab monotherapy as a 2nd line therapy, and weighing 80 kg. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving nivolumab monotherapy with a normal PS status. 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: Eta shrinkage (%): ETA_CL: 11.9; ETA_VC: 28.0; ETA_EMAX: 50.3; EPS shrinkage (%):16.4.

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

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

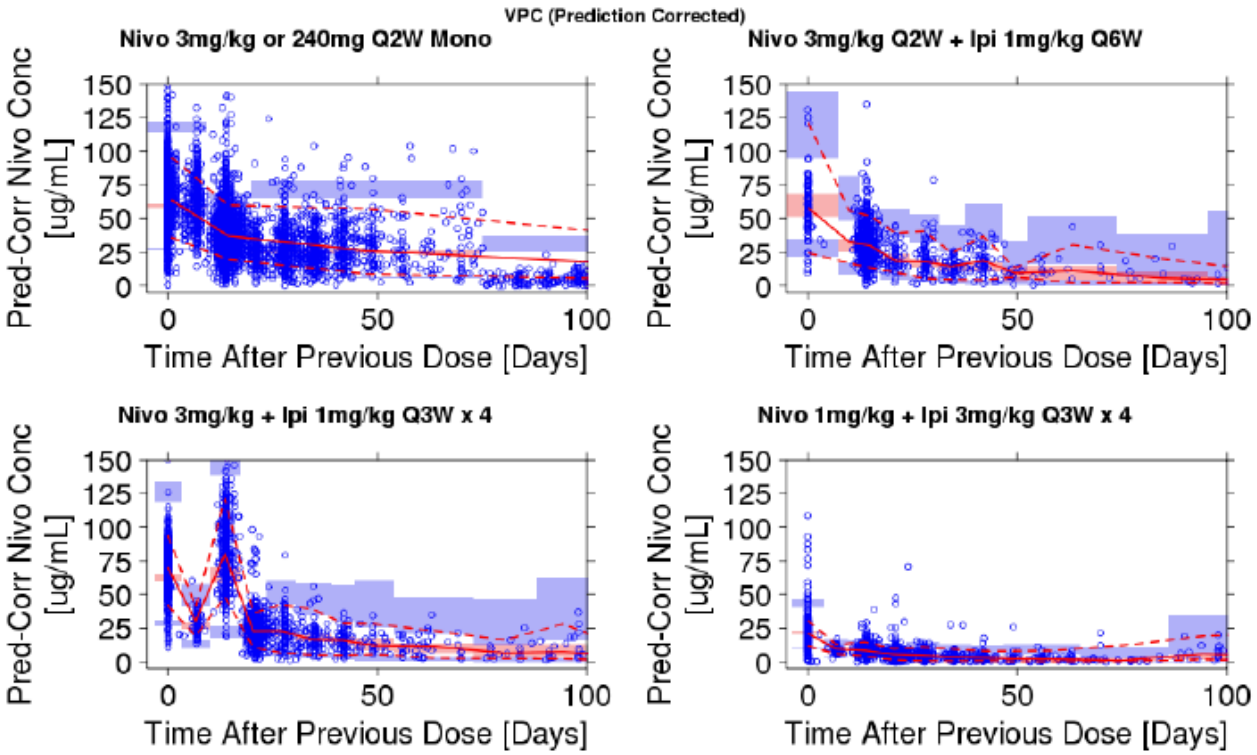
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

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

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

The PPK model provides an adequate description of nivolumab concentration-time data in the target population. The predictive performance of the final PPK model was determined using prediction corrected visual predictive checks (pcVPC) with stratification by the selected nivolumab dosing regimen (nivolumab 3 mg/kg or 240 mg Q2W monotherapy; nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W 4 doses followed by nivolumab 3 mg/kg Q2W; nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W 4 doses followed by nivolumab 3 mg/kg Q2W) in different solid tumors. Figure 1 and Figure 2 show the pcVPC plots of all nivolumab concentration

versus time after the previous dose and trough concentration versus time after the first dose, respectively. A small proportion of the data points were out of the plotted range. The pcVPC plots show that the model adequately characterized the data from the 5th to the 95th percentiles. Most of the lines representing the 5th, 50th, and 95th percentiles of the observed data pass through respective 90% prediction interval (the shaded band) of the PK data up to the first 120 days after the previous dose and first 200 days after the first dose. Thus, data were well characterized enabling the predictions of the model to be used for exposure-response (E-R) efficacy and safety analyses and the final PPK model is appropriate for its intended purpose.



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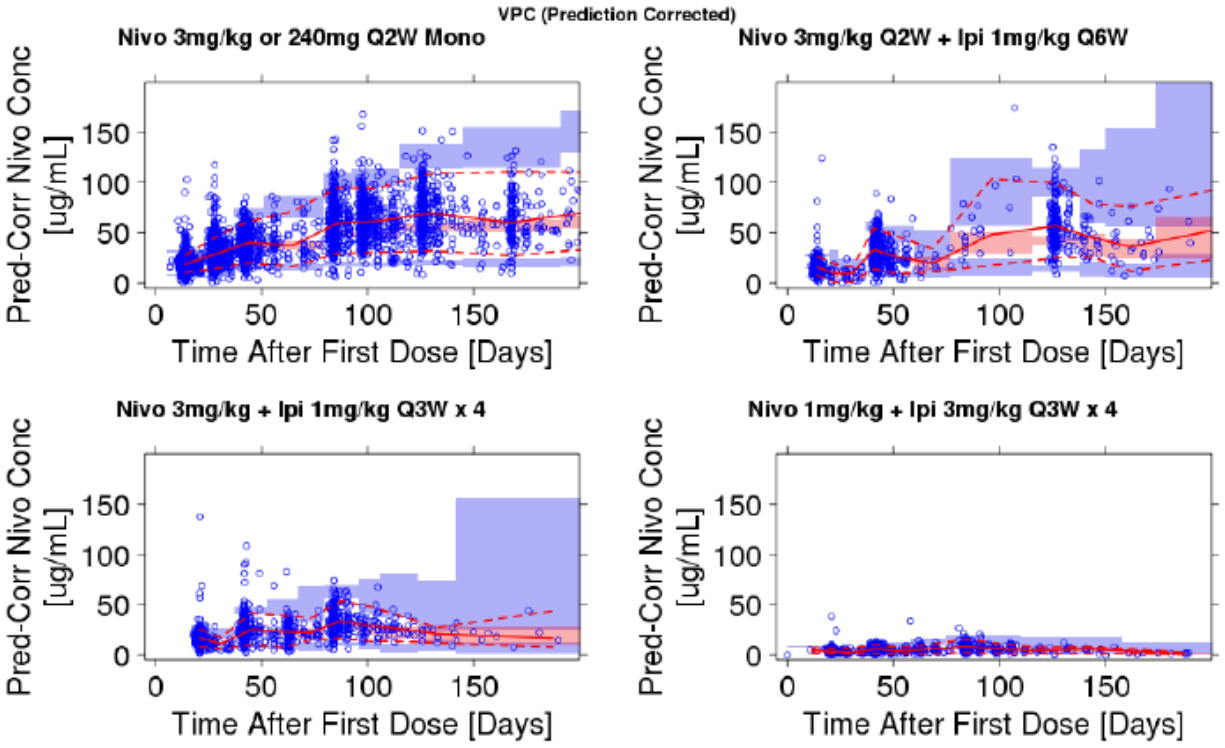
Source: Analysis-Directory/psn/vpc_final_dir5/VPC-plots 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 1: Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose Stratified by Selected Nivolumab Dosing Regimens (Final Nivolumab Population Pharmacokinetic Model)



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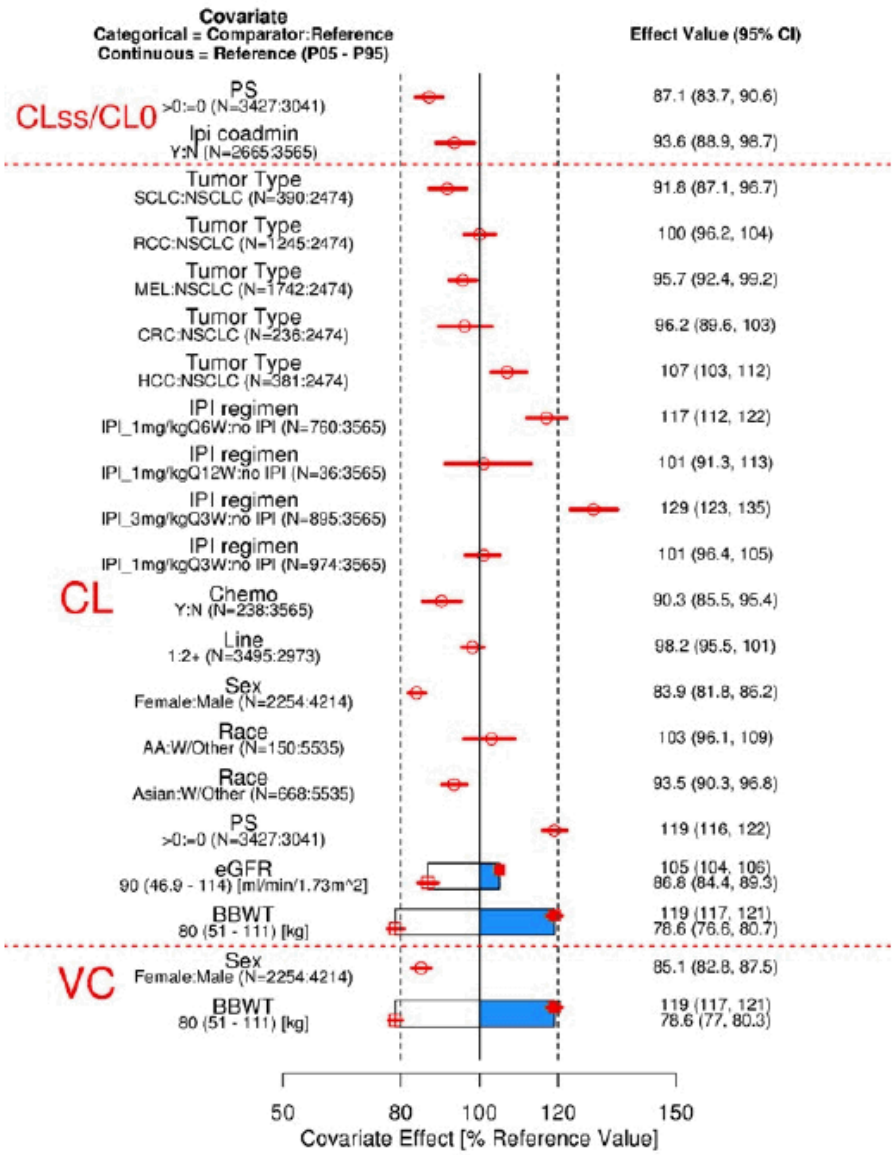
Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 2: Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose Stratified by Selected Nivolumab Dosing Regimens (Final Nivolumab Population Pharmacokinetic Model)

The effect of covariates on nivolumab CL and VC in the full nivolumab PPK model are shown in Figure 1. Nivolumab CL was similar in subjects with melanoma, NSCLC, RCC, SCLC, HCC, and CRC. Ipilimumab 1 mg/kg Q3W or Q12W regimens, when administered with nivolumab, did not have a statistically significant effect on nivolumab CL (95% CI includes 0), whereas ipilimumab 1 mg/kg Q6W resulted in a 17% increase in nivolumab CL and ipilimumab 3 mg/kg Q3W resulted in a 29% increase in nivolumab CL. The CL of nivolumab in combination with chemotherapy was ~10% lower relative to nivolumab monotherapy. Nivolumab CL was higher in subjects with higher baseline body weight and eGFR and lower in female subjects. Nivolumab VC was higher in subjects with higher baseline body weight. Sex, race, PS, and eGFR did not have clinically relevant effect on nivolumab CL; sex did not have a clinically relevant effect on nivolumab VC.



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R-Program Source: Analysis-Directory/R/scripts/cov-eff-plot-full.r
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 m^2, 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: Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 19%, whereas the reduction of nivolumab CL over time was greater in subjects with PS > 0 than subjects with PS = 0 by 13%.

Figure 3: Covariate Effects on Nivolumab Pharmacokinetic Model Parameters (Full Nivolumab PPK Model)

Sensitivity analyses found that nivolumab CL was higher in subjects with higher baseline LDH (BLDH, up to 44%), larger baseline tumor size (BTSIZE, < 20%), and lower BALB (<20%), and was higher (~20%) in the presence of anti nivolumab antibodies.

The effect of tumor mutational burden on nivolumab PK was also assessed graphically. The PK of nivolumab was similar in 1L NSCLC subjects with high, low, or not evaluable baseline TMB status who received nivolumab + ipilimumab combination therapy. Additionally, nivolumab CL decreased more in subjects with a BOR of CR or PR than subjects with a BOR of SD, and CL decreased less in subjects with a BOR of PD than subjects with a BOR of SD.

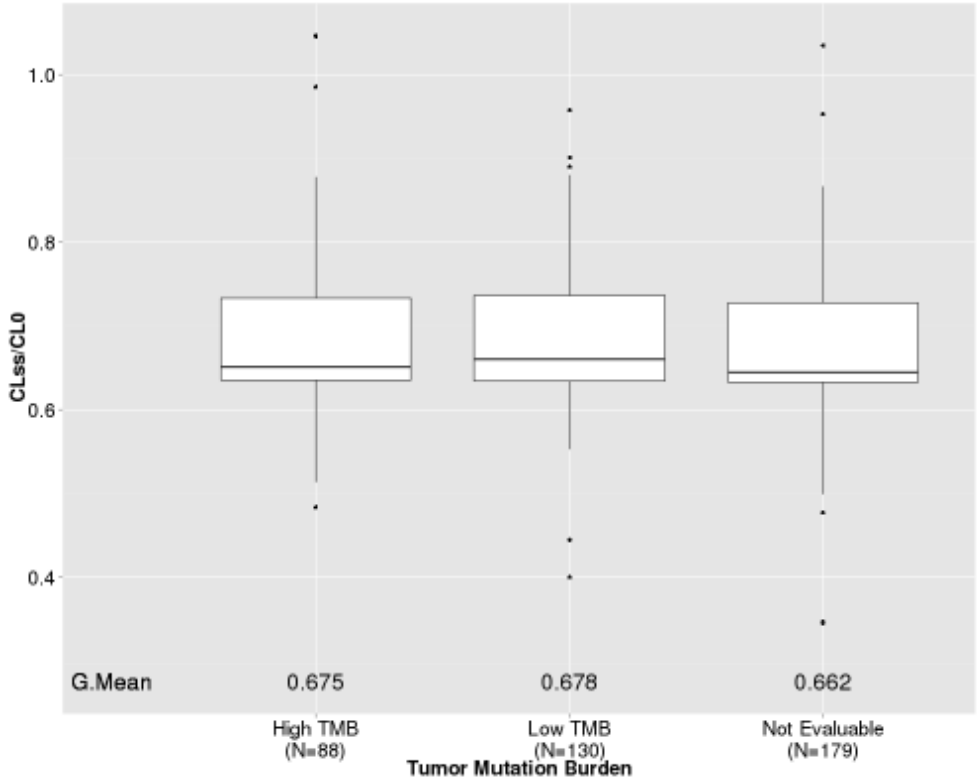


Figure 4: Distribution of Nivolumab Ratio of Steady-State CL to Baseline CL by TMB Status in 1L NSCLC Subjects who Received Nivolumab + Ipilimumab Combination Therapy in Study CA209227

Nivolumab CL decreased with time, and the decrease was greater in subjects with poor PS (~31% and ~21% decrease in subjects with PS > 0 and PS = 0, respectively). The time for half maximal reduction was ~92 days. The EMAX was similar across dose regimens and tumor types.

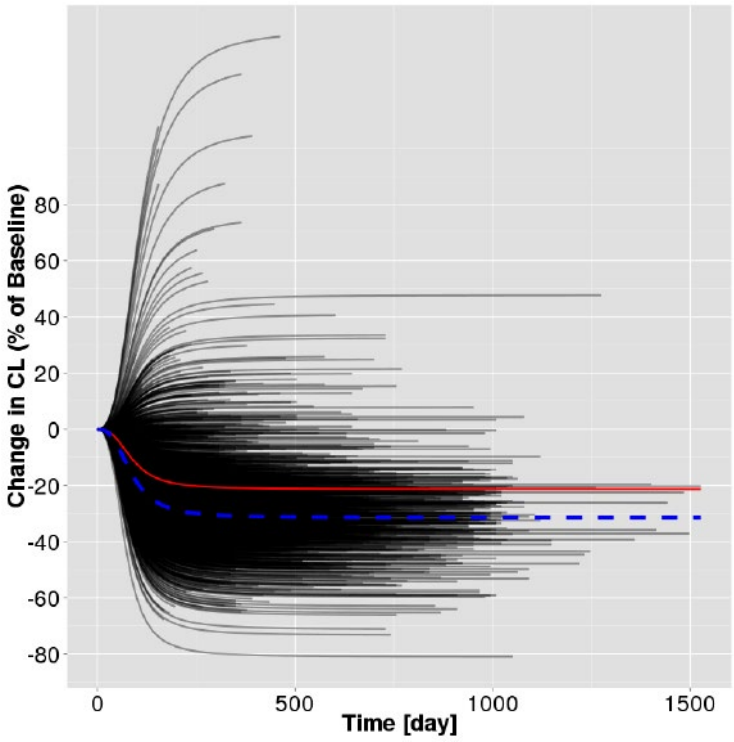


Figure 5: Model Estimated Overall Change in Nivolumab Clearance versus Time from the Final Model

The individual parameter estimates for nivolumab in monotherapy (3 mg/kg or 240 mg Q2W) and in combination (3 mg/kg Q2W) with 1 mg/kg Q6W ipilimumab obtained from the full popPK model and the exposure estimates are summarized in the following tables:

Table 3: Summary Statistics of Individual Measures of Nivolumab Parameters in Monotherapy (3 mg/kg or 240 mg Q2W) Across Tumou Types

Parameters	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CL0 [mL/h]	2907	11.4	10.6	10.6(1.33,47.1)	4.34	38.2
CLSS [mL/h]	2907	8.31	7.75	7.66(0.259,33.4)	3.39	40.7
VC [L]	2907	4.01	3.83	3.93(0.142,11.6)	1.14	28.3
VSS [L]	2907	6.66	6.51	6.55(2.15,14.6)	1.46	21.9
PEMAX[%]	2907	73.4	72.7	70.6(19,169)	10.3	14
T-HALFα [h]	2907	30.3	30	30.5(2.73,44.2)	3.91	12.9
T-HALFα-SS [h]	2907	30.8	30.5	31(2.77,45.6)	3.99	12.9
T-HALFβ -SS[d]	2907	19.3	18.7	19(4.56,213)	6.27	32.4
T-HALFβ [d]	2907	26.8	25.3	25.5(6.13,1100)	22	82.3

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

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

Source: Analysis-Directory/R/plots/para.reg240.csv

VSS was calculated using formula: VSS=VC+VP.

PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.

T-HALF-β and T-HALF-α were calculated using formula as below:

KE = CL/VC; K12 = Q/VC; K21 = Q/VP; AA = KE + K12 + k21

$\beta = (\frac{AA - \sqrt{AA^2 - 4 \times KE \times K21}}{2})$, and $t_{\beta} = (\frac{0.693}{\beta})$

$\alpha = (\frac{AA + \sqrt{AA^2 - 4 \times KE \times K21}}{2})$, and $t_{\alpha} = (\frac{0.693}{\alpha})$

T-HALF-β-SS and T-HALF-α-SS were calculated using parameters estimates at steady state.

Individual estimates of Q, V2 T50 and HILL are 26.3 mL/h, 3.18 L, 2540 hours and 7.43, respectively, as there are no random or covariate effect parameters associated with these parameters in the final PPK model.

Table 4: Summary Statistics of Individual Measures of Nivolumab Exposures in Monotherapy (3 mg/kg or 240 mg Q2W) Across Tumou Types

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	2907	20	19.2	19.3(3.24,64.9)	5.71	28.6
CMAX1	2907	66.9	62.2	60.8(20.7,1500)	49.4	73.9
CAVG1	2907	30	29.2	29.1(11.8,87.1)	7.32	24.4
CMINSS	2907	79.6	71.7	73.4(8.24,2740)	63.7	80
CMAXSS	2907	146	137	136(46.3,2820)	84.5	57.7
CAVGSS	2907	99.6	92.2	93.2(21.4,2760)	65.4	65.6

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

R-Program Source: Analysis-Directory/R/scripts/process-nm-output.r

Source: Analysis-Directory/R/plots/expo.reg240.csv

Table 5: Summary Statistics of Individual Measures of Nivolumab Parameters in Combination Therapy (Nivo: 3 mg/kg Q2W, Ipi: 1 mg/kg Q6W) in Subjects with Non-small Cell Lung Cancer

Parameters	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CL0 [mL/h]	684	13.3	12.4	12.3(2.84,52.7)	5.51	41.4
CLSS [mL/h]	684	8.92	8.26	8.1(1.81,38.9)	3.81	42.7
VC [L]	684	3.82	3.73	3.77(0.986,7.32)	0.834	21.8
VSS [L]	684	6.39	6.27	6.28(1.84,10.4)	1.2	18.8
PEMAX[%]	684	67.3	66.8	64.7(34.9,105)	8.46	12.6
T-HALFα [h]	684	30	29.8	30.1(14.4,42.1)	3.02	10.1
T-HALFα-SS [h]	684	30.7	30.5	30.9(14.4,43.3)	3.2	10.4
T-HALFβ -SS[d]	684	16.2	15.7	16.1(4.18,50)	4.24	26.1
T-HALFβ [d]	684	24.1	22.9	23.5(5.3,139)	8.4	34.9

Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/

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

Source: Analysis-Directory/R/plots/ para.regQ6W.nsclc.csv

VSS was calculated using formula: VSS=VC+VP.

PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.

T-HALF-β and T-HALF-α were calculated using formula as below:

KE = CL/VC; K12 = Q/VC; K21 = Q/VP; AA = KE + K12 + k21

$$\beta = \left(\frac{AA - \sqrt{AA^2 - 4 \times KE \times K21}}{2}\right), \text{ and } t_\beta = \left(\frac{0.693}{\beta}\right)$$

$$\alpha = \left(\frac{AA + \sqrt{AA^2 - 4 \times KE \times K21}}{2}\right), \text{ and } t_\alpha = \left(\frac{0.693}{\alpha}\right)$$

T-HALF-β-SS and T-HALF-α-SS were calculated using parameters estimates at steady state.

Individual estimates of Q, V2 T50 and HILL are 26.3 mL/h, 3.18 L, 2540 hours and 7.43, respectively, as there are no random or covariate effect parameters associated with these parameters in the final PPK model.

Table 6: Summary Statistics of Individual Measures of Nivolumab Exposures in Combination Therapy (Nivo: 3 mg/kg Q2W, Ipi: 1 mg/kg Q6W) in Subjects with Non-small Cell Lung Cancer

Exposure Estimate	N	Mean	GeoMean	Median (min, max)	SD	CV%
CMIN1	684	16.2	15.4	16.1(2.96,63.3)	4.92	30.4
CMAX1	684	57.9	56.9	56(32.3,190)	12.4	21.4
CAVG1	684	25.8	25.3	25.4(14.5,83.4)	5.69	22
CMINSS	684	64.2	57.9	60.9(6.42,490)	32.5	50.6
CMAXSS	684	122	117	117(59.9,578)	40.7	33.4
CAVGSS	684	82.2	76.6	78.6(21.1,515)	34.6	42.1

Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/

R-Program Source: Analysis-Directory/R/scripts/process-nm-output.r

Source: Analysis-Directory/R/export/expo.regQ6W.nsclc.csv

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	426	4.05	3.66	4.07(0.322,13.7)	1.7	41.9
CMAX1	426	21.5	19.6	19.5(9.01,531)	26.3	122
CAVG1	426	7.53	7.3	7.46(3.05,18.6)	1.93	25.7
CMINSS	426	61.3	52.4	56.3(6.21,564)	39.9	65.1
CMAXSS	426	125	115	113(46,1450)	85.6	68.2
CAVGSS	426	80	72.3	75.3(16.8,598)	42.5	53.1

Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/process-nm-output.r
Source: Analysis-Directory/R/plots/expo.regN1I3.sclc.csv

The steady-state exposure estimates for nivolumab in subjects with NSCLC in combination with ipilimumab were slightly (<20%) lower to the exposure estimates following nivolumab monotherapy (Table 7).

The effect of tumour mutational burden on nivolumab PK was also assessed. In more than 40% of the patients, 179 out of 397 for combination therapy and 123 out of 275 for nivolumab monotherapy, TMB status was not evaluable. The PK of nivolumab was similar in 1L NSCLC subjects with high, low, or not evaluable baseline TMB status who received nivolumab + ipilimumab combination therapy Table 7. The ratio CLss to CL0 was 0.675 and 0.678 in subjects with high and low TMB, respectively.

In subjects treated with nivolumab monotherapy in Study CA209227, subjects with high TMB had a slightly higher CL (CL0 and CLss) than subjects with low or not evaluable TMB, and the ratio CLss to CL0 is slightly lower in high TMB subjects compared to low TMB, 0.704 vs 0.725.

Table 7: Summary Statistics of Individual Measures of Nivolumab Exposures by TMB Status in Subjects with 1L NSCLC who Received Nivolumab + Ipilimumab Combination Therapy in Study CA209227 (upper panel) and Nivolumab monotherapy (lower panel) in Study CA209227 Nivolumab + ipilimumab

Exposure Parameter	High TMB (N = 88) GM [µg/mL] (%CV)	Low TMB (N = 130) GM [µg/mL] (%CV)	Not Evaluable (N = 179) GM [µg/mL] (%CV)	All (N = 397) GM [µg/mL] (%CV)
CMIN1	15(30.4)	15.2(27.7)	15.4(36.7)	15.3(32.7)
CMAX1	55.8(18.7)	56.1(15.7)	57(25.4)	56.4(21.3)
CAVG1	24.8(21.7)	24.9(18.9)	25.3(27.1)	25(23.5)
CMINSS	54.7(40.3)	56(44)	58.2(69.1)	56.7(57.3)
CMAXSS	112(28)	115(27.4)	117(45.4)	115(37.3)
CAVGSS	73.1(34.3)	74.5(36.3)	77(57.5)	75.3(47.6)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/tmb-nivo/final
Program Source: Analysis Directory/R/process-nm-output.r
Source: Analysis Directory/R/export/sumstat-exps-227-combo.csv

Exposure Parameter	High TMB (N = 88) GM [µg/mL] (%CV)	Low TMB (N = 130) GM [µg/mL] (%CV)	Not Evaluable (N = 179) GM [µg/mL] (%CV)	All (N = 397) GM [µg/mL] (%CV)
CMIN1	15(30.4)	15.2(27.7)	15.4(36.7)	15.3(32.7)
CMAX1	55.8(18.7)	56.1(15.7)	57(25.4)	56.4(21.3)
CAVG1	24.8(21.7)	24.9(18.9)	25.3(27.1)	25(23.5)
CMINSS	54.7(40.3)	56(44)	58.2(69.1)	56.7(57.3)
CMAXSS	112(28)	115(27.4)	117(45.4)	115(37.3)
CAVGSS	73.1(34.3)	74.5(36.3)	77(57.5)	75.3(47.6)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/tmb-nivo/final
Program Source: Analysis Directory/R/process-nm-output.r
Source: Analysis Directory/R/export/sumstat-exps-227-combo.csv

Nivolumab monotherapy

Exposure Parameter	High TMB (N = 49) GM [µg/mL] (%CV)	Low TMB (N = 103) GM [µg/mL] (%CV)	Not Evaluable (N = 123) GM [µg/mL] (%CV)	All (N = 275) GM [µg/mL] (%CV)
CMIN1	17.2(26.1)	19.3(26)	19.6(29.1)	19(27.8)
CMAX1	60.2(16.8)	63.1(21.7)	64.8(24.1)	63.3(22.4)
CAVG1	27.6(18.7)	29.7(20.9)	30.3(23.6)	29.6(22.1)
CMINSS	61.8(36.6)	70.3(37.6)	69.6(38.8)	68.4(38.2)
CMAXSS	124(24.7)	135(27.1)	136(28.8)	134(27.7)
CAVGSS	81.8(30.9)	91.1(32.2)	90.8(33.5)	89.3(32.8)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/tmb-nivo/final
Program Source: Analysis Directory/R/process-nm-output.r
Source: Analysis Directory/R/export/sumstat-exps-227-mono.csv

Exposure Parameter	High TMB (N = 49) GM [µg/mL] (%CV)	Low TMB (N = 103) GM [µg/mL] (%CV)	Not Evaluable (N = 123) GM [µg/mL] (%CV)	All (N = 275) GM [µg/mL] (%CV)
CMIN1	17.2(26.1)	19.3(26)	19.6(29.1)	19(27.8)
CMAX1	60.2(16.8)	63.1(21.7)	64.8(24.1)	63.3(22.4)
CAVG1	27.6(18.7)	29.7(20.9)	30.3(23.6)	29.6(22.1)
CMINSS	61.8(36.6)	70.3(37.6)	69.6(38.8)	68.4(38.2)
CMAXSS	124(24.7)	135(27.1)	136(28.8)	134(27.7)
CAVGSS	81.8(30.9)	91.1(32.2)	90.8(33.5)	89.3(32.8)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/tmb-nivo/final
Program Source: Analysis Directory/R/process-nm-output.r
Source: Analysis Directory/R/export/sumstat-exps-227-mono.csv

Population Pharmacokinetics of Ipilimumab

Monotherapy

The first PPK analysis was conducted with data from subjects with advanced melanoma participating in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022). The PPK analysis found that the

PK of ipilimumab was linear and exposures were dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters were time-invariant. The ipilimumab CL, T-HALF, and Vss calculated from the PPK analysis were 15.3 mL/h, 14.7 days, and 7.21 L, respectively. Ipilimumab CL and VC were higher in subjects with higher BBWT. In addition, the magnitude of the effects of the following covariates were not considered to be clinically relevant (< 20%): age, gender, prior anti-cancer therapy, ECOG PS, and BLDH.

Combination with nivolumab

The PK of ipilimumab in combination with nivolumab has also been previously characterized using a PPK approach with data from subjects with previously untreated advanced melanoma using a time-invariant model. In an updated analysis of ipilimumab in combination with nivolumab, nivolumab and ipilimumab PK was described by a time-varying model across multiple tumors types including NSCLC, SCLC, melanoma, and RCC. In that analysis, ipilimumab CL was shown to decrease with time (~24%). The CL of ipilimumab combined with nivolumab 0.3 mg/kg Q3W, 1 mg/kg Q2W, and 3 mg/kg Q3W was similar to that of ipilimumab monotherapy, although a statistically significantly higher (5% and 16% respectively) ipilimumab CL was seen with the combination of nivolumab 1 mg/kg Q3W and 3 mg/kg Q2W compared to ipilimumab monotherapy, that was not expected to be clinically relevant. The effect of SCLC, RCC, and NSCLC (squamous and non-squamous) tumor type did not significantly impact ipilimumab CL, as compared to melanoma tumor type. Ipilimumab CL significantly increased with increasing BBWT and BLDH; however, this was not expected to be clinically relevant. Ipilimumab CL was higher in subjects with higher BTSIZE and lower BALB; however, this effect was not expected to be clinically relevant. Ipilimumab CL did not change in the presence of anti-ipilimumab antibodies relative to CL when these antibodies were not detected. Ipilimumab CL and exposures were similar in Japanese and non-Japanese subjects following administration of ipilimumab at 1 mg/kg Q3W or Q6W and 3 mg/kg Q3W in both monotherapy and in combination with nivolumab.

Current combination data with nivolumab

The current ipilimumab integrated PPK analysis dataset included 12653 ipilimumab concentration values from 3411 subjects with melanoma, NSCLC, RCC, HCC, CRC or SCLC who received ipilimumab monotherapy or combination therapy (with nivolumab). The covariates assessed included administration with nivolumab (various regimens), BBWT, baseline LDH, tumor type, and line of therapy on ipilimumab CL, and BBWT on ipilimumab VC. The effect of nivolumab coadministration and PS on EMAX was also assessed.

The analysis demonstrated that the PK of ipilimumab, alone and in combination with nivolumab, was well described by a linear 2-compartment model with time-varying CL.

Table 8: Parameter Estimates for the Final Ipilimumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	14.1	0.231 (1.66)	13.6-14.5
VC_{REF} [L]	θ_2	3.95	0.0255 (0.646)	3.90-4.0
Q_{REF} [mL/h]	θ_3	27.9	2.22 (7.97)	23.9-32.2
VP_{REF} [L]	θ_4	3.18	0.0802 (2.52)	3.04-3.35
CL_{BBWT} [power]	θ_7	0.694	0.0315 (4.55)	0.63-0.75
V_{BBWT} [power]	θ_8	0.600	0.0293 (4.88)	0.54-0.66
CL_{BLDH} [power log]	θ_9	0.703	0.0716 (10.2)	0.57-0.84
$EMAX_{REF}$	θ_{10}	-0.0644	0.0306 (47.4)	-0.12-0.002
T50 [h]	θ_{11}	2540	86.5 (3.41)	2364.0-2727
HILL	θ_{12}	7.43	1.58 (21.3)	4.93-19.3
CL_{SCLC}	θ_{16}	-0.124	0.0317 (25.6)	-0.19--0.06
$CL_{1mg/kg\ Q3W}$				
$CL_{3\ mg/kg\ Q2W}$	θ_{21}	0.191	0.0185 (9.71)	0.15-0.23
CL_{LINE}	θ_{23}	-0.0949	0.0162 (17.1)	-0.12--0.06
$EMAX_{COMBO}$	θ_{24}	-0.202	0.0305 (15.1)	-0.27--0.14
Random Effects				
$\omega 2CL$[-]	$\omega_{1,1}$	0.112 (0.334)	0.00514 (4.60)	0.102-0.123
$\omega 2VC$ [-]	$\omega_{2,2}$	0.0884 (0.297)	0.00939 (10.6)	0.070-0.110
$\omega 2EMAX$	$\omega_{3,3}$	0.0158 (0.126)	0.00797 (50.5)	0.002-0.046
$\omega 2CL$[-]:ω2VC	$\omega_{1,2}$	0.0404 (0.406)	0.00332 (8.22)	0.034-0.123
Residual Error				
Proportional [-]	θ_5	0.223	0.00568 (2.55)	0.21-0.23
Additive [ug/mL]	θ_6	0.607	0.109 (17.9)	0.28-0.77

Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final
Program Source: Analysis Directory/psn/run18_1.dir1NM_run1/psn.lst
Source: Analysis Directory/psn/pirana_reports/run18_1_RTF.rtf
Bootstrap Source: Analysis Directory/psn/bootstrap_dir1/bootstrap_results.csv
Note: $CL0_{REF}$ is the typical value in a reference subject with melanoma, NSCLC, RCC, HCC, or CRC tumor type, receiving ipilimumab monotherapy or combination therapy with nivolumab (0.3 mg/kg Q3W, 3 mg/kg Q3W, or 1 mg/kg Q2W) 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. 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: Eta shrinkage (%): ETA_CL: 12.9; ETA_VC: 29.1; ETA_EMAX: 78.6; EPS shrinkage (%):17.2.

[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

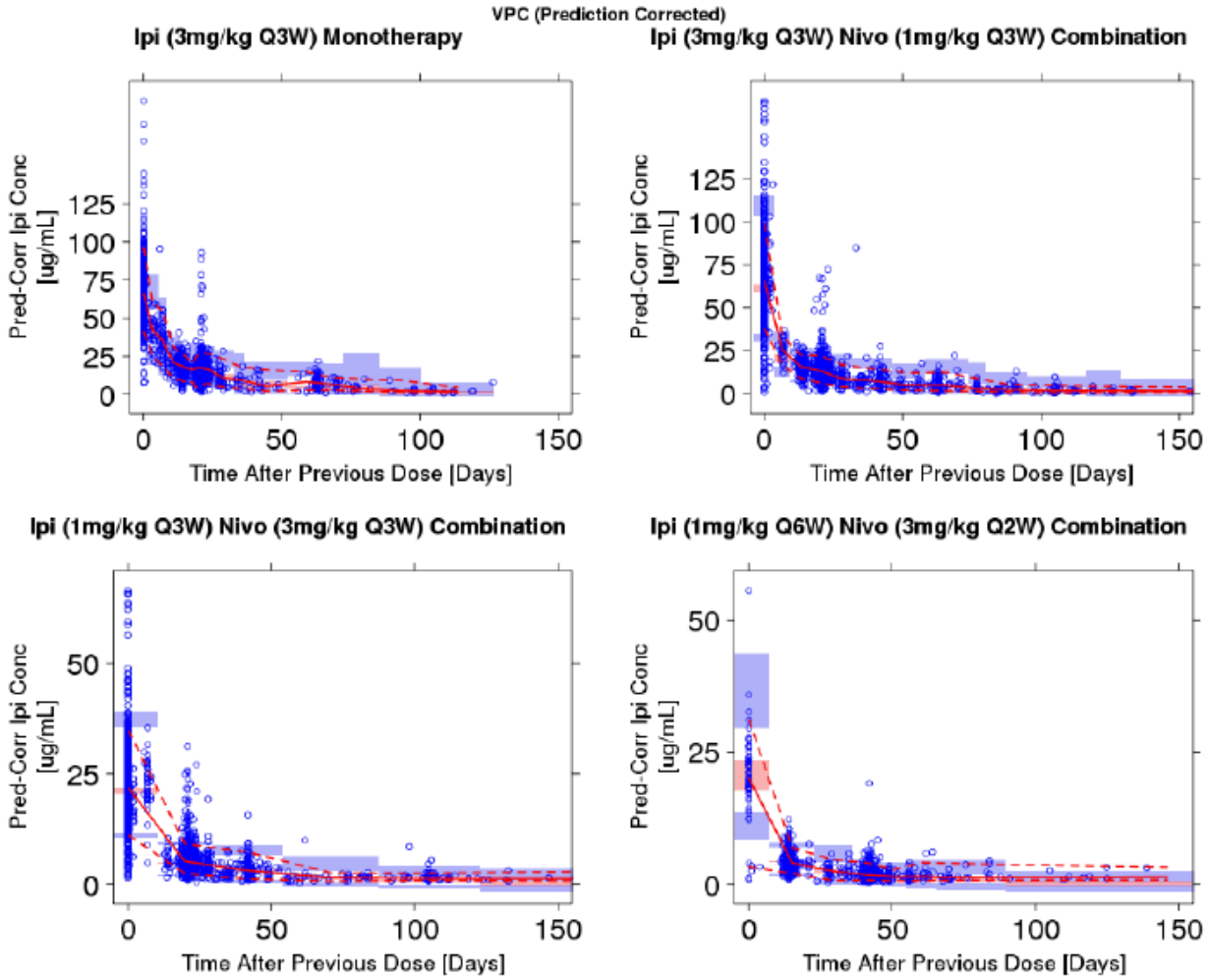
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[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 interval values are taken from bootstrap calculations (982 out of 1000 successful runs)

The predictive performance of the final PPK model was determined using pcVPC with stratification by the selected ipilimumab + nivolumab dosing regimens that are approved or being tested in pivotal studies in different solid tumors. Figure 6 and Figure 7 show the pcVPC plots of all ipilimumab concentrations versus time after the previous dose and ipilimumab trough concentrations after the first dose, respectively. The pcVPC plots show that the model adequately characterized the data from the 5th to the 95th percentiles. The plots show that the solid lines representing the 5th, 50th, and 95th percentiles of the observed data pass through respective 90% prediction interval (the shaded band) of the PK data up to the first 25 days after the previous dose and the first 100 days after the first dose.



Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final

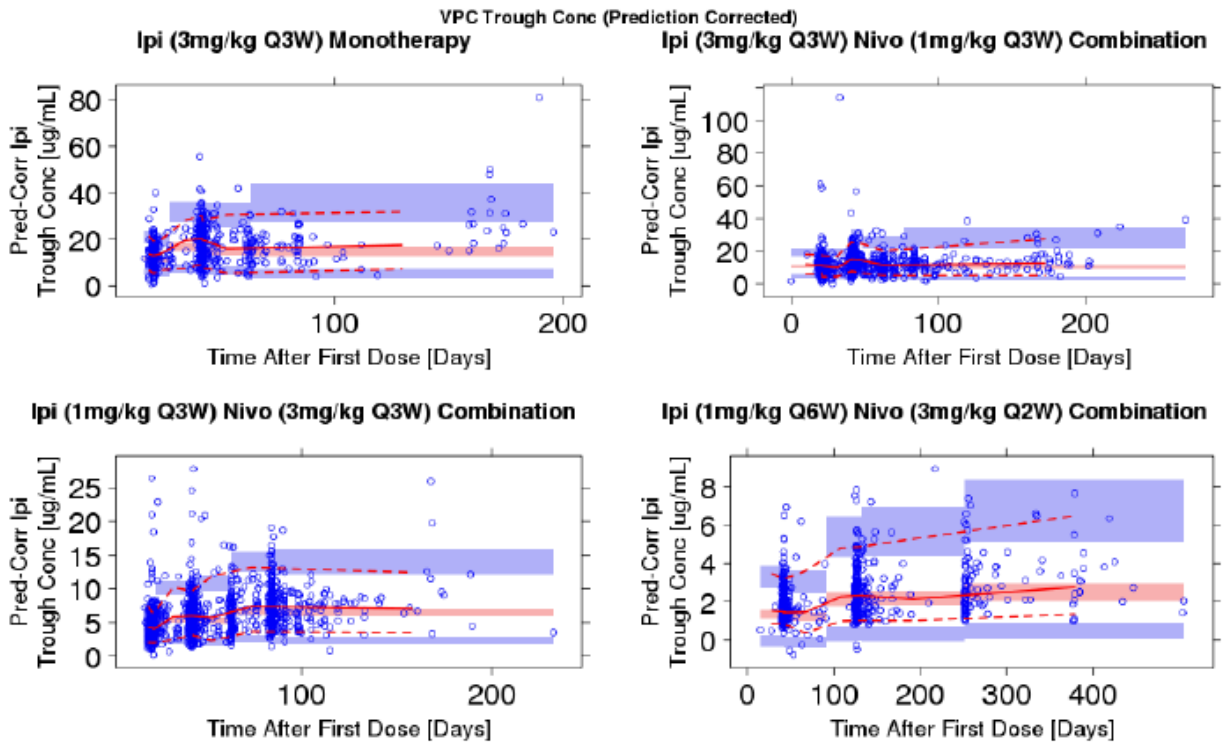
Psn Program Source: Analysis Directory/psn/run19

Program Source: Analysis Directory/R/scripts.vpc-plots.r

Figure Source: Analysis Directory/psn/vpc_full_dir2/VPC-plots1 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 6: Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose Stratified by Selected Ipilimumab Dosing Regimens (Final Ipilimumab Population Pharmacokinetic Model)



Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final

Psn Program Source: Analysis Directory/psn/run20

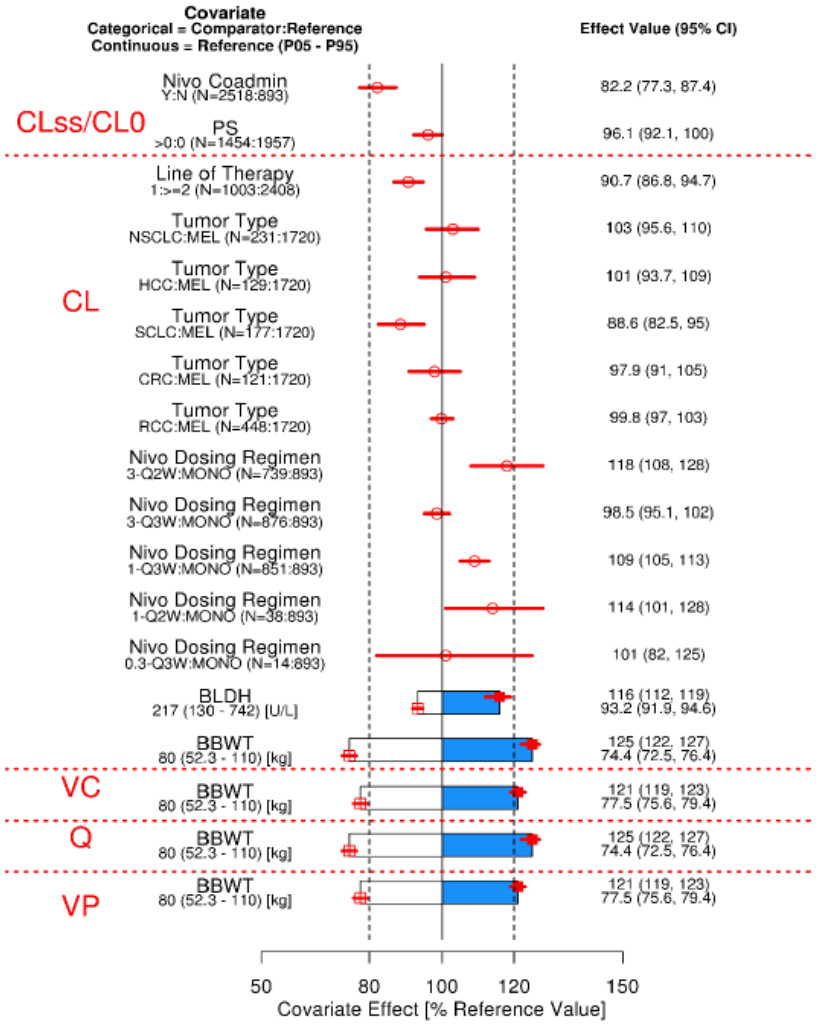
Program Source: Analysis Directory/R/scripts.vpc-plots.r

Figure Source: Analysis Directory/psn/vpc_trough_dir2/VPC-plots1 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 7: Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose Stratified by Selected Ipilimumab Dosing Regimens (Final Ipilimumab Population Pharmacokinetic Model)

The CL of ipilimumab was higher when administered in combination with nivolumab 1 mg/kg Q2W, 1 mg/kg Q3W, or 3 mg/kg Q2W compared to ipilimumab monotherapy; however, the magnitude of these differences are not considered to be clinically relevant (< 20%). Ipilimumab CL when given in combination with nivolumab 0.3 mg/kg or 3 mg/kg Q3W was not significantly different from that seen with ipilimumab monotherapy. Clearance of ipilimumab 1 mg/kg Q6W when administered with nivolumab 3 mg/kg Q2W (the proposed regimen for 1L NSCLC subjects) was 18% greater than with ipilimumab monotherapy. The CL of ipilimumab in subjects with NSCLC was not significantly different relative to subjects with melanoma. Ipilimumab CL was higher in subjects with higher BBWT or higher BLDH; however, the magnitude of these differences are not considered to be clinically relevant.



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

PsN Program Source: Analysis Directory/psn/run4_5.dir3/NM_run1/sdtab4_1

Program Source: Analysis Directory/R/scripts/coveff-plot-full_nregi.r

Figure Source: Analysis Directory/R/plots/full-nivoregi-ppk-coveff-plot-new.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 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.

Figure 8: Covariate Effects on Ipilimumab Pharmacokinetic Model Parameters (Full Ipilimumab Population Pharmacokinetic Model)

In the sensitivity analysis, ipilimumab CL was higher in subjects with larger BTSIZE and lower BALB; however, the magnitude of these differences are not considered to be clinically relevant. Ipilimumab CL was not significantly different in the presence of anti ipilimumab antibodies.

Ipilimumab CL decreased with time and the decrease was greater in subjects receiving ipilimumab in combination with nivolumab (~5% and ~22% in subjects receiving ipilimumab monotherapy and ipilimumab in combination with nivolumab respectively). The time for half maximal reduction was ~106 days. The variability around EMAX predicted by the model was ~38.5%. Although there is no clear mechanistic understanding of the reasons for the time-varying CL of ipilimumab or nivolumab, it is hypothesized that the decrease in ipilimumab CL over the course of treatment may be associated with

improvement in disease status and the corresponding decrease in the rate of cancer related cachexia. This hypothesis is further supported by the finding that ipilimumab CL decreased with higher magnitude in subjects receiving combination with nivolumab compared to monotherapy alone.

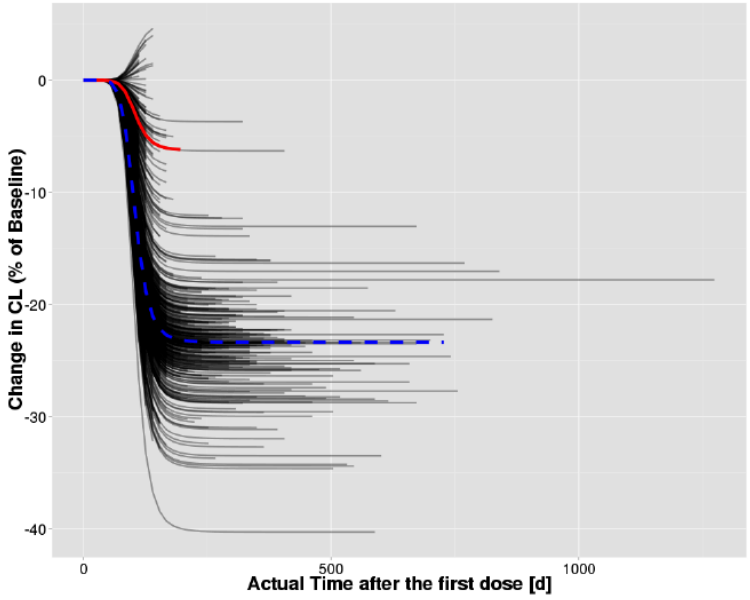


Figure 9: Model Estimated Overall Change in Ipilimumab Clearance versus Time from the Final Model

The red line and blue dashed line are typical change in CL over time in ipilimumab monotherapy and in combination with nivolumab, respectively.

The sensitivity analysis also demonstrated that the magnitude of change in ipilimumab CL over time was higher in responders (CR and PR subjects) compared to non-responders (SD and PD subjects). In addition, the magnitude of change in CL for subjects experiencing a PR was higher compared to those demonstrating PD; however, this difference is not considered to be clinically relevant.

The effect of tumor mutational burden on ipilimumab PK was also assessed graphically. The PK of ipilimumab was similar in 1L NSCLC subjects with high, low, or not evaluable baseline TMB status who received nivolumab + ipilimumab combination therapy.

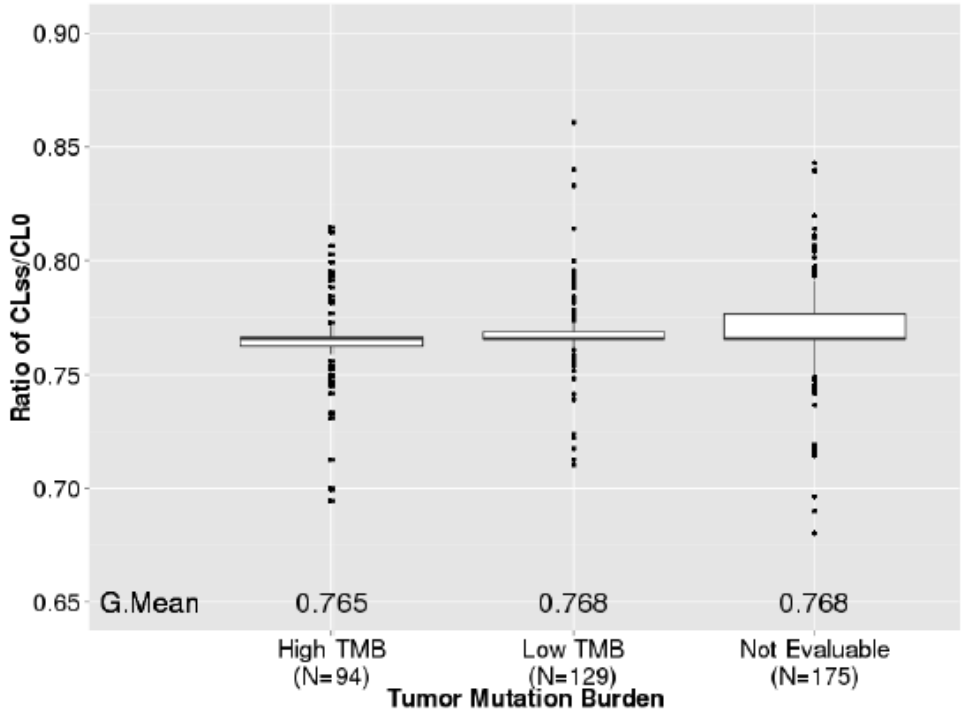


Figure 10: Distribution of Ipilimumab Ratio of Steady-State CL to Baseline CL by TMB Status in Subjects with 1L NSCLC who Received Ipilimumab in Combination with Nivolumab in Study CA209227 Ratio of Steady-State Clearance to Baseline Clearance

The individual parameter estimates for ipilimumab in monotherapy (3 mg/kg Q3W) and in combination (**1 mg/kg Q6W**) with 3 mg/kg Q2W ipilimumab obtained from the full popPK model and the exposure estimates are summarized in the following tables:

Table 9: Summary Statistics of Individual Measures of Ipilimumab Parameters in Monotherapy (3 mg/kg Q3W) Across Tumour Types

Parameters	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CL0 [mL/h]	475	14	12.9	13.2(3.66,52.5)	5.86	41.9
CLSS [mL/h]	475	13.1	12.1	12.2(3.43,49.2)	5.5	42
VC [L]	475	4.01	3.89	3.97(0.99,7.67)	0.97	24.2
VSS [L]	475	7.2	7.09	7.19(4.1,11.8)	1.25	17.3
PEMAX[%]	475	93.8	93.7	93.8(82.4,105)	2.74	2.92
T-HALFα [h]	475	39.4	39.1	39.6(13.3,48.9)	4.17	10.6
T-HALFα-SS [h]	475	39.7	39.4	39.9(13.5,49)	4.18	10.5
T-HALFβ-SS[d]	475	18.2	17.6	18(6.8,45.8)	5.13	28.1
T-HALFβ [d]	475	19.3	18.6	19(7.1,48.7)	5.51	28.5

Source: Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final/

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

Source: Analysis Directory/R/export/stats-para_mono.csv

VSS was calculated using formula: VSS=VC+VP.

PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.

T-HALF-β and T-HALF-α were calculated using formula as below:

KE = CL/VC; K12 = Q/VC; K21 = Q/VP; AA = KE + K12 + k21

$\beta = (\frac{AA - \sqrt{AA^2 - 4 \times KE \times K21}}{2})$, and $t_\beta = (\frac{0.693}{\beta})$

$\alpha = (\frac{AA + \sqrt{AA^2 - 4 \times KE \times K21}}{2})$, and $t_\alpha = (\frac{0.693}{\alpha})$

T-HALF-β-SS and T-HALF-α-SS were calculated using parameters estimates at steady state.

Individual estimates of Q, V2 T50 and HILL are 26.3 mL/h, 3.18 L, 2540 hours and 7.43, respectively, as there are no random or covariate effect parameters associated with these parameters in the final PPK model.

Table 10: Summary Statistics of Individual Measures of Ipilimumab Exposures in Monotherapy (3 mg/kg Q3W) Across Tumor Types

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	475	12	11.3	12.1(1.8,29.5)	3.89	32.4
CMAX1	475	62.8	60.6	59.5(13.7,279)	22.1	35.1
CAVG1	475	22.3	21.8	22.2(9.81,40.3)	4.62	20.7
CMIN4	475	22.9	20.5	22.1(2.19,87.3)	10.5	46
CMAX4	475	84.6	81.7	81.8(42.2,294)	26.3	31.1
CAVG4	475	38.1	36.1	37.2(10.9,108)	12.3	32.4

Source: Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final/

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

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

Table 11: Summary Statistics of Individual Measures of Ipilimumab Parameters in Combination Therapy (Nivo: 3 mg/kg Q2W, Ipi: 1 mg/kg Q6W) in Subjects with Non-small Cell Lung Cancer

Parameters	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CL0 [mL/h]	669	15.3	14.7	14.9(4.5,34)	4.43	29
CLSS [mL/h]	669	11.7	11.2	11.4(3.39,26)	3.43	29.3
VC [L]	669	3.77	3.72	3.73(1.41,6.55)	0.604	16
VSS [L]	669	6.77	6.7	6.69(3.8,10.4)	0.972	14.4
PEMAX[%]	669	76.6	76.6	76.6(65.6,86.1)	2.02	2.64
T-HALFα [h]	669	39.3	39.2	39.4(25.6,45.4)	1.59	4.05
T-HALFα-SS [h]	669	40.5	40.4	40.6(26.7,46.1)	1.67	4.13
T-HALFβ-SS[d]	669	15.2	14.9	14.8(9.17,47.4)	3.33	21.9
T-HALFβ [d]	669	19.4	18.9	18.5(11.4,62.4)	4.52	23.3

Source: Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final/
Program Source: Analysis Directory/R/scripts/exposure-summary.R
Source: Analysis Directory/R/export/stats-para_ipi1.nivo3.2_nsclc.csv
VSS was calculated using formula: VSS=VC+VP.
PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.
T-HALF-β and T-HALF-α were calculated using formula as below:
KE = CL/VC; K12 = Q/VC; K21 = Q/VP; AA = KE + K12 + k21

$$\beta = \left(\frac{AA - \sqrt{AA^2 - 4 \times KE \times K21}}{2}\right), \text{ and } t_\beta = \left(\frac{0.693}{\beta}\right)$$

$$\alpha = \left(\frac{AA + \sqrt{AA^2 - 4 \times KE \times K21}}{2}\right), \text{ and } t_\alpha = \left(\frac{0.693}{\alpha}\right)$$

T-HALF-β-SS and T-HALF-α-SS were calculated using parameters estimates at steady state.
Individual estimates of Q, V2 T50 and HILL are 26.3 mL/h, 3.18 L, 2540 hours and 7.43, respectively, as there are no random or covariate effect parameters associated with these parameters in the final PPK model.

Table 12: Summary Statistics of Individual Measures of Ipilimumab Exposures in Combination Therapy (Nivo: 3 mg/kg Q2W, Ipi: 1 mg/kg Q6W) in Subjects with Non-small Cell Lung Cancer

Exposure Estimate	N	Mean	GeoMean	Median (Min- Max)	SD	%CV
CMIN1	669	1.25	1.13	1.12(0.271,7.2)	0.63	50.3
CMAX1	669	19.3	19.2	19(14,34.9)	2.59	13.4
CAVG1	669	4.3	4.2	4.19(2.43,10.8)	0.931	21.7
CMINSS	669	2.64	2.34	2.27(0.613,22.8)	1.56	59
CMAXSS	669	22	21.7	21.4(14.9,52.4)	3.67	16.7
CAVGSS	669	6.56	6.32	6.2(3.33,29.9)	2.06	31.4

Source: Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final/
Program Source: Analysis Directory/R/scripts/exposure-summary.R
Source: Analysis Directory/R/export/expo.ipi1.6.nivo3.2_nsclc.csv

The PK of ipilimumab was similar in 1L NSCLC subjects with high, low, or not evaluable baseline TMB status who received nivolumab + ipilimumab combination therapy (Table 13). The ratio CLss to CL0 was 0.765 and 0.768 in subjects with high and low TMB, respectively.

Table 13: Summary Statistics of Individual Measures of Ipilimumab Exposures by TMB status in Combination Therapy (Nivo: 3 mg/kg Q2W, Ipi: 1 mg/kg Q6W) in Subjects with 1L NSCLC in Study CA209227

Exposure Estimate	High TMB N = 94 GM [µg/mL] (%CV)	Low TMB N =129 GM [µg/mL] (%CV)	Not Evaluable N = 175 GM [µg/mL] (%CV)	All N = 398 GM [µg/mL] (%CV)
CMIN1	1.16(41.9)	1.14(48.3)	1.11(49.9)	1.13(47.5)
CMAX1	19(12.2)	18.9(11.9)	19.2(14.1)	19.1(13)
CAVG1	4.22(18.8)	4.19(21.4)	4.18(22.9)	4.2(21.4)
CMINSS	2.42(45.8)	2.37(52.3)	2.29(52.4)	2.35(50.7)
CMAXSS	21.6(14.2)	21.4(15.2)	21.7(17.1)	21.6(15.8)
CAVGSS	6.38(25.5)	6.3(29)	6.26(29.7)	6.3(28.4)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/tmb-ipi/final/
R-Program Source: Analysis-Directory/R/scripts/ exposure_summary.R
Source: Analysis-Directory/R/export/summary.table.227.csv

2.3.3. Pharmacodynamics

Mechanism of action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation.

PD-L1 has high affinity for PD-1 but can also bind to CD80 on T-cells and CD80 expression might contribute to PD-L1-induced inactivation of CD8+ T-cells (Rollins 2017). Combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) may thus result in enhanced T-cell function that is greater than the effects of either antibody alone. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity supporting the rationale for the combination of both products.

Primary and secondary pharmacology

Justification of Recommended Nivolumab and Ipilimumab Dose

The nivolumab and ipilimumab combination dose regimen (nivolumab 3 mg/kg over 30 minutes Q2W + ipilimumab 1 mg/kg over 30 minutes Q6W) was chosen based upon data from the Phase 1 Study CA209012. In Study CA209012, Cohorts P and Q used the 3 mg/kg Q2W dose of nivolumab (the approved monotherapy regimen) and lower and less frequent dosing of ipilimumab (1 mg/kg Q6W or Q12W) which provided comparable safety and efficacy. Given no increase in toxicity with the more

frequent dosing, the nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W (Cohort Q) regimen was chosen for further investigation in NSCLC (for further details see Dose Response Study section).

The selected dose and schedule of nivolumab and ipilimumab was further evaluated in CA209568 and CA209227. The assessment of available data from CA209227, CA209568, and CA209012 (Cohort Q) indicates that the selected dose and schedule of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W offers a favorable benefit-risk profile in subjects with previously-untreated recurrent or metastatic NSCLC. This conclusion is based on the improvements in clinical outcomes (PFS, ORR and DoR) with nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W relative to platinum-based doublet chemotherapy in CA209227, and the safety and tolerability of this dose regimen, in addition to longer term clinical follow-up.

The exposure-response modelling using data from Study CA209012 further supports this dose regimen. Specifically, the tumor growth dynamic modelling demonstrated that ipilimumab in combination with nivolumab 3 mg/kg Q2W resulted in enhanced antitumor activity in subjects with NSCLC, compared to nivolumab 3 mg/kg Q2W monotherapy and the exposure-safety analysis demonstrated that the hazard of AE-DC/D with the combination of nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W was not significantly different from nivolumab 3 mg/kg monotherapy.

In addition, this combination dosing regimen is supported by the findings of the population pharmacokinetics analysis that demonstrated nivolumab and ipilimumab clearances that were similar to those seen with monotherapy for both agents.

Overview of Nivolumab and Ipilimumab Immunogenicity

Immunogenicity Results for CA209012

Nivolumab ADA

For cohort Q of CA209012, where nivolumab was administered at a dose of 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W (the recommended dose for nivolumab and ipilimumab in 1L NSCLC), the rate of nivolumab immunogenicity was low (12%) and similar to that seen with nivolumab 3 mg/kg Q2W monotherapy (11.2% from USPI). No subjects were positive for neutralizing ADA and no subjects were considered persistent positive. The highest titer value observed in ADA positive subjects was 32, which occurred in 1 subject. All other ADA positive subjects had titer values of 4 or less.

Ipilimumab ADA

Ipilimumab immunogenicity in cohort Q of CA209012 was low (4%) and similar to ipilimumab monotherapy. Only one subject was ipilimumab ADA positive with a low titer of 1. None of the subjects were persistent positive or neutralizing ADA positive (Table 4.2.1.1-1).

Table 14: Summary of Nivolumab ADA Assessments Based on 16-Week Definition of Persistent Positive - All Treated Subjects with Baseline and at Least One Post-Baseline Assessment - CA209012

Subject ADA Status	Nivolumab ADA Assessments for Cohort Q N = 25	Ipilimumab ADA Assessments for Cohort Q N = 25
Baseline ADA Positive, N (%)	2 (8.0)	1 (4.0)
ADA Positive, N (%)	3 (12.0)	1 (4.0)
Persistent positive (PP), N (%)	0	0
Not PP-Last sample positive, N (%)	2 (8.0)	0
Other positive, N (%)	1 (4.0)	1 (4.0)
Neutralizing ADA positive, N (%)	0	0
ADA Negative, N (%)	22 (88.0)	24 (96.0)

Treatment: Q=IPI1Q6W+NIV3Q2W; S=Squamous; NS=Non-squamous
Baseline ADA Positive: A subject with baseline ADA-positive sample; ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment; Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart; Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint; Other Positive: Not PP but some ADA-positive samples with the last sample being negative; Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline; ADA Negative: A subject with no ADA-positive sample after initiation of treatment

Source: Refer to Table S.8.1A and Table S.8.1B of the CA209012 CSR[9]

Immunogenicity Results from CA209568

Nivolumab ADA

Of the 251 nivolumab ADA evaluable subjects, 21 (8.4%) subjects were nivolumab ADA positive at baseline and 96 (38.2%) subjects were nivolumab ADA positive after start of treatment. In Part 1, 1/251 (0.4%) subject was considered persistent positive and 11 (4.4%) subjects were neutralizing ADA positive. The highest titer value observed in nivolumab ADA positive subjects was 4096, which occurred in 1 subject whose BOR was stable disease.

Ipilimumab ADA

Of the 253 ipilimumab ADA evaluable subjects, 11 (4.3%) subjects were ipilimumab ADA positive at baseline and 30 (11.9%) subjects were ipilimumab ADA positive after the start of treatment. In Part 1, 2/253 (0.8%) subjects were considered persistent positive and no subjects were neutralizing ADA positive. Ipilimumab titers were low, ranging 1 to 256.

Table 15: ADA Assessments Based on 16-Week Definition of Persistent Positive: Nivolumab+ Ipilimumab-treated Subjects in Part 1 with Baseline and at Least One Post-Baseline Assessment

	Number of Subjects (%)	
	Treated Subjects	
	Nivolumab ADA N = 251	Ipilimumab ADA N = 253
BASELINE ADA POSITIVE	21 (8.4)	11 (4.3)
ADA POSITIVE	96 (38.2)	30 (11.9)
PERSISTENT POSITIVE	1 (0.4)	2 (0.8)
NOT PP - LAST SAMPLE POSITIVE	33 (13.1)	6 (2.4)
OTHER POSITIVE	62 (24.7)	22 (8.7)
NEUTRALIZING ADA POSITIVE	11 (4.4)	0
ADA NEGATIVE	155 (61.8)	223 (88.1)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint;
Other Positive: Not PP but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Source: Table S.7.1 of the CA209568 CSR

Immunogenicity Results from CA209227

Nivolumab ADA

Of the 291 nivolumab ADA evaluable subjects in the nivolumab monotherapy group (Arm A), 65 (22.3%) subjects were nivolumab ADA positive after treatment. 2 (0.7%) subjects were considered persistent positive and 5 (1.7%) subjects were positive for neutralizing ADA. Of the 431 nivolumab ADA evaluable subjects in the nivolumab + ipilimumab arm (Arms B + D), 159 (36.9%) subjects were nivolumab ADA positive after start of treatment. 5 (1.2%) subjects were considered persistent positive and 7 (1.6%) subjects were neutralizing ADA (NAb) positive. Of the 132 nivolumab ADA evaluable subjects in the nivolumab + chemotherapy arm (Arm G), 12 (9.1%) subjects were nivolumab ADA positive after start of treatment. 1 (0.8%) subject was neutralizing ADA positive.

Ipilimumab ADA

Of the 424 ipilimumab ADA evaluable subjects in the nivolumab + ipilimumab arm (Arms B + D), 32 (7.5%) subjects were ipilimumab ADA positive after the start of treatment. 3 (0.7%) subjects were considered persistent positive and no subjects were neutralizing ADA positive.

Table 16: ADA Assessments based on 16-Week Definition of Persistent Positive: Nivolumab+ Ipilimumab and Nivolumab-treated Subjects in Part 1 with Baseline and at Least One Post-Baseline Assessment – Study CA209227

	Number of Subjects (%)			
	Nivo + Ipi (Arms B + D)		Arm A: Nivolumab	Arm G: Nivo + Chemo
	Nivolumab ADA N = 431	Ipilimumab ADA N = 424	Nivolumab ADA N = 291	Nivolumab ADA N = 132
BASELINE ADA POSITIVE	34 (7.9)	15 (3.5)	30 (10.3)	6 (4.5)
ADA POSITIVE	159 (36.9)	32 (7.5)	65 (22.3)	12 (9.1)
PERSISTENT POSITIVE	5 (1.2)	3 (0.7)	2 (0.7)	0
NOT PP - LAST SAMPLE POSITIVE	43 (10.0)	11 (2.6)	16 (5.5)	4 (3.0)
OTHER POSITIVE	111 (25.8)	18 (4.2)	47 (16.2)	8 (6.1)
NEUTRALIZING ADA POSITIVE	7 (1.6)	0	5 (1.7)	1 (0.8)
ADA NEGATIVE	272 (63.1)	392 (92.5)	226 (77.7)	120 (90.9)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint; Other Positive: Not PP but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Source: Table 8.7.10.1 of the CA209227 CSR[10]

Effect of Immunogenicity on Safety

The effect of immunogenicity on safety was assessed in the nivolumab + ipilimumab (Arms B + D), nivolumab (Arm A), and nivolumab + chemotherapy (Arm G) arms. Overall, the incidence of nivolumab ADA was low and did not appear to have an effect on safety of the tested regimens.

Nivolumab + Ipilimumab (Arms B + D)

Of all nivolumab-treated subjects in the nivolumab + ipilimumab arm who were evaluable for nivolumab ADA, hypersensitivity/infusion reaction select AEs were experienced by 11/272 (4.0%) ADA negative subjects and 7/159 (4.4%) ADA-positive subjects. In addition, the number of subjects with infusion related and hypersensitivity reactions was comparable between nivolumab ADA positive and nivolumab ADA negative subgroups. Thus, the presence of nivolumab ADA did not appear to be associated with the occurrence of these events. Of all of the nivolumab + ipilimumab-treated subjects who were evaluable for ipilimumab ADA, hypersensitivity/infusion reaction select AEs were experienced by 13/392 (3.3%) ADA negative subjects and 4/32 (12.5%) ADA positive subjects. The proportion of subjects with hypersensitivity/infusion reactions was higher in ipilimumab ADA positive subjects than in ipilimumab ADA negative subjects; however, most of these hypersensitivity/infusion reactions were Grade 1 or 2 and all resolved.

Nivolumab Arm (Arm A)

Of all nivolumab-treated subjects in the nivolumab monotherapy arm who were evaluable for ADA, hypersensitivity/infusion reaction select AEs were experienced by 8/226 (3.5%) ADA negative subjects and 3/65 (4.6%) ADA-positive subjects. The number of subjects with infusion-related and hypersensitivity reactions was comparable between nivolumab ADA positive and ADA negative subgroups. Thus, the presence of ADA did not appear to be associated with the occurrence of these events.

Nivolumab + Chemotherapy Arm (Arm G)

Of all nivolumab-treated subjects in the nivolumab + chemotherapy arm who were evaluable for nivolumab ADA, hypersensitivity/infusion reaction select AEs were experienced by 1/120 (0.8%) ADA-negative subject and 1/12 (8.3%) ADA-positive subject. For nivolumab + chemotherapy treatment, the number of subjects with infusion related and hypersensitivity reactions was comparable between

nivolumab ADA positive and ADA negative subgroups. Thus, the presence of nivolumab ADA did not appear to be associated with the occurrence of these events.

Table 17: Select AEs of Hypersensitivity/Infusion Reaction by ADA Status: All Treated Subjects with ADA Positive or ADA Negative, All Treated Subjects in Part 1

	Nivo + Ipi (Arms B + D)			
	Nivolumab ADA		Ipilimumab ADA	
Preferred Term	Positive N = 159	Negative N = 272	Positive N = 32	Negative N = 392
TOTAL SUBJECTS WITH AN EVENT	7 (4.4)	11 (4.0)	4 (12.5)	13 (3.3)
Anaphylactic reaction	0	1 (0.4)	1 (3.1)	0
Bronchospasm	1 (0.6)	1 (0.4)	0	2 (0.5)
Hypersensitivity	1 (0.6)	1 (0.4)	0	2 (0.5)
Infusion related reaction	5 (3.1)	8 (2.9)	3 (9.4)	9 (2.3)

	Arm A: Nivolumab		Arm G: Nivo + Chemo	
	Nivolumab ADA		Nivolumab ADA	
Preferred Term	Positive N = 65	Negative N = 226	Positive N = 12	Negative N = 120
TOTAL SUBJECTS WITH AN EVENT	3 (4.6)	8 (3.5)	1 (8.3)	1 (0.8)
Anaphylactic reaction	0	1 (0.4)	0	0
Bronchospasm	0	2 (0.9)	0	0
Hypersensitivity	0	1 (0.4)	1 (8.3)	0
Infusion related reaction	3 (4.6)	4 (1.8)	0	1 (0.8)

Source: Table 8.7.238
MedDRA Version: 20.1
CTC Version 4.0
Includes events between first dose and within the last dose of therapy + 100 days

Effect of Nivolumab Immunogenicity on Efficacy

Overall, the incidence of nivolumab neutralizing ADA was low across the treatment arms. No subjects were positive for ipilimumab neutralizing antibodies. Based on assessment of the presence of nivolumab ADA and nivolumab neutralizing antibodies vs BOR, PFS or OS, subjects with nivolumab neutralizing antibodies continued treatment with clinical benefit, and there was no apparent trend showing an effect of neutralizing ADA on the efficacy of the tested regimens. The ORRs for neutralizing ADA positive subjects were 57.0% (4/7) with nivolumab + ipilimumab (Arms B + D), 40.0% (2/5) with nivolumab (Arm A), and 100.0% (1/1) with nivolumab + chemotherapy (Arm G). These results are generally consistent with the ORRs observed in each entire treatment arm (32.2% 188/583 with nivolumab + ipilimumab [Arms B + D], 27.0% [107/396] with nivolumab [Arm A], and 36.7% 65/177 with nivolumab + chemotherapy [Arm G]), which included the neutralizing ADA negative subjects.

Nivolumab + Ipilimumab (Arms B + D)

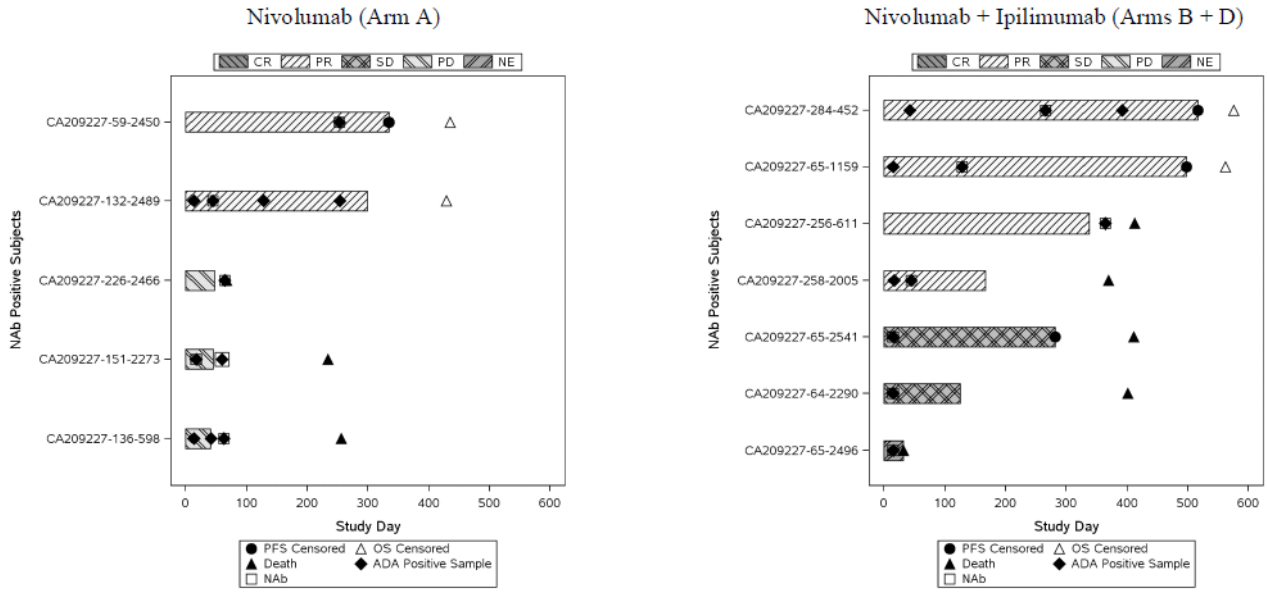
Of the 7 subjects who were nivolumab neutralizing ADA positive, 4 subjects had a BOR of PR, 2 subjects had a BOR of SD, and 1 subject had a BOR reported as NE. The ADA titers in these subjects were low and ranged from 1 to 128.

Nivolumab Arm (Arm A)

Of the 5 subjects who were nivolumab neutralizing ADA positive, 2 subject had a BOR of PR and 3 subjects had a BOR of PD. The ADA titers in these subjects were low and ranged from 1 to 64.

Nivolumab + Chemotherapy (Arm G)

1 subject was nivolumab neutralizing ADA positive, with a BOR of PR. The ADA titers in this subject were 2.



Note: Bar indicates PFS
Source: Figure S.7.2

Figure 11: Nivolumab ADA and Neutralizing Anti-Drug Antibody Occurrence in Relation to PFS and BOR per BICR assessment, and OS: All Nivolumab Neutralizing ADA Positive Subjects Treated with Nivolumab or Nivolumab + Ipilimumab

2.3.4. PK/PD modelling

E-R analyses of safety and efficacy were conducted to assess the relationship between nivolumab and ipilimumab exposure (including potential synergistic interaction of exposure/treatment effects) and safety or TGD in subjects with advanced NSCLC in Study CA209012.

Exposure-Response of Efficacy: Tumor Growth Dynamics

The relationship between nivolumab and ipilimumab exposures and efficacy in subjects with advanced NSCLC was assessed with respect to tumor growth dynamics (TGD). Retrospective tumor-growth dynamic modeling was performed with longitudinal tumor measurements from subjects treated with nivolumab monotherapy or subjects from the nivolumab + ipilimumab combination cohorts in Study CA209012. Data from various regimens of nivolumab and ipilimumab were included in the analysis, with doses ranging from 1 mg/kg to 3 mg/kg and schedules varying from Q2W to Q12W.

Exposure was defined as average drug concentration over the first 12 weeks (Cavg0-12wk). Cavg0-12wk was chosen as the exposure metric because it provided an integer number of dosing intervals across Q2W to Q12W regimens.

Data from a total of 214 NSCLC subjects treated with nivolumab monotherapy or nivolumab + ipilimumab combination were included in the analysis. A total of 35 out of 249 nivolumab or ipilimumab treated subjects (14.06%) were excluded from the analysis due to unavailability of either nivolumab or ipilimumab exposure estimates or post-treatment tumor measures. Table 18 provides a summary description of the treatment regimens for the cohorts included in the E-R analyses. Three other nivolumab monotherapy cohorts were excluded from this analysis: subjects who completed chemotherapy (cohorts K and L), and subjects with asymptomatic brain metastases (cohort M).

Table 18: Summary of Cohorts Included in Exposure-Response Analysis for CA209012

Cohort[a]	No. of Treated Subjects	Regimen[b]
F	52	N3 Q2W
G, H	24	N1+ I3 Q3W x 4 then N3 Q2W
I, J	25	N3 + I1 Q3W x 4 then N3 Q2W
N	31	N1 + I1 Q3W x 4 then N3 Q2W
O	40	N1 Q2W + I1 Q6W
P	38	N3 Q2W + I1 Q12W
Q	39	N3 Q2W + I1 Q6W

[a] Cohorts G-H and I-J had 2 separate cohorts for each histology (SQ vs NSQ). Cohorts N-Q were combined histologies (SQ and NSQ)

[b] Nivolumab and ipilimumab dosing are shown in mg/kg IV (eg, N1 = nivolumab 1 mg/kg IV).

Source: Clinical Study Report CA209012[9]

Abbreviations: **N3 Q2W** = nivolumab 3 mg/kg Q2W; **N1+ I3 Q3W x 4 then N3 Q2W** = nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W x 4 then nivolumab 3 mg/kg Q2W; **N3 + I1 Q3W x 4 then N3 Q2W** = nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W x 4 then nivolumab 3 mg/kg Q2W; **N1 + I1 Q3W x 4 then N3 Q2W** = nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W x 4 then nivolumab 3 mg/kg Q2W; **N1 Q2W + I1 Q6W** = nivolumab 1 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; **N3 Q2W + I1 Q12W** = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W; **N3 Q2W + I1 Q6W** = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

All longitudinal tumor size data were reasonably characterized by the TGD model with exponential decline and linear growth functions. The parameter estimates, and their precisions for the TGD model, are listed in Table 19. All the model parameters including baseline tumor size (TB0), tumor shrinkage rate constant (SR) and progression rate (PR) were precisely estimated with a relative standard error (RSE) less than 15%.

Table 19: Parameter Estimates of TGD Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
TB0 [mm]	θ_1	59.7	2.65 (4.44)	54.5 - 64.9
PR [mm/week]	θ_2	0.357	0.0512 (14.3)	0.257 - 0.457
SR [1/week]	θ_3	0.0146	0.00199 (13.6)	0.0107 - 0.0185
Random Effects				
ω^2-*TB0*	$\omega_{1,1}$	0.404 (0.636)	0.0408 (10.1)	0.324 - 0.484
ω^2-*PR*	$\omega_{2,2}$	2.00 (1.41)	0.268 (13.4)	1.47 - 2.53
ω^2-*SR*	$\omega_{3,3}$	1.18 (1.09)	0.255 (21.6)	0.680 - 1.68
ω^2-*TB0*: ω^2-*PR*	$\omega_{1,2}$	0.552 (0.614)	0.0902 (16.3)	0.375 - 0.729
ω^2-*PR*: ω^2-*SR*	$\omega_{2,3}$	-0.582 (-0.379)	0.128 (22.0)	-0.833 - -0.331
Residual Error				
AERR [mm]	θ_4	2.68	0.158 (5.90)	2.37 - 2.99
PERR [-]	θ_5	0.133	0.00582 (4.38)	0.122 - 0.144

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Source: Analysis Directory/nm/tgdbase.rtf

[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. In this analysis all parameters were estimated.

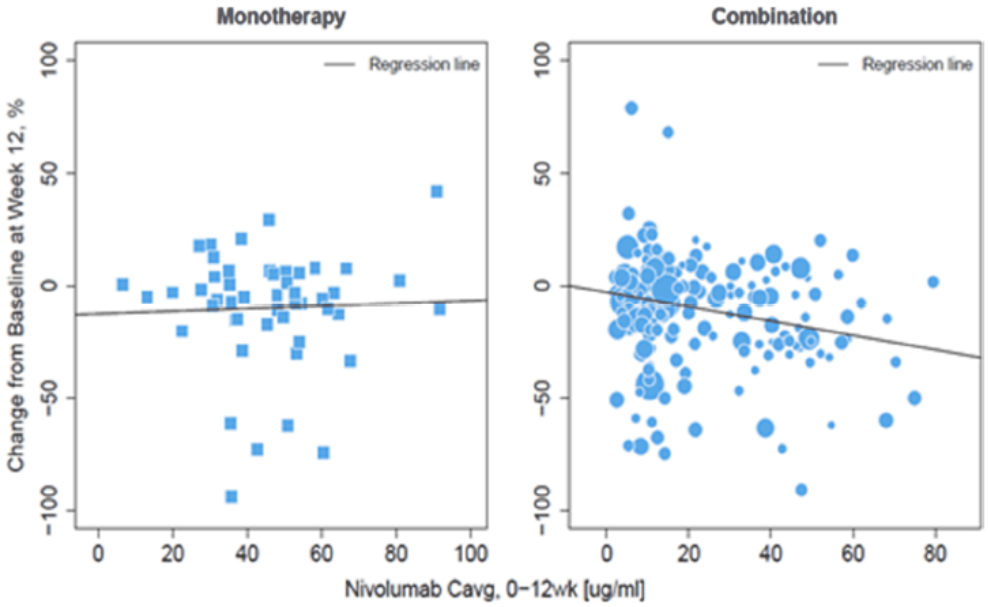
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[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*

In subjects who received nivolumab monotherapy, there was no association of tumor shrinkage with nivolumab exposure based on an exploratory regression analysis (Figure 12). In combination with ipilimumab, higher tumor shrinkage was seen with increased nivolumab exposure, suggesting that ipilimumab may potentiate the effect of nivolumab in NSCLC subjects. However, there was no clear trend between tumor shrinkage and ipilimumab concentration, which is evidenced by the majority of the larger circles that represent higher ipilimumab concentrations being located on the side that did not result in maximal tumor shrinkage (Figure 12).

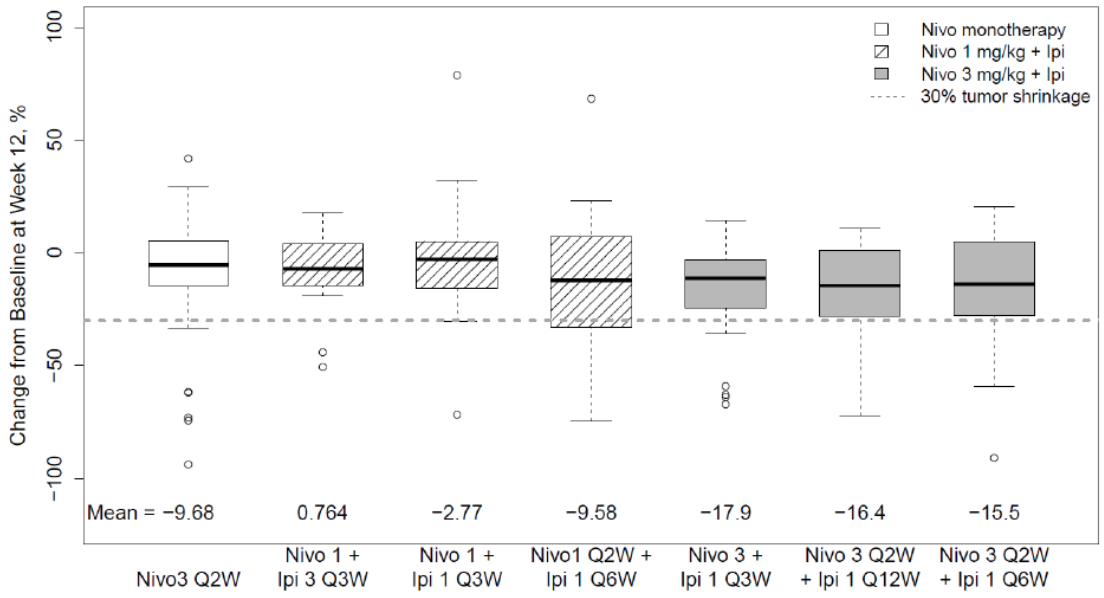


Note: ipilimumab Cavg0-12wk, ranging from 1.57 to 34.3 µg/ml, is reflected by circle size. Lower ipilimumab concentration is indicated by smaller circles, and higher ipilimumab concentration is indicated by larger circles.

Figure 12: Regimen Predicted Percent Change from Baseline in Tumour Size at Week 12 vs.Nivolumab Cavg 0-12wk in Nivolumab Monotherapy and in Combination with Ipilimumab

The potentiating effect of ipilimumab on nivolumab was further explored with respect to alternative combination dosing regimens. The combination of nivolumab 3 mg/kg with ipilimumab regardless of dose and regimen showed greater tumor shrinkage at week 12 (Figure 13) and greater maximum tumor shrinkage (Figure 13: Predicted Percent Change from Baseline in Tumor Size at Week 12, by Regimen

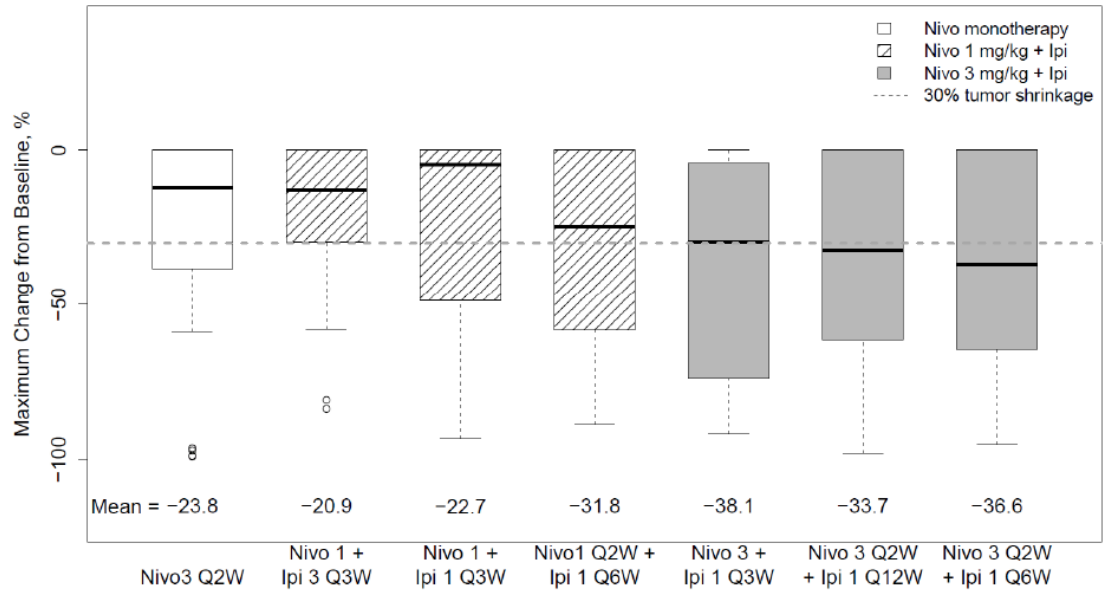
), compared to nivolumab 3 mg/kg monotherapy and nivolumab 1 mg/kg combination groups. Nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W or Q12W showed similar tumor shrinkage at week 12 and at the nadir. Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks also showed greater tumor shrinkage. However, this regimen was not tolerable and the estimated hazard ratio on AE-DC/D was highest among all cohorts. Overall, the exposure-efficacy analyses suggest that ipilimumab dosed at 1 mg/kg Q6W or Q12W in combination with nivolumab 3 mg/kg Q2W resulted in enhanced antitumor activities in subjects with NSCLC, compared to nivolumab 3 mg/kg monotherapy.



Note: The mean value of percent change in tumor size for each regimen is shown at the bottom of each box plot.

The box plots represent the median (bold line), 25th, and 75th percentiles of the distribution of the percent change in tumor size. The whiskers represent the 5th and 95th percentiles of the distribution. There are two subjects whose predicted values are outside of plotting range of the y-axis: 196.2% and 147.8% in Nivo 1 + Ipi 3 Q3W and in Nivo 1 Q2W + Ipi 1 Q6W, respectively.

Figure 13: Predicted Percent Change from Baseline in Tumor Size at Week 12, by Regimen



Note: The mean value of the predicted maximum tumor shrinkage for each regimen is shown at the bottom of each box plot. The predicted maximum tumor shrinkage for each subject was obtained using individual parameter estimates.

The box plots represent the median (bold line), 25th, and 75th percentiles of the distribution of the percent change in tumor size. The whiskers represent the 5th and 95th percentiles of the distribution.

Figure 14: Predicted Maximum Tumor Shrinkage, by Regimen

Exposure-Response of Safety: AE-DC/D

The E-R of safety was characterized with respect to time to occurrence of adverse events leading to death or discontinuation (AE-DC/D). Data from various regimens of nivolumab and ipilimumab were

included in the analysis (from Study CA209012), with doses ranging from 1 mg/kg to 3 mg/kg and schedules varying from Q2W to Q12W. Data from a total of 232 NSCLC subjects treated with nivolumab monotherapy or nivolumab + ipilimumab combination were included in the analysis.

The relationship between nivolumab and ipilimumab exposure (represented by time-varying daily Cavg) and time to AE-DC/D (excluding those related to disease progression) was described by a semi-parametric Cox proportional hazards (CPH) model, and included assessments of the modulatory effect of covariates on the E-R relationship.

A graphical presentation of all the estimated effects in the full model, showing the hazard ratios across the predictor ranges and the associated 95% confidence intervals, is presented in Figure 1.

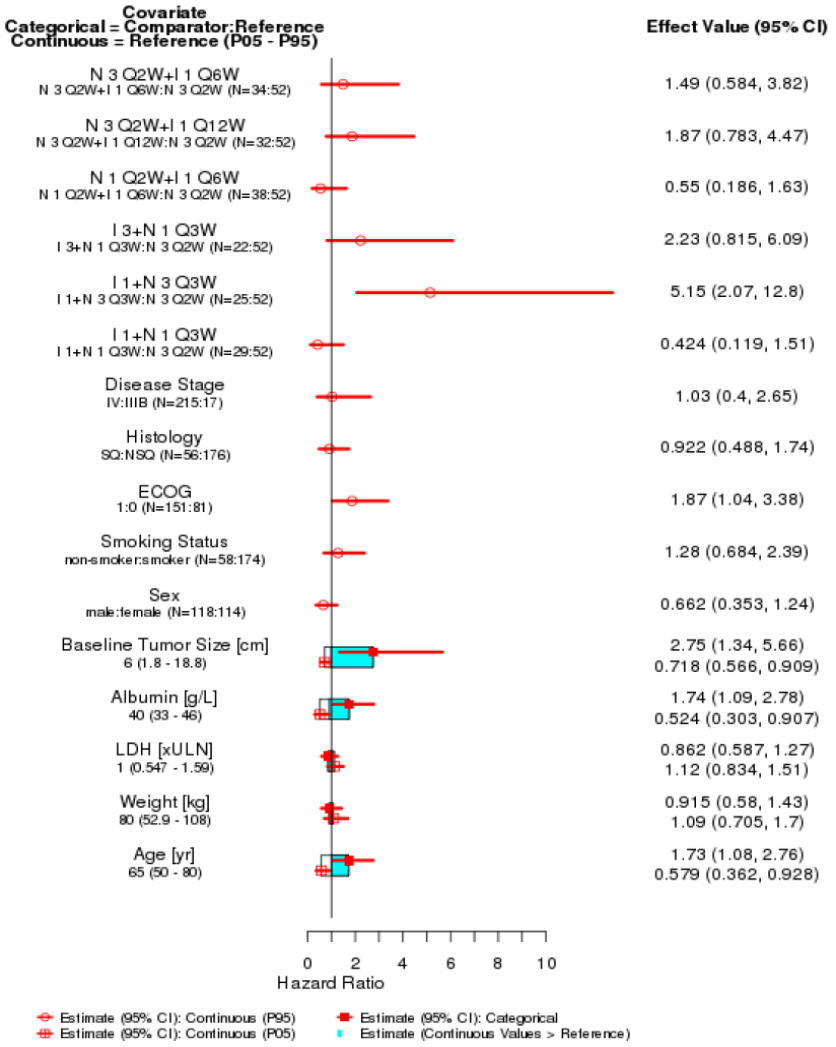


Figure 15: Estimated Covariate Effects of E-R (AE-DC/D) Full Model

The full model estimates are presented in Table 1. There were no significant interaction effects identified in the model that altered the relationship between nivolumab/ipilimumab exposure and AE-DC/D.

Table 20: Parameter Estimates of E-R (AE-DC/D) Full Model

Predictor[a]	Estimate	SE[b]	RSE%[c]	Hazard Ratio (95% CI)[d]
Cavg_nivo [ug/mL]	-0.01579	0.004907	31.07	0.9843 (0.9749, 0.9938)
N 3 Q2W+I 1 Q6W	0.4016	0.479	119.3	1.494 (0.5843, 3.821)
N 3 Q2W+I 1 Q12W	0.6262	0.4444	70.97	1.87 (0.7828, 4.469)
N 1 Q2W+I 1 Q6W	-0.5981	0.5537	92.58	0.5499 (0.1858, 1.628)
N1+ I3 Q3W x 4 then N3 Q2W	0.8009	0.5131	64.06	2.228 (0.8149, 6.09)
N3 + I1 Q3W x 4 then N3 Q2W	1.639	0.465	28.38	5.149 (2.069, 12.81)
N1 + I1 Q3W x 4 then N3 Q2W	-0.8573	0.6475	75.52	0.4243 (0.1193, 1.509)
Disease Status	0.02889	0.4816	1667	1.029 (0.4005, 2.646)
Histology	-0.08157	0.3248	398.2	0.9217 (0.4877, 1.742)
ECOG Status	0.6271	0.3011	48.01	1.872 (1.038, 3.378)
Smoking Status	0.2453	0.3187	129.9	1.278 (0.6843, 2.386)
Sex	-0.4121	0.3212	77.94	0.6623 (0.3529, 1.243)
Tumor Size [cm]	0.07895	0.0289	36.61	1.082 (1.023, 1.145)
ALB [g/L]	0.09228	0.04	43.35	1.097 (1.014, 1.186)
LDH [xULN]	-0.2525	0.3332	132	0.7769 (0.4043, 1.493)
Body Weight [kg]	-0.00319	0.00837	262.6	0.9968 (0.9806, 1.013)
Age [yr]	0.03644	0.01602	43.95	1.037 (1.005, 1.07)

[a] reference values: sex=female, ECOG=0, histology=NSQ, disease stage=IIIB, smoking status=non-smoker

[b] SE: Standard Error

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

[d] For continuous valued predictors (Cavg_nivo, age, BBWT, tumor size, LDH and ALB), the HR represents the change in hazard for a 1-unit increase in the value of the predictor.

Abbreviations: **N1+ I3 Q3W x 4 then N3 Q2W** = nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W x 4 then nivolumab 3 mg/kg Q2W; **N3 + I1 Q3W x 4 then N3 Q2W** = nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W x 4 then nivolumab 3 mg/kg Q2W; **N1 + I1 Q3W x 4 then N3 Q2W** = nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W x 4 then nivolumab 3 mg/kg Q2W; **N1 Q2W + I1 Q6W** = nivolumab 1 mg/kg Q2W + ipilimumab 1 mg/kg Q6W; **N3 Q2W + I1 Q12W** = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W; **N3 Q2W + I1 Q6W** = nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

The model estimates showed that the risk of AE-DC/D in the nivolumab and ipilimumab combination arms was higher than nivolumab 3 mg/kg monotherapy, when either nivolumab or ipilimumab was given as 3 mg/kg with the other drug and administered Q3W during the combination phase. The risk of AE-DC/D was reduced with ipilimumab dosing frequency of Q6W or Q12W in combination with nivolumab 3 mg/kg Q2W as compared to dosing Q3W. The overall risk for these two regimens, Q6W or Q12W, was similar to monotherapy. The predictor variables with a significant effect on the hazard of AE-DC/D were: baseline tumor size, age, albumin (ALB) and Eastern Cooperative Oncology Group (ECOG) status. There was a lack of evidence in the remaining predictor variables to indicate an effect on the risk of AE-DC/D.

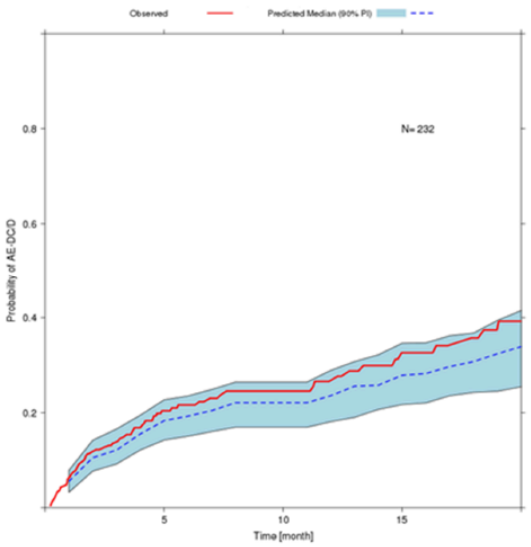


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Figure 16: Model Evaluation of E-R (AE-DC/D) Full Model

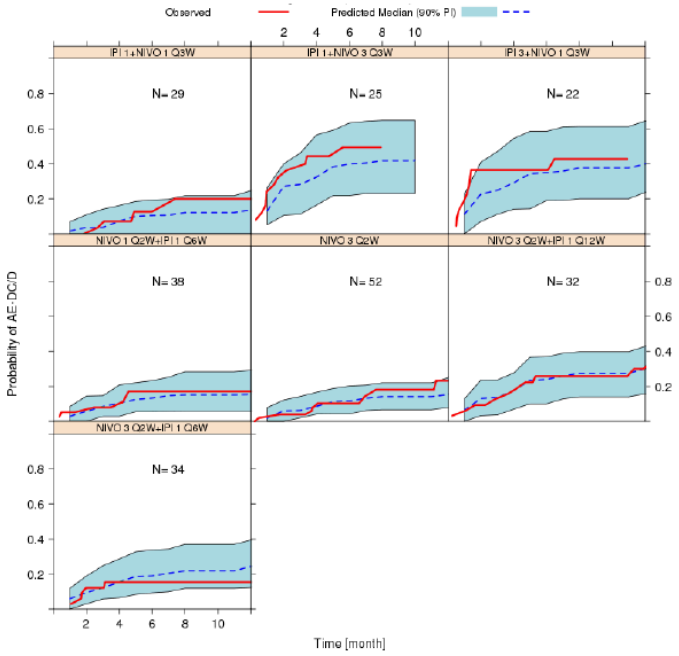

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Figure 17: Model Evaluation of E-R (AE-DC/D) Full Model, by Regimens

2.3.5. Discussion on clinical pharmacology

For this application, the clinical pharmacology program of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W for treatment of 1st line NSCLC was based on data from three studies, i.e. one phase 1 study CA209012 investigating several dosing regimens for the combination of nivolumab, and a phase 2 study CA209568 and a phase 3 study CA209227.

Population Pharmacokinetics – Nivolumab and Ipilimumab

The submitted nivolumab and ipilimumab PPK analyses are updates to a previous analyses describing the nivolumab and ipilimumab PK when administered as monotherapy or in combination (nivolumab and ipilimumab) in subjects with melanoma, NSCLC, SCLC and RCC and included CL as a time-dependent parameter in the model. In the current submitted analyses, the data set were expanded to include two additional tumor types (CRC and HCC), additional data for the existing tumor types, and data for the regimen of nivolumab + chemotherapy.

The previous models were submitted and assessed with variation EMEA/H/C/003985/II/0032. This variation was submitted based on final results from study CA209067 (nivolumab combined with ipilimumab for treatment of advanced (unresectable or metastatic) melanoma in adults). Time varying CL of nivolumab was assessed because the CL of anti-cancer mAbs has been reported to decrease over time. The updated model is the same submitted under WS/1278 for indication of combination of nivolumab and ipilimumab in subjects with previously untreated advanced (not amenable to curative surgery or radiation) or mRCC (AJCC Stage IV). Therefore, although it should be kept in mind that posology for that indication is different to the current proposed posology, this model has been previously assessed.

The PK of both nivolumab and ipilimumab, in monotherapy and in combination, were apparently well described by a linear 2-compartment model with time-varying CL. Diagnostic plots of the both PPK final models, for nivolumab and for ipilimumab, show that a two compartment model with zero-order IV infusion and time-varying CL model (sigmoidal-Emax function) apparently provides an adequate description of nivolumab or ipilimumab concentration-time data in the target population. In the prediction corrected visual predictive check (pcVPC) with stratification by the selected nivolumab or ipilimumab dosing regimen in different solid tumors, a small proportion of the data points were out of the plotted range. The pcVPC plots seem to show that the models adequately characterized the data from the 5th to the 95th percentiles. Most of the lines representing the 5th, 50th, and 95th percentiles of the observed data pass through respective 90% prediction interval of the PK data up to the first 120 days after the previous dose and first 200 days after the first dose in case of nivolumab and up to the first 25 days after the previous dose and the first 100 days after the first dose in case of ipilimumab. Additionally, 90% prediction intervals of 5th, 50th, and 95th percentiles of the observed data seem to be quite narrow, although it should be noted that 90% prediction intervals instead of 95% prediction intervals have been submitted. The inter-individual variability in CL after accounting for all variability was acceptable (39.6% for nivolumab and 33.4% for ipilimumab). However, it should be highlighted that although it is not unexpected due to the difficulties to study Emax, the ETA shrinkage of Emax is high in both models, being specially high for ipilimumab (50.3 for nivolumab and 78.6 for ipilimumab). As CL is calculated using Emax, diagnostic plots of individual CL estimates and covariates on CL could be slightly misleading.

Overall, the model and conclusions obtained from this model can be considered acceptable. The results of this PPK seem to be consistent with the results obtained from previous nivolumab monotherapy analyses and also the previous analysis done in combination with ipilimumab (advanced melanoma EMEA/H/C/003985/II/0003, 1st line RCC EMEA/H/C/WS1278). The intended population in the current application is 1st line NSCLC with tumour mutational burden (TMB) > 10 mut /MB. The PK of nivolumab and ipilimumab was similar in 1L NSCLC subjects with high, low, or not evaluable baseline TMB status who received nivolumab + ipilimumab combination therapy or nivolumab monotherapy.

Exposure-Response

Exposure –Responses on efficacy and safety have been evaluated based on data of study CA209012. This E-R analysis has been mainly used to support the dose and schedule proposed. Data from various regimens of nivolumab and ipilimumab were included in the analysis, with doses ranging from 1 mg/kg

to 3 mg/kg and schedules varying from Q2W to Q12W. However, number of patients by schedule was limited (between 24 and 40). Therefore, results of this Exposure-Response analysis should be interpreted with caution.

E-R Efficacy:

The relationship between nivolumab and ipilimumab exposures and efficacy in subjects with advanced NSCLC was assessed with respect to tumor growth dynamics (TGD) in Study CA209012. Data from various regimens of nivolumab and ipilimumab were included in the analysis, with doses ranging from 1 mg/kg to 3 mg/kg and schedules varying from Q2W to Q12W. Exposure was defined as average drug concentration over the first 12 weeks (Cavg0-12wk). Cavg0-12wk was chosen as the exposure metric because it provided an integer number of dosing intervals across Q2W to Q12W regimens. Hence, subjects discontinuing treatment in early stage had a profound effect on Cave 12 weeks nivolumab and ipilimumab concentrations. This was more pronounced for nivolumab than for ipilimumab as the frequency of dosing for nivolumab was higher. Therefore, this analysis is likely to be confounded by the early discontinuations of subjects and no conclusions on the contribution of ipilimumab to the combination of nivolumab and ipilimumab in NSCLC subjects can be drawn. However, as a nivolumab monotherapy arm was included in the phase 3 study CA209227, the contribution of ipilimumab to the combination can be derived from that study (if data would be provided).

Exposure-Response Safety

The relationship between nivolumab and ipilimumab exposure (represented by time-varying daily Cavg) and time to AE-DC/D (excluding those related to disease progression) was described by a semi-parametric Cox proportional hazards (CPH) model, and included assessments of the modulatory effect of covariates on the E-R relationship. Evaluation of the model has been conducted based on VPC plots.

The E-R safety analysis showed that the risk of AE-DC/D was similar for nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W (the proposed regimen for NSCLC) and nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W, and was numerically higher than nivolumab 3 mg/kg Q2W. Among the studied nivolumab + ipilimumab regimens, the risk of AE-DC/D with nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W or nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W was higher than the others. Analysis also showed that the hazard rate of AE-DC/D increased with increasing baseline tumor size, age and ALB, and was higher with an ECOG of 1 compared to an ECOG of 0. However, results should be interpreted with caution because limited number of patients by schedule have been included.

Immunogenicity

In study CA209227, the incidence of nivolumab immunogenicity in subjects previously-untreated recurrent or metastatic NSCLC similar to that observed in melanoma subjects administered nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg (36.9% vs. 37.8%). 7 subjects (1.6%) were neutralizing ADA positive and 5 subjects (1.2%) were considered persistent positive.

The incidence of ipilimumab immunogenicity in subjects previously-untreated recurrent or metastatic NSCLC was slightly lower than that observed in melanoma subjects administered nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg (7.5% vs 8.3%). No subjects was neutralizing ADA positive and 3 subjects (0.7%) was considered persistent positive.

It should be kept in mind that as happened in subjects with melanoma, the incidence of nivolumab ADA was higher with the combination than with the respective monotherapy (36.9% vs. 12.3%). However, incidence of ipilimumab ADA is similar with the combination and with the monotherapy (7.5 % vs 5.7%). According to the applicant's justification, the nivolumab Fc region includes T-reg specific epitopes (Tregitopes) which can help decrease nivolumab ADA, as Tregitopes induce the activation of

T-regs that suppress an adaptive immune response. Conversely, ipilimumab blocks CTLA-4 leading to T-reg suppression, which can lead to a decline in the ability of T-regs to block antigen driven antibody formation. Thus, an increase in nivolumab immunogenicity with a resultant increase in the probability of the formation of anti-nivolumab ADAs would be expected when nivolumab is administered in conjunction with a T-reg suppressing agent, such as ipilimumab

These results of incidence of immunogenicity with nivolumab and ipilimumab seem to be consistent with the results obtained from the previous analysis done with the combination of nivolumab/ipilimumab and they are also in line with what is expected from the previous nivolumab monotherapy analyses.

Similar to what has been observed with the nivolumab 1 mg/kg + ipilimumab 3 mg/kg regimen in melanoma, there was no impact of nivolumab immunogenicity on nivolumab and ipilimumab PK, safety or efficacy in previously-untreated recurrent or metastatic NSCLC when nivolumab 3 mg/kg Q2W is administered with ipilimumab 1 mg/kg Q6W. In case of ipilimumab ADA in study CA209227, it should be pointed out that the proportion of subjects with hypersensitivity/infusion reactions was higher in ipilimumab ADA positive subjects than in ipilimumab ADA negative subjects, although most of these hypersensitivity/infusion reactions were Grade 1 or 2 and all resolved. These results could be consequence of the limited number of patients with ipilimumab ADA positive (small change in absolute numbers can lead to big differences in relative numbers). Additionally, this trend was not observed in study CA209568, in fact the trend is the opposite in this study. Therefore, this issue is not considered relevant at this point.

Justification of dose

The applicant justification for dose and schedule is accepted based on results of study CA209012, E-R analyses (efficacy and safety) with data of study CA209012 and population PK analysis which suggest that nivolumab and ipilimumab clearances were similar to those seen with monotherapy for both agents. However, several questions are still pending from study CA209012 (see Dose Response section), no firm conclusions on the contribution of ipilimumab to the combination of nivolumab and ipilimumab in NSCLC subjects can be drawn based on E-R Efficacy (see above) and results of pivotal study are still under discussion. Thus, the relative contribution of ipilimumab to the efficacy of the combination regimen nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W is not considered properly justified. More evidence for the contribution of ipilimumab to nivolumab was gathered in the clinical phase III study CA209227, where the nivo+ ipi combination treatment was compared to nivolumab monotherapy in patients with PD-L1 ⩾1%.

2.3.6. Conclusions on clinical pharmacology

The nivolumab and ipilimumab combination dose regimen (nivolumab 3 mg/kg Q2W+ ipilimumab 1 mg/kg Q6W) was selected for treatment of previously-untreated recurrent or metastatic NSCLC patients in the pivotal study CA209227. The relative contribution of ipilimumab to the efficacy of the combination regimen nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W is not considered properly justified based on the dose selection study CA209012 and E-R Efficacy analysis. More evidence for the contribution of ipilimumab to nivolumab was gathered in the clinical phase III study CA209227, where the nivo+ ipi combination treatment was compared to nivolumab monotherapy in patients with PD-L1 ≥ 1%.

2.4. Clinical efficacy

A total of 4 studies were used to support the application for patients with TMB≥ 10 mut/Mb.

The evidence of efficacy of nivolumab in combination with ipilimumab in subjects with TMB≥ 10 mut/Mb regardless of PD-L1 expression presented in this application is based on BICR-assessed PFS, ORR, and DoR, and OS data from Part 1 of pivotal Phase 3 Study CA209227, based on a database lock of 24-Jan-2018.

The contribution of ipilimumab to the activity of the nivolumab + ipilimumab combination in subjects with TMB≥ 10 mut/Mb regardless of PD-L1 expression is supported by the results of the phase 1 study CA209012 nivolumab + ipilimumab cohorts and the phase 2 study CA209568 (nivolumab + ipilimumab vs chemotherapy).

In addition, CA209026, a phase 3 open-label study of nivolumab monotherapy vs chemotherapy provided exploratory analyses supporting TMB as a predictive biomarker and was used to inform the TBM cutoff of ≥13 mut/Mb for nivolumab monotherapy in Part 1a of CA209227

2.4.1. Dose response study

CA209012

Study design

This study was a Phase 1, multiple-cohort study of nivolumab as monotherapy, in combination with ipilimumab, or in combination with chemotherapy or targeted therapy, in chemotherapy naive subjects with stage IIIB/IV NSCLC or recurrent disease.

The study included adult patients ≥ 18 years with newly diagnosed and confirmed stage IIIb/IV NSCLC with measurable disease, without brain metastasis and a life expectancy ≥ 3 months. The ECOG score was 0 or 1.

Primary Objective was to assess the safety and tolerability of nivolumab in combination with ipilimumab in chemotherapy-naïve subjects with Stage IIIB/IV NSCLC.

Secondary Objectives were to determine the ORR and PFS rate at 24 weeks in chemotherapy-naive subjects with Stage IIIB/IV NSCLC treated with nivolumab in combination with ipilimumab. Cohorts P and Q were based on IRRC assessment.

Key exploratory objectives include assessments of OS and immunogenicity. An additional pre-specified analysis of efficacy by programmed death ligand-1 (PD-L1) expression level was also performed. Tumor responses were assessed using RECIST v1.1 criteria beginning 11 weeks after first dose of study drug, and then occurred at weeks 17 and 23, and then every 12 weeks until disease progression.

Subjects were treated until progression, unacceptable toxicity, or other protocol-defined reasons. Nivolumab treatment (or nivolumab and and ipilimumab treatment in cohorts O, P, and Q) beyond initial investigator-assessed RECIST v1.1-defined progression was permitted if the subject had an investigator-assessed clinical benefit and was tolerating study drug.

8 cohorts received treatment with nivolumab in combination with ipilimumab.

Table 21: Study Design

Cohort[a]	Subjects	Treatment
A	Chemotherapy-naive SQ subjects; dose de-escalation design	GEM 1250 mg/m^2 Days 1 and 8 with CIS 75 mg/m^2 on Day 1 of a Q3W cycle for up to 4 cycles + Nivo 10 mg/kg Q3W until progression after cycle 4
B	Chemotherapy-naive NSQ subjects; dose de-escalation design	PEM 500 mg/m^2 with CIS 75 mg/m^2, both on Day 1 of a Q3W cycle for up to 4 cycles + Nivo 10 mg/kg Q3W until progression after cycle 4
C	Chemotherapy-naive subjects with any histology; dose de-escalation design	PAC 200 mg/m^2 with CAR AUC 6, both on Day 1 of a Q3W cycle for up to 4 cycles + Nivo 10 mg/kg Q3W until progression after cycle 4[b]
D	NSQ subjects who completed ≥ 4 cycles of chemotherapy and are non-progressors	BEV 15 mg/kg + Nivo 5 mg/kg Q3W until progression
E	Chemotherapy-naive, subjects with EGFR mutations	ERL 150 mg PO, daily + Nivo 3 mg/kg Q2W until progression
F	Chemotherapy-naive subjects with any histology	Nivo 3 mg/kg Q2W until progression
G	**Chemotherapy-naive SQ subjects**	**Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W until progression**
H	**Chemotherapy-naive NSQ subjects**	**Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W until progression**
I	**Chemotherapy-naive SQ subjects**	**Nivo 3 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W until progression**
J	**Chemotherapy-naive NSQ subjects**	**Nivo 3 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W until progression**
K	SQ subjects who completed ≥ 4 cycles of chemotherapy and are non-progressors	Nivo 3 mg/kg Q2W as switch maintenance therapy until progression
L	NSQ subjects who completed ≥ 4 cycles of chemotherapy and are non-progressors	Nivo 3 mg/kg Q2W as switch maintenance therapy until progression
M	Subjects with any histology and untreated, asymptomatic brain metastases	Nivo 3 mg/kg Q2W until progression
N	**Chemotherapy-naive subjects with any histology**	**Nivo 1 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W until progression**
O	**Chemotherapy-naive subjects with any histology**	**Nivo 1 mg/kg Q2W + Ipi 1 mg/kg Q6W until progression or unacceptable toxicity**
P	**Chemotherapy-naive subjects with any histology**	**Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W until progression or unacceptable toxicity**
Q	**Chemotherapy-naive subjects with any histology**	**Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W until progression or unacceptable toxicity**

Abbreviations: BEV: bevacizumab, CAR: carboplatin, CIS: cisplatin, EGFR: epidermal growth factor, ERL: erlotinib, GEM: gemcitabine, Ipi: ipilimumab, Nivo: nivolumab, NSQ: non-squamous, PAC: paclitaxel, PEM: pemetrexed, Q: every, SQ: squamous, W: weeks

[a] Cohorts R and S, described in the protocol (Appendix 1.1), were not opened since safety in cohorts O and P was acceptable.

[b] Nivolumab dose was de-escalated to 5 mg/kg Q3W.

Source: Appendix 1.1

In cohorts G, H, I, and J, subjects received concurrent treatment with nivolumab and ipilimumab for 4 doses every 3 weeks (Q3W) during induction, followed by nivolumab at 3 mg/kg every two weeks (Q2W) thereafter. Cohorts G and H received nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during induction. Cohorts I and J received nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg during induction.

Based on preliminary safety data from cohorts G, H, I, and J, cohort N was opened to evaluate the combination of nivolumab and ipilimumab both at a lower dose (nivolumab 1 mg/kg and ipilimumab 1 mg/kg, both Q3W during induction, followed by nivolumab 3 mg/kg Q2W thereafter) in order to improve safety in chemotherapy-naive subjects. Given the improved tolerability observed in cohort N, subjects (N=12) were randomly assigned to receive different combinations of nivolumab and ipilimumab in cohorts O, P, and Q in which ipilimumab was dosed less frequently. A lower and less frequent dose of ipilimumab was chosen since across cohorts GH and IJ, the higher dose of ipilimumab appeared to be a key driver of toxicity. Furthermore, data from MDX1106-03 (CA209003) showed a dose-response relationship for nivolumab in NSCLC, with better activity achieved with nivolumab 3 mg/kg than 1 mg/kg, and less frequent dosing of ipilimumab might allow for a full (approved) dose of nivolumab of 3 mg/kg. Cohort O received both nivolumab and ipilimumab at 1 mg/kg, but nivolumab was given Q2W while ipilimumab was given every 6 weeks (Q6W). In cohort P, nivolumab was dosed at 3 mg/kg Q2W and ipilimumab was dosed at 1 mg/kg every 12 weeks (Q12W). In cohort Q, nivolumab was dosed at 3 mg/kg Q2W and ipilimumab at 1 mg/kg Q6W.

Disposition and Baseline/Demographic Characteristics

Results are based on the 19-Sep-2016 database lock with a last patient last visit date of 20-Jul-2016. The database lock was on 19 sept 2016.

A summary of the subject status for subjects treated with nivolumab in combination with ipilimumab is presented in Table 22.

Baseline demographic and disease characteristics for pooled cohorts GH and IJ were consistent with a typical advanced/metastatic NSCLC population. Among all treated subjects, the median age was 61.0 years and 60.0 years in pooled cohorts GH and IJ, respectively. Most subjects had Stage IV disease at baseline. Per protocol, cohorts G and I enrolled subjects with SQ histology while cohorts H and J enrolled NSQ subjects. The proportion of subjects with SQ vs NSQ histology in pooled cohorts GH and IJ was similar. The majority of subjects had tumors that were EGFR mutation negative. Most subjects were either former or current smokers. 62.5% and 60.0% of subjects in pooled cohorts GH and IJ, respectively, had an ECOG PS of 1. Baseline demographic and disease characteristics in cohorts N and O were consistent with a typical advanced/metastatic NSCLC population. Among all treated subjects, the median age was 63.0 years and 65.5 years in cohorts N and O, respectively. Most subjects had Stage IV disease at baseline. 80.6% and 80.0% of subjects in cohorts N and O had tumors with non-squamous histology, respectively, and most subjects had tumors that were EGFR mutation negative. The majority of subjects were either former or current smokers. 61.3% and 67.5% of subjects in cohorts N and O, respectively, had an ECOG PS of 1.

Table 22: Subject Status Summary - All Treated Subjects in Cohorts GH, IJ, N, O, P, and Q

Subjects, n (%)	Pooled Cohorts GH N = 24	Pooled Cohorts IJ N = 25	Cohort N N = 31	Cohort O N = 40	Cohort P N = 38	Cohort Q N = 39
Subjects continuing in the treatment period	2 (8.3)	0	4 (12.9)	7 (17.5)	4 (10.5)	3 (7.7)
Subjects not continuing treatment in the treatment period	22 (91.7)	25 (100.0)	27 (87.1)	33 (82.5)	34 (89.5)	36 (92.3)
Reason for not completing treatment						
Disease progression	11 (45.8)	12 (48.0)	21 (67.7)	26 (65.0)	19 (50.0)	22 (56.4)
Study drug toxicity	9 (37.5)	10 (40.0)	4 (12.9)	3 (7.5)	7 (18.4)	7 (17.9)
Death	0	0	0	0	1 (2.6)	0
Adverse event unrelated to study drug	1 (4.2)	1 (4.0)	0	1 (2.5)	4 (10.5)	3 (7.7)
Subject request to discontinue study treatment	0	1 (4.0)	0	1 (2.5)	0	2 (5.1)
Subject withdrew consent	0	1 (4.0)	0	2 (5.0)	1 (2.6)	0
Maximum clinical benefit	1 (4.2)	0	0	0	2 (5.3)	0
Subject no longer meets study criteria	0	0	1 (3.2)	0	0	0
Other[a]	0	0	1 (3.2)	0	0	2 (5.1)

Percentages based on subjects treated.

[a] The 1 subject in cohort N listed as Other did not complete treatment because they relocated. For the 2 subjects in cohort Q listed as Other, 1 subject did not complete treatment due to investigator determined "anti-tumor effect" and 1 subject stopped at the discretion of the investigator.

Baseline demographics and disease characteristics for cohorts P and Q are summarized in Table 23. The only notable imbalances observed in demographics was cohort P had fewer never smokers (2 [5.3%] vs 9 [23.1%]) and fewer male subjects (17 [44.7%] vs 24 [61.5%]) compared with cohort Q.

Table 23: Baseline Characteristics - All Treated Subjects in Cohorts P and Q

	Cohort P N = 38	Cohort Q N = 39
AGE		
N	38	39
MEAN	65.9	64.4
MEDIAN	68.0	62.0
MIN , MAX	50 , 91	47 , 87
Q1 , Q3	58.0 , 73.0	57.0 , 73.0
STANDARD DEVIATION	9.36	9.95
AGE CATEGORIZATION (%)		
< 65	17 (44.7)	21 (53.8)
>= 65	21 (55.3)	18 (46.2)
GENDER (%)		
MALE	17 (44.7)	24 (61.5)
FEMALE	21 (55.3)	15 (38.5)
DISEASE STAGE (%)		
STAGE IIIB	4 (10.5)	1 (2.6)
STAGE IV	34 (89.5)	38 (97.4)
NOT REPORTED	0	0
CELL TYPE (%)		
ADENOCARCINOMA	32 (84.2)	30 (76.9)
BRONCO-ALVEOLAR CARCINOMA	0	0
LARGE CELL CARCINOMA	0	2 (5.1)
SQUAMOUS CELL CARCINOMA	6 (15.8)	6 (15.4)
OTHER	0	1 (2.6)
NOT REPORTED	0	0
ECOG [%]		
0	11 (28.9)	16 (41.0)
1	27 (71.1)	23 (59.0)
SMOKING STATUS (%)		
NEVER	2 (5.3)	9 (23.1)
CURRENT	6 (15.8)	4 (10.3)
FORMER	30 (78.9)	25 (64.1)
UNKNOWN	0	0
NOT REPORTED	0	1 (2.6)
EGFR MUTATION STATUS (%)		
POSITIVE	6 (15.8)	6 (15.4)
NEGATIVE	28 (73.7)	25 (64.1)
UNKNOWN	4 (10.5)	8 (20.5)
PD-L1		
< 1%	10 (26.3)	9 (23.1)
>= 1%	23 (60.5)	23 (59.0)
>= 50%	6 (15.8)	7 (17.9)
Unknown	5 (13.2)	7 (17.9)

Treatment: P=IPI1Q12W+NIV3Q2W; Q=IPI1Q6W+NIV3Q2W.

Efficacy and Safety results

The cohorts G-J showed a high incidence of drug related AE ≥ 3 leading to discontinuation (24-40%) (Table 24). The ORRs (± 21%) were comparable with an approved nivolumab monotherapy dose of cohort F (Table 25).

The Cohort N shows improved tolerability compared to cohort G-J because fewer patients stopped because of study drug toxicity, and the incidence of AEs leading to discontinuation were lower (6.5 % vs 24-33%) (Table 24). The response rate was 24%, comparable to the approved nivolumab monotherapy arm of cohort F (Table **25**).

The cohorts O, P, and Q used a comparable dosing scheme. The highest, and a comparable number of patients discontinuation treatment is shown in the cohort P and Q (90%) compared to dose O (83%); both cohorts use a higher dose of nivolumab than cohort O, while the number of patients that discontinued treatment because of drug related AEs was comparable in these 3 cohorts (±7.5%). Also drug related Serious AE ≥ 3 are comparable in these three cohorts (± 22%) (Table 24).

All three cohorts showed a higher response rate (33-47%) than with nivolumab monotherapy (23%). The highest response rate was observed in cohort P (47%) (Table 25).

These cohorts have a comparable minimum follow-up period, 15.7-16.4 months. Cohort O and Q show the same PFS range at week 24, (47-48%), the highest PFS rate at week 24 was observed in cohort P (68%). The median OS for cohort P is not yet reached; for cohort O and Q is the observed median OS somewhat smaller than with nivolumab monotherapy (Table 25).

No subgroup analyses are provided for the patient populations with TMB ≥ 10 mut/MB and those with TMB < 10 mut/MB.

Table 24: Summary of the key safety results of all treated subjects in cohorts G-J, N—Q

	Pooled Cohorts	Pooled Cohorts					IRRC-Assessed Efficacy	
	GH[a] N = 24	IJ[b] N = 25	Cohort N[c] N = 31	Cohort O[d] N = 40	Cohort P[e] N = 38	Cohort Q[f] N = 39	Cohort P[e] N = 38	Cohort Q[f] N = 39
Rate at 12 months (95% CI)	66.7 (44.3, 81.7)	44.0 (24.5, 61.9)	64.2 (44.7, 78.4)	66.1 (47.9, 79.2)	83.3 (66.4, 92.1)	69.0 (51.8, 81.0)	-	-
Minimum follow-up, months	34.5	34.8	29.7	16.4	15.7	16.0	-	-
SAFETY[j], n (%)								
Deaths	15 (62.5)	17 (68.0)	14 (45.2)	17 (42.5)	15 (39.5)	20 (51.3)	-	-
Within 30 days of last dose	2 (8.3)	3 (12.0)	1 (3.2)	1 (2.5)	4 (10.5)	2 (5.1)	-	-
Within 100 days of last dose	3 (12.5)	10 (40.0)	3 (9.7)	6 (15.0)	8 (21.1)	7 (17.9)	-	-
Due to study drug toxicity	1 (4.2)	2 (8.0)	0	0	0	0	-	-
Drug-related SAEs, Grade 3-4	10 (41.7)	7 (28.0)	5 (16.1)	9 (22.5)	10 (26.3)	9 (23.1)	-	-
Drug-related AEs leading to DC, Grade 3-4	8 (33.3)	6 (24.0)	2 (6.5)	3 (7.5)	3 (7.9)	3 (7.7)	-	-
Drug-related AEs, Grade 3-4	14 (58.3)	12 (48.0)	9 (29.0)	13 (32.5)	15 (39.5)	11 (28.2)	-	-

Abbreviation: AE: adverse event, CI: confidence interval, DC: discontinuation, SAE: serious adverse event.

Percentages based on subjects treated.

[a] Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; [b] Nivo 3 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; [c] Nivo 1 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; [d] Nivo 1 mg/kg Q2W + Ipi 1 mg/kg Q6W; [e] Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W; [f] Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W

[g] Investigator-assessed efficacy unless otherwise noted.

[h] One of these subjects (CA209012-xx in cohort G) developed radiographic PR and later had excisional biopsy of radiographic residue lesion. Pathological evaluation showed no viable tumor and pathological CR was determined by investigator. The other subject in cohort GH with a CR was radiographically determined and confirmed (per RECIST v1.1 criteria).

[i] Subjects CA209012-xx, CA209012-xx (both in cohort P) and CA209012-xx (cohort Q) developed radiographic PR and later had excisional biopsy of radiographic residue lesion or autopsy (for unrelated death of subject CA209012-xx). Pathological evaluation showed no residual viable tumor and pathological CR was determined by investigator. The other 3 subjects with CRs (2 in cohort P and 1 in cohort Q) were radiographically determined and confirmed (per RECIST v1.1 criteria).

[j] Includes events reported between first dose date and 30 days after the last dose of nivolumab or ipilimumab (whichever happened last) unless otherwise noted.

Table 25: Summary of the key efficacy results of the cohorts GJ, N-Q and F – study CA209012

								IRRC assessed efficacy	
Cohort	**GH N=24**	**IJ N=25**	**N N=31**	**O N= 40**	**P N=38**	**Q N=39**	**F N=52**	**P**	**Q**
ORR n (%) 95% CI	5 (21) (7.1-42.2)	6 (24) (9.4-45.1)	7 (23) (9.6, 41.1)	13 (33) (18.6, 49.1)	18 (47) (31.0, 64.2)	15 (39) (23.4, 55.4)	12 (23) (12.5 - 36.8)	19 (50) (33, 65)	14 (36) (24, 55)
PFS (median months)	3.78 (1.97, 7.98)	3.55 (2.17, 6.80)	5.16 (2.07, 12.09)	5.09 (2.73, 9.69)	8.11 (5.55, 16.69)	3.94 (2.56, 13.17)	3.59 (2.30 , 6.64)	12.78 (6.44 , NA)	3.68 (2.6, 9.00
Estimated PFS rate (%) 24 weeks	42.8 (22.4, 61.8)	37.3 (18.1, 56.7)	49.1 (30.3,65.5)	48.0 (31.6, 62.7	67.6 (50.0, 80.1	47.1 (30.7, 61.9)	39.7 (26.0 , 53.1)	72.4 (54,7 , 84.1)	39.5 (24.2 , 54.4)

(95% CI)									
OS (median months) (95% CI)	19.78 (10.94,N.A.)	11.01 (3.98,37.75)	NR (11.50,N.A.)	17.68 (11.04,N.A.)	NR (14.42,N.A.)	18.46 (13.31,N.A.)	21.82 (15.05, 25.59	NR (14.42, NA	18.46 (13.31, NA)
OS rate 12 months (95% CI)	66.7 (44.3,81.7)	44.0 (24.5, 61.9)	64.2 (44.7, 78.4)	66.1 (47.9,79.2)	83.3 (66.4,92.1)	69.0 (51.8,81.0)			

Source table 3.3.1 SoCE; table 6.1 and 9.3.1.1 final study report study CA 209012

According the MAH, the nivolumab and ipilimumab combination cohort Q, i.e. nivolumab 3 mg/kg over 30 minutes Q2W + ipilimumab 1 mg/kg over 30 minutes Q6W was selected for studies CA209227 and CA209568 because:

- Cohorts G-J that used the melanoma or RCC dose and schedule (nivolumab 3 mg/kg + ipilimumab 1 mg/kg or ipilimumab 1 mg/kg + nivolumab 3 mg/kg Q3W; followed by nivolumab 3 mg/kg Q2W maintenance) were not as well tolerated as other regimens.
- Cohorts N and O, which had a lower dose (1 mg/kg) of both nivolumab and ipilimumab, demonstrated improved tolerability; however, the ORR was similar to nivolumab monotherapy.
- Cohorts P and Q used the 3 mg/kg Q2W dose of nivolumab (the approved monotherapy regimen) and lower and less frequent dosing of ipilimumab (1 mg/kg Q6W or Q12W), and were well tolerated and showed promising efficacy.

Based on the totality of the data, Cohorts P and Q provided comparable safety and efficacy in CA209012; however, cohort sizes were small. More frequent dosing of ipilimumab might be important for maintaining long-term response, and based on similar tolerability of the Q6W and Q12W schedule, appears feasible. There is evidence that higher ipilimumab exposures are associated with higher activity for other tumor types, suggesting that the more frequent ipilimumab dosing regimen of Q6W might be important for maintaining long-term responses.[1,2] The nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W regimen was chosen for further development in NSCLC.

Discussion on dose selection study CA209012

Study's CA209012 primary objective was to explore the safety and efficacy of various nivolumab + ipilimumab combinations in patients with chemo-naive stage IV NSCLC, regardless of PD-L1 and TMB expression. The primary endpoint was the tolerability of the treatment schedules, while the efficacy was a secondary endpoint.

The cohorts G-J used the melanoma/renal cell carcinoma dose and schedule with a frequent dosing interval of ipilimumab [Q3W], but these treatments were not well tolerated leading to a high percentage of patients who did not complete treatment because of drug toxicity (33-40%) (Table 22).

Cohort N used a lower dose of nivolumab than the cohorts G-J. This cohort showed an improved tolerability compared to cohort G-J, with a lower incidence of patients that discontinued treatment because of drug toxicity (6.5%). The ORRs (± 21%) and PFS rate at week 24 (37-49%) of cohorts GH, IJ and N were comparable with nivolumab monotherapy (cohort F). Without added efficacy, the additional value of ipilimumab to the monotherapy is hard to determine.

The cohorts O, P, and Q used a comparable dosing scheme with less frequent dosing of ipilimumab [6-12W] compared with the cohorts G-J. The dosing scheme of cohort O, using a lower dose of nivolumab

(1 mg/kg) was best tolerated, with the lowest incidence of patients that discontinued treatment because of drug toxicity (Table 22).

The cohorts O, P, and Q showed a higher ORR than with nivolumab monotherapy, with durable responses, which may point towards improvement of efficacy of the combination over the monocomponent. The estimated outcome measures (PFS rate and OS rate at 12 months) were comparable between cohort O and cohort Q. The best outcome measures were shown with cohort P, in which ipilimumab was administered at the lowest dosing frequency [Q12W dosing] (Table 25). It should be noted that a discrepancy is seen between ORR, PFS and OS efficacy data. When focusing on PFS and OS median data no beneficial effect of the combination therapy (cohort O and Q) is seen compared to nivolumab monotherapy. With the current data it is not clear if the ORR will be predictive for the overall survival. The OS data is limited to the OS rate on 12 months. Based on this data, cohort P shows the highest OS rate at 12 months.

The applicant decided to continue with the posology of cohort Q. Given the comparable efficacy and better tolerability of cohort O compared to cohort Q and the better efficacy with comparable safety of cohort P compared to cohort Q, the choice for cohort Q nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W is disputable.

Nevertheless, the applicant decided to further develop dosing scheme Q, based the evidence provided by melanoma and small cell lung cancer that indicate that higher ipilimumab exposure was associated with higher activity, suggesting that the more frequent ipilimumab dosing regimen of Q6W might be important for maintaining long-term responses. In these studies, nivolumab was administered with 1 or 3 mg/kg ipilimumab Q3W for 4 cycles, a quite different dosing regimen from the current proposal, and the results indicated that combination with 3 mg/kg ipilimumab showed longer responses than the combination with 1 mg/kg. Therefore, it is not understood how these data support the Q6W frequency of 1 mg/kg ipilimumab. Moreover, this reasoning does not seem to be confirmed in the current study CA209012 with NSCLC.).

In conclusion

The dose finding is based on an unselected NSCLC population, which taking into account the all comers indication now applied for, seems reasonable.

The data of the dose finding study show a large variability, which hampers the dose selection. The choice for the selected posology of nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/hg Q6W would need to be further substantiated considering the apparent inconsistent results for ORR, PFS and OS. Furthermore, based on PFS and OS data from this study the contribution of ipilimumab to long term responses of the combination is not known and would need further substantiation knowing that ipilimumab increases the toxicity compared to monotherapy nivolumab. However, bearing in mind the outcome in terms of OS, the theoretical contribution of ipilimumab to the combination would be supported by the previous precedent in RCC.

2.4.2. Main study

CA209227 is an ongoing, open-label, randomized, Phase 3 trial of nivolumab monotherapy, nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy vs platinum doublet chemotherapy in subjects with chemotherapy-naive stage IV or recurrent NSCLC with no known EGFR or ALK positive tumor mutations, who were previously untreated for advanced disease. The trial consists of three parts: Part 1a (subjects with PD-L1 expressing tumors ≥ 1%), Part 1b (subjects with PD-L1 non-expressing tumors < 1%), and Part 2 (all comers). This report will focus on subjects in Part 1 (Part 1a + Part 1b) of this study randomized to nivolumab + ipilimumab or chemotherapy. Subjects within each group (Part 1a and Part 1b) were enrolled simultaneously at the same sites, and randomized to the

following treatment arms in a 1:1:1 ratio and stratified by histology (squamous [SQ] vs non-squamous [NSQ]).

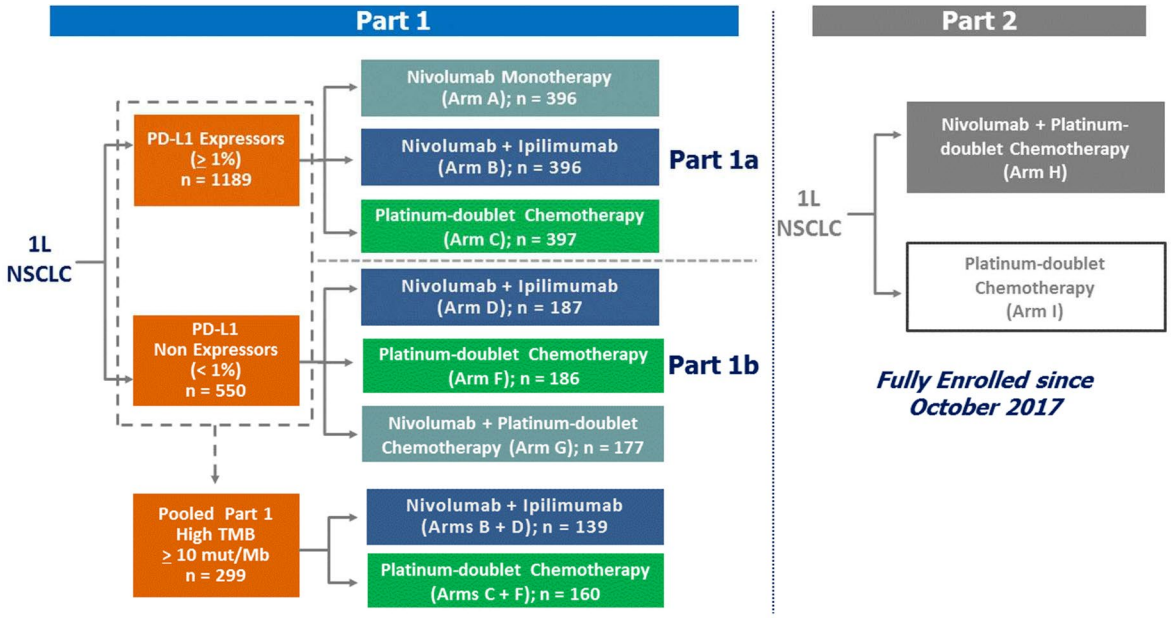


Figure 18: CA209227 Study Design Schematic

Part 1 platinum-doublet chemotherapy options include: NSQ: pem/cis, pem/carbo; SQ: gem/cis, gem/carbo. Part 2 platinum-doublet chemotherapy options include NSQ: pem/carbo, pem/cis; SQ: carbo/taxol.

Methods

Study participants

The study included adults (≥18 years) with 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. Subjects with known EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy were excluded.

PD-L1 status was required prior to randomization for all subjects in Part 1. Immunohistochemical testing (Dako 28-8 IHC) was performed by the central lab during the screening period. In Part 1a and Part 1b, subjects were required to have ≥1% and < 1% tumor PD-L1 expression, respectively.

PD-L1 expression in the tumor was assessed and categorized into 4 groups:

- PD-L1 ≥1%: ≥1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells
    - PD-L1 ≥50% (≥50% tumor cell membrane staining in a minimum of 100 evaluable tumor cells). This is a subset of subjects in all treated PD-L1 ≥1% subjects.
- PD-L1 < 1%: < 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells
- PD-L1 not quantifiable (tumor biopsy specimens without quantifiable PD-L1 expression)

TMB refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. High TMB has been hypothesized to correlate with high efficacy in patients treated with immuno-oncology therapies. In this study, TMB was to be tested for all treated subjects with available tumor specimens, categorizing subjects as high TMB vs low TMB using a TMB cutoff of 10 mutations per megabase [1 million bases] of exome sequence (mut/Mb). The prospective selection of a cutoff of

10 mut/Mb for nivolumab + ipilimumab and 13 mut/Mb for nivolumab in CA209227 was based on data from clinical studies CA209568 and CA209026, respectively.

Key inclusion criteria:

- ECOG performance status of ≤ 1.
- Patients with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.
- Measurable disease by CT or MRI per RECIST 1.1 criteria.

Key Exclusion Criteria

- Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy.
- Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy.
- Subjects with untreated CNS metastases are excluded, even if asymptomatic.
- Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Treatments

Part 1a:

Subjects with PD-L1 expressing (≥ 1%) NSCLC were randomized and treated with 1 of the following open-label treatments:

- Arm A: nivolumab 240 mg over 30 minutes every 2 weeks (Q2W)
- Arm B: nivolumab 3 mg/kg over 30 minutes Q2W + ipilimumab 1 mg/kg over 30 minutes every 6 weeks (Q6W)
- Arm C: 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). 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.

Part 1b:

Subjects with PD-L1 non-expressing (< 1%) NSCLC were randomized and treated with 1 of the following open-label treatments:

- Arm D: nivolumab 3 mg/kg over 30 minutes Q2W + ipilimumab 1 mg/kg over 30 minutes every 6 weeks (Q6W)

- Arm 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). 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.
- Arm G: 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). Choice of platinum-doublet regimens was dependent on NSCLC histology:
    - SQ:
        - Nivolumab 360 mg administered IV over 30 minutes, followed by gemcitabine (1000 or 1250 mg/m2) with cisplatin (75 mg/m2). Gemcitabine was administered on Day 1 and Day 8 of each cycle, o
        - Nivolumab 360 mg administered IV over 30 minutes, followed by gemcitabine (1000 mg/m2) with carboplatin (AUC 5). Gemcitabine was administered on Day 1 and Day 8 of each cycle.
    - NSQ:
        - Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle, or
        - Nivolumab 360 mg administered IV over 30 minutes, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle.

Subjects in Arms A, B, D, and G were treated until disease progression, unacceptable toxicity, or up to 24 months in subjects without disease progression. Treatment beyond initial investigator assessed RECIST 1.1 defined progression was permitted if the subject had investigator-assessed clinical benefit and was tolerating nivolumab (Arms A and G) or nivolumab + ipilimumab (Arms B and D), as specified in the protocol.

Objectives

Hypothesis:

- Part 1a: Treatment with nivolumab plus ipilimumab (Arm B) will improve overall survival (OS) compared with platinum doublet chemotherapy (Arm C) in subjects with PD-L1 expressing stage IV or recurrent NSCLC.
- Part 1: Treatment with nivolumab plus ipilimumab (Arms B + D), will improve progression-free survival (PFS) compared with platinum doublet chemotherapy (Arms C + F) in subjects with stage IV or recurrent NSCLC and tumor mutational burden (TMB) ≥ 10 mutations per megabase [1 million bases] of exome sequence (mut/Mb), regardless of PD-L1 tumor expression level.

OBJECTIVES FOR PART 1:

Primary Objectives:

- In subjects with programmed cell death ligand 1 (PD-L1) ≥1% tumors: To compare overall survival (OS) of nivolumab in combination with ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C).
- In subjects with high baseline tumor mutational burden (TMB ≥ 10 mutations per megabase [mut/Mb]): To compare progression-free survival (PFS, based on blinded independent central review [BICR] assessment) of nivolumab in combination with ipilimumab (Arms B + D) to platinum-doublet chemotherapy (Arms C + F) regardless of programmed cell death ligand 1 (PD-L1) expression level.

Secondary Objectives:

The following objectives were to be hierarchically tested if the co-primary objective of OS for nivolumab + ipilimumab (Arm B) vs chemotherapy (Arm C) in subjects with PD-L1 ≥1% (Part 1a) crossed the boundary for statistical significance.

1. To compare PFS (per BICR) of nivolumab in combination with platinum-doublet chemotherapy (Arm G) to platinum-doublet chemotherapy (Arm F) in subjects with PD-L1 < 1% tumors. No formal testing was performed for this objective.
2. To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum doublet chemotherapy (Arm F) in subjects with PD-L1 < 1% tumors
3. To compare OS of nivolumab (Arm A), to platinum-doublet chemotherapy (Arm C) in subjects whose tumors express high PD-L1 (≥50%)

The following objectives were to be hierarchically tested in subjects with high baseline TMB (≥10 mut/Mb for nivolumab + ipilimumab; ≥13 mut/Mb for nivolumab) if the co-primary objective of PFS for nivolumab + ipilimumab vs chemotherapy in subjects with high TMB (≥10 mut/Mb) was positive.

1. To compare PFS (based on BICR assessment) of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥1% PD-L1 expression and with high baseline TMB (≥13 mut/Mb)
2. To compare OS of nivolumab in combination with ipilimumab (Arms B + D) to platinum-doublet chemotherapy (Arms C plus F) in subjects with high baseline TMB (≥10 mut/Mb) regardless PD-L1 expression level
3. To compare OS of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and with high baseline TMB (≥13 mut/Mb)

Key exploratory objectives:

These include the assessment of safety, tolerability, and immunogenicity of nivolumab + ipilimumab, nivolumab, and nivolumab + chemotherapy.

Outcomes/endpoints

The **2 co-primary** objectives of Part 1 were

1) To compare OS of nivolumab in combination with ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C) in subjects with ≥ 1% PD-L1 tumors in Part 1a

2) To compare PFS (BICR-assessed, primary definition) of nivolumab in combination with ipilimumab (Arms B + D) to platinum-doublet chemotherapy (Arms C + F) in subjects with baseline TMB ≥ 10 mut/Mb regardless of PD-L1 expression level in Part 1.

Other efficacy endpoints included objective response rate (ORR), time to response (TTR), and duration of response (DoR). The first tumor assessment was to be performed at 6 weeks (± 7 days) from first

dose date and subsequent tumor assessments were to occur every 6 weeks (± 7 days) up to the first 12 months (Week 48), then every 12 weeks until disease progression.

- PFS (primary definition) was defined as the time between the date of randomization and the first date of documented progression, as determined by BICR, or death due to any cause, whichever occurred first. Subjects who died with no reported progression were considered to have progressed on the date of death. Subjects who did not progress or die were censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die were censored on their date of randomization. Subjects who had palliative local therapy or initiated anti-cancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment on or prior to the initiation of subsequent anti-cancer therapy or palliative local therapy. PFS per investigator assessment and PFS (secondary definition, which accounts for the tumor scans post subsequent therapies) were also provided.
- ORR was defined as the proportion of randomized subjects who achieved a best response of complete response (CR) or partial response (PR) using the RECIST v1.1 criteria based on BICR assessment.
- DOR was defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented progression per BICR (using RECIST v1.1), or death due to any cause, whichever occurs first. Subjects who did not progress or die were censored on the date of their last evaluable tumor assessment. DOR was evaluated for responders only.
- TTR was defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the BICR. TTR was evaluated for responders only.
- The test for TMB (FoundationOne CDx [F1CDx] assay) used in CA209227 Part 1 was developed by Foundation Medicine, Inc. (Cambridge, MA), and is a validated next-generation sequencing (NGS)-based comprehensive genomic profile (CGP) assay for detection of genomic alterations, as well as genomic signatures including microsatellite instability (MSI) and TMB using deoxyribonucleic acid (DNA) isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. TMB results are presented overall and by two different baseline TMB cutoffs: 10.09 mutations per megabase (1 million bases of exome sequence; mut/Mb) and 12.61 mut/Mb. For computational derivation purposes, TMB 10.09 mut/Mb was categorized as TMB 10 mut/Mb, and TMB 12.61 mut/Mb was categorized as TMB 13 mut/Mb.

Sample size

Co-primary Endpoint: OS of nivolumab + ipilimumab (Arm B) vs chemotherapy (Arm C) in Part 1a

The sample size of Part 1a was calculated to compare OS between nivolumab + ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) under a 2-sided 0.0249 type I error with 90% power consideration for PD-L1 ≥ 1% subjects. Note that an alpha of 0.0001 (2-sided) was spent for an interim analysis of ORR for Part 1a. The number of events was estimated assuming an exponential distribution for OS in each arm. Approximately 1200 subjects were to be randomized to Arms A, B and C in a 1:1:1 ratio. Approximately 554 events (ie, deaths), observed among approximately 800 subjects between Arm B and C would provide 90% power to detect a hazard ratio (HR) of 0.74 with a type I error of 0.0249 (2-sided). The HR of 0.74 corresponds to a 35% increase in the median OS, assuming a median OS of 13.8 months for chemotherapy (Arm C) and 18.6 months for nivolumab + ipilimumab (Arm B) respectively. One interim OS analysis was planned at 70% of total events (ie, 388 events) observed at final analysis. The stopping boundaries at the interim and final analysis 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 388 events,

the nominal significance level for OS superiority would be 0.0056. The nominal significance level for the final look of OS after 553 events would then be 0.023.

Sample size justification to support co-primary objective of PFS comparison of nivolumab + ipilimumab vs chemotherapy in subjects with high TMB regardless of PD-L1 expression:

Approximately 1167 subjects were expected to be randomized to nivolumab + ipilimumab (pooled Arm B and Arm D) and chemotherapy (pooled Arm C and Arm F) regardless of baseline PD-L1 expression level. It was estimated that approximately 265 subjects would have a TMB ≥10.09 mutations/megabase per the FoundationOne CDx [F1CDx] assay; this would comprise the target population.

Approximately 221 PFS events observed among the TMB ≥10 mut/Mb subjects would provide 80% power to detect a HR of 0.66 (nivolumab + ipilimumab vs chemotherapy) with a 2-sided type 1 error of 0.025. The HR of 0.66 corresponds to a 52% increase in the median PFS, assuming a median of 6 months for chemotherapy and 9.1 months for nivolumab + ipilimumab. No formal interim analysis of PFS was planned. To achieve 221 PFS events, a sample size of at least 265 subjects will be required.

Assuming a piecewise accrual rate with a18-month accrual period, it will take approximately 25 months from the randomization of the first subject to observed the required number of events for PFS analysis. The number of events needed for the analyses will be monitored by the un-blinded independent statistician supporting the DMC.

Table 26: Sample Size Justification in Part 1 of the Study

Primary Endpoint	**PFS**
Primary analysis Comparison population	Subjects with TMB high: nivolumab+ipilimumab (Pooled Arm B and Arm D) and chemotherapy (pooled Arm C and Arm F)
Power	80%
Alpha	0.025
Hypothesized Median PFS of chemotherapy (pooled Arm C and Arm F) vs. nivolumab+ipilimumab (pooled Arm B and Arm D)	6 vs. 9.1
Hypothesized Hazard ratio	0.66
Accrual Duration (months)	18
Timing of final analysis (FA) from randomization of first subject (months)	25
Estimated sample size	At least 265
Expected number of events for final analysis	221

Randomisation

In Part 1 of the study, the overall enrolled population meeting the inclusion/exclusion criteria is categorized into PD-L1 expression level defined parts: PD-L1 expressing as Part 1A and PD-L1 non expressing (<1%) as Part 1B. Subjects categorized within these pre-defined groups are then stratified by their histology status and randomized to the respective treatment arms in 1:1:1 ratio.

Blinding (masking)

Not applicable.

Statistical methods

On 24-Jan-2018, the clinical database was locked for the following protocol-specified analyses of Part 1:

1) a formal planned interim analysis of OS for nivolumab + ipilimumab- vs chemotherapy-treated subjects in Part 1a and

2) a final analysis of PFS for nivolumab + ipilimumab- vs chemotherapy-treated subjects in Part 1 with TMB ≥10 mut/Mb.

On 02-Feb-2018, the independent DMC reviewed the data from the 24-Jan-2018 database lock, and confirmed that the pre-specified boundary for OS (nominal significance level $p < 0.007$) was not crossed with no new safety signals identified that would affect continuation of the study. The final analysis for the co-primary objective of PFS among subjects with TMB ≥ 10 mut/Mb between nivolumab + ipilimumab vs chemotherapy met the pre-criteria of statistical significance and these data are reported in this SCE. OS was not reported at the 24-Jan-2018 database lock.

The following objectives were to be hierarchically tested in subjects with baseline TMB ≥10 mut/Mb for nivolumab + ipilimumab and ≥13 mut/Mb for nivolumab if the co-primary objective of PFS for nivolumab + ipilimumab (Arms B + D) vs chemotherapy (Arms C + F) in subjects with TMB ≥10 mut/Mb was significant:

1. To compare BICR-assessed PFS between nivolumab (Arm A) and chemotherapy (Arm C) in subjects whose tumors have ≥1% PD-L1 expression and TMB ≥13 mut/Mb.
2. To compare OS of nivolumab + ipilimumab (Arms B + D) and chemotherapy (Arms C + F) in subjects with TMB ≥10 mut/Mb regardless of PD-L1 expression level.
3. To compare OS of nivolumab (Arm A) and chemotherapy (Arm C) in subjects whose tumors have ≥ 1% PD-L1 expression and TMB ≥13 mut/Mb.

However, nivolumab did not demonstrate a statistically significant improvement in PFS compared with chemotherapy. This comparison was pre-planned as part of the TMB testing hierarchy and, as such, further formal statistical testing was stopped in the TMB hierarchy.

To further characterize the long-term benefit of nivolumab + ipilimumab in subjects with TMB ≥10 mut/Mb observed in the co-primary PFS analysis, OS was analyzed for nivolumab + ipilimumab vs chemotherapy in subjects with TMB ≥10 mut/Mb based on a 15-Mar-2018 database lock (minimum follow-up of 14.1 months).

OS for nivolumab vs chemotherapy was not formally tested because a statistically significant improvement of PFS was not observed in subjects with TMB ≥13 mut/Mb based on the 24-Jan-2018 database lock. Therefore, the nominal p-value of OS was included for descriptive purposes only.

The OS analysis based on the 15-Mar-2018 database lock, with 14.1 months minimum follow-up (i.e., the expected median OS in the chemotherapy control arm), provides an additional 3 months of data to investigate any effect or trend for OS, including in scenarios with late separation. No other analyses of OS, including sub-group analyses, were conducted based on this lock to maintain the integrity of Part 1a.

The exploratory objective of BICR-assessed ORR of nivolumab in combination with ipilimumab (Arms B + D) and platinum-doublet chemotherapy (Arms C + F) in subjects with TMB ≥10 mut/Mb regardless of PD-L1 expression level will also be reported in this SCE.

Co-primary Endpoint: OS of nivolumab + ipilimumab (Arm B) vs chemotherapy (Arm C) in Part 1a

The sample size of Part 1a was calculated to compare OS between nivolumab + ipilimumab (Arm B) and platinum doublet chemotherapy (Arm C) under a 2-sided 0.0249 type I error with 90% power consideration for PD-L1 ≥1% subjects. Note that an alpha of 0.0001 (2-sided) was spent for an interim analysis of ORR for Part 1a. The number of events was estimated assuming an exponential distribution for OS in each arm. Approximately 1200 subjects were to be randomized to Arms A, B and C in a 1:1:1 ratio. Approximately 554 events (ie, deaths), observed among approximately 800 subjects between Arm B and C would provide 90% power to detect a hazard ratio (HR) of 0.74 with a type I error of 0.0249 (2-sided). The HR of 0.74 corresponds to a 35% increase in the median OS, assuming a median OS of 13.8 months for chemotherapy (Arm C) and 18.6 months for nivolumab + ipilimumab (Arm B) respectively. One interim OS analysis was planned at 70% of total events (ie, 388 events) observed at final analysis. The stopping boundaries at the interim and final analysis 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 388 events, the nominal significance level for OS superiority would be 0.0056. The nominal significance level for the final look of OS after 553 events would then be 0.023.

On 02-Jul-2019, the clinical database was locked for the pre-specified final analysis of this OS co-primary endpoint, which has a minimum follow-up of 29.3 months

Co-primary Endpoint: PFS of nivolumab + ipilimumab (Arm B + D) vs chemotherapy (Arm C + F) in subjects with High TMB (≥10 mut/Mb) in Part 1

Approximately 1167 subjects were expected to be randomized to nivolumab + ipilimumab (pooled Arm B and Arm D) and chemotherapy (pooled Arm C and Arm F) regardless of baseline PD-L1 expression level. It was estimated that approximately 265 subjects would have a TMB ≥10.09 mutations/megabase per the FoundationOne CDx [F1CDx] assay; this would comprise the target population.

Approximately 221 PFS events observed among the high TMB (≥10 mut/Mb) subjects would provide 80% power to detect a HR of 0.66 (nivolumab + ipilimumab vs chemotherapy) with a 2-sided type 1 error of 0.025. The HR of 0.66 corresponds to a 52% increase in the median PFS, assuming a median of 6 months for chemotherapy and 9.1 months for nivolumab + ipilimumab. No formal interim analysis of PFS was planned.

PFS (per BICR) co-primary hypothesis testing for nivolumab + ipilimumab (Arms B + D) to chemotherapy (Arms C + F) in subjects with baseline high TMB (≥10 mut/Mb) regardless of PD-L1 expression level was based on an unstratified log-rank test using a 2-sided alpha 0.025 level. Hazard ratios (HRs) of PFS (nivolumab + chemotherapy vs chemotherapy, and nivolumab + ipilimumab vs chemotherapy) and corresponding 2-sided 97.5% CIs were estimated using a Cox proportional hazard model, with treatment arm as a single covariate. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, and 24 months with 95% CIs were estimated using Kaplan-Meier (KM) methodology.

BICR-determined ORR was estimated by treatment arm and its corresponding 95% exact two-sided CIs was calculated using the Clopper Pearson method. The unweighted differences in ORR between the two treatment groups and corresponding 95% two-sided CI using the method of Newcombe was provided. Best overall response (BOR) as determined by BICR was summarized by response category for each treatment group. Summary statistics of time to objective response were provided for each treatment arm for subjects who achieved partial response (PR) or complete response (CR). **Duration of response** in each treatment arm was estimated using KM product-limit method for subjects who achieved PR or CR, including median values, 2-sided 95% CIs, and range. A "forest" plot by baseline subgroups of the BICR-determined unweighted differences in ORR (between nivolumab containing

arms and chemotherapy arm) and corresponding 95% CIs using the method of Newcombe was provided.

Hierarchical Testing Procedure: There are 2 parallel hierarchical testing paradigms in Part 1 as indicated by the co-primary objectives: a PD-L1 paradigm (2-sided type I error rate = 0.0249) and a TMB paradigm (2-sided type I error rate = 0.025).

An interim analysis of ORR of the first 484 subjects for Part 1a was performed in Jan-2017; BMS study personnel remained blinded. An alpha of 0.0001 was spent for this analysis.

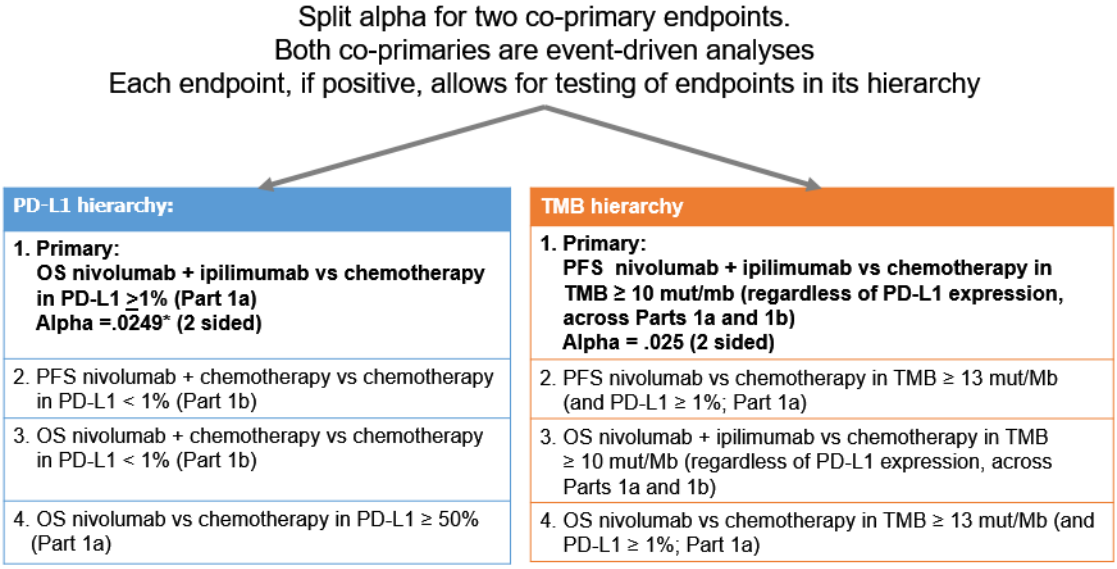
Safety was summarized for treated subjects. The safety profile was assessed through summaries and by-subject listings of deaths, SAEs, AEs leading to discontinuation or dose modification, overall AEs, select AEs, and laboratory abnormalities. The percentage of subjects who received immune-modulating concomitant medications for management of AEs or IMAEs was reported. The total duration of all immune-modulating medications (excluding overlaps) given for select AE management was reported.

Immunogenicity analyses included all nivolumab + ipilimumab-treated subjects with a baseline and at least 1 post-baseline assessment for ADA.

PFS (per BICR) co-primary hypothesis testing for nivolumab + ipilimumab (Arms B + D) to chemotherapy (Arms C + F) in subjects with baseline TMB ≥10 mut/Mb regardless of PD-L1 expression level was based on an unstratified log-rank test using a 2-sided alpha 0.025 level.

Hazard ratios (HRs) of PFS (nivolumab + chemotherapy vs chemotherapy, and nivolumab + ipilimumab vs chemotherapy) and corresponding 2-sided 97.5% CIs were estimated using a Cox proportional hazard model, with treatment arm as a single covariate. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, and 24 months with 95% CIs were estimated using KM methodology.

Figure 19: CA209227 Part 1 Co-primary Endpoints and Testing Hierarchy for Secondary Endpoints



* An alpha of 0.0001 (2-sided) was spent for a planned interim analysis of ORR in Part 1a

Results

Participant flow

A total of 1739 subjects were randomized at 239 sites in 32 countries.

Table 27: Subject Disposition by Arm - Part 1

End of Treatment Period Subject Status Summary
All Treated Subjects in Part 1

	Arm B: Nivo + Ipi N = 391	Arm A: Nivolumab N = 391	Arm C: Chemotherapy N = 387
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	0	2 (0.5)	5 (1.3)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	391 (100.0)	389 (99.5)	382 (98.7)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)			
DISEASE PROGRESSION	212 (54.2)	240 (61.4)	198 (51.2)
STUDY DRUG TOXICITY	79 (20.2)	51 (13.0)	30 (7.8)
DEATH	4 (1.0)	7 (1.8)	0
ADVERSE EVENT UNRELATED TO STUDY DRUG	23 (5.9)	29 (7.4)	22 (5.7)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	5 (1.3)	3 (0.8)	15 (3.9)
SUBJECT WITHDREW CONSENT	5 (1.3)	5 (1.3)	3 (0.8)
LOST TO FOLLOW-UP	0	0	1 (0.3)
MAXIMUM CLINICAL BENEFIT	3 (0.8)	3 (0.8)	1 (0.3)
POOR/NON-COMPLIANCE	1 (0.3)	0	2 (0.5)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.3)	1 (0.3)	0
ADMINISTRATIVE REASON BY SPONSOR	0	3 (0.8)	0
OTHER	5 (1.3)	6 (1.5)	11 (2.8)
COMPLETED TREATMENT	45 (11.5)	36 (9.2)	94 (24.3)
NOT REPORTED	8 (2.0)	5 (1.3)	5 (1.3)
SUBJECTS CONTINUING IN THE STUDY (%) (A)	123 (31.5)	107 (27.4)	82 (21.2)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (A)	268 (68.5)	284 (72.6)	305 (78.8)
DEATH	245 (62.7)	260 (66.5)	283 (73.1)
SUBJECT WITHDREW CONSENT	14 (3.6)	14 (3.6)	13 (3.4)
LOST TO FOLLOW-UP	7 (1.8)	9 (2.3)	7 (1.8)
OTHER	2 (0.5)	1 (0.3)	2 (0.5)

End of Treatment Period Subject Status Summary
All Treated Subjects in Part 1

	Arm D: Nivo + Ipi N = 185	Arm G: Nivo + Chemo N = 172	Arm F: Chemotherapy N = 183	Total N = 1709
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	1 (0.5)	2 (1.2)	1 (0.5)	11 (0.6)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	184 (99.5)	170 (98.8)	182 (99.5)	1698 (99.4)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)				
DISEASE PROGRESSION	93 (50.3)	112 (65.1)	97 (53.0)	952 (55.7)
STUDY DRUG TOXICITY	39 (21.1)	11 (6.4)	25 (13.7)	235 (13.8)
DEATH	0	1 (0.6)	2 (1.1)	14 (0.8)
ADVERSE EVENT UNRELATED TO STUDY DRUG	18 (9.7)	11 (6.4)	14 (7.7)	117 (6.8)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	5 (2.7)	3 (1.7)	6 (3.3)	37 (2.2)
SUBJECT WITHDREW CONSENT	3 (1.6)	1 (0.6)	3 (1.6)	20 (1.2)
LOST TO FOLLOW-UP	1 (0.5)	0	0	2 (0.1)
MAXIMUM CLINICAL BENEFIT	1 (0.5)	2 (1.2)	0	10 (0.6)
POOR/NON-COMPLIANCE	0	0	1 (0.5)	4 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.6)	1 (0.5)	4 (0.2)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	3 (0.2)
OTHER	7 (3.8)	5 (2.9)	0	34 (2.0)
COMPLETED TREATMENT	14 (7.6)	21 (12.2)	32 (17.5)	242 (14.2)
NOT REPORTED	3 (1.6)	2 (1.2)	1 (0.5)	24 (1.4)
SUBJECTS CONTINUING IN THE STUDY (%) (A)	60 (32.4)	34 (19.8)	24 (13.1)	430 (25.2)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (A)	125 (67.6)	138 (80.2)	159 (86.9)	1279 (74.8)
DEATH	110 (59.5)	132 (76.7)	148 (80.9)	1178 (68.9)
SUBJECT WITHDREW CONSENT	10 (5.4)	3 (1.7)	9 (4.9)	63 (3.7)
LOST TO FOLLOW-UP	4 (2.2)	3 (1.7)	1 (0.5)	31 (1.8)
OTHER	1 (0.5)	0	1 (0.5)	7 (0.4)

	Nivo + Ipi Arm B	Nivolumab Arm A	Chemotherapy Arm C	Nivo + Ipi Arm D	Nivo + Chemo Arm G	Chemotherapy Arm F
SUBJECTS RANDOMIZED	396	396	397	187	177	186
SUBJECTS TREATED	391	391	387	185	172	183
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	74 (18.9)	69 (17.6)	28 (7.2)	28 (15.1)	36 (20.9)	4 (2.2)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	317 (81.1)	322 (82.4)	359 (92.8)	157 (84.9)	136 (79.1)	179 (97.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)						
DISEASE PROGRESSION	200 (51.2)	228 (58.3)	183 (47.3)	85 (45.9)	101 (58.7)	96 (52.5)
STUDY DRUG TOXICITY	72 (18.4)	46 (11.8)	28 (7.2)	36 (19.5)	11 (6.4)	23 (12.6)
DEATH	5 (1.3)	7 (1.8)	0	1 (0.5)	1 (0.6)	2 (1.1)
AE UNRELATED TO STUDY DRUG	20 (5.1)	28 (7.2)	21 (5.4)	19 (10.3)	8 (4.7)	14 (7.7)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	4 (1.0)	2 (0.5)	13 (3.4)	5 (2.7)	2 (1.2)	6 (3.3)
SUBJECT WITHDREW CONSENT	5 (1.3)	6 (1.5)	3 (0.8)	3 (1.6)	1 (0.6)	3 (1.6)
LOST TO FOLLOW-UP	0	0	1 (0.3)	1 (0.5)	0	0
MAXIMUM CLINICAL BENEFIT	1 (0.3)	0	0	2 (1.1)	1 (0.6)	0
POOR/NON-COMPLIANCE	1 (0.3)	0	1 (0.3)	0	0	1 (0.5)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.3)	0	0	0	1 (0.6)	1 (0.5)
OTHER	6 (1.5)	3 (0.8)	10 (2.6)	5 (2.7)	4 (2.3)	0
COMPLETED TREATMENT	2 (0.5)	0	94 (24.3)	0	5 (2.9)	32 (17.5)
NOT REPORTED	0	2 (0.5)	5 (1.3)	0	1 (0.6)	1 (0.5)
SUBJECTS CONTINUING IN STUDY (%) (A)	192 (49.1)	169 (43.2)	162 (41.9)	90 (48.6)	78 (45.3)	62 (33.9)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (A)	199 (50.9)	222 (56.8)	225 (58.1)	95 (51.4)	94 (54.7)	121 (66.1)
DEATH	180 (46.0)	200 (51.2)	204 (52.7)	84 (45.4)	89 (51.7)	109 (59.6)
SUBJECT WITHDREW CONSENT	9 (2.3)	13 (3.3)	11 (2.8)	6 (3.2)	4 (2.3)	9 (4.9)
LOST TO FOLLOW-UP	8 (2.0)	8 (2.0)	8 (2.1)	4 (2.2)	1 (0.6)	2 (1.1)
OTHER	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.5)	0	1 (0.5)

Percentages based on subjects entering treatment period
(A) Subject status at the end of treatment

Results of TMB Testing in Part 1 of CA209227:

Archival or current subject specimens were sent to Foundation Medicine, Inc. (Cambridge, MA) for determination of TMB using the validated FoundationOne CDx (F1CDx) assay. FMI performed sample processing, next-generation sequencing (NGS) testing, and analysis using the F1CDx assay on samples from 1649 of the 1739 (94.8%) subjects randomized in CA209227 Part 1.

All 1649 randomized subjects with a sample provided to FMI had a categorical result (TMB valid [n = 1004], lower bound [n = 201], or unknown [n = 444]).

In the nivolumab + ipilimumab arms (Arms B + D) and the chemotherapy arms (Arms C + F) in Part 1, 330/583 (56.6%) and 349/583 (59.9%) of randomized subjects, respectively, were included in the TMB evaluable population, and 398/583 (68.3%) and 415/583 (71.2%) of randomized subjects, respectively, were included in the TMB evaluable sensitivity population. The TMB evaluable sensitivity population was used for missing TMB data sensitivity analyses of PFS in the TMB ≥ 10 mut/Mb population.

Recruitment

239 sites in 32 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea, Lebanon, Mexico, Netherlands, Peru, Poland, Romania, Russia Federation, South Africa, Spain, Switzerland, Taiwan, United Kingdom, and United States [US]). Part 1a and Part 1b of the study were open at the same time, at the same sites. Subjects with PD-L1 expressing tumors (≥1%) were randomized in Part 1a while subjects with PD-L1 non-expressing tumors (< 1%) were randomized in Part 1b. The last subject was randomized on 06-Jan-2017 and LPLV (clinical cutoff) for this CSR occurred on 15-May-2019, providing a minimum follow-up of 28.3 months for all subjects in Part 1.

On 24-Jan-2018, the clinical database was locked for the following protocol-specified analyses or Part 1:

1) A formal planned interim analysis of OS for nivolumab + ipilimumab- vs chemotherapy-treated subjects in Part 1a and

2) A final analysis of PFS for nivolumab + ipilimumab- vs chemotherapy-treated subjects in Part 1 with TMB ≥ 10 mut/Mb.

On 02-Feb-2018, the independent DMC reviewed the data from the 24-Jan-2018 database lock, and confirmed that the pre-specified boundary for OS (nominal significance level $p < 0.007$) was not crossed with no new safety signals identified that would affect continuation of the study. The final analysis for the co-primary objective of PFS among subjects with TMB ≥ 10 mut/Mb between nivolumab + ipilimumab vs chemotherapy met the pre-criteria of statistical significance. OS was not reported at the 24-Jan-2018 database lock.

On 02-Jul-2019, the clinical database was locked for the pre-specified final analysis of this OS co-primary endpoint, which has a minimum follow-up of 29.3 months

Conduct of the study

The original CA209227 protocol, dated 29-May-2015, contained two substudies, one in subjects with PD-L1 expressing tumors (≥1%) and one in subjects with PD-L1 non-expressing tumors (< 1%), each randomizing to three arms (including one control arm), with an OS/PFS co-primary endpoint for each experimental arm versus the respective control. Each substudy had an independent alpha of 0.05 for addressing the primary and salient secondary objectives within each substudy. The protocol underwent 4 major revisions based on emerging data from other studies in first-line NSCLC. A description and rationale for the major protocol amendments relevant to Part 1 are provided below.

- **Replacement of Arm E (Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg) with Arm G (Nivolumab + Chemotherapy) in Part 1b (Amendment 09, 21-Oct-2015):**

  Based on new data from Phase 1 study CA 209012, Arm E regimen (which included lower dose of nivolumab and more frequent ipilimumab) was reported less efficacious and removed from Part 1b. Arm E was replaced by Arm G, which evaluated nivolumab plus platinum-doublet chemotherapy, using the same chemotherapy regimens as in the control arms. The addition of Arm G was based on the ORR and OS observed in the nivolumab plus chemotherapy cohorts of CA209012. For subjects with PD-L1 non- expressing tumors (< 1%), the response rates with nivolumab + chemotherapy were greater than with nivolumab monotherapy, or nivolumab + ipilimumab, and appeared to be similar between subjects with PD-L1 expressing tumors and PD-L1 non-expressing tumors.

  No subjects were randomized to Arm E. 20 subjects were randomized in Part 1b (10 to Arm D and 10 to Arm F) before the first subject was randomized to Arm G. Given the overall size of the study, randomization to Arm G and Arms D and F was considered as nearly contemporaneous, and for this reason, all randomized subjects are included in the analysis.

- **Addition of Part 2, and Organization into 3 Substudies, and Changes to the Co-primary Endpoints (Amendment 12, 17-Nov-2016):**

  Based on emerging data from KEYNOTE-021 (pembrolizumab + chemotherapy showing superior PFS vs chemotherapy in NSQ subjects in a PD-L1 unselected population), Part 2 was added to CA209227 to investigate nivolumab + chemotherapy versus chemotherapy in a PD-L1 unselected population. For increased clarity, the original substudies were named Part 1a and Part 1b. The sample size for Part 1a was increased from 990 to 1200. Part 1b was amended so that it would close enrolment after Part 1a was fully accrued, decreasing the sample size to ~540. As mentioned above, an alpha of 0.05 was allocated to each substudy (Part 1a and Part 1b).

In this protocol amendment, endpoints for Part 1a and Part 1b were revised as follows:

- In Part 1a: PFS was removed as a co-primary objective, leaving the OS comparison of nivolumab + ipilimumab vs chemotherapy as the single primary objective. In addition, the population for the primary endpoint of OS (nivolumab + ipilimumab vs chemotherapy) was changed to subjects with tumors expressing PD-L1 ⩾ 50%, based on anti-PD-1 monotherapy data showing increased OS in this population in KEYNOTE 024, but not in the PD-L1 ⩾1% population in CA209026.
- In Part 1b: OS was removed as a co-primary objective, leaving the comparison of PFS (per BICR) of nivolumab + chemotherapy vs chemotherapy as the single primary objective. This was based on KEYNOTE-021, suggesting PFS may adequately capture benefit with anti-PD-1 therapy + chemotherapy. Furthermore, with reduced size of the Part 1b substudy, PFS was considered more appropriate and would allow for an analysis at approximately the time OS in Part 1a had matured.

- **Change of the Primary Objective of OS with Nivolumab + Ipilimumab vs Chemotherapy Back to the Original PD-L1 ≥1% Population (Amendment 19, 05-Oct-2017):**

  The primary objective comparison of OS for nivolumab + ipilimumab vs chemotherapy was changed from the PD-L1 ⩾50% population to the ⩾1% population, which was the comparison in the original protocol. This was supported by emerging data from CA209568 (that confirmed data first observed in CA209012), showing an ORR of > 40% in subjects with PD-L1 ⩾1%, ie, higher than the ORR historically observed with chemotherapy. The higher ORR, combined with increased durability, was expected to translate into an OS benefit in this broader PD-L1 selected population. In contrast, based on data from KEYNOTE-024 and CA209026, benefit from nivolumab monotherapy over chemotherapy was likely to be observed only in a more selected population. To test this, an OS comparison of nivolumab vs chemotherapy in subjects with PD-L1 ⩾50% was added to Part 1a as a secondary objective.

- **Addition of TMB PFS Co-primary Objective (Amendment 19 dated 05-Oct-2017):**

  In 2017, during the conduct of CA209227, based on emerging science and evidence from multiple other studies, including analyses from Phase 2 study CA209568 (nivolumab + ipilimumab) and Phase 3 study CA209026 (nivolumab monotherapy), TMB was identified as an important potential biomarker (independent of PD-L1) to help identify patients most likely to benefit from immunotherapy. To further enhance and optimize patient selection, an additional co-primary analysis was incorporated into Part 1 of the study to test whether nivolumab + ipilimumab prolongs PFS versus chemotherapy in subjects with TMB ⩾10 mut/Mb per the F1CDx assay, regardless of PD-L1 expression. The original co-primary endpoint of OS with nivolumab + ipilimumab versus chemotherapy in subjects with PD-L1 ⩾1% was maintained. To ensure sufficient power for the two co-primary endpoints, the comparison of nivolumab + chemotherapy versus chemotherapy was demoted to a secondary endpoint.

  Subjects were pooled across Parts 1a and 1b for analysis of TMB. Subjects in Parts 1a and 1b were enrolled simultaneously using the same inclusion/exclusion criteria at the same sites and countries. Subjects in both Parts 1a and 1b were randomized 1:1:1 to nivolumab + ipilimumab, chemotherapy, or a third arm (nivolumab monotherapy in Part 1a, nivolumab + chemotherapy in Part 1b). While Parts 1a and 1b had separate randomization, the simultaneous enrollment of both parts facilitates pooling, with PD-L1 status functionally acting as a stratification factor.

Of note, in the original statistical analysis plan (SAP), a separate alpha of 0.05 was allocated to each substudy (Part 1a and Part 1b), as they were considered separate studies. However, since subjects with TMB ⩾10 mut/Mb were to be pooled across Parts 1a and 1b, in the revised SAP (version 1.1) and protocol (version 4.0), the alpha (type-1 error) for assessing the co-primary efficacy endpoints within Part 1 was set at a two-sided 0.05 level (alpha of 0.0001 for the planned interim analysis of ORR, 0.0249 for the co-primary analysis of OS in PD-L1 ⩾1%, and 0.025 for the co-primary analysis of PFS in TMB ⩾10 mut/Mb). A hierarchical hypothesis testing approach for the secondary endpoints was used to preserve the type I error rates.

Baseline data

Baseline demographics and disease characteristics in all randomized subjects were representative of a first-line recurrent or metastatic NSCLC population.

Among subjects with TMB ≥ 10 mut/Mb, in both the nivolumab + ipilimumab and chemotherapy groups, there was a higher proportion of smokers (former or current) and subjects with SQ histology compared with the all randomized population, as expected based on the underlying biology. Baseline demographic and disease characteristics were well balanced between the nivolumuab + ipilimumab and the chemotherapy groups, with the exception of the proportion of subjects with an ECOG PS of 0, which was numerically higher in the nivolumab + ipilimumab group than in the chemotherapy group (40.3% vs 30.6%, respectively).

Table: Key Baseline Characteristics in Subjects with PD-L1> 1% (Part 1A)

	Nivolumab + Ipilimumab Arm B (N = 396)	Nivolumab Arm A (N = 396)	Chemotherapy Arm C (N = 397)
Age (years)			
Median	64.0	64.0	64.0
< 65 (n, %)	199 (50.3)	210 (53.0)	207 (52.1)
≥ 65 and < 75 (n, %)	157 (39.6)	129 (32.6)	149 (37.5)
≥ 65 (n, %)	197 (49.7)	186 (47.0)	190 (47.9)
≥ 75 (n, %)	40 (10.1)	57 (14.4)	41 (10.3)
Male (n, %)	255 (64.4)	272 (68.7)	260 (65.5)
Race (n, %)			
White	299 (75.5)	317 (80.1)	305 (76.8)
Black	4 (1.0)	6 (1.5)	5 (1.3)
Asian	84 (21.2)	67 (16.9)	82 (20.7)
Other	5 (1.3)	6 (1.5)	3 (0.8)
Cell Type (n, %)			
SQ Carcinoma	117 (29.5)	117 (29.5)	116 (29.2)
NSQ Carcinoma			
Adenocarcinoma	267 (67.4)	267 (67.4)	269 (67.8)
Large Cell Carcinoma	6 (1.5)	5 (1.3)	4 (1.0)
Other	6 (1.5)	7 (1.8)	8 (2.0)

	Nivolumab + Ipilimumab Arm B (N = 396)	Nivolumab Arm A (N = 396)	Chemotherapy Arm C (N = 397)
Age (years)			
Median	64.0	64.0	64.0
< 65 (n, %)	199 (50.3)	210 (53.0)	207 (52.1)
≥ 65 and < 75 (n, %)	157 (39.6)	129 (32.6)	149 (37.5)
≥ 65 (n, %)	197 (49.7)	186 (47.0)	190 (47.9)
≥ 75 (n, %)	40 (10.1)	57 (14.4)	41 (10.3)
Male (n, %)	255 (64.4)	272 (68.7)	260 (65.5)
Race (n, %)			
White	299 (75.5)	317 (80.1)	305 (76.8)
Black	4 (1.0)	6 (1.5)	5 (1.3)
Asian	84 (21.2)	67 (16.9)	82 (20.7)
Other	5 (1.3)	6 (1.5)	3 (0.8)
Cell Type (n, %)			
SQ Carcinoma	117 (29.5)	117 (29.5)	116 (29.2)
NSQ Carcinoma			
Adenocarcinoma	267 (67.4)	267 (67.4)	269 (67.8)
Large Cell Carcinoma	6 (1.5)	5 (1.3)	4 (1.0)
Other	6 (1.5)	7 (1.8)	8 (2.0)

	Nivolumab + Ipilimumab Arm B (N = 396)	Nivolumab Arm A (N = 396)	Chemotherapy Arm C (N = 397)
Metastasis Site			
Liver	71 (17.9)	92 (23.2)	85 (21.4)
Brain	41 (10.4)	42 (10.6)	40 (10.1)
ECOG PS (n, %)			
0	135 (34.1)	142 (35.9)	134 (33.8)
1	260 (65.7)	252 (63.6)	259 (65.2)
≥ 2	1 (0.3)	0	3 (0.8)
Not Reported	0	2 (0.5)	1 (0.3)
Smoking Status (n, %)			
Never smoker	56 (14.1)	50 (12.6)	51 (12.8)
Smoker[a]	334 (84.3)	342 (86.4)	340 (85.6)
Unknown	6 (1.5)	4 (1.0)	6 (1.5)
PD-L1 Level (n, %)			
≥ 50%	205 (51.8)	214 (54.0)	192 (48.4)
1% – 49%	191 (48.2)	182 (46.0)	205 (51.6)
≥ 1%	396 (100.0)	396 (100.0)	397 (100.0)

[a] Includes former and current smokers

Table: Key Baseline Characteristics in Subjects with PD-L1 < 1% (Part 1b)

	Nivolumab + Ipilimumab Arm D (N = 187)	Nivolumab + Chemotherapy Arm G (N = 177)	Chemotherapy Arm F (N = 186)
Age (years)			
Median	63.0	64.0	64.0
< 65 (n, %)	107 (57.2)	91 (51.4)	98 (52.7)
≥ 65 and < 75 (n, %)	62 (33.2)	71 (40.1)	74 (39.8)
≥ 65 (n, %)	80 (42.8)	86 (48.6)	88 (47.3)
≥ 75 (n, %)	18 (9.6)	15 (8.5)	14 (7.5)
Male (n, %)	138 (73.8)	130 (73.4)	125 (67.2)
Race (n, %)			
White	143 (76.5)	136 (76.8)	133 (71.5)
Black	0	2 (1.1)	2 (1.1)
Asian	41 (21.9)	38 (21.5)	45 (24.2)
Other	1 (0.5)	1 (0.6)	5 (2.7)
Cell Type (n, %)			
SQ Carcinoma	46 (24.6)	42 (23.7)	46 (24.7)
NSQ Carcinoma			
Adenocarcinoma	132 (70.6)	127 (71.8)	135 (72.6)
Large Cell Carcinoma	3 (1.6)	3 (1.7)	2 (1.1)
Other/Not Reported	6 (3.2)	5 (2.8)	3 (1.6)
Metastasis Site			
Liver	51 (27.3)	39 (22.0)	45 (24.2)
Brain	23 (12.3)	16 (9.0)	11 (5.9)
ECOG PS (n, %)			
0	69 (36.9)	59 (33.3)	57 (30.6)
1	117 (62.6)	116 (65.5)	127 (68.3)
≥ 2/ Not Reported	1 (0.5)	2 (1.1)	2 (1.1)
Smoking Status (n, %)			
Never smoker	23 (12.3)	27 (15.3)	27 (14.5)
Smoker[a]	163 (87.2)	147 (83.1)	159 (85.5)
Unknown/Not Reported	1 (0.5)	3 (1.7)	0
PD-L1 Level (n, %)			
≥ 1%	0	1 (0.6)[b]	0
< 1%	187 (100.0)	176 (99.4)	186 (100.0)

[a] Includes former and current smokers

Prior Cancer Therapies

In all randomized subjects in Part 1, no subjects received prior systemic anticancer therapy in the setting of metastatic disease, which is consistent with the inclusion criteria. Overall, 6.0% and 2.1% of subjects received prior systemic therapy in the adjuvant or neoadjuvant setting, respectively. The most frequent prior systemic cancer therapies overall were cisplatin (5.0%), vinorelbine (3.5%), and carboplatin (2.6%).

Numbers analysed

Table: Analysis Populations in this Final Clinical Study Report for CA209227 Part 1

Population	Arm A (Nivo)	Arm B (Nivo + Ipi)	Arm C (Chemo)	Arm D (Nivo + Ipi)	Arm G (Nivo+ Chemo)	Arm F (Chemo)	Arms B +D (Pooled Nivo + Ipi)	Arms C + F (Pooled Chemo)	Total n/N (%)
Enrolled: Enrolled subjects who signed an informed consent form (ICF) and were registered in Interactive Web Response System (IWRS) (used for pre-treatment disposition).	--	--	--	--	--	--	--	--	2876
Randomized: Subjects randomized to any treatment arm in Part 1 (used for demography, protocol deviations, baseline characteristics, efficacy).	396	396	397	187	177	186	583	583	1739
PD-L1 ≥ 1%: Randomized subjects with PD-L1 membranous staining in ≥ 1% tumor cells	396	396	397	--	1	--	396	397	1190
PD-L1 < 1%: Randomized subjects with PD-L1 membranous staining in < 1% tumor cells	--	--	--	187	176	186	187	186	549
PD-L1 ≥ 50%: Randomized subjects with PD-L1 membranous staining in ≥ 50% tumor cell (subset of PD-L1 ≥ 1% subjects)	214	205	192	--	--	--	205	192	611
Tumor Mutational Burden (TMB) ≥ 10 mut/Mb: randomized subjects with TMB ≥ 10 mut/Mb	102	101	112	38	43	48	139	160	444
Low TMB < 10 mut/Mb: randomized subjects with TMB < 10 mut/Mb	126	139	130	52	54	59	191	189	560
Treated: Treated subjects, who received at least 1 dose of study drug (used for drug exposure and safety)	391	391	387	185	172	183	576	570	1709
Immunogenicity subjects: treated subjects with baseline and at least 1 post-baseline assessment for anti-drug antibody (ADA) (used for immunogenicity).									
Nivolumab ADA Evaluable	322	334	--	157	148	--	491	--	961
Ipilimumab ADA Evaluable	--	329	--	154	--	--	483	--	483

Outcomes and estimation

Table: Results of the Statistical Testing Hierarchy for Part 1

	p-Value Threshold	Actual p-Value	Met the Threshold
PD-L1 Hierarchy (2-sided type I error rate = 0.0228 for the final analysis)			
Co-primary objective: In subjects with PD-L1 ≥ 1% tumors, compare OS of nivo + ipi (Arm B) to chemo (Arm C)	< 0.0228	0.0066	Yes
Secondary Objectives (2-sided type I error rate = 0.0228)			
1. Compare PFS of nivo + chemo (Arm G) to chemo (Arm F) in subjects with PD-L1 < 1%	< 0.0228	0.0070	Yes
2. Compare OS of nivo + chemo (Arm G) to chemo (Arm F) in subjects with PD L1 < 1%	< 0.0228	0.0352	No (Statistical testing was stopped)
3. Compare OS of nivo (Arm A) to chemo (Arm C) in subjects with PD L1 ≥ 50%	< 0.0228	NA	NA
TMB Hierarchy (2-sided type I error rate = 0.025 for the interim analysis)			
Co-primary objective: In subjects with TMB ≥ 10 mut/Mb, compare PFS (per BICR) of nivo + ipi (Arms B + D) to chemo (Arms C + F) regardless of PD-L1 expression	< 0.025	0.0002[a]	Yes
Secondary Objectives (2-sided type I error rate = 0.025)			
1. Compare PFS between nivo (Arm A) and chemo (Arm C) among subjects with TMB ≥ 13 mut/Mb	< 0.025	0.7776[a]	No (statistical testing was stopped)
2. Compare OS of nivo + ipi (Arms B and D) and chemo (Arms C and F) in subjects with TMB ≥ 10 mut/Mb regardless of PD L1 expression	< 0.025	NA	NA
3. Compare OS of nivo (Arm A) and chemo (Arm C) in subjects with TMB ≥ 13 mut/Mb	< 0.025	NA	NA

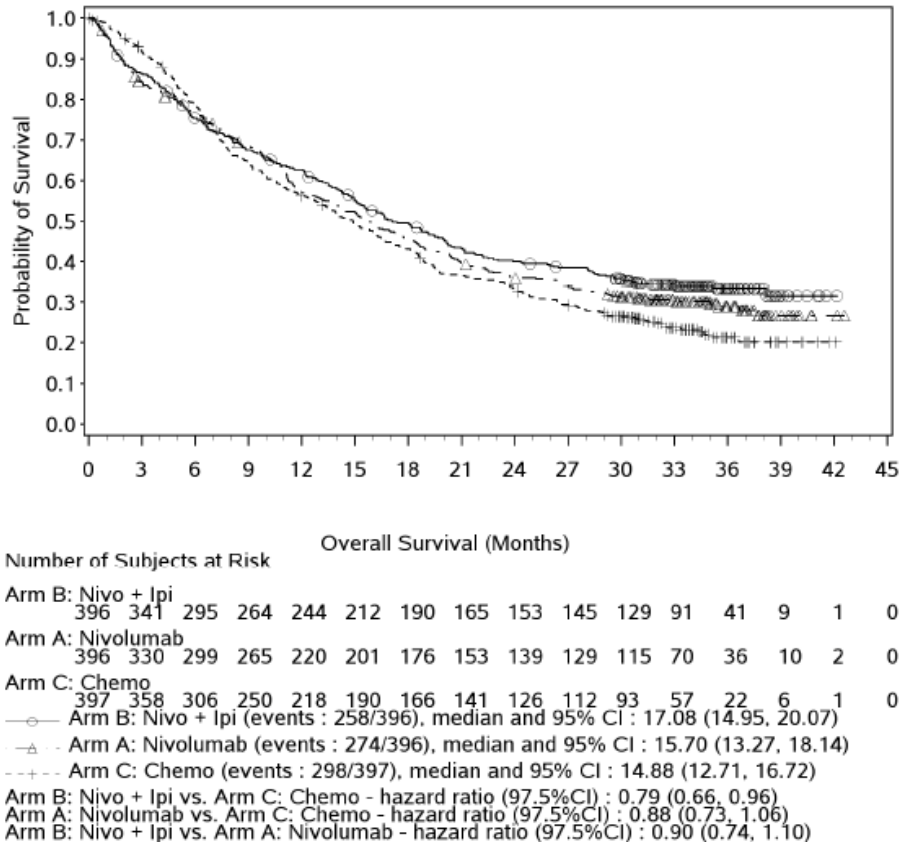
[a] Data from the 24-Jan-2018 database lock, reported in the CA209227 Interim Part 1 CSR.

Abbreviations: BICR - blinded independent central review, mut/Mb- mutations per megabase, NA - not applicable, OS - overall survival, PD-L1 - programmed cell death ligand 1, PFS - progression-free survival, TMB - tumor mutational burden

Nivolumab + Ipilimumab vs Chemotherapy

Co-Primary Endpoint: Nivolumab + ipilimumab demonstrated a statistically significant improvement in OS compared with chemotherapy alone: HR = 0.79 (97.72% CI: 0.65, 0.96); stratified log-rank test p-value = 0.0066. In subjects with PD-L1 > 1% in Part 1a, median OS (95% CI) was 17.08 (14.95, 20.07), 15.70 (13.27, 18.14), and 14.88 (12.71, 16.72) months in the nivolumab + ipilimumab (Arm B), nivolumab (Arm A), and chemotherapy (Arm C) arms, respectively

Figure: Kaplan-Meier Plot of Overall Survival - Nivolumab + Ipilimumab (Arm B), Nivolumab (Arm A), and Chemotherapy (Arm C) – All Randomized Subjects in Part 1a



Efficacy of Nivolumab + Ipilimumab, Nivolumab, and Chemotherapy in Subjects with PD-L1 ≥ 1% (CA209227 Part 1a)

Table: Efficacy in Randomized Subjects with PD-L1-Expressing (≥ 1%) Tumors - CA209227 Part 1a

	Nivolumab + Ipilimumab Arm B (N = 396)	Nivolumab Arm A (N = 396)	Chemotherapy Arm C (N = 397)
Overall Survival (OS)			
Events, n (%)	258 (65.2)	274 (69.2)	298 (75.1)
Nivo + Ipi vs Chemo			
HR (97.72% CI)[a]		0.79 (0.65, 0.96)	
Stratified log-rank test p value		0.0066	
HR (97.5% CI)[a]		0.79 (0.66, 0.96)	
HR (95% CI)[a]		0.79 (0.67, 0.94)	
Nivo vs Chemo			
HR (97.5% CI)[a]		0.88 (0.73, 1.06)	
HR (95% CI)[a]		0.88 (0.75, 1.04)	
Nivo + Ipi vs Nivo			
HR (97.5% CI)[a]		0.90 (0.74, 1.10)	
HR (95% CI)[a]		0.90 (0.76, 1.07)	
Median OS (95% CI), mo.[b]	17.08 (14.95, 20.07)	15.70 (13.27, 18.14)	14.88 (12.71, 16.72)
OS Rates (95% CI), %[b]			
12 months	62.6 (57.7, 67.2)	57.0 (51.9, 61.7)	56.2 (51.1, 61.0)
18 months	49.4 (44.4, 54.3)	45.6 (40.6, 50.4)	43.0 (38.0, 47.9)
24 months	40.0 (35.1, 44.9)	36.2 (31.5, 41.0)	32.8 (28.2, 37.5)
PFS per BICR (1° Definition)			
Events, n (%)	288 (72.7)	311 (78.5)	286 (72.0)
Nivo + Ipi vs Chemo			
HR (97.5% CI)[a]		0.82 (0.67, 0.99)	
HR (95% CI)[a]		0.82 (0.69, 0.97)	
Nivo vs Chemo			
HR (97.5% CI)[a]		0.99 (0.82, 1.19)	
HR (95% CI)[a]		0.99 (0.84, 1.17)	
Nivo + Ipi vs Nivo			
HR (97.5% CI)[a]		0.83 (0.69, 1.00)	
HR (95% CI)[a]		0.83 (0.71, 0.97)	
Median PFS (95% CI), mo.[b]	5.06 (4.07, 6.31)	4.17 (3.02, 5.32)	5.55 (4.63, 5.82)
PFS Rates (95% CI), %[b]			
12 months	33.0 (28.1, 37.9)	25.8 (21.3, 30.5)	18.6 (14.3, 23.3)
18 months	26.7 (22.1, 31.4)	18.2 (14.3, 22.5)	10.6 (7.2, 14.8)
24 months	22.2 (17.9, 26.7)	14.3 (10.8, 18.3)	7.0 (4.2, 10.8)

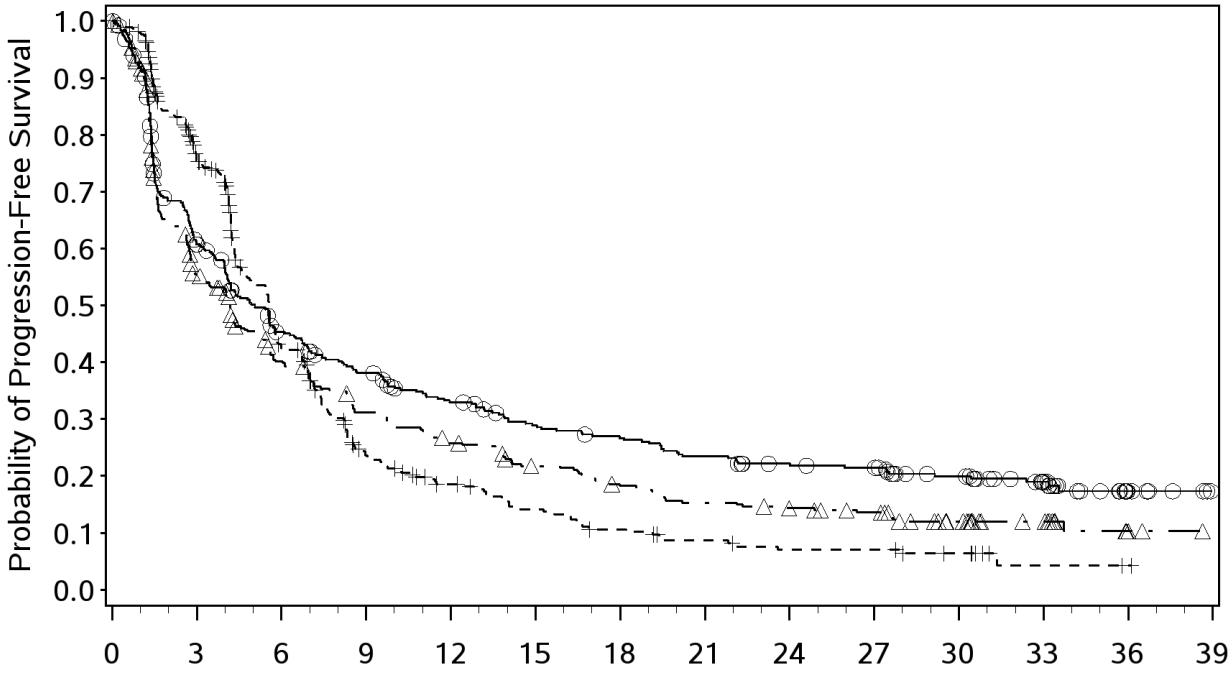
Table: Efficacy in Randomized Subjects with PD-L1-Expressing (≥ 1%) Tumors - CA209227 Part 1a

	Nivolumab + Ipilimumab Arm B (N = 396)	Nivolumab Arm A (N = 396)	Chemotherapy Arm C (N = 397)
ORR per BICR (CR + PR)[c]			
N responders (%)	142 (35.9%)	109 (27.5%)	119 (30.0%)
95% CI	(31.1, 40.8)	(23.2, 32.2)	(25.5, 34.7)
Complete Response, n (%)	23 (5.8)	12 (3.0)	7 (1.8)
TTR per BICR			
Median (min, max), mo.	1.95 (1.0, 16.6)	2.69 (1.2, 16.4)	1.61 (1.1, 21.8)
DoR per BICR			
N events/N responders (%)	74/142 (52.1)	65/109 (59.6)	82/119 (68.9)
Median (95% CI), mo.[b]	23.16 (15.21, 32.16)	15.54 (12.71, 23.52)	6.24 (5.59, 7.39)
Min, Max, mo.	1.4+, 37.6+	1.5+, 35.9+	1.2+, 34.5+
% subjects with DoR (95% CI)[b] of:			
≥ 6 months	79 (71, 85)	81 (72, 87)	53 (43, 62)
≥ 12 months	64 (55, 72)	63 (53, 72)	28 (19, 38)
≥ 18 months	54 (45, 62)	43 (33, 52)	16 (9, 25)
≥ 24 months	49 (41, 58)	40 (30, 49)	11 (5, 20)

[a] Hazard ratios are based on a stratified Cox proportional hazard model.
[b] Kaplan-Meier estimate
[c] Proportion with CR or PR; confidence interval based on the Clopper and Pearson method

Symbol + indicates a censored value.
Database lock: 02-Jul-2019; minimum follow-up of 28.3 months (29.3 months for OS)
Abbreviations: BICR - blinded independent central review, CI - confidence interval, CR - complete response, DoR - duration of response, HR - hazard ratio, ORR - objective response rate, OS - overall survival, PD-L1 - programmed cell death ligand 1, PFS - progression-free survival, PR - partial response, TTR - time to response.
Source: Table 7.1.1-1 of the CA209227 Part 1 Final CSR

Figure: Kaplan-Meier Plot of Progression-Free Survival (Primary Definition) per BICR - All Randomized Subjects in CA209227 Part 1a



Number of Subjects at Risk

Arm B: Nivo + Ipi	396	221	158	130	108	91	83	73	65	62	47	31	7	0
Arm A: Nivolumab	396	199	136	104	85	68	56	47	42	37	24	15	3	0
Arm C: Chemo	397	253	130	63	44	32	23	17	12	12	8	2	1	0

Arm B: Nivo + Ipi (events : 288/396), median and 95% CI : 5.06 (4.07, 6.31)
Arm A: Nivolumab (events : 311/396), median and 95% CI : 4.17 (3.02, 5.32)
Arm C: Chemo (events : 286/397), median and 95% CI : 5.55 (4.63, 5.82)
Arm B: Nivo + Ipi vs. Arm C: Chemo - hazard ratio (97.5%CI) : 0.82 (0.67, 0.99)
Arm A: Nivolumab vs. Arm C: Chemo - hazard ratio (97.5%CI) : 0.99 (0.82, 1.19)
Arm B: Nivo + Ipi vs. Arm A: Nivolumab - hazard ratio (97.5%CI) : 0.83 (0.69, 1.00)

Symbols represent censored observations.
Hazard Ratios (Nivo + Ipi vs Chemo, Nivo vs Chemo and Nivo + Ipi vs Nivo) are based on a stratified Cox proportional hazard model

Source: Figure 7.2.2-1 of the CA209227 Part 1 Final CSR

Figure ~~0-1~~: Forest Plot of Treatment Effect on OS in Pre-Defined Subsets - Nivolumab + Ipilimumab (Arm B) and Chemotherapy (Arm C) - All Randomized Subjects in CA209227 Part 1a

	N	Nivo + Ipi (Arm B) N of Events (N of subjects)	mOS (95% CI)	Chemotherapy (Arm C) N of Events (N of subjects)	mOS (95% CI)	Unstratified Hazard Ratio (97.5% CI) Nivo + Ipi vs. Chemo
Overall	793	258(396)	17.08 (14.95, 20.07)	298(397)	14.88 (12.71, 16.72)	0.80 (0.66, 0.97)
Age Categorization						
< 65	406	116(199)	19.68 (15.34, 28.09)	152(207)	16.03 (13.17, 18.23)	0.70 (0.53, 0.93)
>= 65 and < 75	306	109(157)	16.62 (13.57, 19.94)	111(149)	14.49 (10.84, 18.86)	0.91 (0.67, 1.24)
>= 75 and < 85	79	33(40)	13.50 (6.60, 20.07)	33(39)	11.43 (8.61, 15.21)	0.91 (0.52, 1.59)
>= 85	2	0(0)	N.A.	2(2)	18.50 (6.67, 30.32)	N.A.
>= 75	81	33(40)	13.50 (6.60, 20.07)	35(41)	11.43 (8.61, 15.21)	0.92 (0.53, 1.59)
>= 65	387	142(197)	15.51 (13.37, 18.76)	146(190)	13.47 (10.74, 17.54)	0.91 (0.70, 1.19)
Gender						
Male	515	164(255)	18.66 (14.95, 21.72)	201(260)	13.96 (10.84, 16.72)	0.75 (0.59, 0.95)
Female	278	94(141)	16.59 (12.81, 20.24)	97(137)	16.20 (12.42, 18.79)	0.91 (0.66, 1.26)
Race						
White	604	210(299)	15.51 (12.81, 18.69)	242(305)	12.81 (10.51, 14.92)	0.81 (0.65, 1.00)
Black	9	1(4)	N.A. (8.15, N.A.)	4(5)	10.05 (1.97, N.A.)	0.28 (0.02, 3.46)
Asian	166	39(84)	N.A. (16.62, N.A.)	48(82)	24.84 (18.86, 32.53)	0.76 (0.47, 1.24)
Other	14	8(9)	20.24 (0.53, 28.19)	4(5)	17.15 (0.33, N.A.)	1.28 (0.32, 5.21)
Region						
North America	95	26(40)	18.23 (8.57, 38.18)	40(55)	15.70 (7.66, 25.72)	0.85 (0.48, 1.49)
Europe	400	138(199)	16.20 (12.81, 19.09)	159(201)	11.93 (9.72, 14.49)	0.78 (0.60, 1.02)
Asia	162	37(81)	N.A. (16.62, N.A.)	47(81)	24.84 (19.48, 32.53)	0.76 (0.46, 1.24)
Rest of World	136	57(76)	15.01 (9.30, 20.57)	52(60)	13.90 (8.44, 17.18)	0.76 (0.49, 1.16)
Baseline ECOG Performance Status						
0	269	74(135)	24.44 (19.15, N.A.)	96(134)	17.51 (14.92, 22.87)	0.66 (0.46, 0.93)
1	519	183(260)	14.62 (11.30, 16.69)	199(259)	12.71 (10.51, 15.67)	0.89 (0.71, 1.12)
> 1	4	1(1)	4.30 (N.A., N.A.)	2(3)	7.00 (1.12, N.A.)	
Not Reported	1	0(0)	N.A.	1(1)	6.08 (N.A., N.A.)	

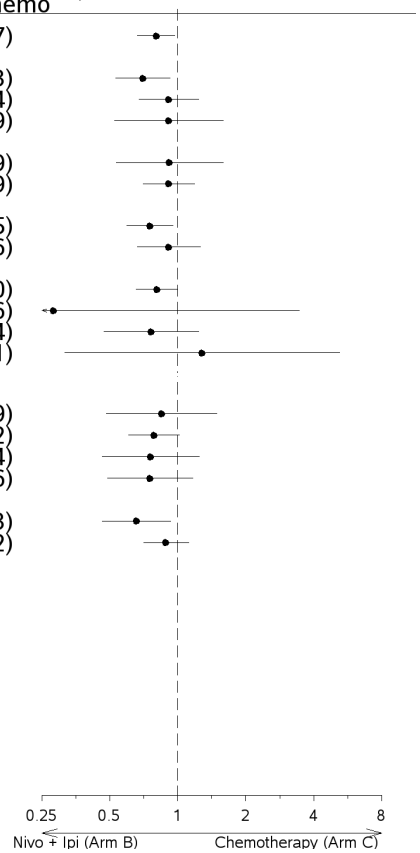
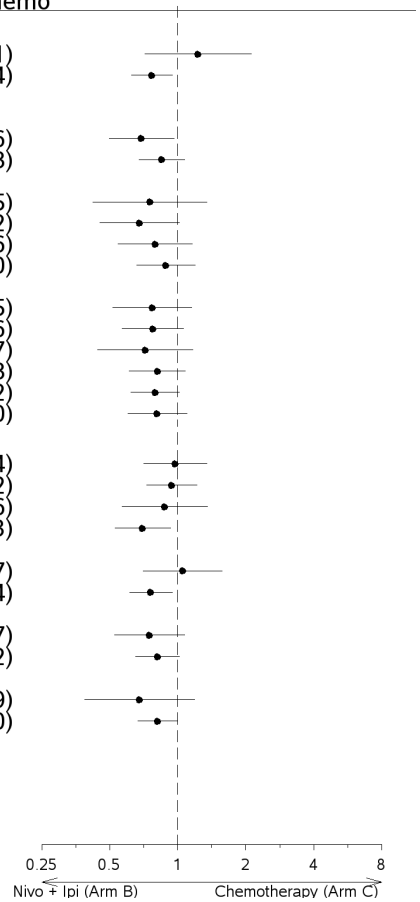


Figure: **Forest Plot of Treatment Effect on OS in Pre-Defined Subsets - Nivolumab + Ipilimumab (Arm B) and Chemotherapy (Arm C) - All Randomized Subjects in CA209227 Part 1a**

	N	Nivo + Ipi (Arm B) N of Events (N of subjects)	mOS (95% CI)	Chemotherapy (Arm C) N of Events (N of subjects)	mOS (95% CI)	Unstratified Hazard Ratio (97.5% CI) Nivo + Ipi vs. Chemo
Tobacco Use						
Never Smoker	107	38(56)	15.21 (9.46, 29.57)	31(51)	19.65 (12.71, 31.90)	1.23 (0.71, 2.11)
Smoker	674	217(334)	18.14 (14.95, 20.24)	262(340)	14.06 (11.66, 16.43)	0.77 (0.63, 0.94)
Unknown	12	3(6)	N.A. (11.53, N.A.)	5(6)	6.95 (1.81, N.A.)	
IVRS Histology						
Squamous	236	85(118)	14.78 (12.09, 18.66)	103(118)	9.23 (7.59, 13.86)	0.69 (0.50, 0.96)
Non-Squamous	557	173(278)	19.45 (15.64, 24.34)	195(279)	17.18 (14.29, 19.65)	0.85 (0.67, 1.08)
Intended Investigator's Choice Therapy Prior to Randomized from IVRS						
Gemcitabine/Cisplatin	80	30(43)	16.69 (12.94, 23.03)	30(37)	14.52 (7.20, 19.42)	0.75 (0.42, 1.35)
Gemcitabine/Carboplatin	156	55(75)	12.81 (7.39, 16.62)	73(81)	8.53 (6.37, 11.10)	0.68 (0.45, 1.02)
Pemetrexed/Cisplatin	214	63(104)	19.94 (14.13, 30.65)	80(110)	18.86 (15.80, 21.72)	0.80 (0.55, 1.16)
Pemetrexed/Carboplatin	343	110(174)	19.15 (14.95, 25.95)	115(169)	15.67 (12.42, 22.34)	0.89 (0.66, 1.20)
TMB Cutoff						
>= 10 Mutations/MB	213	54(101)	24.44 (15.61, N.A.)	75(112)	18.14 (12.71, 24.61)	0.77 (0.52, 1.15)
< 10 Mutations/MB	269	100(139)	16.20 (13.50, 19.48)	105(130)	12.14 (8.08, 15.08)	0.78 (0.57, 1.06)
>= 13 Mutations/MB	155	37(76)	30.85 (17.08, N.A.)	51(79)	19.91 (14.92, 29.14)	0.72 (0.44, 1.17)
< 13 Mutations/MB	327	117(164)	16.20 (12.62, 19.09)	129(163)	11.66 (8.90, 15.08)	0.81 (0.61, 1.08)
TMB Evaluable	482	154(240)	18.00 (15.11, 21.82)	180(242)	14.49 (11.37, 16.72)	0.80 (0.62, 1.02)
TMB Not Evaluable	311	104(156)	16.62 (13.21, 20.24)	118(155)	14.95 (11.93, 18.79)	0.81 (0.60, 1.10)
PD-L1 Subgroups						
1 - 19%	259	91(123)	14.95 (11.30, 19.09)	106(136)	16.16 (13.34, 18.63)	0.97 (0.71, 1.34)
1 - 49%	396	142(191)	15.08 (12.16, 18.66)	161(205)	15.08 (13.34, 17.54)	0.94 (0.73, 1.22)
20 - 49%	137	51(68)	16.59 (10.58, 19.45)	55(69)	13.47 (9.23, 16.30)	0.88 (0.57, 1.36)
>= 50%	397	116(205)	21.19 (15.51, 38.18)	137(192)	13.96 (10.05, 18.60)	0.70 (0.53, 0.93)
Liver Metastasis						
Yes	156	58(71)	9.46 (5.55, 15.08)	67(85)	11.86 (8.08, 14.49)	1.05 (0.70, 1.57)
No	637	200(325)	19.94 (16.59, 22.21)	231(312)	16.30 (13.37, 18.60)	0.76 (0.61, 0.94)
Bone Metastasis						
Yes	208	77(108)	13.36 (9.72, 18.17)	81(100)	10.05 (7.69, 13.01)	0.75 (0.52, 1.07)
No	585	181(288)	18.76 (15.64, 21.19)	217(297)	16.72 (14.88, 18.83)	0.81 (0.65, 1.02)
CNS Metastasis						
Yes	81	29(41)	16.85 (8.57, 21.72)	36(40)	13.42 (8.71, 18.56)	0.68 (0.39, 1.19)
No	712	229(355)	17.12 (14.95, 20.17)	262(357)	14.92 (12.42, 17.18)	0.82 (0.67, 1.00)



HR is not computed for subsets (except age, race, region, and gender) with fewer than 10 subjects per treatment group

For computational derivation purposes, for TMB 10 and TMB 13 cutoffs values of 10.09 and 12.61 respectively are used.

Source: Figure 7.2.1.2-1 of the CA209227 Part 1 Final CSR

Efficacy of Nivolumab + Ipilimumab, Nivolumab + Chemotherapy, and Chemotherapy in Subjects with PD-L1 < 1% (Part 1b)

As part of the hierarchical testing, PFS and OS for nivolumab + chemotherapy vs chemotherapy in Part 1b were tested. The PFS analysis met the statistical threshold; however, the OS analysis did not meet the criteria for statistical significance. Any results in Part 1b other than the comparison of PFS and OS between nivolumab + chemotherapy vs chemotherapy are descriptive in nature.

Table: Efficacy in Randomized Subjects with PD-L1 Non-Expressing (< 1%) Tumors in CA209227 Part 1b

	Nivolumab + Ipilimumab Arm D (N = 187)	Nivolumab + Chemotherapy Arm G (N = 177)	Chemotherapy Arm F (N = 186)
Overall Survival (OS)			
Events, n (%)	119 (63.6)	137 (77.4)	156 (83.9)
Nivo + Chemo vs Chemo			
HR (97.5% CI)[a]		0.78 (0.60, 1.02)	
Stratified log-rank p-value		0.0352	
HR (95% CI)[a]		0.78 (0.62, 0.98)	
Nivo + Ipi vs Chemo			
HR (97.5% CI)[a]		0.62 (0.47, 0.81)	
HR (95% CI)[a]		0.62 (0.48, 0.78)	
Stratified log-rank descriptive p-value		< 0.0001	
Nivo + Ipi vs Nivo + Chemo			
HR (97.5% CI)[a]		0.77 (0.58, 1.02)	
HR (95% CI)[a]		0.77 (0.60, 0.98)	
Median OS (95% CI), mo.[b]	17.15 (12.85, 22.05)	15.21 (12.29, 19.78)	12.19 (9.17, 14.32)
OS Rates (95% CI), %[b]			
12 months	59.5 (52.1, 66.2)	59.0 (51.3, 65.9)	50.6 (43.2, 57.6)
18 months	48.1 (40.7, 55.1)	45.1 (37.6, 52.3)	34.1 (27.3, 41.0)
24 months	40.4 (33.3, 47.4)	34.7 (27.7, 41.8)	23.0 (17.2, 29.3)
PFS per BICR (1° Definition)			
Events, n (%)	137 (73.3)	146 (82.5)	151 (81.2)
Nivo + Chemo vs Chemo			
HR (97.72% CI)[a]		0.73 (0.56, 0.95)	
Stratified log-rank p-value		0.0070	
HR (97.5% CI)[a]		0.73 (0.56, 0.95)	
HR (95% CI)[a]		0.73 (0.58, 0.92)	
Nivo + Ipi vs Chemo			
HR (97.5% CI)[a]		0.75 (0.57, 0.99)	
HR (95% CI)[a]		0.75 (0.59, 0.96)	

Table: Efficacy in Randomized Subjects with PD-L1 Non-Expressing (< 1%) Tumors in CA209227 Part 1b

	Nivolumab + Ipilimumab Arm D (N = 187)	Nivolumab + Chemotherapy Arm G (N = 177)	Chemotherapy Arm F (N = 186)
Nivo + Ipi vs Nivo + Chemo			
PFS HR (97.5% CI)[a]		0.98 (0.74, 1.28)	
PFS HR (95% CI)[a]		0.98 (0.77, 1.24)	
Median PFS (95% CI), mo.[b]	5.06 (3.15, 6.37)	5.55 (4.63, 6.90)	4.70 (4.21, 5.59)
PFS Rates (95% CI), %[b]			
12 months	30.6 (23.5, 37.9)	25.6 (19.2, 32.5)	14.3 (9.1, 20.5)
18 months	23.2 (16.8, 30.3)	14.0 (9.0, 20.1)	7.3 (3.6, 12.8)
24 months	16.3 (10.8, 22.9)	10.5 (6.0, 16.3)	4.6 (1.8, 9.4)
ORR per BICR (CR + PR)[c]			
N responders (%)	51 (27.3%)	67 (37.9%)	43 (23.1%)
95% CI	(21.0, 34.3)	(30.7, 45.4)	(17.3, 29.8)
Complete Response, n (%)	4 (2.1)	3 (1.7)	2 (1.1)
TTR per BICR			
Median (min, max), mo.	2.83 (1.3, 24.9)	1.71 (1.0, 8.5)	1.51 (0.5, 22.4)
DoR per BICR			
N events/N responders (%)	28/51 (54.9)	53/67 (79.1)	35/43 (81.4)
Median (95% CI), mo.[b]	17.97 (12.42, 28.65)	8.31 (5.88, 9.43)	4.83 (3.71, 5.78)
Min, Max, mo.	1.2+, 35.9+	1.2+, 35.0+	1.3+, 26.5+
% subjects with DoR (95% CI)[d]			
≥ 6 months	85 (71, 93)	62 (49, 72)	31 (17, 46)
≥ 9 months	78 (63, 88)	41 (29, 53)	25 (13, 40)
≥ 12 months	71 (55, 82)	32 (21, 43)	25 (13, 40)
≥ 18 months	48 (32, 62)	23 (13, 34)	9 (2, 22)
≥ 24 months	40 (25, 55)	16 (8, 27)	5 (0, 18)

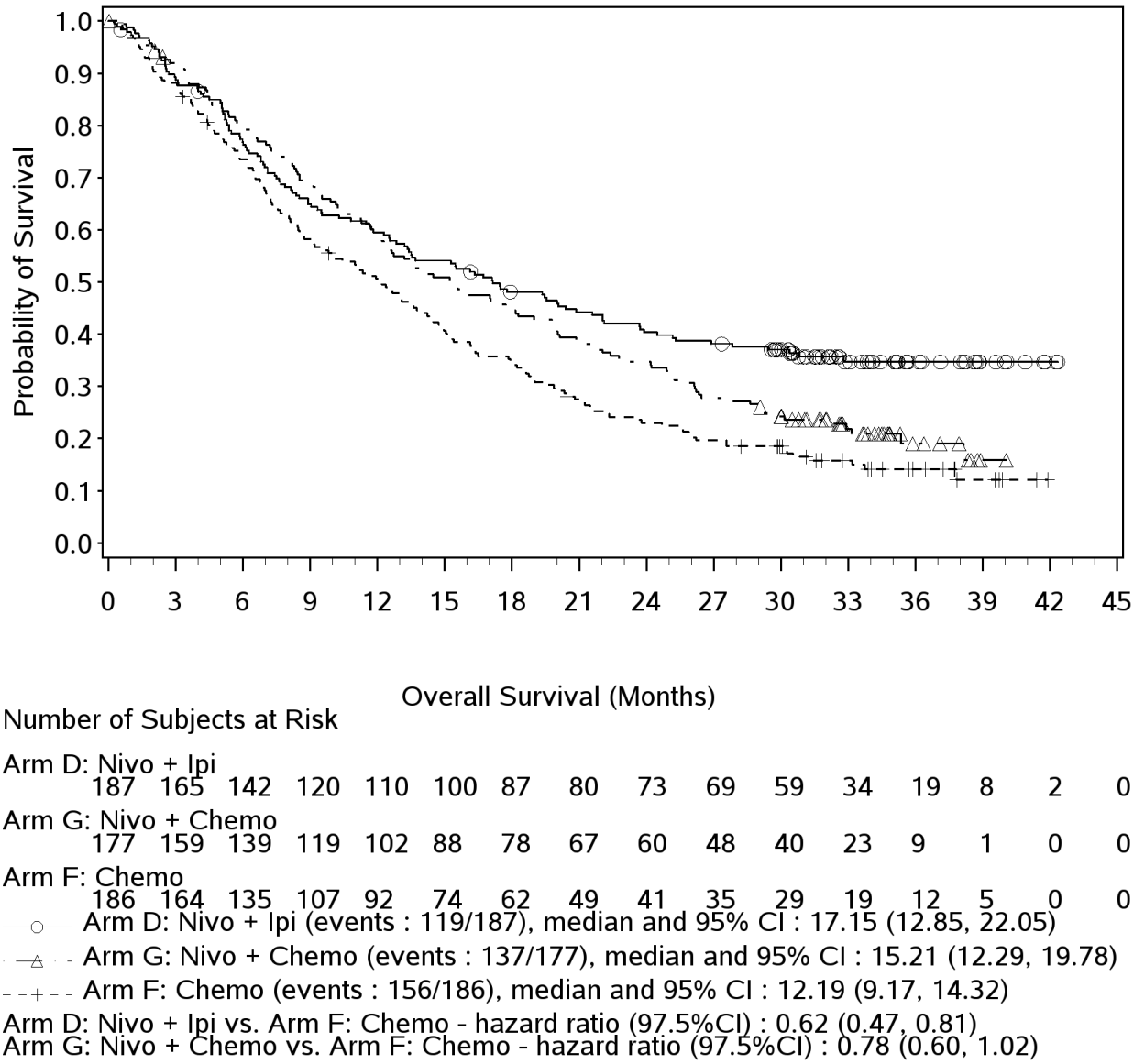
[a] Hazard ratios based on a stratified Cox proportional hazard model.
[b] Kaplan-Meier estimate
[c] Proportion with CR or PR; CI based on the Clopper and Pearson method
[d] Based on Kaplan-Meier estimates of duration of response

Symbol + indicates a censored value. Database lock: 02-Jul-2019; Minimum follow-up: 29.3 months for OS

Abbreviations: BICR - blinded independent central review, CI - confidence interval, CR - complete response, DoR - duration of response, HR - hazard ratio, , ipi - ipilimumab, max - maximum, min - minimum, nivo - nivolumab, ORR - objective response rate, OS - overall survival, PD - L1 - programmed cell death ligand 1, PFS - progression-free survival, PR - partial response, TTR - time to response

Source: Table 7.1.2-1 of the CA209227 Part 1 Final CSR

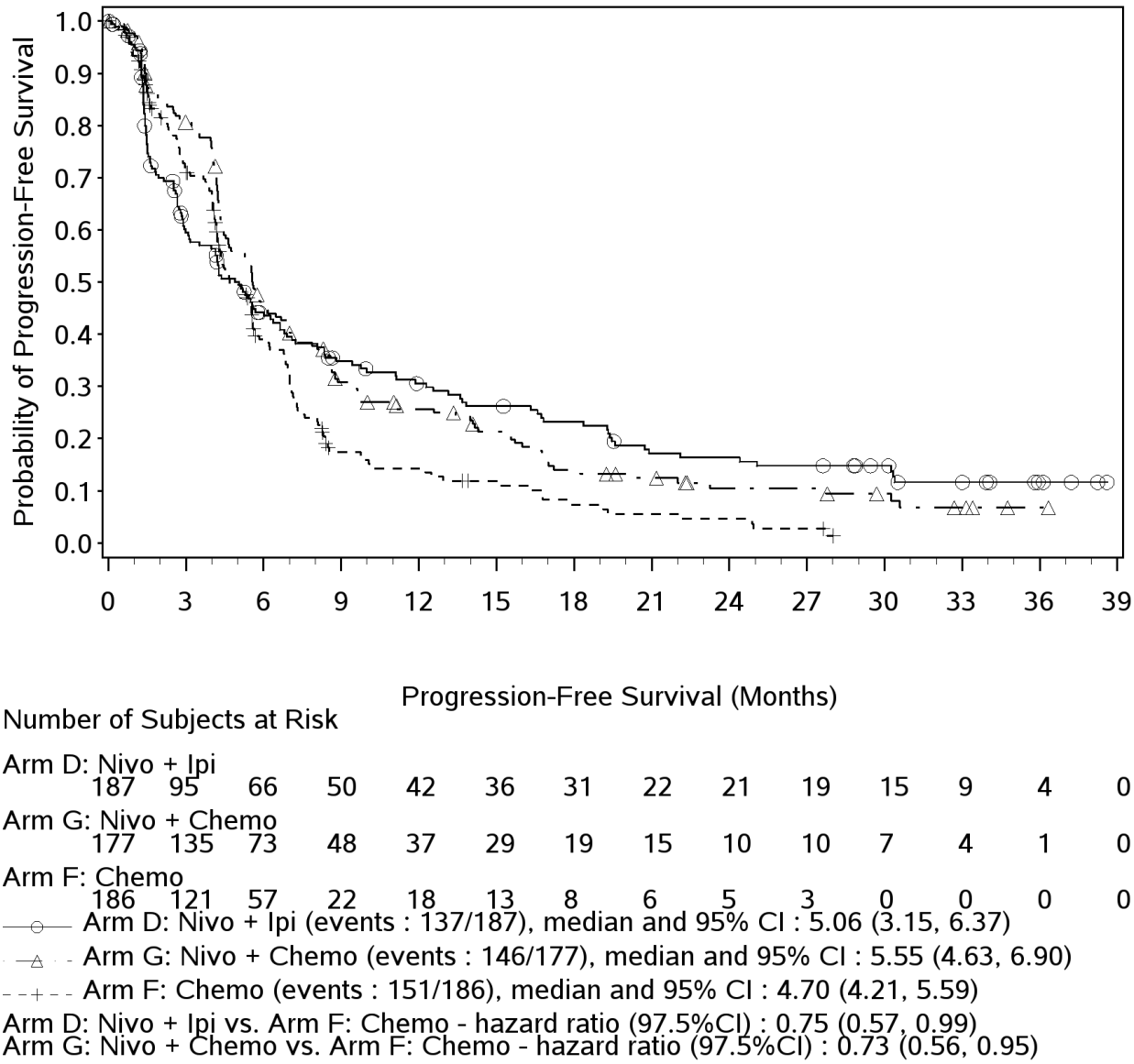
Figure: Kaplan-Meier Plot of Overall Survival - Nivolumab + Ipilimumab (Arm D), Nivolumab + Chemotherapy (Arm G), and Chemotherapy (Arm F) - All Randomized Subjects in CA209227 Part 1b



Symbols represent censored observations.

Source: Figure S.5.125.2 of the CA209227 Part 1 Final CSR

Figure: Kaplan-Meier Plot of Progression-Free Survival per BICR (Primary Definition) - All Randomized Subjects in CA209227 Part 1b



Symbols represent censored observations.

Hazard Ratios (Nivo + Chemo over Chemo and Nivo + Ipi over Chemo) are based on a stratified Cox proportional hazard model.

Source: Figure S.5.122.5 of the CA209227 Part 1 Final CSR

Table: Efficacy Results - Nivolumab + Ipilimumab and Chemotherapy - Randomized Subjects in CA209227 Part 1

	PD-L1 ≥ 1%		PD-L1 < 1%	
	Nivo + Ipi (n = 396)	**Chemo** (n = 397)	**Nivo + Ipi** (n = 187)	**Chemo** (n = 186)
OS				
Events (%)	258 (65.2)	298 (75.1)	119 (63.6)	156 (83.9)
Median OS (95% CI), mo.[b]	17.1 (15, 20.1)	14.9 (12.7, 16.7)	17.2 (12.9, 22.1)	12.2 (9.2, 14.3)

Table: Efficacy Results - Nivolumab + Ipilimumab and Chemotherapy - Randomized Subjects in CA209227 Part 1

	PD-L1 ≥ 1%		PD-L1 < 1%	
Hazard ratio [a] (97.72% CI) (95% CI)	0.79 (0.65, 0.96) (0.67, 0.94)		0.62 -- (0.48, 0.78)	
p value [c]	0.0066		< 0.0001	
2-year OS rate (95% CI), % [b]	40.0 (35.1, 44.9)	32.8 (28.2, 37.5)	40.4 (33.3, 47.4)	23.0 (17.2, 29.3)
PFS				
Events (%)	288 (72.7)	286 (72.0)	137 (73.3)	151 (81.2)
Median (95% CI), mo. [b]	5.1 (4.1, 6.3)	5.6 (4.6, 5.8)	5.1 (3.2, 6.4)	4.7 (4.2, 5.6)
Hazard ratio (95% CI) [a]	0.82 (0.69, 0.97)		0.75 (0.59, 0.96)	
ORR, n (%) [d]	142 (35.9)	119 (30.0)	51 (27.3)	43 (23.1%)
(95% CI)	(31.1, 40.8)	(25.5, 34.7)	(21.0, 34.3)	(17.3, 29.8)
CR, n (%)	23 (5.8)	7 (1.8)	4 (2.1)	2 (1.1)
Median **TTR**, mo. [b]	1.95	1.61	2.83	1.51
Median **DoR**, mo. (95% CI) [b]	23.2 (15.2, 32.2)	6.2 (5.6, 7.4)	18.0 (12.4, 28.7)	4.8 (3.7, 5.8)
% with DoR ≥ 12 mo.	64 (55, 72)	28 (19, 38)	71 (55, 82)	25 (13, 40)
% with DoR ≥ 24 mo.	49 (41, 58)	11 (5, 20)	40 (25, 55)	5 (0, 18)

[a] Hazard ratios are based on an unstratified (stratified for all randomized) Cox proportional hazard model.

[b] Kaplan-Meier estimate

[c] Stratified log-rank test p value (p values for PD-L1 < 1% and all randomized subjects are descriptive).

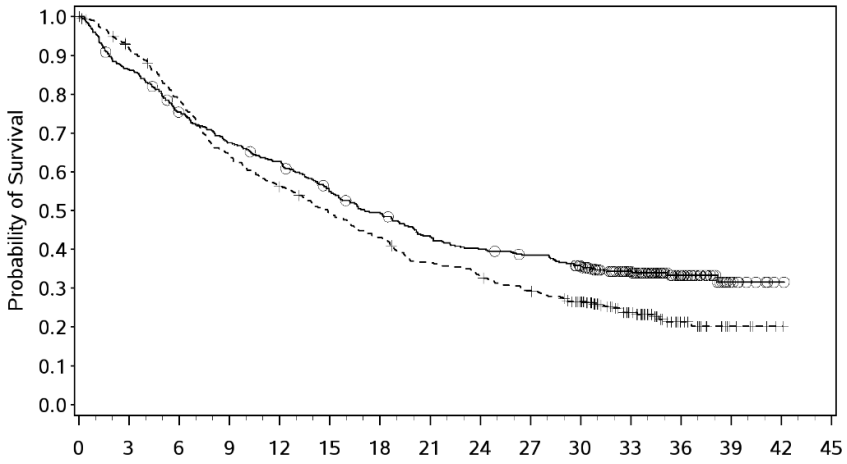
[d] Proportion with CR or PR; CI based on Clopper and Pearson method

Minimum follow-up: 28.3 months (29.3 months for OS)

Source: Table and Table

Figure: **Kaplan-Meier Plot of Overall Survival by PD-L1 Expression Status - All Randomized Nivolumab + Ipilimumab and Chemotherapy Subjects in CA209227 Part 1**

PD-L1 ≥ 1% (Part 1a)



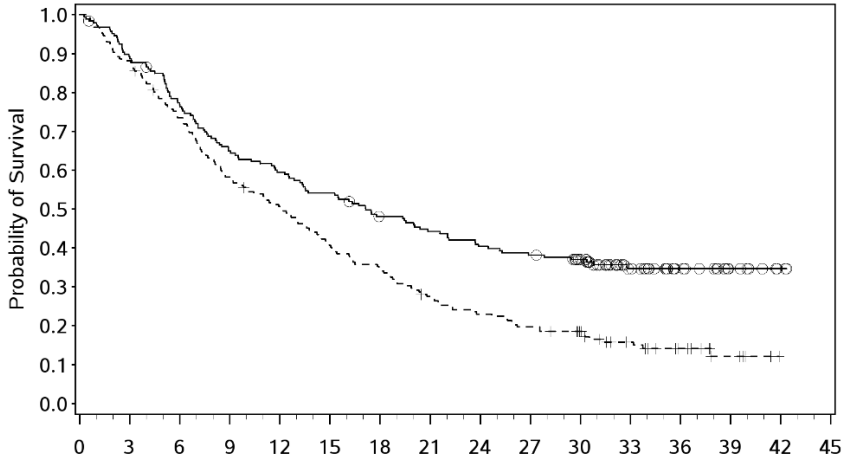
Number of Subjects at Risk

Arm B: Nivo + Ipi	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Arm 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 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 (97.72%CI) : 0.79 (0.65, 0.96)

Stratified log-rank test p-value : 0.0066

PD-L1 < 1% (Part 1b)



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 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 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)

Stratified log-rank test p-value : <0.0001

Figure: **Kaplan-Meier Plot of Overall Survival by PD-L1 Expression Status - All Randomized Nivolumab + Ipilimumab Subjects in CA209227 Part 1**

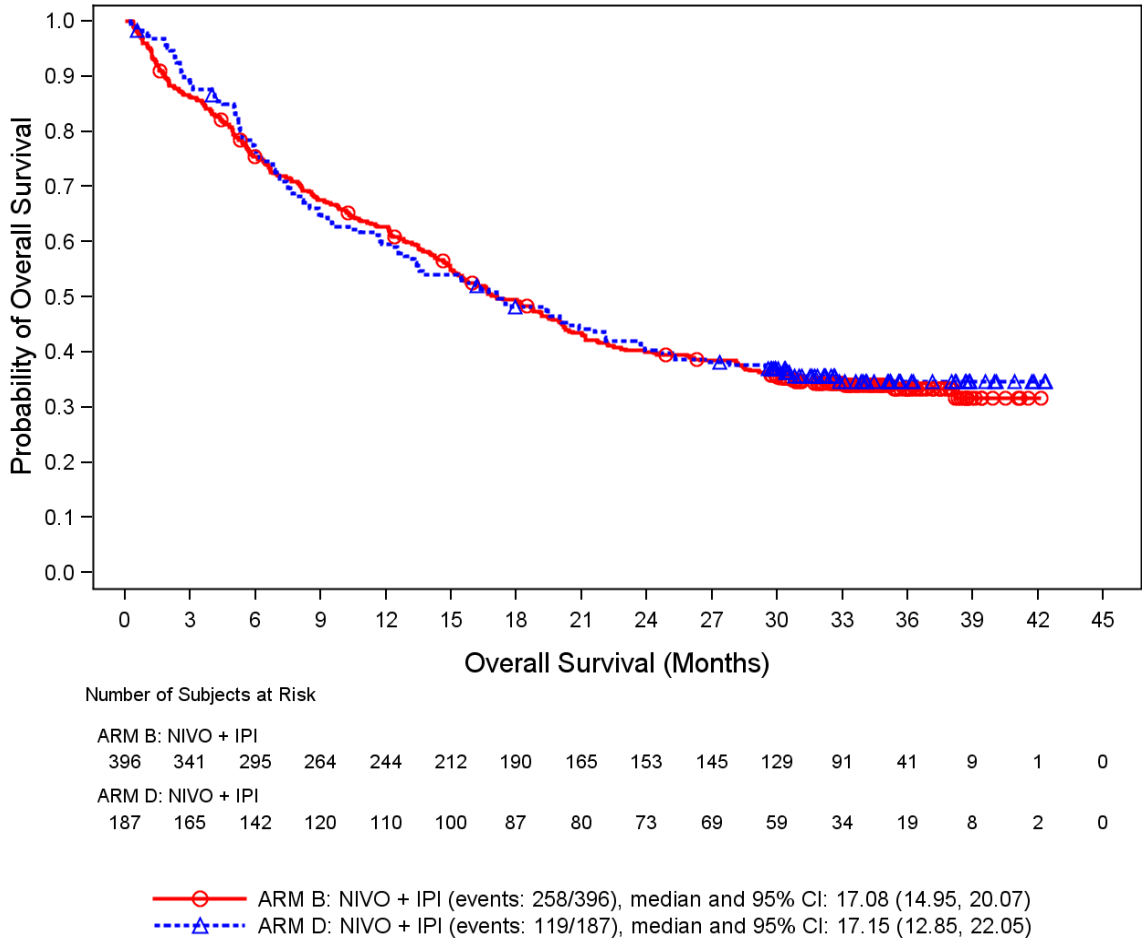


Table: **Efficacy by PD-L1 Expression for Nivolumab + Ipilimumab (Arm B) vs Nivolumab (Arm A) in Part 1a**

	PD-L1 ≥ 1%		PD-L1 1-49%		PD-L1 ≥ 50%	
	Nivo+Ipi N = 396	Nivo N = 396	Nivo+Ipi N = 191	Nivo N = 182	Nivo+Ipi N = 205	Nivo N = 214
OS						
HR (97.5% CI)	0.90 (0.74, 1.10)		0.93 (0.71, 1.21)		0.87 (0.66, 1.16)	
Events, n (%)	258 (65.2)	274 (69.2)	142 (74.3)	141 (77.5)	116 (56.6)	133 (62.1)
Median (95% CI), mo.	17.08 (14.95, 20.07)	15.70 (13.27, 18.14)	15.08 (12.16, 18.66)	13.04 (11.17,16.23)	21.19 (15.51, 38.18)	18.14 (14.36, 22.14)
PFS per BICR (1° Definition)						
HR (97.5% CI)	0.82 (0.69, 0.99)		0.80 (0.62, 1.04)		0.80 (0.62, 1.04)	

Events, n (%)	288 (72.7)	311 (78.5)	151 (79.1)	150 (82.4)	137 (66.8)	161 (75.2)
Median (95% CI), mo.	5.06 (4.07, 6.31)	4.17 (3.02, 5.32)	4.01 (2.99, 5.52)	2.86 (2.53, 4.17)	6.74 (4.53, 11.01)	5.55 (4.17, 8.34)
ORR per BICR (CR + PR)						
N responders (%)	142 (35.9)	109 (27.5)	51 (26.7)	30 (16.5)	91 (44.4)	79 (36.9)
95% CI	(31.1, 40.8)	(23.2, 32.2)	(20.6, 33.6)	(11.4, 22.7)	(37.5, 51.5)	(30.4. 43.8)

OS and PFS HRs for nivolumab + ipilimumab vs nivolumab are unstratified.
Source: refer to Figure S.5.500.3 (OS), Figure S.5.500.1 (PFS), and Figure S.5.500.2 (ORR) of the CA209227 Part 1 Final CSR

PFS of nivolumab + ipilimumab vs chemotherapy in subjects with TMB ≥ 10 mut/Mb, regardless of PD-L1 level (co-primary endpoint)

In subjects with TMB ≥10 mut/Mb, regardless of PD-L1 expression level, nivolumab + ipilimumab (Arms B + D) demonstrated a clinically meaningful and statistically significant improvement in PFS (per BICR and censoring for subsequent therapy: primary PFS definition) compared with chemotherapy (Arms C + F): HR = 0.58 (97.5% CI: 0.41, 0.81); unstratified log-rank test p-value = 0.0002. At 1.5 and 3 months, the PFS rate was lower for nivolumab + ipilimumab than with chemotherapy, but higher from 4.5 months onwards, with increasing and sustained separation at later timepoints.

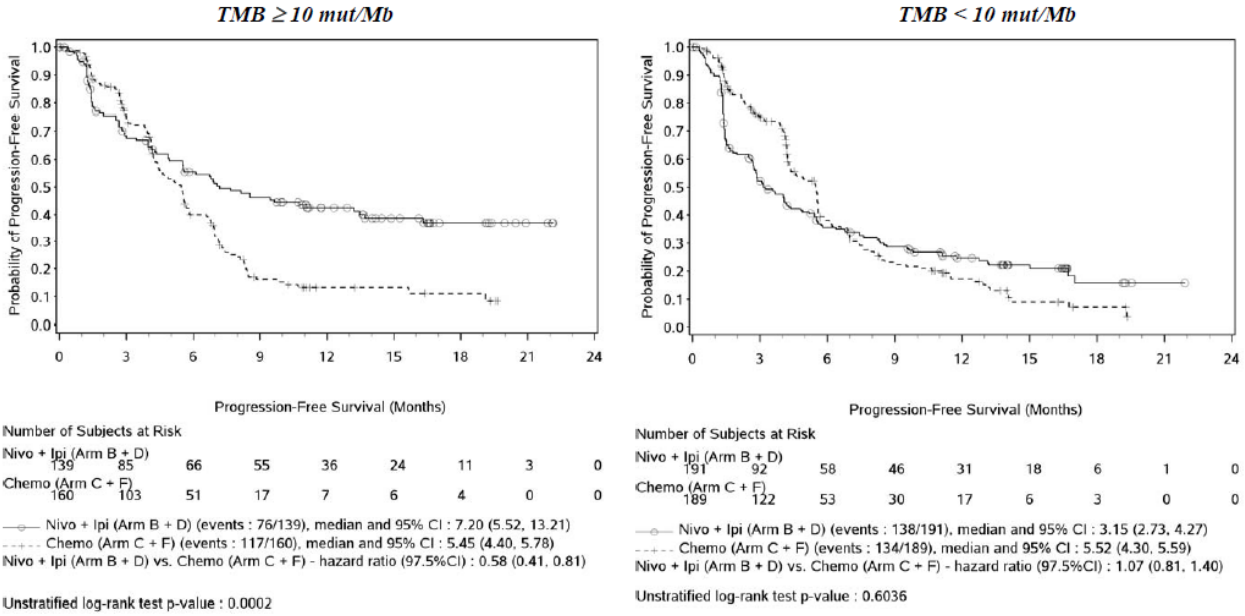
Censoring:

63 (45.3%) subjects in the nivolumab + ipilimumab arms and 43 (26.9%) subjects in the chemotherapy arms with TMB ≥10 mut/Mb were censored. For most censored subjects, their PFS time was censored on either the date of last on-study tumor assessment or date of last assessment prior to subsequent anticancer therapy. The higher frequency of censoring in the nivolumab + ipilimumab arms was mainly due to the fact that fewer subjects in the nivolumab + ipilimumab arms had progression or died in comparison to the chemotherapy arms. In addition, fewer nivolumab + ipilimumab subjects received subsequent anticancer therapy compared to chemotherapy (9.4% vs 16.9%, respectively). More nivolumab + ipilimumab treated subjects were either still on randomized treatment or were in follow-up without evidence of progression compared to chemotherapy treated subjects (33.8% vs 7.5%, respectively).

Sensitivity analyses:

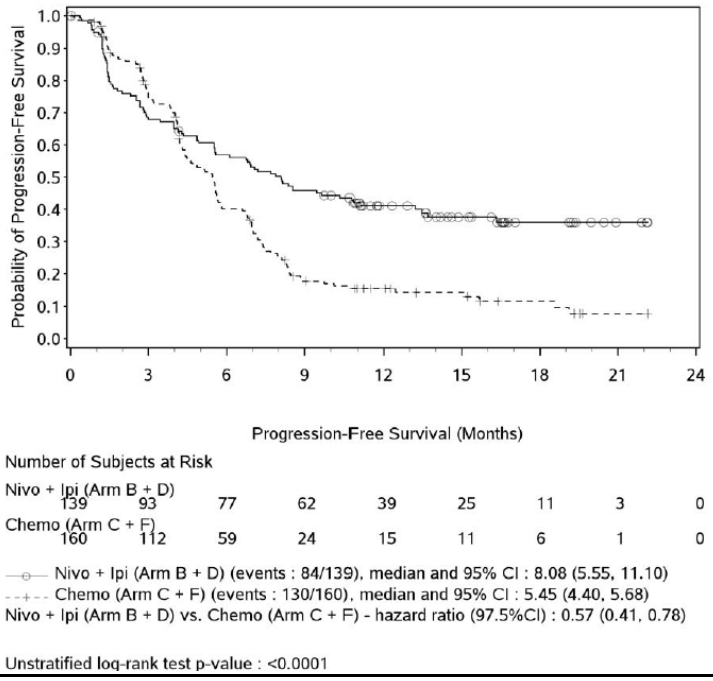
Results of the following sensitivity analyses were consistent with the primary PFS (per BICR) analysis

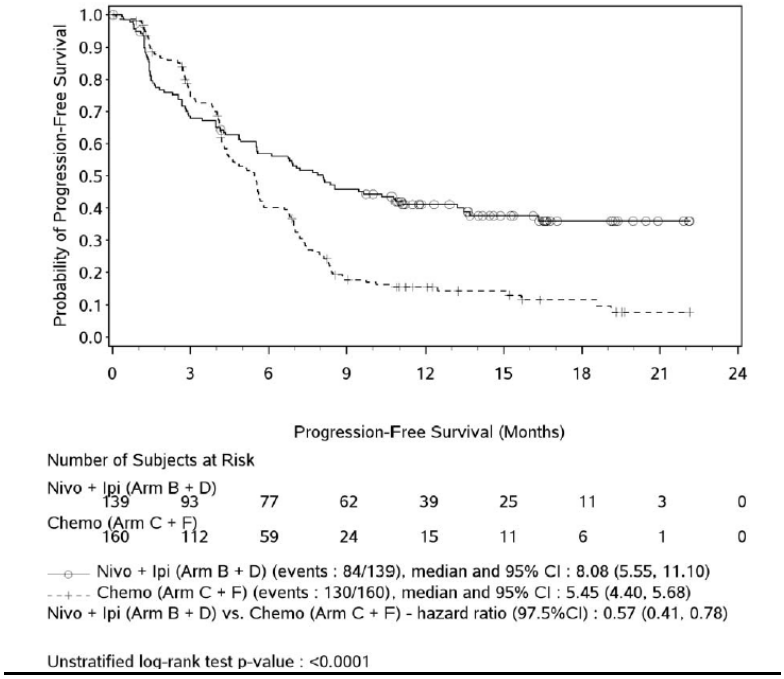
- Results of an analysis of PFS (secondary definition) using the investigator assessment were consistent with the analysis of PFS per BICR (secondary definition): HR = 0.48 (97.5% CI: 0.35, 0.66); unstratified log-rank test p-value <0.0001. There was less censoring in the analysis of PFS per investigator than per BICR but the estimated HRs were similar, indicating the censoring did not influence the outcome.



Symbols represent censored observations.
Hazard Ratios (Nivolumab + Ipilimumab over Chemotherapy) are based on an unstratified Cox proportional hazard model.
For computational derivation purposes, subjects with TMB ≥ 10.09 mut/Mb are categorized as TMB ≥ 10 mut/Mb.
The p-value for the TMB < 10 mut/Mb is for descriptive purposes only.
Source: Refer to Figure 7.2.1-1 (TMB ≥ 10 mut/Mb) and Figure S.5.100.6 (TMB < 10 mut/Mb) of the CA209227 Part 1 Interim CSR

Figure 20: Kaplan-Meier Plot of Progression-Free Survival per BICR (Primary Definition) for Nivolumab + Ipilimumab (Arms B + D) and Chemotherapy (Arms C + F) by TMB Cutoff (10 mut/Mb): TMB Evaluable Subjects in Part 1 of CA209227





Symbols represent censored observations.
Hazard Ratio (Nivolumab + Ipilimumab over Chemotherapy) is based on an unstratified Cox proportional hazard model.
For computational derivation purposes, subjects with TMB ≥10.09 mut/Mb are categorized as TMB ≥10 mut/Mb.
Source: Figure 7.2.1-2 of the CA209227 Part 1 Interim CSR

Figure 21: Kaplan-Meier Plot of Progression-Free Survival per BICR (Secondary Definition) Nivolumab + Ipilimumab (Arms B + D) and Chemotherapy (Arms C + F) in Subjects with TMB ≥ 10 mut/Mb in Part 1 of CA209227

Efficacy of nivolumab vs chemotherapy in subjects with TMB ≥ 13 mut/Mb (Part 1a)

PFS per BICR of nivolumab vs chemotherapy in subjects with TMB ≥ 13 mut/Mb in Part 1a (secondary endpoint)

In subjects with TMB ≥13 mut/Mb and PD-L1 ≥1%, nivolumab (Arm A) did not demonstrate a statistically significant improvement in PFS (per BICR) compared with chemotherapy (Arm C): HR = 0.95 (97.5% CI: 0.61, 1.48); unstratified log-rank test p value = 0.7776. This comparison was pre-planned as part of the TMB testing hierarchy and, as such, further formal statistical testing was stopped in the TMB hierarchy.

Table 28: Efficacy of Nivolumab (Arm A) vs Chemotherapy (Arm C) by TMB Cutoff (13 mut/Mb) in Part 1a of CA209227

	TMB ≥ 13 mut/Mb		TMB < 13 mut/Mb	
	Nivo (N = 71)	Chemo (N = 79)	Nivo (N = 157)	Chemo (N = 163)
PFS per BICR (1° Definition)				
Events, n (%)	50 (70.4)	56 (70.9)	116 (73.9)	111 (68.1)
Unstratified log-rank test p-value	0.7776		0.4411[c]	
HR (97.5% CI)[a]	0.95 (0.61, 1.48)		1.11 (0.82, 1.50)	
HR (95% CI)[a]	0.95 (0.64, 1.40)		1.11 (0.85, 1.44)	
Median (95% CI), mo.[b]	4.21 (2.66, 8.34)	5.55 (4.47, 6.97)	4.17 (2.66, 5.36)	5.45 (4.24, 5.59)
Rate at 6 mo. (95% CI), %	45.5 (33.4, 56.9)	44.2 (32.2, 55.5)	38.0 (30.0, 45.9)	36.5 (28.2, 44.9)
Rate at 12 mo. (95% CI), %	24.4 (14.3, 36.1)	17.0 (8.8, 27.5)	22.2 (15.6, 29.6)	16.4 (10.0, 24.1)

a Comparison of nivolumab vs chemotherapy. Hazard ratios are based on an unstratified Cox proportional hazard

model.
b Kaplan-Meier estimate
c Descriptive p-value, not formally tested in the hierarchy
Database lock: 24-Jan-2018; Minimum follow-up: 11.2 months
Abbreviations: BICR - blinded independent central review, CI - confidence interval, HR - hazard ratio, mut/Mbmutations per megabase, PFS - progression-free survival, TMB - tumor mutational burden
Source: Refer to Table 7.1.1-4 of the CA209227 Part 1 Interim CSR

ORR per BICR of nivolumab + ipilimumab vs chemotherapy in subjects with TMB ≥ 10 mut/Mb, regardless of PD-L1 expression (exploratory endpoint)

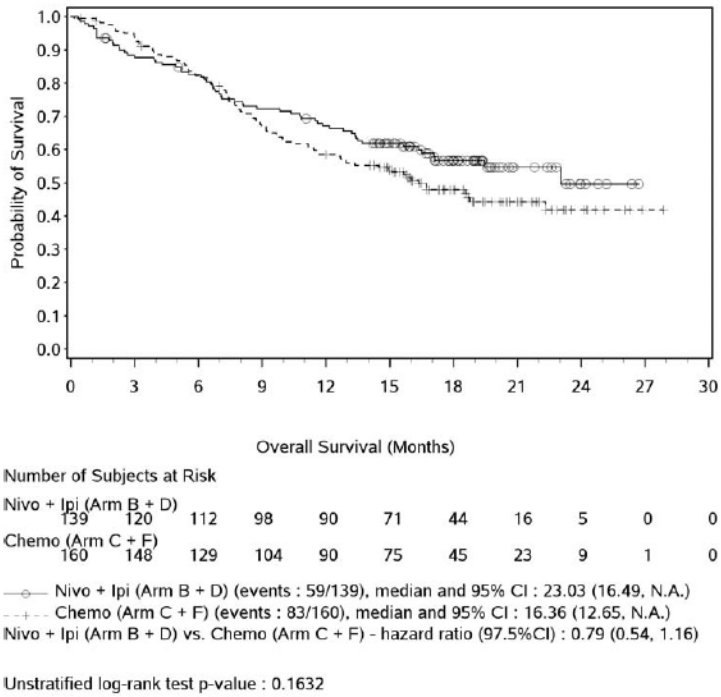
ORR (95% CI) was higher with nivolumab + ipilimumab than with chemotherapy: 45.3% (36.9, 54.0) vs 26.9% (20.2, 34.4).

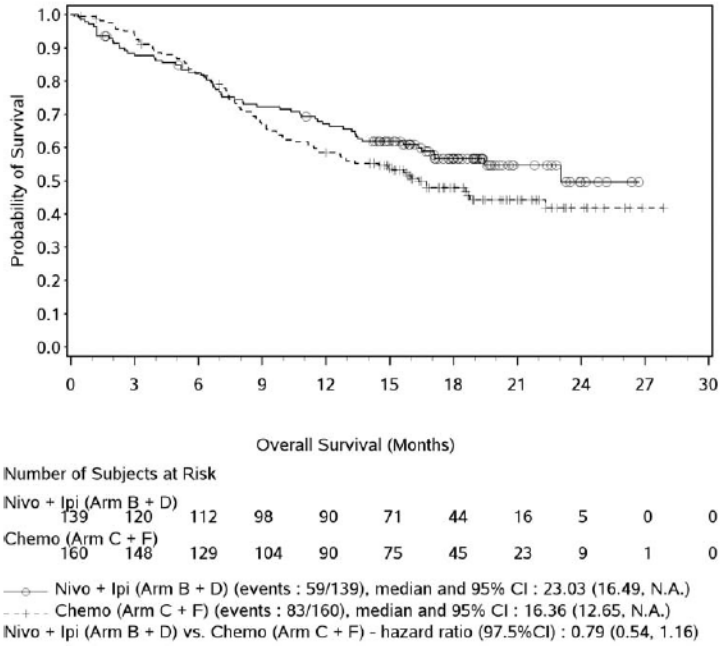
Median TTR per BICR was 2.69 and 1.48 months for all confirmed responders treated with nivolumab + ipilimumab and chemotherapy, respectively. Note that the first tumor assessment was to be performed at 6 weeks (≥7 days) from first dose date and subsequent tumor assessments were to occur every 6 weeks (≥7 days) up to the first 12 months (Week 48), then every 12 weeks until disease progression.

The median DoR was longer for all confirmed responders treated with nivolumab + ipilimumab than with chemotherapy (not reached vs 5.42 months). Based on Kaplan-Meier estimates, 77% and 44% of subjects in the nivolumab + ipilimumab and chemotherapy arms, respectively, had a DoR of at least 6 months and 68% and 25% of subjects, respectively, had a DoR of at least 12 months. For the actual proportion of subjects in the nivolumab + ipilimumab and chemotherapy arms with duration of response ≥ 6 months, ≥9 months, and ≥12 months for all responders with TMB ≥10 mut/Mb.

OS of nivolumab + ipilimumab vs chemotherapy in subjects with TMB ≥ 10 mut/Mb (secondary endpoint)

In a descriptive early analysis of OS based on a database lock of 15-Mar-2018 (minimum follow-up of 14.1 months), median OS was 23.03 months (95% CI: 16.49, NA) with nivolumab + ipilimumab versus 16.36 months (95% CI: 12.65, NA) with chemotherapy: OS HR = 0.79 (97.5% CI: 0.54, 1.16). The 1-year OS rate was 67.0% (95% CI: 58.5, 74.2) with nivolumab + ipilimumab vs 58.5% (95% CI: 50.3, 65.7) with chemotherapy.





Symbols represent censored observations. Hazard Ratio (Nivolumab + Ipilimumab over Chemotherapy) is based on an unstratified Cox proportional hazard model. For computational derivation purposes, subjects with TMB ≥10.09 mut/Mb are categorized as TMB ≥10 mut/Mb. The p-value is for descriptive purposes only. Source: Figure 3.3-1 of Addendum 01 to the CA209227 Part 1 Interim CSR

Figure 22: Kaplan-Meier Plot of Overall Survival - Nivolumab + Ipilimumab (Arms B + D) and Chemotherapy (Arms C + F) - Subjects with TMB ≥ 10 mut/Mb in Part 1 of CA209227

Ancillary analyses

Efficacy results of nivolumab + ipilimumab vs chemotherapy (Part 1) by PD-L1 and TMB

PFS for nivolumab + ipilimumab vs chemotherapy vs nivolumab by PD-L1 and TMB

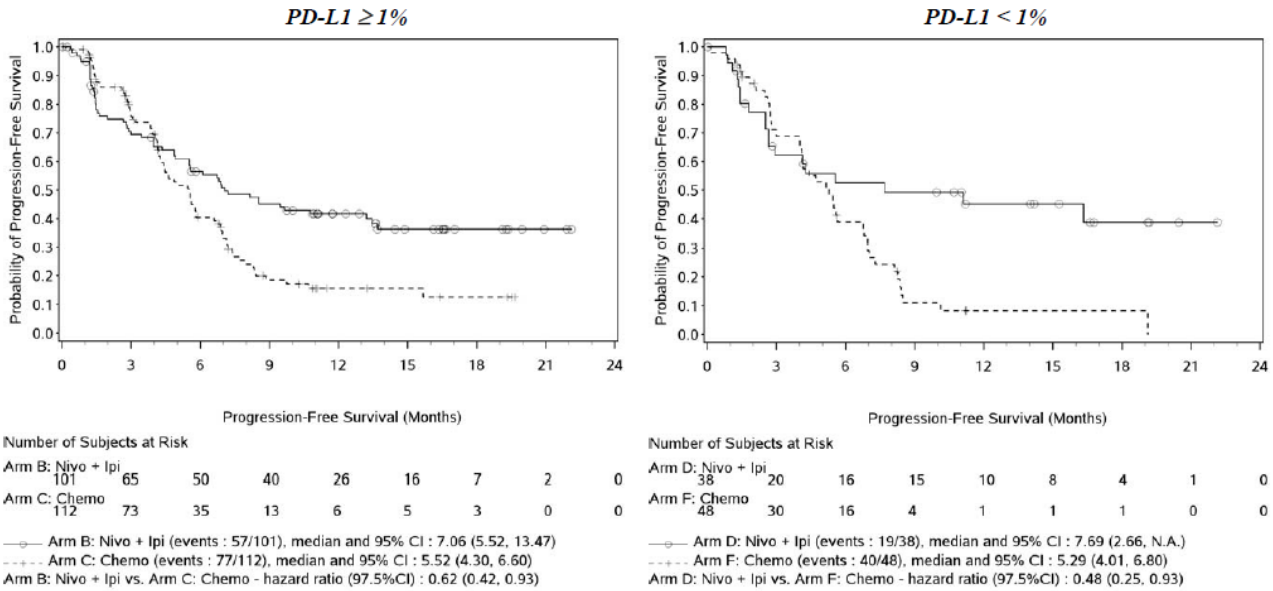
In subjects with TMB ≥10 mut/Mb in Part 1, the HRs for PFS by PD-L1 status favoured nivolumab + ipilimumab (Arms B + D) over chemotherapy (Arms C + F) regardless of subgroup defined by PD-L1 expression. In subjects with TMB < 10 mut/Mb, the HR still favored nivolumab + ipilimumab as long as PD-L1 expression was high (≥50%), suggesting that TMB and PD-L1 are independent biomarkers.

Across all PD-L1 expression levels (< 1%, 1 - 49%, ≥50%), subjects whose tumors had TMB ≥10 mut/Mb derived more benefit from nivolumab + ipilimumab vs chemotherapy than subjects whose tumors had TMB < 10 mut/Mb. (forest plot en Efficacy, PFS co-primary, subpopulations)

Table 29: Progression-Free Survival by PD-L1 and TMB: Comparison of Nivolumab + Ipilimumab (Arms B + D) vs Chemotherapy (Arms C + F) in Part 1 of CA209227

	HR (97.5% CI) for Nivolumab + Ipilimumab vs Chemotherapy			
	n	TMB ≥ 10 mut/Mb	n	TMB < 10 mut/Mb
PD-L1 (≥ 1%)	213	0.62 (0.42, 0.93)	269	1.05 (0.75, 1.45)
PD-L1 (< 1%)	86	0.48 (0.25, 0.93)	111	1.17 (0.71, 1.92)
PD-L1 (1-49%)	102	0.85 (0.48, 1.49)	144	1.71 (1.11, 2.64)
PD-L1 (≥ 50%)	111	0.47 (0.26, 0.83)	125	0.64 (0.38, 1.06)

Abbreviations: CI - confidence interval, HR - hazard ratio, mut/Mb- mutations per megabase, PD - L1 - programmed cell death ligand 1, TMB - tumor mutational burden
Source: Refer to Table 7.7.1-1 of the CA209227 Part 1 Interim CSR



Symbols represent censored observations.
Hazard Ratio (Nivolumab + Ipilimumab over Chemotherapy) is based on an unstratified Cox proportional hazard model.
For computational derivation purposes, subjects with TMB ≥10.09 Mutations/MB are categorized as TMB ≥10 Mutations/MB.
Source: Figure 7.7.1-1 of the CA209227 Part 1 Interim CSR

Figure 23: Kaplan-Meier Plot of Progression-Free Survival per BICR (Primary Definition) for Nivolumab + Ipilimumab (Arms B + D) and Chemotherapy (Arm C + F): TMB ≥ 10 mut/Mb Subjects with PD-L1 ≥ 1% and < 1% in Part 1 of CA209227

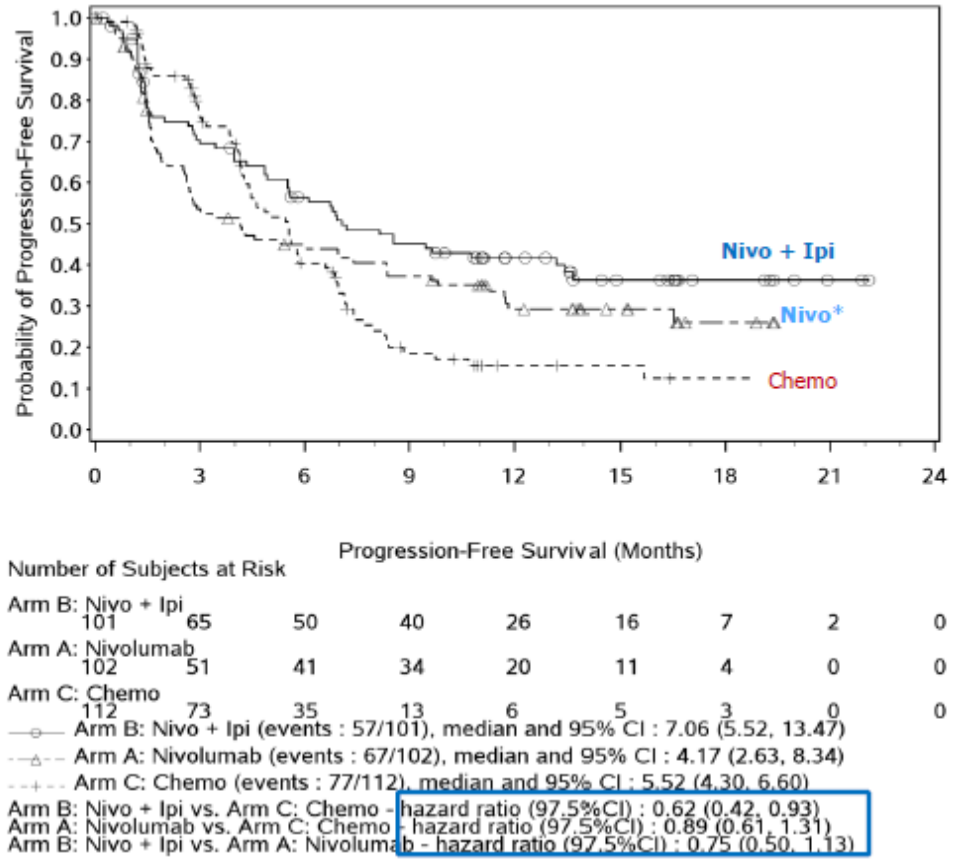


Figure 24: Kaplan-Meier Plot of Progression-Free Survival per BICR (Primary Definition) for Nivolumab + Ipilimumab (Arms B) Nivolumab (Arm A) and Chemotherapy (Arm C): TMB ≥ 10 mut/Mb Subjects with PD-L1 ≥ 1%

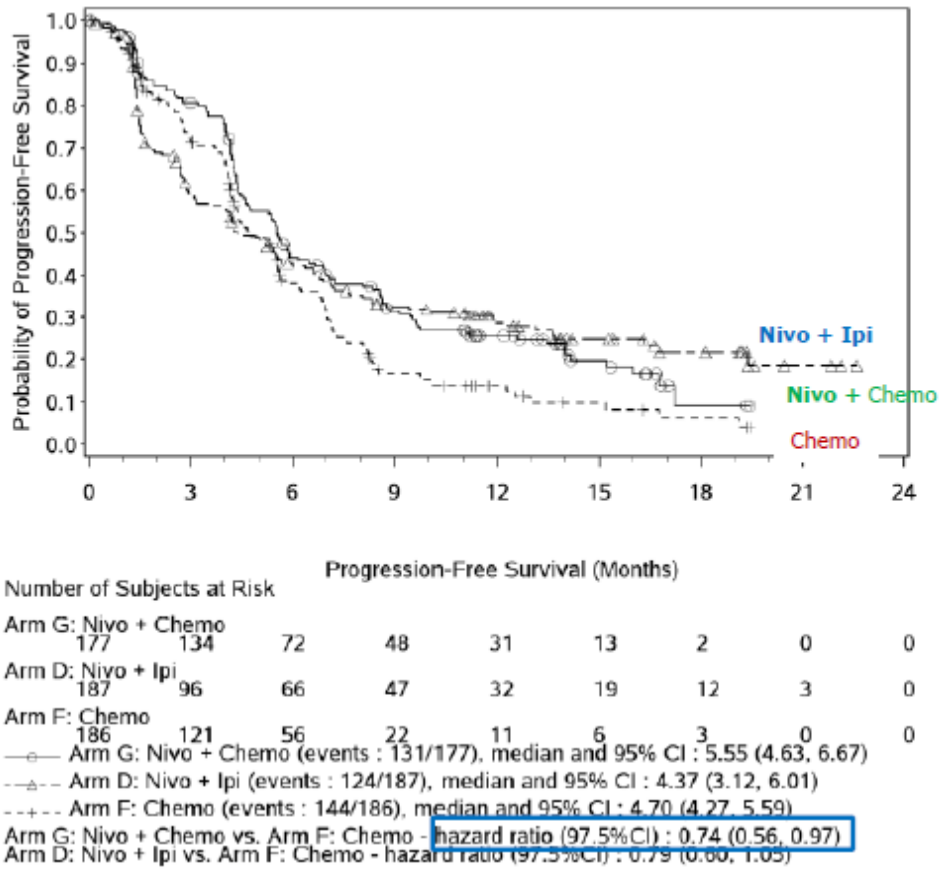
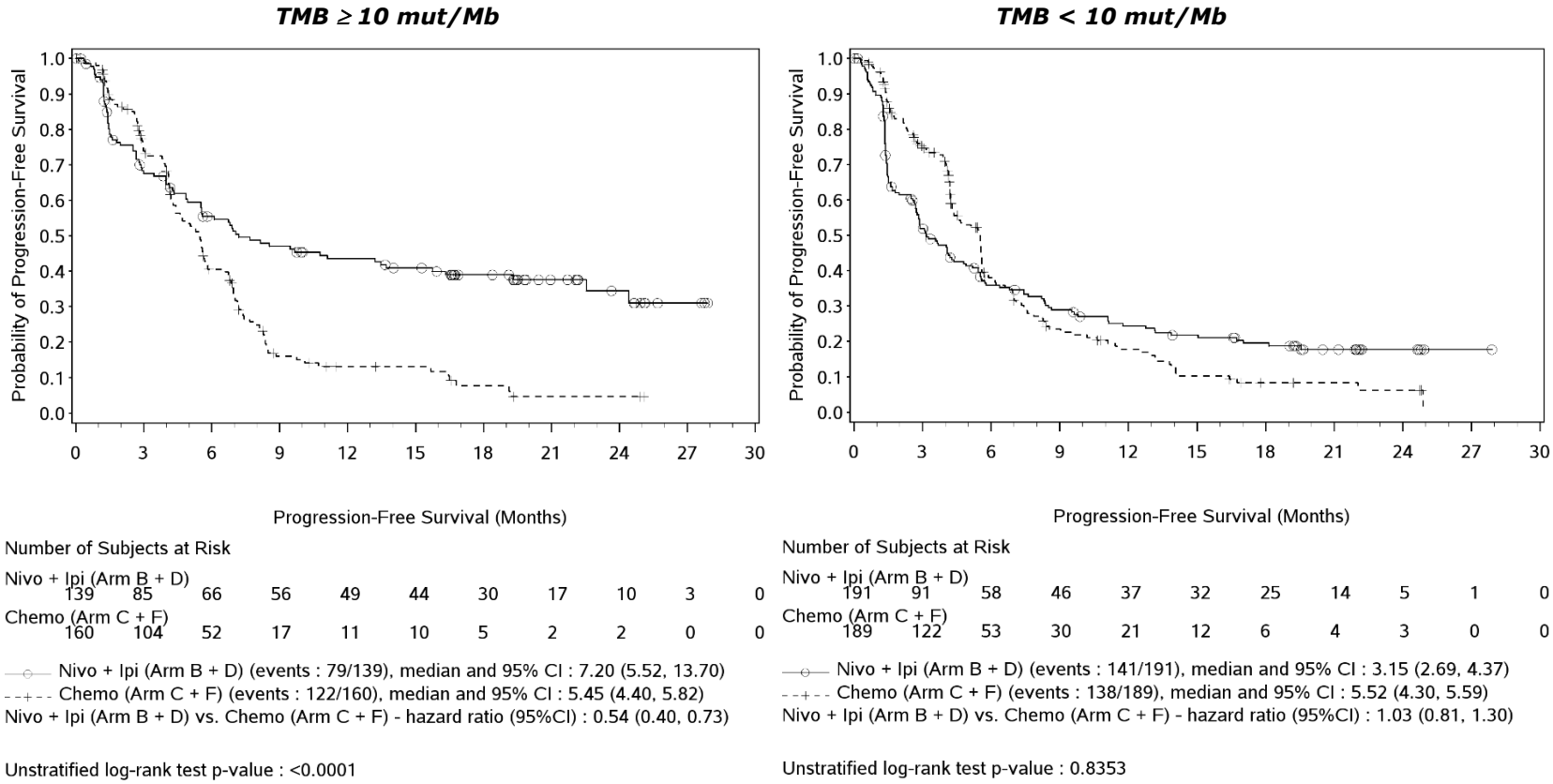


Figure 25: Kaplan-Meier Plot of Progression-Free Survival per BICR (Primary Definition) for Nivolumab + Ipilimumab (Arms D) Nivolumab + Chemotherapy (Arm G) and Chemotherapy (Arm F): TMB ≥ 10 mut/Mb Subjects with PD-L1 < 1%

ORR for nivolumab + ipilimumab vs chemotherapy by PD-L1 and TMB

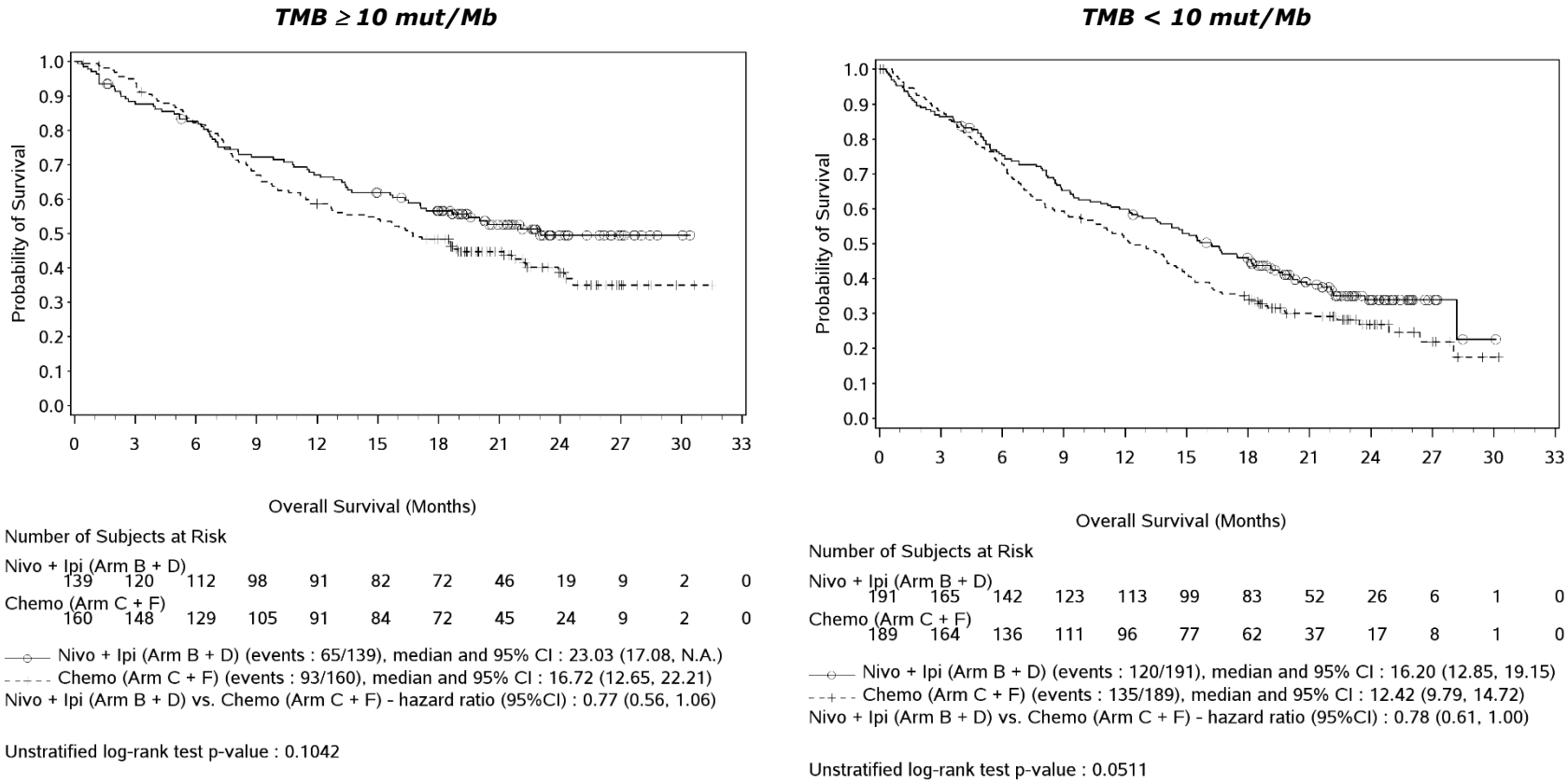
In subjects with TMB ≥10 mut/Mb, the BICR-assessed ORR (97.5% CI) increased across the spectrum of PD-L1 expression and was higher with nivolumab + ipilimumab (Arms B + D) than with chemotherapy (Arms C + F) across all PD-L1 expression levels: < 1% PD-L1: 36.8% (21.8, 54.0) vs 20.8% (10.5, 35.0); 1 - 49% PD-L1: 41.7% (27.6, 56.8) vs 22.2% (12.0, 35.6), and ≥50% PD-L1: 54.7% (40.4, 68.4) vs 36.2% (24.0, 49.9), respectively.

Updated efficacy analyses and new efficacy analyses from the CA209227 study were performed using a database lock of 09-Jul-2018, with a minimum follow-up of 18 months. The 09-Jul-2018 database lock was not pre-specified; it was conducted to fulfil the Request for Supplementary Information from the CHMP/EMA (dated 26-Jul-2018). Upon review of this data, additional new analyses of OS were conducted in TMB evaluable, TMB not evaluable, and all randomized subjects to confirm the validity and consistency of the results.



Symbols represent censored observations.
Hazard Ratio (Nivolumab + Ipilimumab vs Chemotherapy) is based on an unstratified Cox proportional hazard model.
For computational derivation purposes, subjects with TMB ≥ 10.09 and < 10.09 mut/Mb are categorized as TMB ≥ 10 mut/Mb and < 10 mut/Mb, respectively.
Source: Figure S.5.100.1 (TMB ≥ 10 mut/Mb) and Figure R-Q1-2 (TMB < 10 mut/Mb)

Figure 26: Kaplan-Meier Plot of Progression-Free Survival per BICR (Primary Definition) for Nivolumab + Ipilimumab (Arms B + D) and Chemotherapy (Arms C + F) by TMB Cutoff (10 mut/Mb) - All TMB Evaluable Subjects in CA209227 Part 1 - 09-Jul-2018 Database Lock

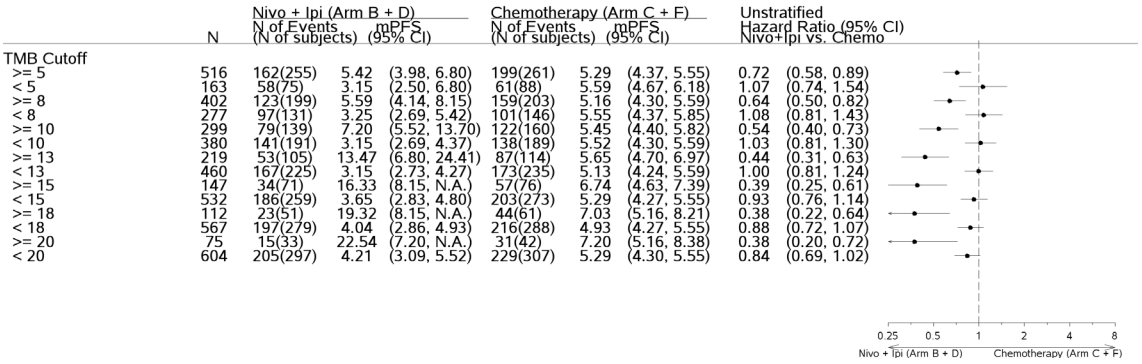


Symbols represent censored observations.

Hazard Ratio (Nivolumab + Ipilimumab vs Chemotherapy) is based on an unstratified Cox proportional hazard model.
For computational derivation purposes, subjects with TMB ≥ 10.09 and < 10.09 mut/Mb are categorized as TMB ≥ 10 mut/Mb and < 10 mut/Mb, respectively.
Source: Figure S.5.120.1.1 (TMB ≥ 10 mut/Mb) and Figure R-Q1-1 (TMB < 10 mut/Mb)

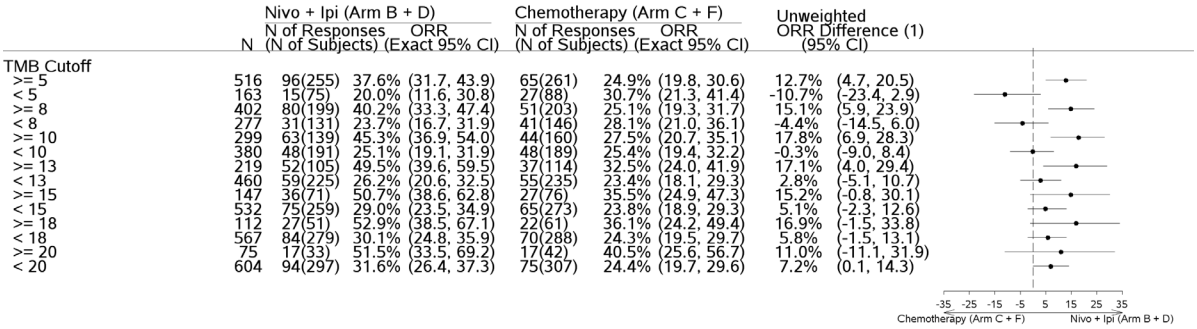
Figure 27: Kaplan-Meier Plot of Overall Survival for Nivolumab + Ipilimumab (Arms B + D) and Chemotherapy (Arms C + F) by TMB Cutoff (10 mut/Mb) - All TMB Evaluable Subjects in CA209227 Part 1 - 09-Jul-2018 Database Lock

The following TMB levels for nivolumab + ipilimumab versus chemotherapy in CA209227 Part 1 were explored using updated PFS and ORR data from the 09-Jul-2018 database lock (minimum follow-up of 18 months): TMB < and ≥ 5, 8, 10, 13, 15, 18, and 20 mut/Mb; and TMB < 5, ≥ 5 to < 10, ≥ 10 to < 15, ≥ 15 to < 20, and ≥ 20 mut/Mb.



Based on database lock: 09-Jul-2018.
Subgroups defined based on baseline TMB levels.
For computational derivation purposes, subjects with TMB >= 5.04, 7.57, 10.09, 12.61, 15.13, 17.65, 20.17 Mutations/MB are categorized as TMB >=5, 8, 10, 13, 15, 18, 20 Mutations/MB.

Figure 28: Forest Plot of PFS (Primary Definition, BICR) by TMB Levels at Baseline - Nivolumab + Ipilimumab and Chemotherapy - All TMB Evaluable Subjects in CA209227 Part 1 - 09-Jul-2018 Database Lock



Based on database lock: 09-Jul-2018.
Subgroups defined based on baseline TMB levels.
(1) Unweighted ORR difference (Nivolumab + Ipilimumab vs. Chemotherapy) and associated 95% CI
For computational derivation purposes, subjects with TMB >= 5.04, 7.57, 10.09, 12.61, 15.13, 17.65, 20.17 Mutations/MB are categorized as TMB >=5, 8, 10, 13, 15, 18, 20 Mutations/MB.

Figure 29: Forest Plot of ORR (per BICR) by TMB Levels at Baseline - Nivolumab + Ipilimumab and Chemotherapy - All TMB evaluable Subjects in CA209227 Part 1 - 09-Jul-2018 Database Lock

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). This table has not been updated with the new efficacy data from Part1A and Part1B.

Table 30: Summary of Efficacy for trial CA209227 (Part 1)

Title: A phase III, open-label, randomized, trial of nivolumab monotherapy, nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy vs platinum doublet chemotherapy in subjects with chemotherapy-naive stage IV or recurrent NSCLC with no known EGFR or ALK positive tumor mutations, who were previously untreated for advanced disease.		
Study identifier	CA209227	
Design	Phase III, open-label, randomised study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	05-Aug-2015 / 13-Dec-2017 (LPLV) – ongoing <time> <not applicable> <time> <not applicable>

Hypothesis	Superiority of nivolumab + ipilimumab over chemotherapy in patients with high TMB (≥ 10 mut/Mb), regardless of PD-L1 expression.		
Treatments groups	Nivolumab + ipilimumab (pooled Part 1: arms B+D)		Nivolumab 3 mg/kg over 30 minutes Q2W + ipilimumab 1 mg/kg over 30 minutes every 6 weeks (Q6W) 583 patients randomised (396 in Arm B and 187 in Arm D), 576 treated (391 in Arm B and 185 in Arm D). Patients with evaluable TMB: 330(240 in Arm B and 90 in Arm D). Pooled part 1 (Arms B + D) with high TMB (≥ 10 mut/Mb): 139 subjects.
	Chemotherapy (pooled Part 1: arms C + F)		Histology-based platinum-doublet in 3-week cycles for a maximum of 4 cycles or until disease progression or unacceptable toxicity: - SQ: gemcitabine (1000 or 1230 mg/m2) with cisplatin (75 mg/m2) or gemcitabine (1000 mg/m2) with carboplatin (AUC 5). - NSQ: pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) or pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6). 583 patients randomised (397 in Arm C and 186 in Arm F), 270 treated (387 in Arm C and 183 in Arm F). Patients with evaluable TMB: 349(242 in Arm B and 107 in Arm D). Pooled part 1 (Arms C + F) with high TMB (≥ 10 mut/Mb): 160 subjects.
Endpoints and definitions	Co-primary endpoint	PFS	Nivolumab + ipilimumab vs chemotherapy in subjects with TMB ≥ 10 mut/Mb, regardless of PD-L1 expression. PFS defined as the time between the date of randomisation and the first date of documented progression, as determined by BICR, or death due to any cause, whichever occurred first. Subjects who did not have any on study tumor assessments and did not die were censored on their date of randomization. Subjects who had palliative local therapy or initiated anti-cancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment on or prior to the initiation of subsequent anticancer therapy or palliative local therapy.
	Secondary endpoint	OS	Nivolumab + ipilimumab vs chemotherapy in subjects with TMB TMB ≥ 10 mut/Mb, regardless of PD-L1 expression. OS defined as the time from randomization to the date of death. A subject who had not died was censored at the last known alive date. OS was censored at the date of randomization for subjects who were randomized but had no follow-up.
	Secondary endpoint	PFS	Nivolumab vs chemotherapy in subjects with TMB ≥ 13 mut/Mb and PD-L1 expression ≥ 1% (Part 1a) See description for PFS above.
	Exploratory endpoint	ORR	Nivolumab + ipilimumab (Arms B+D) and chemotherapy (C+F) in subjects with TMB ≥ 10 mut/Mb regardless of PD-L1 expression level. Nivolumab (Arm A) vs chemotherapy (Arm C) with TMB ≥ 13 mut/Mt and PD-L1 ≥ 1%. ORR was defined as the proportion of randomized subjects who achieved a best response of CR or PR using the RECIST v1.1 criteria based on BICR assessment.
Database lock	24-Jan-2018 (15-Mar-2018 for OS in high TMB Part 1 secondary endpoint)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Patients with high TMB (≥ 10 mut/Mb), regardless of PD-L1 expression		

Descriptive statistics and estimate variability	Treatment group	Nivolumab + ipilimumab	Chemotherapy
	Number of subjects	139	160
	PFS per BICR, median (95% CI)	7.20 months (5.52, 13.21)	5.45 months (4.40, 7.78)
	ORR per BICR, % responders (95% CI)	45.3 (36.9, 54.0)	26.9 (20.2, 34.4)
	OS, median (95% CI)	23.03 months (16.49, NA)	16.36 months (12.65, NA)
	Treatment group (Part 1a)	Nivolumab	Chemotherapy
	Number of subjects	71	79
	PFS per BICR, median (95% CI) (Part 1a)	4.21 months (2.66, 8.34)	5.55 months (4.47, 6.97)
Effect estimate per comparison	Co-primary endpoint: PFS	Comparison groups	Nivolumab + ipilimumab vs chemotherapy
		HR	0.58
		95% CI	0.43, 0.77
		P-value	0.0002
	Secondary endpoint: OS	Comparison groups	Nivolumab + ipilimumab vs chemotherapy
		HR	0.79
		95% CI	0.56, 1.10
		P-value	0.1632
	Exploratory endpoint: ORR	Comparison groups	<group descriptors>
			<point estimate>
		<variability statistic>	<variability>
		P-value	<P-value>
	Secondary endpoint: PFS (Part 1a)	Comparison groups	Nivolumab vs chemotherapy
		HR	0.95
		95% CI	0.64, 1.40
		P-value	0.7776

Supportive study: CA209568

Study CA209568 is ongoing Phase 2, 2-part study to evaluate the efficacy of nivolumab plus ipilimumab (Part 1) and safety of nivolumab plus ipilimumab in combination with chemotherapy (Part 2) in subjects with stage IV NSCLC, previously untreated for advanced disease. Part 1 is completed and Part 2 is ongoing. A final CSR for Part 1 was completed based on a database lock of 25-Aug-2017; the data from subjects with TMB ≥ 10 mut/Mb in Part 1 are supportive of this submission and include efficacy data with a minimum follow-up of 6 months.

Objectives

Hypothesis:

In subjects with PD-L1+ stage IV NSCLC, the administration of nivolumab in combination with ipilimumab as first line treatment will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR).

Primary objective:

- To determine the ORR by BICR per RECIST 1.1 in PD-L1 + (membranous staining in ≥ 1% tumor cells) stage IV NSCLC subjects treated with nivolumab in combination with ipilimumab as first line therapy.

Secondary objectives:

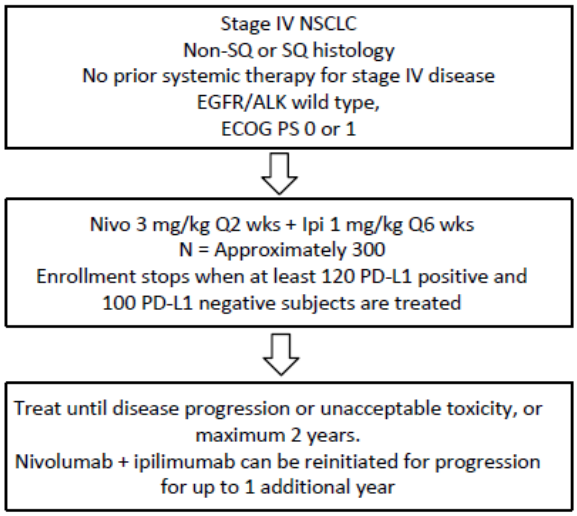
- To assess PFS, PFS rate at 6 months and DOR based on BICR in PD L1+ treated subjects.

Exploratory objectives:

- To assess safety and tolerability, pharmacokinetics and immunogenicity of nivolumab in combination with ipilimumab as first line therapy.
- To assess ORR, PFS, PFS rate at 6 months, and DOR in PD L1- (membranous staining in < 1% tumor cells) treated subjects.
- To assess median OS in PD-L1+ and PD-L1- treated subjects.

Methodology

The study included adults (≥ 18 years) who have 1) histologically confirmed Stage IV NSCLC or locally advanced disease with recurrence after chemoradiation therapy, 2) SQ or NSQ histology, 3) measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.1 criteria, and 4) no prior systemic anticancer therapy (including epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] inhibitors) given as primary therapy for advanced or metastatic disease. Prior adjuvant or neoadjuvant chemotherapy for early stage lung cancer was permitted if completed at least 6 months prior to initiating study treatment.



Source: Figure 3.1-1 of the CA209568 Part 1 Final CSR

Figure 30: Study design schematic for Part 1 of CA209568

In both parts of the study, subjects were to have tumor tissue sample available for PD-L1 testing. TMB was also to be tested for all treated subjects with available baseline tumor specimens using Foundation Medicine Inc.'s FoundationOneDx (F1CDx) assay, categorizing subjects using a TMB cutoff of 10 mut/Mb (≥☐10 mut/Mb and < 10 mut/Mb). This cutoff was chosen based on a preliminary analysis of data from CA209568 (12-May-2017 database lock) and has been confirmed in the final analysis (25-Aug-2017 database lock).

- Choice of cutoff for Tumor Mutational Burden (TMB):

Receiver operating characteristic (ROC) curves were used to aid in determination of the optimal cutoff for TMB. ROC curves can indicate optimal predictive performance; however, to investigate whether a specific cutoff would yield a clinically meaningful enrichment, with an ORR higher than what has been

historically reported with chemotherapy, clinical efficacy (ORR) was summarized for a range of cutoffs (5, 10, and 15 mut/Mb) representing the full spectrum of TMB.

Based on results from a preliminary analysis using data from the 12-May-2017 database lock (clinical cutoff of 31-Mar-2017, minimum follow-up of 3 months), a TMB cutoff off of 10.09 mutations per megabase (1 million bases of exome sequence; mut/Mb) was chosen; this cutoff was supported by results from the current 25-Aug-2017 database lock. For computational derivation purposes, subjects with TMB ≥□10.09 mut/Mb were categorized as TMB ≥10 mut/Mb, subjects with TMB < 10.09 mut/Mb were categorized as TMB < 10 mut/Mb.

In Part 1, subjects received nivolumab 3 mg/kg IV over 30 minutes Q2W + ipilimumab 1 mg/kg IV over 30 minutes Q6W for up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment beyond initial investigator-assessed RECIST v1.1 defined progression was permitted if the subject had investigator assessed clinical benefit and was tolerating nivolumab and ipilimumab.

The primary objectives of Part 1 were to determine the ORR per BICR in all treated PD-L1 ≥ 1% and PD-L1 < 1% subjects treated with nivolumab in combination with ipilimumab. Secondary objectives include BICR-assessed PFS, OS, efficacy by PD-L1 expression levels and TMB as a potential predictive biomarker of efficacy. Tumor assessments using RECIST v1.1 criteria were performed every 6 weeks from the first dose of study drug for the first 48 weeks, and then every 12 weeks until BICR-assessed progression.

Number of subjects

Subjects from 30 sites in the US and Canada were treated in Part 1 of CA209568, 261 (90.6%) subjects from the US and 27 (9.4%) subjects from Canada. The last patient first treatment occurred on 28-Dec-2016 and LPLV (clinical cutoff) occurred on 30-Jun-2017, providing a minimum follow-up of 6 months for all nivolumab + ipilimumab-treated subjects in Part 1. For all nivolumab + ipilimumab-treated subjects, the median extent of follow-up (time between the first dose date and last known date alive [for subjects who are alive]) was 8.77 months (range: 0.2 to 17.5).

Of the 288 treated subjects, 69.4% of subjects discontinued study drugs as of the 25-Aug-2017 database lock. The most common reasons for discontinuation was disease progression (41.7%). Of the 288 nivolumab + ipilimumab-treated subjects, 23 (8.0%) subjects discontinued ipilimumab, only (refer to Table S.4.1.2 of the CA209568 Part 1 Final CSR). These subjects continued to receive nivolumab for a mean (standard deviation [SD]) of 116.7 (76.80) days. Note that ipilimumab could be discontinued and nivolumab continued; however, if nivolumab was discontinued, ipilimumab could not be continued alone as monotherapy.

- Results of TMB testing in Part 1 of CA209568

Per protocol, archival or current formalin-fixed, paraffin-embedded tumor tissue was to be sent to the central vendor/laboratory (Foundation Medicine, Inc. Cambridge, MA) for determination of TMB expression using the validated FoundationOne CDx (F1CDx) assay.

As of the 25-Aug-2017 database lock:

- 120/288 (41.7%) treated subjects had a baseline tumor tissue sample available for TMB testing
    - 98/120 (81.7%) success rate in generating evaluable TMB by Foundation Medicine
    - 22/120 (18.3%) not evaluable due to technical reasons

- Overall, 98/288 (34.0%) treated subjects had an evaluable TMB result and 190/288 (66.0%) had a non-evaluable TMB result.

Among all treated subjects (N = 288) in Part 1, 98 (34.0%) subjects had tumors that were TMB evaluable. Among TMB evaluable subjects (n = 98), the median number of mut/Mb was 8.830 (range 0 to 98.35); 48 (49.0%) subjects had tumors that were categorized as having TMB ≥ 10 mut/Mb and 50 (51.0%) subjects had tumors that were categorized as having TMB < 10 mut/Mb.

Baseline demographics and disease characteristics

Baseline characteristics for the subgroups by TMB expression (≥ 10 mut/Mb, < 10 mut/Mb, evaluable, and not evaluable) were generally consistent with those for all treated subjects in Part 1.

Table 31: Baseline Characteristics in Tumor Mutational Burden (TMB) Subgroups: Treated Subjects in Part 1 of CA209568

	TMB ≥ 10 mut/Mb (N = 48)	TMB < 10 mut/Mb (N = 50)	TMB Evaluable (N = 98)	TMB Not Evaluable (N = 190)	Total (N = 288)
Age (years)					
Median	63.5	66.0	65.0	65.0	65.0
< 65 (n, %)	25 (52.1)	22 (44.0)	47 (48.0)	88 (46.3)	135 (46.9)
≥ 65 (n, %)	23 (47.9)	28 (56.0)	51 (52.0)	102 (53.7)	153 (53.1)
Male (n, %)	23 (47.9)	31 (62.0)	54 (55.1)	88 (46.3)	142 (49.3)
Race (n, %)					
White	44 (91.7)	44 (88.0)	88 (89.8)	171 (90.0)	259 (89.9)
Black	3 (6.3)	5 (10.0)	8 (8.2)	11 (5.8)	19 (6.6)
Other	1 (2.1)	1 (2.0)	2 (2.0)	8 (4.2)	10 (3.5)
Cell Type (n, %)					
Adenocarcinoma	26 (54.2)	35 (70.0)	61 (62.2)	140 (73.7)	201 (69.8)
Squamous Cell Carcinoma	20 (41.7)	14 (28.0)	34 (34.7)	42 (22.1)	76 (26.4)
Other	2 (4.2)	1 (2.0)	3 (3.0)	8 (8.2)	11 (3.8)
ECOG PS (n, %)					
0	23 (47.9)	14 (28.0)	37 (37.8)	70 (36.8)	107 (37.2)
1	24 (50.0)	35 (70.0)	59 (60.2)	119 (62.6)	178 (61.8)
2	1 (2.1)	1 (2.0)	2 (2.0)	1 (0.5)	3 (1.0)
Smoking Status (n, %)					
Former	44 (91.7)	38 (76.0)	82 (83.7)	123 (64.7)	205 (71.2)
Current	4 (8.3)	7 (14.0)	11 (11.2)	45 (23.7)	56 (19.4)
Never/Unknown	0	5 (10.0)	5 (5.1)	22 (11.6)	27 (9.4)
PD-L1 Expression					
≥ 50%	9 (18.8)	10 (20.0)	19 (19.4)	49 (25.8)	68 (23.6)
≥ 1%	26 (54.2)	28 (56.0)	54 (55.1)	84 (44.2)	138 (47.9)
< 1%	19 (39.6)	22 (44.0)	41 (41.8)	73 (38.4)	114 (39.6)
Not quantifiable	3 (6.25)	0	3 (3.1)	33 (17.4)	36 (12.5)

	TMB ≥ 10 mut/Mb (N = 48)	TMB < 10 mut/Mb (N = 50)	TMB Evaluable (N = 98)	TMB Not Evaluable (N = 190)	Total (N = 288)
Age (years)					
Median	63.5	66.0	65.0	65.0	65.0
< 65 (n, %)	25 (52.1)	22 (44.0)	47 (48.0)	88 (46.3)	135 (46.9)
≥ 65 (n, %)	23 (47.9)	28 (56.0)	51 (52.0)	102 (53.7)	153 (53.1)
Male (n, %)	23 (47.9)	31 (62.0)	54 (55.1)	88 (46.3)	142 (49.3)
Race (n, %)					
White	44 (91.7)	44 (88.0)	88 (89.8)	171 (90.0)	259 (89.9)
Black	3 (6.3)	5 (10.0)	8 (8.2)	11 (5.8)	19 (6.6)
Other	1 (2.1)	1 (2.0)	2 (2.0)	8 (4.2)	10 (3.5)
Cell Type (n, %)					
Adenocarcinoma	26 (54.2)	35 (70.0)	61 (62.2)	140 (73.7)	201 (69.8)
Squamous Cell Carcinoma	20 (41.7)	14 (28.0)	34 (34.7)	42 (22.1)	76 (26.4)
Other	2 (4.2)	1 (2.0)	3 (3.0)	8 (8.2)	11 (3.8)
ECOG PS (n, %)					
0	23 (47.9)	14 (28.0)	37 (37.8)	70 (36.8)	107 (37.2)
1	24 (50.0)	35 (70.0)	59 (60.2)	119 (62.6)	178 (61.8)
2	1 (2.1)	1 (2.0)	2 (2.0)	1 (0.5)	3 (1.0)
Smoking Status (n, %)					
Former	44 (91.7)	38 (76.0)	82 (83.7)	123 (64.7)	205 (71.2)
Current	4 (8.3)	7 (14.0)	11 (11.2)	45 (23.7)	56 (19.4)
Never/Unknown	0	5 (10.0)	5 (5.1)	22 (11.6)	27 (9.4)
PD-L1 Expression					
≥ 50%	9 (18.8)	10 (20.0)	19 (19.4)	49 (25.8)	68 (23.6)
≥ 1%	26 (54.2)	28 (56.0)	54 (55.1)	84 (44.2)	138 (47.9)
< 1%	19 (39.6)	22 (44.0)	41 (41.8)	73 (38.4)	114 (39.6)
Not quantifiable	3 (6.25)	0	3 (3.1)	33 (17.4)	36 (12.5)

Abbreviations: ECOG - Eastern Cooperative Oncology Group; mut/Mb - mutations per megabase [1 million bases] of exome sequence TMB - tumor mutational burden
Source: Refer to Table 5.3.2-1 of the CA209568 Part 1 Final CSR

In Part 1 of CA209568, 1 (0.3%) subject received prior systemic anticancer therapy in the setting of metastatic disease; this subject was considered a protocol deviation. Overall, 8.7% of subjects received prior systemic therapy in the adjuvant setting and 3.1% of subjects received prior systemic therapy in the neoadjuvant setting. The most frequent prior systemic cancer therapies were cisplatin (9.0%), carboplatin (3.8%), and etoposide, paclitaxel, and pemetrexed (3.5% each).

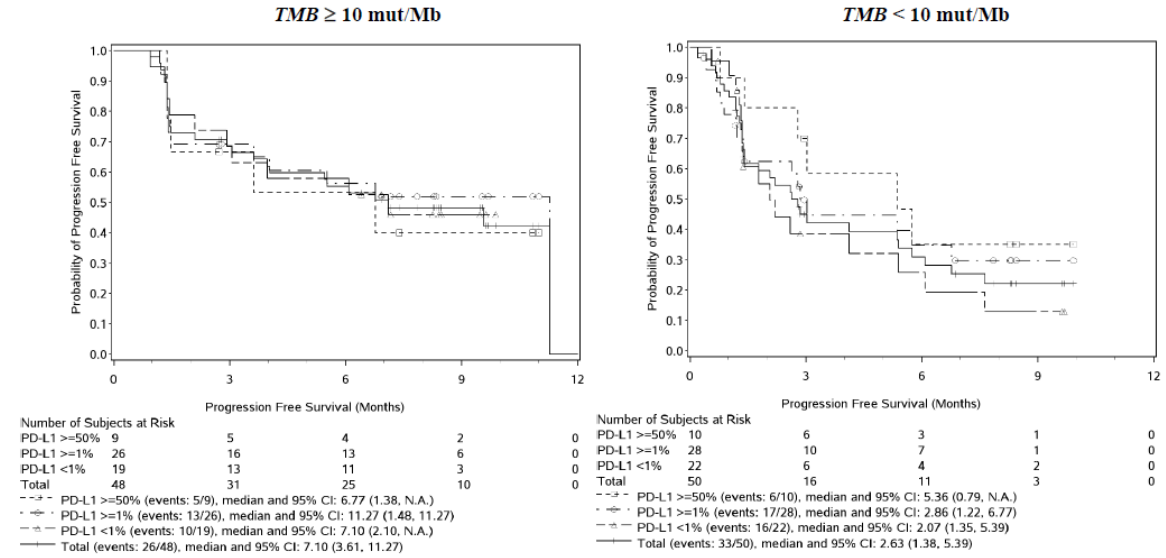
Efficacy results

TMB evaluable or TMB not evaluable subjects had efficacy results that were similar to those for the whole study population. Among TMB evaluable subjects, TMB ≥ 10 mut/Mb was associated with greater anti-tumor activity than TMB < 10 mut/Mb regardless of PD-L1 expression.

Table 32: Efficacy Summary Overall and by Tumor Mutational Burden: Subjects Treated with Nivolumab + Ipilimumab in Part 1 of CA209568

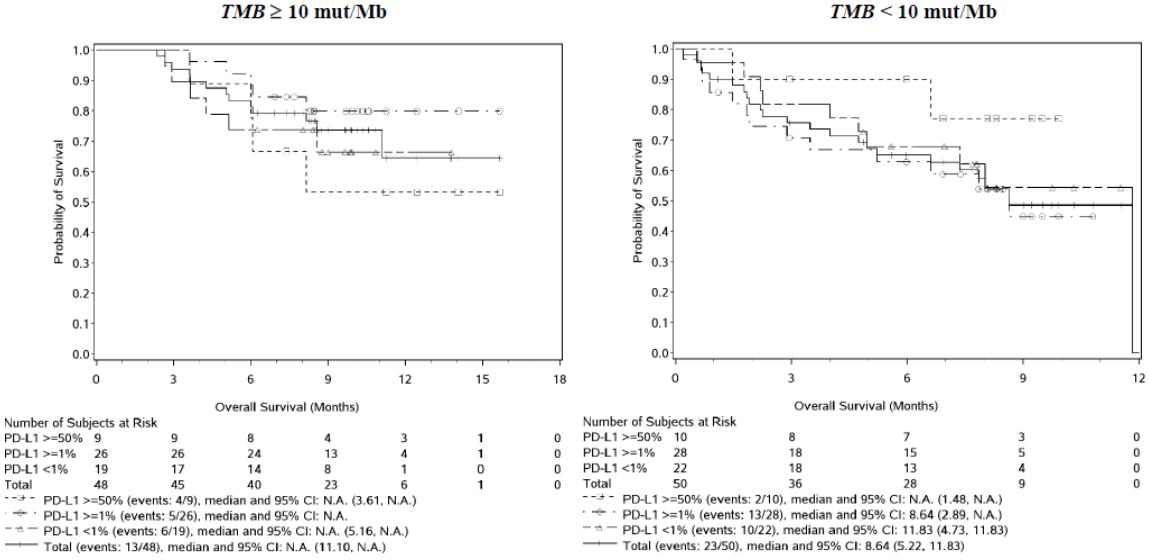
	TMB ≥ 10 mut/Mb (N = 48)	TMB < 10 mut/Mb (N = 50)	TMB Evaluable (N = 98)	TMB Not Eval. (N = 190)	Total (N = 288)
ORR (per BICR)					
Responders/Total, n/N	21/48	6/50	27/98	59/190	86/288
Objective Response	43.8%	12.0%	27.6%	31.1%	29.9%
95% CI	(29.5, 58.8)	(4.5, 24.3)	(19.0, 37.5)	(24.6, 38.2)	(24.6, 35.5)
Best Overall Response, n (%)					
Complete Response	4 (8.3)	1 (2.0)	5 (5.1)	2 (1.1)	7 (2.4)
Partial Response	17 (35.4)	5 (10.0)	22 (22.4)	57 (30.0)	79 (27.4)
Stable Disease	14 (29.2)	23 (46.0)	37 (37.8)	67 (35.3)	104 (36.1)
Progression	13 (27.1)	13 (26.0)	26 (26.5)	50 (26.3)	76 (26.4)
Unable to Determine	0	8 (16.0)	8 (8.2)	14 (7.4)	22 (7.6)
Time to Response[a]					
Median, mos	2.56	2.07	2.56	2.30	2.43
(Min, Max)	1.2, 5.6	1.2, 4.1	1.2 , 5.6	1.2, 8.3	1.2, 8.3
Duration of Response					
≥ 6 mos, % (95% CI)	76 (51, 89)	78 (20, 97)	82 (55, 89)	72 (65, 88)	78 (67, 86)
Median, months (95% CI)	NA (NA, NA)	NA (4.17, NA)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
Min, Max	2.7 , 9.6+	3.8+, 8.5+	2.7 , 9.6+	1.2+, 14.0+	1.2+, 14.0+
PFS (per BICR)					
Events, n/N	26/48	33/50	59/98	114/190	173/288
6-month PFS Rate	55.3%	30.9%	43.7%	42.3%	42.8%
Median, months	7.10	2.63	4.11	4.17	4.17
(95% CI)	(3.61, 11.27)	(1.38, 5.39)	(2.63, 6.77)	(2.83, 5.88)	(3.02, 5.65)
Overall Survival					
Events, n/N	13/48	23/50	36/98	66/190	102/288
6-month OS Rate, %	83.3	65.0	74.1	75.1	74.7
Median, mos	NA	8.64	11.83	NA	NA
(95% CI)	(11.10, NA)	(5.22, 11.83)	(11.10, NA)	(NA, NA)	(NA, NA)

a Note that the first tumor assessment was to be performed at 6 weeks (≥7 days) from first dose date and subsequent tumor assessments were to occur every 6 weeks (≥7 days) up to first 12 months (Week 48), then every 12 weeks until disease progression.
Database lock: 25-Aug-2017; Minimum follow-up: 6 months
Abbreviations: BICR - blinded independent central review, CI - confidence interval, mut/Mb - mutations per megabase [1 million bases] of exome sequence, ORR - objective response rate, OS - overall survival, PFS - progression-free survival, TMB - tumor mutational burden
Source: Refer to Table 7.1-2, Table S.9.13A, Table S.9.13B, Table S.9.13C, and Table S.9.13D of the CA209568 Part 1 Final CSR



Symbols represent censored observations.
Source: Figure 7.3.2-1 of the CA209568 Part 1 Final CSR

Figure 31: Kaplan-Meier Plot of Progression Free Survival per BICR by TMB Cutoff (10 mut/Mb): TMB Evaluable Subjects in Part 1 of CA209568



Symbols represent censored observations
Source: Figure 7.3.3-1 of the CA209568 Part 1 Final CSR

Figure 32: Kaplan-Meier Plot of Overall Survival by TMB Cutoff (10 mut/Mb): TMB Evaluable Subjects in Part 1 of CA209568

Although the numbers were small, BICR-assessed ORR was 42.3% (11/26) in subjects who had both TMB ≥10 mut/Mb and PD-L1 ≥1% vs 4.5% (1/22) in subjects with TMB < 10 mut/Mb and PD-L1 < 1%.

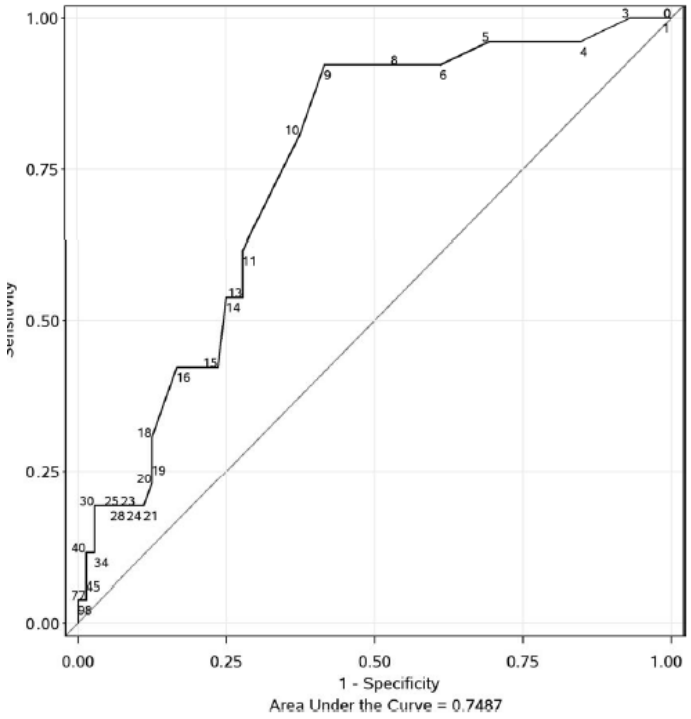
- BICR-assessed ORR was 47.4% (9/19) in TMB ≥10 mut/Mb and PD-L1 <1% subjects and 17.9% (5/28) in TMB < 10 mut/Mb and PD-L1 ≥1% subjects.
- Subjects with TMB ≥10 mut/Mb who were PD-L1 ≥1% had a median PFS of 11.27 months.
- Subjects with TMB < 10 mut/Mb who were PD-L1 < 1% had a median PFS of 2.07 months.

• Choice of baseline TMB cutoff (≥ 10 mut/Mb)

To aid in the investigation and determination of an optimal TMB cutoff for nivolumab + ipilimumab combination therapy, preliminary analyses of ORR by TMB were conducted using data from a 12-May-2017 database lock; minimum follow-up of 3 months.

TMB in association with ORR classification performance ROC curves were used to evaluate TMB as a continuous variable over the full spectrum of observed values. The ROC curves showed that TMB was an informative classifier of response with nivolumab + ipilimumab in TMB evaluable subjects (N = 98; AUC = 0.7487), TMB evaluable subjects with PD-L1 ≥1% (n = 54; AUC = 0.7056), and TMB evaluable subjects with PD-L1 < 1% (n = 41; AUC = 0.8819). The observed shoulder for True Positive Fraction (TPF) in the TMB ROC curves supports the choice of 10 mut/Mb as the TMB cutoff.

Although the ROC curve indicated that 10 mut/Mb was the optimal cutoff for TMB, ORR also was summarized using various TMB cutoffs chosen to represent the full spectrum of TMB values (5, 10, and 15 mut/Mb). In the TMB ≥10 mut/Mb population (all treated), ORR was 43.8% and did not increase further with TMB higher than 10 mut/Mb, supporting the choice of 10 mut/Mb as the TMB cutoff.



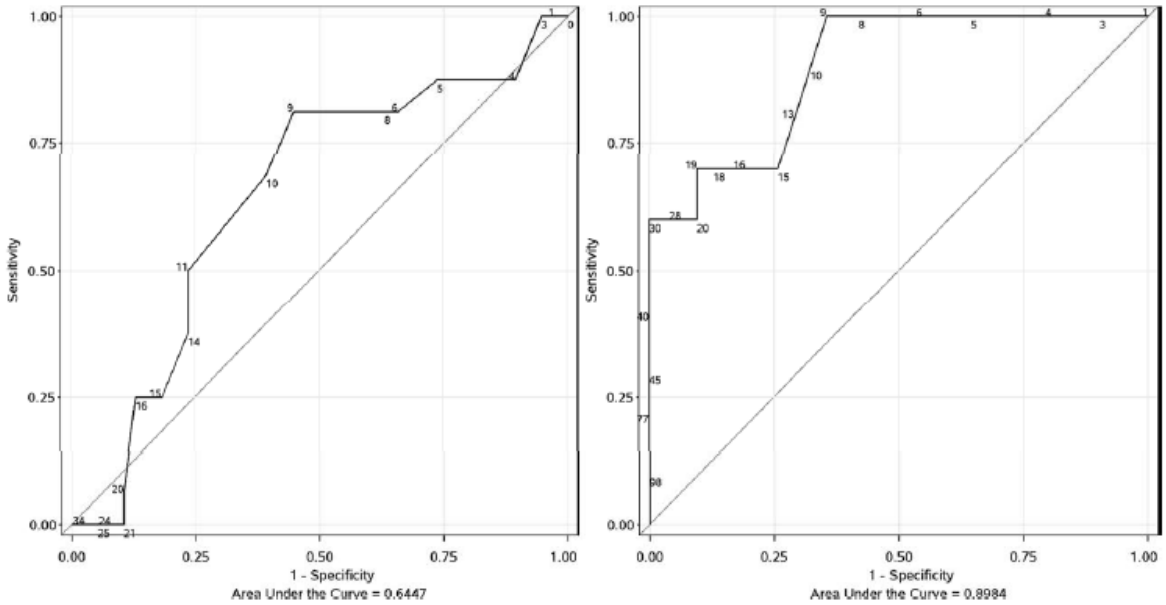
Annotation shows the level of TMB.

Figure 33: Receiver Operating Characteristic Curve (ROC) for TMB Based on Objective Response (per BICR) Regardless of PD-L1 Expression – All TMB Evaluable Subjects - CA209568 Preliminary Analysis

The ORR data from the current database lock (25-Aug-2017) support the selection of 10 mut/Mb as the TMB cutoff. TMB classification performance ROC curves show that TMB is an informative classifier of response with nivolumab + ipilimumab in TMB evaluable subjects (N = 98; AUC = 0.7280), TMB evaluable subjects with PD-L1 ≥ 1% (n = 54; AUC = 0.6447), and TMB evaluable subjects with PD-L1 < 1% (n = 41; AUC = 0.8984) (Figure 7.3.1.1-1-3 and Figure 7.3.1.1-4). The observed shoulder for TPF in the TMB ROC curves supports the choice of 10 mut/Mb as the TMB cutoff.

BICR-assessed ORR generally increased with increasing TMB level up to 10 mut/Mb, irrespective of PD-L1 expression (≥ 1%, < 1%, and all treated subjects) with an ORR in subjects with TMB

≥ 10 mut/Mb ranging from 42% (in PD-L1 ≥ 1% subjects) to 47% (in PD-L1 < 1% subjects). Moreover, with a higher TMB cutoff, there was no incremental ORR benefit.



Annotation shows the level of TMB.

Figure 34: Receiver Operating Characteristic (ROC) Curve Based on ORR (per BICR) by PD-L1 Expression and TMB Level: All TMB Evaluable Subjects with PD-L1 ≥ 1% (N = 54) and PD-L1 < 1% (N = 41) Expression at Baseline

Table 33: ORR per BICR by TMB and PD-L1: All Treated Subjects

	ORR % (n/N)				
	All Treated	PD-L1 < 1%	PD-L1 ≥ 1%	PD-L1 ≥ 50%	PD-L1 not quantifiable
All treated	29.9 (86/288)	14.9 (17/114)	41.3 (57/138)	50.0 (34/68)	33.3 (12/36)
TMB evaluable	27.6 (27/98)	24.4 (10/41)	29.6 (16/54)	36.8 (7/19)	33.3 (1/3)
TMB < 5 mut/Mb	8.7 (2/23)	0/11	16.7 (2/12)	33.3 (2/6)	0/0
TMB ≥ 5 mut/Mb	33.3 (25/75)	33.3 (10/30)	33.3 (14/42)	38.5 (5/13)	33.3 (1/3)
TMB ≥ 10 mut/Mb	**43.8 (21/48)**	**47.4 (9/19)**	**42.3 (11/26)**	**33.3 (3/9)**	**33.3 (1/3)**
TMB ≥ 15 mut/Mb	39.3 (11/28)	46.7 (7/15)	36.4 (4/11)	50.0 (1/2)	0/2

Abbreviations: BICR - blinded independent central review, mut/Mb - mutations/megabase, ORR - objective response rate, PD-L1 - programmed death-ligand 1, TMB - tumor mutational burden
Source: Table S.5.1, Table S.9.13A, Table S.9.13B, Table S.9.13E, Table S.9.13F, and Table S.9.13G

2.4.3. Discussion on clinical efficacy

The initial application concerned an extension of indication to include the first-line combination treatment with nivolumab and ipilimumab of adult patients with metastatic non-small cell lung cancer (NSCLC) in adults who have tumour mutational burden ≥ 10 mutations per megabase with no known EGFR or ALK positive tumour mutations. However, with the full and final data of CA209227 Part 1, an updated indication has been now proposed. "OPDIVO in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations (see sections 4.4 and 5.1)."

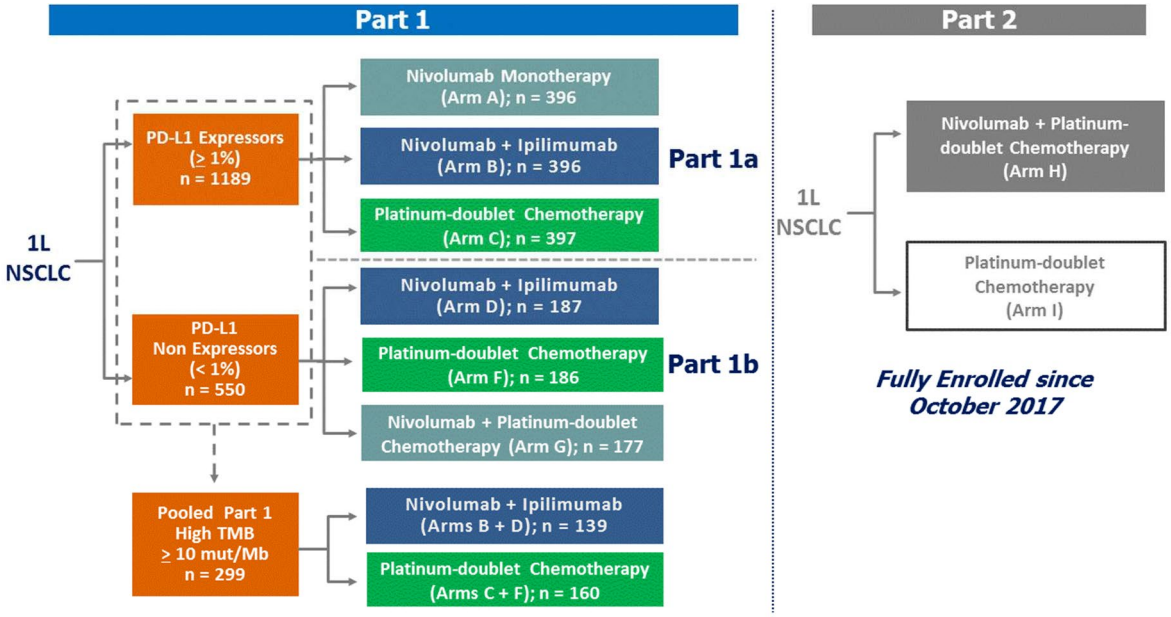
The recommended dose is 3 mg/kg nivolumab administered as an intravenous infusion every 2 weeks in combination with 1 mg/kg ipilimumab administered intravenously every 6 weeks (see Table

1.1-1). Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression

Design and conduct of clinical studies

CA209227 is an open-label, randomized, Phase 3 study of nivolumab monotherapy, nivolumab plus ipilimumab, nivolumab plus platinum-doublet chemotherapy, or platinum-doublet chemotherapy alone in subjects with previously untreated recurrent or metastatic NSCLC. The nivolumab + ipilimumab (Arms B and D) and chemotherapy (Arms C and F) treatment regimens were identical in Parts 1a and 1b, respectively.

Subjects were first assessed for PD-L1 expression, using a 1% cut-off, and categorized into 2 separate groups (PD-L1 expressing and PD-L1 non-expressing). Subjects within each group were to be stratified by histology (squamous [SQ] vs non-squamous [NSQ]). Subjects with PD-L1 ≥1% tumors were randomized in a 1:1:1 ratio to Arms A, B, and C. Subjects with PD-L1 < 1% tumors were initially randomized to Arms D, F and G in a 1:1:1 ratio.



The original CA209227 protocol, dated 29-May-2015, contained two substudies, one in subjects with PD-L1 expressing tumors (≥1%) and one in subjects with PD-L1 non-expressing tumors (< 1%), each randomizing to three arms (including one control arm), with an OS/PFS dual primary endpoint for each experimental arm versus the respective control (nivolumab + ipilimumab vs chemotherapy in part 1A and nivolumab + chemotherapy vs chemotherapy in part 1B). Each substudy had an independent alpha of 0.05 for addressing the primary and salient secondary objectives within each substudy.

The primary PFS analyses censored the patients for palliative local therapy and initiation of new anti-cancer therapy. This is not in line with the preferred EU definition, in the EU definition is the time of the progression or recurrence event is determined using the first date when there is documented evidence that the criteria have been met, even in situations where progression is observed after one or more missed visits, treatment discontinuation, or new anti-cancer treatment [EMA/CHMP/27994/2008/Rev.1]
The provided secondary definition of the PFS is in line with EU definition. The data from the secondary analyses were provided as additional sensitivity analyses.

The study did not include an ipilimumab treatment arm, which was justified by the absence of an additive effect of ipilimumab when added to a backbone in chemotherapy in first line SQ -NSCLC patients (Study CA184104) and possible additive effects of ipilimumab with nivolumab. However, following the latest amendment, the target population was redefined to the subgroup of patients with TMB ≥10 mut/MB. No supportive clinical data is provided that shows that ipilimumab has no effect in this target population when added to chemotherapy. Therefore, with the current study design the contribution of ipilimumab to the proposed target population cannot be determined and remains an uncertainty.

The protocol underwent 4 major revisions based on emerging data from other studies in first-line NSCLC. In November 2016, PFS was removed as a co-primary objective, leaving the OS comparison of nivolumab + ipilimumab vs chemotherapy as the single primary objective in the part 1A. In addition, the population for the primary endpoint of OS (nivolumab + ipilimumab vs chemotherapy) was changed to subjects with tumors expressing PD-L1 ≥50%. In part 1B, OS was removed as a co-primary objective, leaving the comparison of PFS (per BICR) of nivolumab + chemotherapy vs chemotherapy as the single primary objective. Multiplicity corrections were modified and the error type I was split between the new co-primary endpoints. This major amendment introduced a major change in the primary endpoint and in the definition of the population for the primary analysis.

In addition to that, another important amendment was introduced in October 2017 (amendment 19). The primary objective comparison of OS for nivolumab + ipilimumab vs chemotherapy was changed from the PD-L1 ≥50% population to the ≥1% population, which was the comparison in the original protocol. According to the MAH, this was due to the data from the phase II study CA209568, which showed a high ORR in subjects with PD-L1 ≥1%. However, this amendment also introduced a relevant change in the protocol, an additional co-primary analysis was incorporated into Part 1 of the study to test whether nivolumab + ipilimumab prolongs PFS versus chemotherapy in subjects with TMB ≥10 mut/Mb per the F1CDx assay, regardless of PD-L1 expression (primary OS endpoint was kept). To ensure sufficient power for the dual primary endpoints, the comparison of nivolumab + chemotherapy versus chemotherapy was demoted to a secondary endpoint. This change in the protocol is considered critical given the modification in the population to be analysed and keeping in mind that was carried out in the last part of the study (Oct 2017 / last patient last visit Dec 2017). Importantly, before this amendment an interim analysis of ORR for Part 1a was carried out in January 2017, but also included an analysis for PFS. The PFS results of the interim analysis data were submitted in an annex to CSR. Together, this raises concerns about the integrity of the study, especially bearing in mind that the amendment was made during the conduct of this open-label trial and subsequent to an interim analysis. In order to address the uncertainties related to these changes in the design of the clinical study during the conduct of the trial a triggered GCP inspection was requested.

A GCP inspection was conducted at Sponsor site Bristol-Myers Squibb ([BMS], Lawrenceville, NJ, US; from 07-May-2019 to 10-May-2019) and at two vendors, one CRO responsible for some data management activities, from 02-Apr-2019 to 04-Apr-2019 and another CRO, responsible for preparation of the statistical outputs, from 08-Apr-2019 to 11-Apr-2019). The inspectors shared the integrated inspection report GCP/2018/040 dated 14-Jun-19 with the rapporteurs and the Committee for Medicinal Products for Human Use (CHMP).

The inspection team concluded that the sponsor and the CRO processes were having weaknesses on their systems that led to the departures on ICH GCP observed (lack of solid measures to prevent dissemination of information to authorised/non authorised personnel within a non-robust and immature risk management system). Overall, the MAH was not able to demonstrate that the addition of the TMB endpoint was not informed by the interim analysis.

The inspection team considers that as a result of the departures from GCP noted the consistency on the trial data could have been compromised and therefore inspectors cannot confirm that trial data is reliable with adequate quality to be used in support of the Marketing Authorisation Application submitted to the Agency, due to the weaknesses on the processes used for handling this data.

Efficacy data and additional analyses

Baseline demographics and disease characteristics are overall representative of a first-line metastatic NSCLC population and seem to be evenly balanced among arms. Liver metastasis is more frequent in PD-L1 negative in the immune combo vs PD-L1 positive. This is a population treatment naïve not candidate to receive ALKi or TKI with either squamous or non-squamous NSCLC. Due to the exclusion of patients with ECOG>1 and brain metastases, there is uncertainty to what extent the potential benefit of this combination could be extrapolated to further groups of patients. This information needs to be reflected in the SmPC section 4.2. Patients with non-quantifiable PD-L1 expression were not allowed into the Part 1.

A total of 1739 subjects were randomized at 239 sites in 32 countries. Fifty eight (58) % of the ITT population encompasses the TMB evaluable population. Among the main reasons for this loss of patients/samples are the pre-analytical QC check, sample QC failure and TMB lower bound (minimum tumour content in a sample). Others reason include problems with the tissue collection and issues with the NGS analysis.

The pre-defined co-primary objectives of Part 1 are:

1. In subjects with PD-L1 ≥ 1% tumors: To compare OS of nivolumab in combination with ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C) (alpha = 0.0249, Part 1a)
2. In subjects with high baseline tumor mutational burden (TMB ≥ 10 mut/Mb): To compare PFS (based on blinded independent central review [BICR] assessment) of nivolumab in combination with ipilimumab (Arms B + D) to platinum-doublet chemotherapy (Arms C + F) (alpha = 0.025, Part 1).

1) The use of the combination of Nivolumab + ipilimumab in Part 1A showed a statistically significant improvement in OS compared with chemotherapy alone: HR = 0.79 (97.72% CI: 0.65, 0.96); stratified log-rank test p-value = 0.0066. This result is considered successful as the threshold according to the hierarchical testing with alfa protection was established in < 0.0228. In terms of median OS, the was a gain of roughly 2 months (17.08 (14.95, 20.07) vs 14.88 (12.71, 16.72) nivolumab + ipilimumab and chemotherapy, respectively

Majority of censored patients are still in follow-up.

Status of Censored Subjects, Overall Survival
All Randomized Subjects in Part 1

	Arm B: Nivo + Ipi N = 396	Arm A: Nivolumab N = 396	Arm C: Chemotherapy N = 397	Arm D: Nivo + Ipi N = 187	Arm G: Nivo + Chemo N = 177	Arm F: Chemotherapy N = 186
NUMBER OF DEATHS (%)	258 (65.2)	274 (69.2)	298 (75.1)	119 (63.6)	137 (77.4)	156 (83.9)
NUMBER OF SUBJECTS CENSORED (%)	138 (34.8)	122 (30.8)	99 (24.9)	68 (36.4)	40 (22.6)	30 (16.1)
STATUS OF CENSORED SUBJECTS (%)						
STILL ON TREATMENT	0	2 (0.5)	5 (1.3)	1 (0.5)	2 (1.1)	1 (0.5)
NOT PROGRESSED	0	2 (0.5)	5 (1.3)	0	2 (1.1)	1 (0.5)
PROGRESSED (1)	0	0	0	1 (0.5)	0	0
IN FOLLOW-UP	123 (31.1)	106 (26.8)	78 (19.6)	59 (31.6)	32 (18.1)	23 (12.4)
OFF STUDY	15 (3.8)	14 (3.5)	16 (4.0)	8 (4.3)	6 (3.4)	6 (3.2)
LOST TO FOLLOW-UP	5 (1.3)	5 (1.3)	4 (1.0)	2 (1.1)	2 (1.1)	1 (0.5)
SUBJECT WITHDREW CONSENT	9 (2.3)	9 (2.3)	12 (3.0)	6 (3.2)	4 (2.3)	5 (2.7)
OTHER	1 (0.3)	0	0	0	0	0

Status of Censored Subjects, Overall Survival
All Randomized Subjects in Part 1

	Arm B: Nivo + Ipi N = 396	Arm A: Nivolumab N = 396	Arm C: Chemotherapy N = 397	Arm D: Nivo + Ipi N = 187	Arm G: Nivo + Chemo N = 177	Arm F: Chemotherapy N = 186
NUMBER OF DEATHS (%)	258 (65.2)	274 (69.2)	298 (75.1)	119 (63.6)	137 (77.4)	156 (83.9)
NUMBER OF SUBJECTS CENSORED (%)	138 (34.8)	122 (30.8)	99 (24.9)	68 (36.4)	40 (22.6)	30 (16.1)
STATUS OF CENSORED SUBJECTS (%)						
STILL ON TREATMENT	0	2 (0.5)	5 (1.3)	1 (0.5)	2 (1.1)	1 (0.5)
NOT PROGRESSED	0	2 (0.5)	5 (1.3)	0	2 (1.1)	1 (0.5)
PROGRESSED (1)	0	0	0	1 (0.5)	0	0
IN FOLLOW-UP	123 (31.1)	106 (26.8)	78 (19.6)	59 (31.6)	32 (18.1)	23 (12.4)
OFF STUDY	15 (3.8)	14 (3.5)	16 (4.0)	8 (4.3)	6 (3.4)	6 (3.2)
LOST TO FOLLOW-UP	5 (1.3)	5 (1.3)	4 (1.0)	2 (1.1)	2 (1.1)	1 (0.5)
SUBJECT WITHDREW CONSENT	9 (2.3)	9 (2.3)	12 (3.0)	6 (3.2)	4 (2.3)	5 (2.7)
OTHER	1 (0.3)	0	0	0	0	0

Results for sensitivity analyses using a 2-sided unstratified log-rank test were consistent with the primary OS analysis (HR 0.80; 95% CI 0.66, 0.97, p value 0.0100)

In a multivariate Cox regression, the treatment effect of nivolumab + ipilimumab vs chemotherapy when adjusted for the following baseline factors: ECOG PS, gender (male, female), and histology (SQ, NSQ) was consistent with the primary OS analysis (HR = 0.80 [97.5% CI: 0.66, 0.97], multivariate Cox model p-value: 0.0101). Baseline ECOG PS and histology were significant prognostic variables in this model for OS.

However, further analyses shown a larger effect on the OS, PFS, ORR and DOR in the subgroup of PD-L1 ≥ 50% compared with the subgroup of patients with PDL1-49%. The magnitude of effect size is also larger compared with the comparative chemotherapy group, except for the overall survival in the PD-L1 1-49%. This subgroup shows a comparable OS for nivolumab + ipilimumab and chemotherapy is comparable.

Table: Efficacy by PD-L1 Expression for Nivolumab + Ipilimumab vs Chemotherapy in CA209227 for subgroup of patients with PD-L1 ≥ 1% i.e PD-l1 1-49% vs PD-L1 ≥ 50%

	PD-L1 1-49%		**PD-L1 ≥ 50%**	
	Nivolumab + ipilimumab N = 191	**Chemo N = 205**	**Nivolumab + ipilimumab N = 205**	**Chemo N = 192**
OS				
HR (97.5% CI)	0.94 (0.73, 1.22)		0.70 (0.53, 0.93)	
Events, n (%)	142 (74.3)	161 (78.5)	116 (56.6)	137 (71.4)
Median (95% CI), mo.	15.08 (12.16, 18.66)	15.08 (13.34, 17.54)	21.19 (15.51, 38.18)	13.96 (10.05, 18.60)
PFS				
HR (97.5% CI)	1.15 (0.89, 1.50)		0.62 (0.47, 0.82)	
Events, n (%)	151 (79.1)	142 (69.3)	137 (66.8)	144 (75.0)
Median (95% CI), mo.	4.01 (2.99, 5.52)	5.49 (4.37, 5.82)	6.74 (4.53, 11.01)	5.59 (4.57, 6.60)
Responders (%)	51 (26.7)	51 (24.9)	91 (44.4)	68 (35.4)
95% CI	(20.6, 33.6)	(19.1, 31.4)	(37.5, 51.5)	(28.7. 42.6)
DoR per BICR				

Median (95% CI), mo.	12.22 (6.14, 16.07)	7.59 (6.24, 12.45)	31.84 (18.66, N.A.)	5.75 (4.47, 6.90)

1. Abbreviations: BICR: blinded independent central review; chemo: chemotherapy; DoR: duration of response; HR: hazard ratio; nivolumab + ipilimumab: nivolumab + ipilimumab; ORR: objective response rate; OS: overall survival

2. Source: (OS), Figure S.5.120.5.309 (PFS), Figure S.5.326.4 (ORR), Table S.5.128.2 (PD-L1 < 1% DoR), Table S.5.7.2 (PD-L1 ≥ 1 % DoR), Table S.5.500.12 (PD-L1 1-49% DoR), Table S.5.128.1 (PD-L1 ≥ 50% DoR) of the CA209227 Part 1 Final CSR

The Applicant's table abbreviated

The applicant further investigated the demographic and baseline characteristics in the complementary subgroups of PD-L 1 ≥ 1%. The subgroup of patient with PD-L1 1-49% included 396 and the subgroup of PD-L1 ≥ 50% a total of 397 patients. No obvious imbalances in known prognostic factors were observed.

Furthermore, the effect of the OS by incremental cut of points for PD-L1 expression was explored. Overall these results did not show a consistent improvement if the PD-L1 expression was increased, but the overall number of patients in each group were small. No significant differences were observed.

Two other phase II studies (CA 209568 and CA 209817) supported the finding of the pivotal study CA 209227: they showed also a lower efficacy of nivolumab + ipilimumab in the subgroup with PD-L1-49 compared with PD-L1 50. This effect was seen for the OS, PFS , OR and DoR. However, they lack the comparison with chemotherapy and as such will not be conclusive. Nevertheless they do show that numerically larger effect might be observed in patients with high PD-L1 expression.

The subgroup analyses in part 1A showed overall larger responses for the SQ population compared with the NSQ population. In the SQ population, the largest improvement of OS and ORR was observed, although this was not supported with an improvement in PFS over chemotherapy.

The observed improvement is OS was about 5.55 months for SQ population (0.69 (0.50, 0.96)), and 2.22 months (HR 0.85 (0.67, 1.08)) for the NSQ population.

The observed improvement for the OS is modest for the NSQ population but can be regarded as clinically relevant for the NSQ population.

Secondary endpoints seem to support the benefit of the combination over chemotherapy. PFS per BICR (HR = 0.82 [97.5% CI: 0.67, 0.99]), ORR per BICR (35.9% vs 30.0%), CR rate (5.8% vs 1.8%), and median DoR (23.16 vs 6.24 months).

In the Part1B of the study, Nivolumab + ipilimumab showed an improvement in OS compared with chemotherapy alone: HR = 0.62 (97.5% CI: 0.47, 0.81); stratified log-rank descriptive p-value < 0.0001. However, this analysis was not part of the hierarchical testing strategy and there was not adjustment for multiplicity. So, conclusions from this analysis should be considered exploratory in nature.

On analysing the OS curves for the combination vs chemotherapy it is noted the overlapping curves for the immune combo regardless of the cutoff of 1% in PD-L1 expression, whereas the chemotherapy curves are clearly different with a poorer performance in the PD-L1 < 1%. This fact is probably reflecting the better benefit for those patients treated with second line checkpoint inhibitors in the context of a positivity in terms of PD-L1 expression. Indeed, the reports median OS data for the chemotherapy arm in the PD-L1 <1% is in line with previous data obtained before the approval of second line immunotherapy (9-12 months), while the observed OS data for the PD-L1 > 1% is larger (14.9 months). Also the percentage of patients using immunotherapy as subsequent therapy was lower in the chemotherapy arm of Part1B as compared to same arm in Part1A.

The effect of the combination of nivolumab+Ipilimumab in the Part1B is also observed in PFS as compared to chemotherapy (HR = 0.75 (97.5% CI: 0.57,0.99). However, the positive trend of the

combo seems to be lost in antitumor activity (ORR) (nivolumab +ipilimumab (Arm D: 27.3%; 21.0, 34.3); nivolumab + chemotherapy (Arm G: 37.9%; 30.7, 45.4); chemotherapy (Arm G: 23.1%; 17.3, 29.8)

Regarding the contribution of the monocomponents, the data shows that for the overall group, the OS, PFS, ORR, DOR show numerical improvement with the combination nivolumab + ipilimumab therapy compared to the monotherapy nivolumab. These improvements show the contributively effect of ipilimumab.

The Kaplan-Meier curves for the OS and PFS are indicating that a subgroup of patients is at risk for an earlier disease progression/death. Apparently, using an age cut-off at 65 years showed a signal that the combinations of age and having pretreatment Grade ⩾ 3 or not could be important to predict for which patients chemotherapy would be advised instead of nivolumab+ipilimumab to prevent early death. Kaplan-Meier curves for the corresponding subgroups should be provided, or, at least, the group "<65 year and baseline Grade ⩾ 3 events" versus the rest should be provided. To further investigate the sensitivity of this interaction, the estimates of a model using an age cut-of at 75 years should be provided

2) In the subpopulation of patients considered TMB evaluable and with a cutoff > 10 mut/Mb, and pooling the arms B+D, the combination of nivolumab and ipilimumab provides a longer PFS than those subjects treated with chemotherapy alone. The HR of 0.58 (97.5% CI: 0.41, 0.81) is statistically significant, which in terms of medians is translated in a gain of almost 2 months (1.75 months), that is likely not capturing the benefit observed in the whole Kaplan Meier plot. On the other hand, in the complementary subgroup of patients (those with TMB < 10 mut/Mb) the HR does not seem to point out a benefit for the combination of immunotherapy (HR 1.07 CI 0.81-1.40).

The cut-off chosen of 10 mut/Mb was mainly based on data from study CA209568 and basically upon the observation of increasing BICR-assessed ORR with increasing TMB cut-off up to 10 mut/Mb. The relationship between PD-L1 expression and TMB is not clear. Of note, the TMB evaluable population in the study CA209568 represents about 1/3 of the treated patients (98/288). Nevertheless, and due to further exploratory analyses of additionally TMB levels for nivolumab + ipilimumab versus chemotherapy in CA209227 Part 1 using updated PFS and ORR data from the 09-Jul-2018 database lock, the cut-off chosen of ≥ 10 mut/Mb is deemed sufficiently substantiated as a biomarker to select patients who derive PFS benefit from nivolumab + ipilimumab versus chemotherapy.

Updated efficacy results by TMB (10 mut/Mb cutoff) in CA209227 Part 1 based on the 02-Jul-2019 database lock were consistent with those previously reported in the responses to the first Request for Supplementary Information (RSI 1) dated 26-Jul-2018 based on the 09-Jul-2018 database lock.

Nivolumab + ipilimumab demonstrated a clinically meaningful improvement in OS compared with chemotherapy in subjects with TMB ≥ 10 mut/Mb (HR = 0.68 [97.5% CI: 0.49, 0.95]; unstratified log-rank test descriptive p value = 0.0091) and in subjects with TMB < 10 mut/Mb (HR = 0.75 [97.5% CI: 0.57, 0.97]), with similar HRs. So, these analyses seem to demonstrate that unlike prior results based on PFS and ORR, TMB at a cutoff of 10 mut/Mb did not appear to be predictive of OS benefit.

2.4.4. Conclusions on the clinical efficacy

Based on this update results, the company is seeking an all comers indication, "OPDIVO in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations (see sections 4.4 and 5.1)". However, the discussion about the acceptability of this new data and the subsequent updated indication is beyond the efficacy data reported at this stage. The validity of the data is called into question due to triggered GCP inspection findings.

2.5. Clinical safety

Introduction

The Summary of Clinical Safety presented provides safety data from Part 1 of the Phase 3 study CA209227, in which nivolumab and ipilimumab combination was used to treat chemotherapy-naïve subjects with stage IV or recurrent non-small cell lung cancer (NSCLC), versus nivolumab and platinum doublet chemotherapy. Safety data are presented for Part 1 of CA209227 with all treated subjects in the nivolumab + ipilimumab (Arms B + D, n = 576), nivolumab (Arm A, n = 391), nivolumab+chemotherapy (Arm G, n=172) and chemotherapy (Arms C + F, n = 570) groups, based database lock date of 02-Jul-2019, with a minimum follow-up of 28.3 months.

Supportive safety data have been presented from studies:

- CA209012, cohorts P (N = 38) and Q (N = 39), in which nivolumab 3 mg/kg (Q2W) + ipilimumab 1 mg/kg (Q12W in cohort P and Q6W in cohort Q) were used.
- CA209568 Part 1 (N = 288), NSCLC subjects were treated with the same nivolumab + ipilimumab regimen and schedule as that in Part 1 of the pivotal first-line study CA209227.
- CA209817 Cohort A (N=391, NSCLC subjects with recurrent or metastatic NSCLC treated with nivolumab 240 mg Q2W (flatdose) + ipilimumab 1 mg/kg Q6W.

Only data from the pivotal study CA209227 have been summarized in this AR as this is considered the main safety data set.

Table 34: BMS-Sponsored studies of nivolumab in combination with ipilimumab as first-line treatment for advanced or recurrent NSCLC –Safety population supporting the proposed indication

Study/Phase/ Status	Study Population	Design	Test Drugs and Dose	Safety Population/Number of Treated Subjects
Pivotal Phase 3 Study for Nivolumab in Combination with Ipilimumab in Subjects with TMB ≥ 10 mut/Mb				
CA209227 Phase 3 **Part 1** Completed for TMB PFS co-primary objective in Part 1; Ongoing for PD-L1 ≥ 1% OS co-primary objective in Part 1a (Part 1 DBL: 24-Jan-2018) **Part 2** ongoing	Previously untreated NSCLC Patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	**Part 1a (PD-L1 ≥ 1%)**: nivo, nivo + ipi, or chemo (1:1:1 randomization; SQ vs NSQ stratification). **Part 1b (PD-L1 < 1%)**: nivo+ipi, nivo+chemo or chemo (1:1:1 randomization; SQ vs NSQ stratification).	•Nivo 240 mg Q2W •Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W •Platinum-doublet chemo in 3-wk cycles for a maximum of 4 cycles ± pemetrexed maintenance •Nivo 360 mg + platinum-doublet chemo Q3W, up to 4 doses, followed by nivo 360 mg Q3W ± pemetrexed maintenance	**Part 1**: 1537 treated in Nivo + ipi arms: 576 treated (135 TMB ≥ 10 mut/Mb) Nivo arm: 391 treated Chemo arms: 570 treated (159 TMB ≥ 10 mut/Mb)
Supportive Phase 1 Study for Nivolumab in Combination with Ipilimumab (Dose Selection)				
CA209012 Phase 1 **Nivo + Ipi Cohorts** Completed (DBL: 19-Sep-2016)	Chemotherapy-naive NSCLC regardless of PD-L1 expression Patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	Multiple cohorts including cohorts of nivo+ipi	Cohorts with various regimens of nivo+ipi (Cohorts G-J, N-Q) Cohort P: nivo 3 mg/kg Q2W + ipi 1 mg/kg Q12W Cohort Q: nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	**nivo 3 mg/kg + ipi 1 mg/kg**: 77 treated in Cohort P: 38 treated Cohort Q: 39 treated
Supportive Phase 2 Study for Nivolumab in Combination with Ipilimumab in Subjects with TMB ≥ 10 mut/Mb				
CA209568 Phase 2 **Part 1** Completed (Part 1 DBL: 25-Aug-2017) **Part 2** ongoing	Previously untreated NSCLC Patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	**Part 1** Nivo + ipi (regardless of PD-L1 expression)	Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	**Part 1**: 288 treated (48 TMB ≥ 10 mut/Mb)

Abbreviations: ALK: anaplastic lymphoma kinase; chemo: platinum-doublet chemo; DBL: database lock; EGFR: epidermal growth factor receptor; ipi: ipilimumab; Mb: megabase; mut: mutation; nivo: nivolumab; NSQ: non-squamous; PD-L1: programmed cell death ligand 1; SQ: squamous; QxW: every x weeks; TMB: tumour mutational burden

Source: Refer to the CA209227 Part 1 Interim CSR, the CA209012 Nivo + Ipi Final CSR, and the CA209568 Part 1 Final CSR.

Patient exposure

In Part 1 of CA209227, the last subject was randomized on 06-Jan-2017 and last patient last visit date (clinical cut-off) for this report occurred on 15-May-2019, providing a minimum follow-up of 28.3 months for all subjects in Part 1.

In all treatment arms, the most frequent reasons for discontinuation were disease progression (55.7%), completed treatment (14.2%) and study drug toxicity (13.8%). The overall rates of discontinuation were:

- Nivolumab + ipilimumab (Arms B + D, discontinuation of both nivolumab and ipilimumab): 99.8% (100% in PD-L1 ≥ 1% subjects [Part 1a] and99.5% in PD-L1 < 1% subjects [Part 1b]; 1 subject in Arm D was counted as still on treatment because site did not enter an off-treatment date, although study treatment was discontinued when subject reached the 2-year limit.))
- Nivolumab (Arm A): 99.5% (2 subjects were counted as still on treatment because site did not enter off-treatment dates, although last dose of medication was received each subject reached the 2-year limit.)
- Nivolumab + chemotherapy (Arm G): 98.8%
- Chemotherapy (Arms C + F): 98.9% (98.7% in PD-L1 ≥ 1% subjects [Part 1a] and 99.5% in PD-L1 < 1% subjects [Part 1b])

In Part 1 of CA209227, the proportion of subjects who received ≥ 90% of the planned dose intensity was as follows:

- Nivolumab + ipilimumab (Arms B + D): 73.6% for the nivolumab dose and 87.2% for the ipilimumab dose
    - PD-L1 ≥ 1% (Part 1a): 72.7% for the nivolumab dose and 86.7% for the ipilimumab dose
    - PD-L1 < 1% (Part 1b): 75.7% for the nivolumab dose and 88.1% for the ipilimumab dose
- Nivolumab (Arm A): 79.8%
- Nivolumab + chemotherapy (Arm G)-treated subjects: 81.4% of the nivolumab dose, 42.5% for gemcitabine, 83.0% for cisplatin, 71.5% for carboplatin, 72.7% for pemetrexed
- Chemotherapy (Arms C + F): 44.7% of the gemcitabine dose, 78.3% for cisplatin, 67.2% for carboplatin, 72.9% for pemetrexed.
    - PD-L1 ≥ 1% (Part 1a): 49.1% of the gemcitabine dose, 77.5% for cisplatin, 66.5% for carboplatin, 73.4% for pemetrexed
    - PD-L1 < 1% (Part 1b): 33.3% of the gemcitabine dose, 79.7% for cisplatin, 69.5% for carboplatin, 71.7% for pemetrexed

Per protocol, chemotherapy was to be given up to 4 cycles (12 weeks); hence, most subjects with chemotherapy were off treatment after 3 months, except those on pemetrexed maintenance therapy.

The median (95% CI) duration of therapy was as follows:

- Nivolumab + ipilimumab (Arms B + D): 4.19 (3.71, 5.09) months
    - PD-L1 ≥ 1% (Arm B): 4.24 (3.68, 5.22) months
    - PD-L1 < 1% (Arm D): 3.98 (2.99, 5.03) months
- Nivolumab (Arm A): 4.63 (3.75, 5.22) months
- Nivolumab + chemotherapy (Arm G)-treated subjects: 5.82 (4.90, 7.16) months
- Chemotherapy (Arms C + F): 2.63 (2.56, 2.79) months.
    - PD-L1 ≥ 1% (Arm C): 2.66 (2.56, 2.83) months
    - PD-L1 < 1% (Arm F): 2.60 (2.33, 3.25) months

A total of 64.3% of chemotherapy-treated subjects (Arms C + F) received pemetrexed maintenance therapy (66.1% in Arm C, 60.9% in Arm F and 72.7% in arm G (combination with nivolumab).

A small proportion of subjects had at least one dose infusion interruption:

- Nivolumab + ipilimumab (Arms B + D): 4.5% nivolumab, 0.3% ipilimumab
    - PD-L1 ≥ 1% (Arm B): 5.1% nivolumab, 0.3% ipilimumab
    - PD-L1 < 1% (Arm D): 3.2% nivolumab, 0.5% ipilimumab
- Nivolumab (Arm A): 7.4%
- Nivolumab + chemotherapy (Arm G): 4.7% nivolumab, 5% gemcitabine, 0% cisplatin, 0.9% carboplatin, 0% pemetrexed.
- Chemotherapy (Arms C + F): 1.2% gemcitabine, 1.9% cisplatin, 0.5% carboplatin, 1.2% pemetrexed.
    - PD-L1 ≥ 1% (Arm C): 1.7% gemcitabine, 2.2% cisplatin, 0.8% carboplatin, 1.5% pemetrexed.
    - PD-L1 < 1% (Arm F): 0% gemcitabine, 1.4% cisplatin, 0% carboplatin, 0.7 % pemetrexed.

The proportion of subjects who had at least one infusion rate reduction were as follows:

- Nivolumab + ipilimumab (Arms B + D): 6.8% nivolumab, 2.3% ipilimumab
    - PD-L1 ≥ 1% (Arm B): 7.2% nivolumab, 2.6% ipilimumab
    - PD-L1 < 1% (Arm D): 5.9% nivolumab, 1.6% ipilimumab
- Nivolumab (Arm A): 7.9%
- Nivolumab + chemotherapy (Arm G): 7.0% nivolumab, 7.5% gemcitabine, 6.2% cisplatin, 7.1% carboplatin, 7.6% pemetrexed.
- Chemotherapy (Arms C + F): 6.8% gemcitabine, 2.4% cisplatin, 3.7% carboplatin, 3.7% pemetrexed.
    - PD-L1 ≥ 1% (Arm C): 6.0% gemcitabine, 3.6% cisplatin, 2.7% carboplatin, 3.0% pemetrexed
    - PD-L1 < 1% (Arm F): 8.9% gemcitabine, 0% cisplatin, 5.1% carboplatin, 5.1% pemetrexed

Dose delays of study drug were reported as follows (proportion of subjects with at least 1 dose delay), with the most common cause of dose delay for all drugs being AE:

- Nivolumab + ipilimumab (Arms B + D): 543.5% nivolumab, 41.3% ipilimumab
    - PD-L1 ≥ 1% (Arm B): 54.5% nivolumab, 41.4% ipilimumab
    - PD-L1 < 1% (Arm D): 51.4% nivolumab, 41.1% ipilimumab
- Nivolumab (Arm A): 47.3%
- Nivolumab + chemotherapy arm (Arm G): 62.8% nivolumab, 40.0% gemcitabine, 24.6% cisplatin, 31.3% carboplatin, and 57.6% pemetrexed
- Chemotherapy (Arms C + F): 43.5% gemcitabine, 27.5% cisplatin, 38.1% carboplatin, 49.6% pemetrexed.

- PD-L1 ≥ 1% (Arm C): 42.2% gemcitabine, 27.5% cisplatin, 37.7% carboplatin, 50.2% pemetrexed
- PD-L1 < 1% (Arm F): 46.7% gemcitabine, 27.5% cisplatin, 39.0% carboplatin, 47.8% pemetrexed

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

- Nivolumab + chemotherapy arm (Arm G): 30.0% gemcitabine, 4.6% cisplatin, 32.1% carboplatin, 11.4% pemetrexed
- Chemotherapy arms (C+F):
  - Chemotherapy Arm C: 29.3% gemcitabine, 13.8% cisplatin, 36.5% carboplatin, 12.5% pemetrexed
  - Chemotherapy Arm F: 22.2% gemcitabine, 5.8% cisplatin, 29.7% carboplatin, 18.1% pemetrexed

Table 35: Dose delay summary: nivolumab + ipilimumab and chemotherapy – All treated subjects in Part 1 (updated table 02-Jul-2019 Database lock)

	Nivo + Ipi (Arm B + D)		Chemotherapy (Arm C + F)			
	Nivolumab N = 576	Ipilimumab N = 576	Gemcitabine N = 161	Cisplatin N = 207	Carboplatin N = 378	Pemetrexed N = 409
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	308 (53.5)	238 (41.3)	70 (43.5)	57 (27.5)	144 (38.1)	202 (49.4)
NUMBER OF DOSES DELAYED PER SUBJECT						
0	268 (46.5)	338 (58.7)	91 (56.5)	150 (72.5)	234 (61.9)	207 (50.6)
1	154 (26.7)	136 (23.6)	57 (35.4)	47 (22.7)	108 (28.6)	111 (27.1)
2	73 (12.7)	57 (9.9)	10 (6.2)	6 (2.9)	28 (7.4)	41 (10.0)
3	35 (6.1)	24 (4.2)	3 (1.9)	4 (1.9)	8 (2.1)	25 (6.1)
>=4	46 (8.0)	21 (3.6)	0	0	0	25 (6.1)
TOTAL NUMBER DOSES DELAYED/ TOTAL NUMBER DOSES RECEIVED (%) (A)	635/8546 (7.4)	427/2577 (16.6)	86/842 (10.2)	71/484 (14.7)	188/893 (21.1)	424/3266 (13.0)
REASON FOR DOSE DELAY (B)						
ADVERSE EVENT	412 (64.9)	218 (51.1)	73 (84.9)	55 (77.5)	161 (85.6)	296 (70.3)
OTHER	217 (34.2)	171 (40.0)	11 (12.8)	16 (22.5)	25 (13.3)	121 (28.5)
NOT REPORTED	6 (0.9)	38 (8.9)	2 (2.3)	0	2 (1.1)	5 (1.2)
LENGTH OF DELAY (B)						
4 - 7 DAYS	248 (39.1)	187 (43.8)	59 (68.6)	44 (62.0)	122 (64.9)	267 (63.0)
8 - 14 DAYS	201 (31.7)	128 (30.0)	21 (24.4)	17 (23.9)	50 (26.6)	104 (24.5)
15 - 42 DAYS	162 (25.5)	96 (22.2)	6 (7.0)	10 (14.1)	16 (8.5)	53 (12.5)
> 42 DAYS	24 (3.8)	17 (4.0)	0	0	0	0

A dose is considered delayed if the delay is exceeding 3 days from previous dose for any given study medication
(A) Total number doses received is excluding first dose.
(B) Percentages are computed out of the total number of doses delayed
Program Source: /opt/sfs001/prd/bms231196/stats/plface/prog/tables/rt-ex-delay.sas 23JUL2019:23:18:32

Adverse events

Table 36: Safety results - Treated subjects in CA209227 Part 1 (updated table 02-Jul-2019 Database lock)

Safety Parameters	Nivolumab + Ipilimumab (Arms B + D) (N = 576)		Nivolumab (Arm A) (N = 391)		Nivolumab+Chemotherapy (Arm G) (N = 172)		Chemotherapy (Arms C + F) (N = 570)	
Deaths	372 (64.6)		270 (69.1)		134 (77.9)		445 (78.1)	
Disease	304 (52.8)		219 (56.0)		115 (66.9)		364 (63.9)	
Due to Study Drug Toxicity[a]	8 (1.4)		2 (0.5)		4 (2.3)		6 (1.1)	
Unknown	14 (2.4)		12 (3.1)		4 (2.3)		27 (4.7)	
Other	46 (8.0)		37 (9.5)		11 (6.4)		48 (8.4)	
	Adverse Event Grades							
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All Causality SAEs	355 (61.6)	259 (45.0)	207 (52.9)	142 (36.3)	91 (52.9)	71 (41.3)	228 (40.0)	164 (28.8)
Drug-related SAEs	141 (24.5)	106 (18.4)	44 (11.3)	32 (8.2)	36 (20.9)	33 (19.2)	79 (13.9)	61 (10.7)
All Causality AEs leading to DC	190 (33.0)	141 (24.5)	94 (24.0)	68 (17.4)	42 (24.4)	27 (15.7)	122 (21.4)	72 (12.6)
Drug-Related AEs leading to DC	104 (18.1)	71 (12.3)	48 (12.3)	28 (7.2)	22 (12.8)	13 (7.6)	52 (9.1)	28 (4.9)
All Causality AEs	568 (98.6)	360 (62.5)	385 (98.5)	208 (53.2)	172 (100.0)	121 (70.3)	554 (97.2)	311 (54.6)
Drug-related AEs	442 (76.7)	189 (32.8)	256 (65.5)	76 (19.4)	159 (92.4)	96 (55.8)	467 (81.9)	205 (36.0)
≥ 15% Drug-related AEs in Any Treatment arm								
Rash	98 (17.0)	9 (1.6)	43 (11.0)	3 (0.8)	26 (15.1)	1 (0.6)	30 (5.3)	0
Diarrhea	98 (17.0)	10 (1.7)	49 (12.5)	2 (0.5)	17 (9.9)	2 (1.2)	55 (9.6)	4 (0.7)
Fatigue	83 (14.4)	10 (1.7)	44 (11.3)	2 (0.5)	43 (25.0)	8 (4.7)	108 (18.9)	8 (1.4)
Decreased Appetite	76 (13.2)	4 (0.7)	26 (6.6)	0	39 (22.7)	4 (2.3)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	24 (6.1)	1 (0.3)	67 (39.0)	4 (2.3)	206 (36.1)	12 (2.1)
Vomiting	28 (4.9)	2 (0.3)	11 (2.8)	1 (0.3)	26 (15.1)	4 (2.3)	77 (13.5)	13 (2.3)
Constipation	26 (4.5)	0	6 (1.5)	0	38 (22.1)	0	85 (14.9)	2 (0.4)
Anemia	22 (3.8)	8 (1.4)	11 (2.8)	2 (0.5)	70 (40.7)	30 (17.4)	188 (33.0)	66 (11.6)
Neutrophil count decreased	4 (0.7)	0	0	0	27 (15.7)	17 (9.9)	64 (11.2)	36 (6.3)
Neutropenia	1 (0.2)	0	1 (0.3)	0	41 (23.8)	23 (13.4)	98 (17.2)	54 (9.5)
All Causality Select AEs								
Endocrine	151 (26.2)	27 (4.7)	57 (14.6)	3 (0.8)	22 (12.8)	1 (0.6)	13 (2.3)	1 (0.2)
Gastrointestinal	145 (25.2)	18 (3.1)	87 (22.3)	4 (1.0)	41 (23.8)	4 (2.3)	94 (16.5)	5 (0.9)
Hepatic	126 (21.9)	56 (9.7)	70 (17.9)	29 (7.4)	31 (18.0)	10 (5.8)	68 (11.9)	7 (1.2)
Pulmonary	49 (8.5)	19 (3.3)	34 (8.7)	6 (1.5)	8 (4.7)	3 (1.7)	10 (1.8)	5 (0.9)
Renal	56 (9.7)	7 (1.2)	21 (5.4)	6 (1.5)	22 (12.8)	2 (1.2)	40 (7.0)	3 (0.5)
Skin	240 (41.7)	29 (5.0)	116 (29.7)	5 (1.3)	62 (36.0)	3 (1.7)	81 (14.2)	1 (0.2)
Hypersensitivity/Infusion Reactions	29 (5.0)	1 (0.2)	18 (4.6)	2 (0.5)	6 (3.5)	1 (0.6)	7 (1.2)	1 (0.2)
Drug-Related Select AEs								
Endocrine	137 (23.8)	24 (4.2)	51 (13.0)	2 (0.5)	18 (10.5)	1 (0.6)	1 (0.2)	0
Gastrointestinal	105 (18.2)	14 (2.4)	50 (12.8)	4 (1.0)	20 (11.6)	3 (1.7)	57 (10.0)	4 (0.7)
Hepatic	91 (15.8)	47 (8.2)	42 (10.7)	15 (3.8)	21 (12.2)	5 (2.9)	42 (7.4)	2 (0.4)
Pulmonary	48 (8.3)	19 (3.3)	30 (7.7)	6 (1.5)	8 (4.7)	3 (1.7)	7 (1.2)	4 (0.7)
Renal	25 (4.3)	4 (0.7)	6 (1.5)	3 (0.8)	14 (8.1)	1 (0.6)	29 (5.1)	2 (0.4)
Skin	196 (34.0)	24 (4.2)	83 (21.2)	4 (1.0)	49 (28.5)	2 (1.2)	55 (9.6)	0
Hypersensitivity/Infusion Reactions	23 (4.0)	0	17 (4.3)	2 (0.5)	4 (2.3)	1 (0.6)	6 (1.1)	1 (0.2)
All Causality IMAEs within 100 days of last dose Treated with Immune Modulating Medication								
Diarrhea/Colitis	48 (8.3)	17 (3.0)	18 (4.6)	3 (0.8)	4 (2.3)	1 (0.6)	0	0
Hepatitis	46 (8.0)	37 (6.4)	16 (4.1)	14 (3.6)	3 (1.7)	3 (1.7)	1 (0.2)	1 (0.2)
Pneumonitis	50 (8.7)	23 (4.0)	24 (6.1)	8 (2.0)	10 (5.8)	5 (2.9)	3 (0.5)	1 (0.2)
Nephritis/Renal Dysfunction	6 (1.0)	2 (0.3)	4 (1.0)	3 (0.8)	2 (1.2)	2 (1.2)	1 (0.2)	1 (0.2)
Rash	106 (18.4)	21 (3.6)	30 (7.7)	3 (0.8)	17 (9.9)	2 (1.2)	6 (1.1)	0
Hypersensitivity/Infusion Reactions	4 (0.7)	0	3 (0.8)	1 (0.3)	1 (0.6)	1 (0.6)	0	0

All Causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication								
Adrenal Insufficiency	27 (4.7)	13 (2.3)	3 (0.8)	1 (0.3)	3 (1.7)	1 (0.6)	0	0
Hypophysitis	20 (3.5)	9 (1.6)	4 (1.0)	0	1 (0.6)	0	0	0
Hypothyroidism/Thyroiditis	81 (14.1)	4 (0.7)	33 (8.4)	1 (0.3)	9 (5.2)	0	1 (0.2)	0
Hyperthyroidism	50 (8.7)	0	15 (3.8)	0	6 (3.5)	0	2 (0.4)	1 (0.2)
Diabetes Mellitus	6 (1.0)	5 (0.9)	2 (0.5)	2 (0.5)	1 (0.6)	1 (0.6)	0	0
All-causality OESIs within 100 days of last dose With or Without Immune Modulating Medication								
Myasthenic Syndrome	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Pancreatitis	6 (1.0)	4 (0.7)	0	0	0	0	0	0
Uveitis	2 (0.3)	0	0	0	0	0	0	0
Encephalitis	2 (0.3)	2 (0.3)	0	0	0	0	0	0
Myocarditis	2 (0.3)	2 (0.3)	0	0	1 (0.6)	0	0	0
Myositis	2 (0.3)	1 (0.2)	2 (0.5)	2 (0.5)	1 (0.6)	0	1 (0.2)	0
Rhabdomyolysis	1 (0.2)	1 (0.2)	0	0	0	0	0	0

[a] **Nivolumab + ipilimumab arms**: myocarditis, acute tubular necrosis, pneumonitis [4 subjects], circulatory collapse [shock], and cardiac tamponade; **nivolumab arm**: pneumonitis and neutropenia/sepsis; **nivolumab + chemotherapy arm**: hypovolemic shock, pulmonary embolism, respiratory failure, pancytopenia; **chemotherapy arms**: sepsis (2 subjects), multiple brain infarctions, interstitial lung disease, thrombocytopenia, and febrile neutropenia with sepsis

MedDRA version 22.0; CTC version 4.0.

All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Abbreviations: AEs - adverse events, CTC - Common Toxicity Criteria, DC - discontinuation, IMAEs - immune-mediated adverse events, MedDRA - Medical Dictionary for Regulatory Activities, OESI - other events of special interest, SAEs - serious adverse events

Source: Table S.6.15.1 and Table S.6.15.3 (deaths), Table S.6.18.1.1 and Table S.6.18.3.1 (all causality SAEs), Table S.6.18.1.3 and Table S.6.18.3.3 (drug-related SAEs), Table S.6.23.1.1 and Table S.6.23.3.1 (all causality AEs leading to DC), Table S.6.23.1.2 and Table S.6.23.3.2 (drug-related AEs leading to DC), Table S.6.2.1 and Table S.6.2.3 (all causality AEs), Table S.6.3.1 and Table S.6.3.3.1 (drug-related AEs), Table S.6.101.1.1 and Table S.6.101.3.1 (all causality select AEs), Table S.6.101.1.2 and Table S.6.101.3.2 (drug-related select AEs), Table S.6.105.1.1 and Table S.6.105.3.1 (all causality endocrine select AEs), Table S.6.105.1.2 and Table S.6.105.3.2 (drug-related endocrine select AEs), Table S.6.204.1 and Table S.6.204.3 (all causality endocrine IMAEs), Table S.6.202.1 and Table S.6.202.3 (all causality IMAEs with exception of endocrine), and Table S.6.300.1.1 and Table S.6.300.2.1 (OESIs)

Common adverse events

Any-grade AEs (regardless of causality) were reported in 568 (98.6%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 385 (98.5%) subjects in the nivolumab arm (Arm A), 172 (100%) in the nivolumab+chemotherapy arm (Arm G) and 554 (97.2%) subjects in the chemotherapy arms (Arms C + F).

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

- Nivolumab + ipilimumab (Arms B + D): decreased appetite (30.9%), fatigue (25.0%), dyspnoea (24.8%), diarrhea (24.1%), asthenia (21.5%), rash (20.7%), nausea (20.7%) and pruritis (20.0%)
    - PD-L1 ≥ 1% (Arm B): decreased appetite (30.9%), fatigue (27.4%), dyspnoea (24.8%), diarrhoea (23.8%), asthenia (21.7%), rash (22.8%), nausea (21.7%) and pruritis (22.8%)
    - PD-L1 < 1% (Arm D): decreased appetite (30.8%), fatigue (20.0%), dyspnoea (24.9%), diarrhoea (24.9%), asthenia (21.1%), rash (16.2%), nausea (18.4%) and pruritis (14.1%)
- Nivolumab (Arm A): dyspnoea (23.0%), decreased appetite (22.5%), fatigue (22.3%), diarrhoea (22.0%), cough (20.2%) and asthenia (19.7%)
- Nivolumab + Chemotherapy (Arm G): Anaemia (48.3%), nausea (45.9%), constipation (35.5%), decreased appetite (34.9%) fatigue (31.4%), neutropenia (26.2%), cough (25.6%), Diarrhoea (22.1%), dyspnoea (21.5%) and Asthenia (20.3%).
- Chemotherapy (Arms C + F): nausea (42.1%), anaemia (40.0%), constipation (26.8%), decreased appetite (26.0%), and fatigue (24.9%)
    - PD-L1 ≥ 1% (Arm C): nausea (44.2%), anemia (39.5%), constipation (26.1%), decreased appetite (26.4%), and fatigue (25.3%)
    - PD-L1 < 1% (Arm F): nausea (37.7%), anemia (41.0%), constipation (28.4%), decreased appetite (25.1%), and fatigue (24.0%)

Any-grade drug-related AEs were reported in 442 (76.7%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 256 (65.5%) subjects in the nivolumab arm (Arm A), 159 (92.4%) in the nivolumab+chemotherapy arm (Arm G) and 467 (81.9%) subjects in the chemotherapy arms (Arms C + F).

The most frequently reported drug-related AEs were:

- Nivolumab + ipilimumab: rash and diarrhea (17.0% each), fatigue (14.4%), pruritus (14.2%), decreased appetite (13.2%), and hypothyroidism (12.5%)
    - PD-L1 ≥ 1% (Arm B): rash (18.7), diarrhea (17.9%), fatigue (14.3%), pruritus (15.9%), decreased appetite (13.6%), and hypothyroidism (14.3%)
    - PD-L1 < 1% (Arm D): rash (13.5), diarrhea (15.1%), fatigue (14.6%), pruritus (10.8%), decreased appetite (12.4%), and hypothyroidism (10.3%)
- Nivolumab: diarrhoea (12.5%), rash (11.0%), fatigue (11.3%), pruritus (8.2%), increased ALT (7.9%), and asthenia (7.7%)
- Nivolumab + chemotherapy: anaemia (40.7%), nausea (39.0%), fatigue (25.0%), and neutropenia (23.8%), decreased appetite (22.7%), and constipation (22.1%)
- Chemotherapy: nausea (36.1%), anemia (33.0%), decreased appetite (19.6%), and fatigue (18.9%)
    - PD-L1 ≥ 1% (Arm C): nausea (37.5%), anaemia (32.3%), decreased appetite (18.9%), and fatigue (19.1%)
    - PD-L1 < 1% (Arm F): nausea (33.3%), anaemia (34.4%), decreased appetite (21.3%), and fatigue (18.6%)

Grade 3-4 adverse events

Grade 3-4 AEs (regardless of causality) were reported in 360 (62.5%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 208 (53.2%) subjects in the nivolumab arm (Arm A), 121 (70.3%) in the nivolumab+chemotherapy arm (Arm G) and 311 (54.6%) subjects in the chemotherapy arms (Arms C + F). The most frequently reported Grade 3-4 AEs (regardless of causality) were:

- Nivolumab + ipilimumab (Arms B + D): malignant neoplasm progression (11.8%), hyponatraemia (5.6%), pneumonia (5.2%) , lipase increased (5.4%), and increased amylase (4.4%), increased ALT and dyspnoea(4%
    - PD-L1 ≥ 1% (Arm B): malignant neoplasm progression (12%), hyponatraemia (5.6%), pneumonia (5.6%), lipase increased (4.3%), and increased amylase (3.3%), increased ALT (4.6%), dyspnoea (4.3%)
    - PD-L1 < 1% (Arm D): malignant neoplasm progression (11.4%), hyponatraemia (5.4%), pneumonia (4.3%), lipase increased (7.6%), and increased amylase (5.4%), increased ALT (2.7%) and dyspnoea (3.2%)
- Nivolumab (Arm A): malignant neoplasm progression (10.7%), pneumonia (5.4%), increased lipase (4.3%), dyspnoea (3.3%), and hyponatremia (3.1%)
- Nivolumab + Chemotherapy (Arm G): anemia (20.9%), neutropenia (15.1%), neutrophil count decreased (9.9%), malignant neoplasm progression (8.1%), and white blood cell count decreased (5.2%)

- Chemotherapy (Arms C + F): anemia (13.9%), malignant neoplasm progression (10%) neutropenia (10.7%), neutrophil count decreased (6.7%), thrombocytopenia (4.3%) and platelet count decreased (4%)
    - PD-L1 ≥ 1% (Arm C): anaemia (12.4%), malignant neoplasm progression (7.5%) neutropenia (8.8%), neutrophil count decreased (7.5%), thrombocytopenia (5.2%) and platelet count decreased (3.1%)
    - PD-L1 < 1% (Arm F): anaemia (15.3%), malignant neoplasm progression (4.4%) neutropenia (12.6%), neutrophil count decreased (4.9%), thrombocytopenia (3.3%) and platelet count decreased (4.9%)

Grade 3-4 drug-related AEs were reported in 189 (32.8%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 76 (19.4%) subjects in the nivolumab arm (Arm A), 96 (55.8%) in the nivolumab+chemotherapy arm (Arm G) and 205 (36.0%) subjects in the chemotherapy arms (Arms C + F). The most frequently reported Grade 3-4 drug-related AEs were:

- Nivolumab + ipilimumab (Arms B + D): Lipase increased (4.0%), AST increased (3.1%), ALT increased (3.3%), amylase increased (3.0%) and pneumonitis (2.8%),
    - PD-L1 ≥ 1% (Arm B): Lipase increased (3.3%), AST increased (3.6%), ALT increased (3.8%), amylase increased (2.6%), pneumonitis (3.6%)
    - PD-L1 < 1% (Arm D): Lipase increased (5.4%), AST increased (3.8%), ALT increased (3.2%), amylase increased (4.3%), pneumonitis (2.2%).
    -
- Nivolumab (Arm A): Lipase increased (3.6%), amylase increased (2.3%), ALT increased (1.5%), AST increased (1.3%), pneumonitis (1.3%).

- Nivolumab + Chemotherapy (Arm G): anaemia (17.4%), neutropenia (13.4%), neutrophil count decreased (9.9%), platelet count decreased (6.4%), white blood cell count decreased (5.2%).

- Chemotherapy (Arms C + F): anaemia (11.6%), neutropenia (9.5%), neutrophil count decreased (6.3%), thrombocytopenia (4.4%), platelet count decreased (3.7%)

    - PD-L1 ≥ 1% (Arm C): anaemia (10.9%), Neutropenia (8.5%), neutrophil count decreased (7.0%), platelet count decreased (3.4%), thrombocytopenia (5.2%).

    - PD-L1 < 1% (Arm F): anaemia (13.7%), neutropenia (11.5%), neutrophil count decreased (4.9%), platelet count decreased (4.9%), thrombocytopenia (2.7%).

<u>Serious adverse events</u>

Any-grade SAEs (regardless of causality) were reported in 355 (61.6%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 207 (52.9%) subjects in the nivolumab arm (Arm A), 91 (52.9%) subjects in the nivolumab+chemotherapy arm (Arm G) and 228 (40.0%) subjects in the chemotherapy arms (Arms C + F). Grade 3-4 SAEs were reported in 259 (45%) subjects in the nivolumab + ipilimumab arms, 142 (36.3%) subjects in the nivolumab arm, 71 (41.3%) subjects in the nivolumab+chemotherapy arm (Arm G) and 164 (28.8%) subjects in the chemotherapy arm.

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

- Nivolumab + ipilimumab: malignant neoplasm progression (16.5%), pneumonia (6.6%), pneumonitis (4.2%), diarrhoea (2.4%), and adrenal insufficiency and pulmonary embolism (2.3% each)
    - PD-L1 ≥ 1% (Arm B): malignant neoplasm progression (17.1%), pneumonia (6.6%), pneumonitis (4.6%), diarrhoea (1.3%), and adrenal insufficiency (2.3%) and pulmonary embolism (2.8%)
    - PD-L1 < 1% (Arm D): malignant neoplasm progression (15.1%), pneumonia (6.5%), pneumonitis (3.2%), diarrhoea (4.9%), and adrenal insufficiency (2.2%) and pulmonary embolism (1.1%)
- Nivolumab: malignant neoplasm progression (16.4%), pneumonia (6.1%), pneumonitis (2.6%), and dyspnoea (1.5%)
- Nivolumab + chemotherapy: malignant neoplasm progression (14.0%), anemia and pneumonia (4.7% each), and lung infection, cellulitis, fatigue, pancytopenia, and thrombocytopenia (2.3% each)
- Chemotherapy arms: malignant neoplasm progression (7.5%), pneumonia (3.3%), anemia (2.8%), and febrile neutropenia (2.3%)
    - PD-L1 ≥ 1% (Arm C): malignant neoplasm progression (8.3%), pneumonia (3.4%), anaemia (2.1%), and febrile neutropenia (1.8%)
    - PD-L1 < 1% (Arm F): malignant neoplasm progression (6.0%), pneumonia (3.3%), anaemia (4.4%), and febrile neutropenia (3.3%)

Any-grade drug-related SAEs were reported in 141 (24.5%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 44 (11.3%) subjects in the nivolumab arm (Arm A), 36 (20.9%) subjects in the nivolumab+chemotherapy arm (Arm G) and 79 (13.9%) subjects in the chemotherapy arms (Arms C + F).

Grade 3-4 drug-related SAEs were reported in 106 (18.4%) subjects in the nivolumab + ipilimumab arms, 32 (8.2%) subjects in the nivolumab arm, 33 (19.2%) subjects in the nivolumab+chemotherapy arm (Arm G) and 61 (10.7%) subjects in the chemotherapy arm. The most frequently reported drug-related SAEs were:

- Nivolumab + ipilimumab: pneumonitis (4.2%), diarrhoea and adrenal insufficiency (2.1% each), colitis (1.7%), and hepatitis and hypophysitis (1.4% each)
    - PD-L1 ≥ 1% (Arm B): pneumonitis (4.6%), diarrhoea (1.3%), adrenal insufficiency (2.0%), colitis (2.0%), and hepatitis (0.5%) and hypophysitis (1.5%)
    - PD-L1 < 1% (Arm D): pneumonitis (3.2%), diarrhoea (3.8%) , adrenal insufficiency (2.2%), colitis (1.1%), and hepatitis (3.2%) and hypophysitis (1.1%)
- Nivolumab: pneumonitis (2.6%), colitis and hepatitis (0.8%), diarrhoea, and pericardial effusion, increased ALT and rash (0.5% each)
- Nivolumab + chemotherapy: anaemia (4.1%), thrombocytopenia (2.3%), and pneumonitis and pancytopenia (1.7% each)
- Chemotherapy: anemia (2.5%), febrile neutropenia (1.9%), vomiting (1.2%), and nausea and thrombocytopenia (1.1% each)
    - PD-L1 ≥ 1% (Arm C): febrile neutropenia (1.6%), vomiting (1.6%), and nausea (1%) and thrombocytopenia (1.3%)

- PD-L1 < 1% (Arm F): febrile neutropenia (2.7%), vomiting (0.5%), and nausea (1.1%) and thrombocytopenia (0.5%)

Deaths

As of the 02-Jul-2019 database lock, a lower proportion of treated subjects in the nivolumab + ipilimumab arms (Arms B + D) died compared with the chemotherapy arms (Arms C + F): 64.6% vs 78.1%. Disease progression was the most common cause of death in all arms.

Table 37: Death summary – Treated subjects in CA209227 Part 1 (updated table 02-Jul-2019 Database lock)

	Nivo + Ipi (Arm B + D) N = 576	Chemotherapy (Arm C + F) N = 570
NUMBER OF SUBJECTS WHO DIED (%)	372 (64.6)	445 (78.1)
PRIMARY REASON FOR DEATH (%)		
DISEASE	304 (52.8)	364 (63.9)
STUDY DRUG TOXICITY	8 (1.4)	6 (1.1)
UNKNOWN	14 (2.4)	27 (4.7)
OTHER	46 (8.0)	48 (8.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	75 (13.0)	37 (6.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	48 (8.3)	16 (2.8)
STUDY DRUG TOXICITY	5 (0.9)	5 (0.9)
UNKNOWN	2 (0.3)	5 (0.9)
OTHER	20 (3.5)	11 (1.9)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	154 (26.7)	144 (25.3)
PRIMARY REASON FOR DEATH (%)		
DISEASE	110 (19.1)	105 (18.4)
STUDY DRUG TOXICITY	7 (1.2)	6 (1.1)
UNKNOWN	6 (1.0)	9 (1.6)
OTHER	31 (5.4)	24 (4.2)
	Arm A: Nivolumab N = 391	**Arm G: Nivo + Chemo N = 172**
NUMBER OF SUBJECTS WHO DIED (%)	270 (69.1)	134 (77.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	219 (56.0)	115 (66.9)
STUDY DRUG TOXICITY	2 (0.5)	4 (2.3)
UNKNOWN	12 (3.1)	4 (2.3)
OTHER	37 (9.5)	11 (6.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	51 (13.0)	17 (9.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	31 (7.9)	9 (5.2)
STUDY DRUG TOXICITY	1 (0.3)	2 (1.2)
UNKNOWN	5 (1.3)	1 (0.6)
OTHER	14 (3.6)	5 (2.9)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	113 (28.9)	51 (29.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	79 (20.2)	38 (22.1)
STUDY DRUG TOXICITY	2 (0.5)	4 (2.3)
UNKNOWN	6 (1.5)	1 (0.6)
OTHER	26 (6.6)	8 (4.7)

Source: Table S.6.15.1 and Table S.6.15.3

20 deaths were attributed to study drug toxicity in the following arms.

- 8 (1.4%) subjects in the nivolumab + ipilimumab arms (Arms B + D): pneumonitis (4 subjects), and myocarditis, acute tubular necrosis, shock, and cardiac tamponade (1 subject each)
- 2 (0.5%) subjects in the nivolumab arm (Arm A): pneumonitis and neutropenia/sepsis (1 subject each)
- 4 (2.3%) subjects in the nivolumab + chemotherapy arm (Arm G): hypovolemic shock, pulmonary embolism, respiratory failure, and pancytopenia (1 subject each)

- 3 of the 4 deaths (the deaths due to hypovolemic shock, pulmonary embolism, and pancytopenia) were related only to chemotherapy.

- 6 (1.1%) subjects in the chemotherapy arms (Arms C + F): sepsis (2 subjects), and multiple brain infarctions, interstitial lung disease, thrombocytopenia, and febrile neutropenia with sepsis (1 subject each)

Deaths attributed to other reasons were reported in 8.0% of subjects in the nivolumab + ipilimumab arms (Arms B + D), 9.5% of subjects in the nivolumab arm (Arm A), 6.4% of subjects in the nivolumab + chemotherapy arm (Arm G), and 8.4% of subjects in the chemotherapy arms (Arms C + F).

In CA209012 Cohorts P and Q, there were no deaths attributed to study drug toxicity as of the 19-Sep-2016 database lock in subjects treated with nivolumab + ipilimumab.

In CA209568, there were 3 deaths attributed to study drug toxicity by the investigator in subjects treated with nivolumab + ipilimumab (toxicities related to an immune response, dyspnoea/hypoxia, and pneumonitis).

Select Adverse Events

Select AEs are AEs of special clinical interest that are potentially associated with the use of nivolumab + ipilimumab and nivolumab. These adverse events are immunorelated and include amongst others, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis and hypersensitivity reactions.

Some endocrine select AEs, though well-controlled with hormone replacement therapy, were not considered resolved due to the continuing need for hormone replacement therapy.

Most events were manageable with resolution occurring when immune–modulation medications (mainly systemic corticosteroids) were administered.

A summary of drug-related select AEs in the 4 treatments arms in provided in Table 38.

Table 38: Frequency of the selected drug related adverse events (any grade, grade 3-5) - Study CA209227 (updated table 02-Jul-2019 Database lock)

	Nivolumab+ Ipilimumab N=576		**Nivolumab N=391**		**Nivolumab + Chemotherapy N=172**		**Chemotherapy N= 570**	
	any grade	grade 3-4	any grade	grade 3-4	any grade	grade 3-4	any grade	grade 3-4
Endocrine	137 (24)	24 (4)	51 (13)	2 (1)	18 (11)	1 (1)	1 (0)	0
Gastro intestinal	105 (18)	14 (2)	50 (13)	4 (1)	20 (12)	3 (2)	57 (10)	4 (1)
Hepatic	91 (16)	47 (8)	42 (11)	15 (4)	21 (12)	5 (3)	42 (7)	2 (0)
Pulmonary	48 (8)	19 (3)	30 (8)	6 (2)	8 (5)	3 (2)	7 (1)	4 (1)
Renal	25 (4)	4 (1)	6 (2)	3 (1)	14 (8)	1 (1)	29 (5)	2 (0)
Skin events	196 (34)	24 (4)	83 (21)	4 (1)	49 (29)	2 (1)	55 (10)	0 (0)
Hypersensitivity	23 (4)	0	17 (4)	2 (1)	4 (2)	1 (1)	6 (1)	1 (0)

Source table 2.5.1 -1– 2.5.7-1- summary of clinical safety

Other events of special interest (OESIs)

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

OESIs were infrequent in both the nivolumab + ipilimumab (2.6%) and nivolumab (0.5%) arms, and 12/16 OESIs with nivolumab + ipilimumab (events not resolved myasthenia gravis, encephalitis, myocarditis and myositis) and 1/2 OESIs with nivolumab were resolved (event not resolved myositis).

14/16 OESIs in the nivolumab + ipilimumab arms and 2/2 OESIs in the nivolumab arm required immune-modulating medication (IMM).

Table 39: Other events of special interest (regardless of causality or immune-modulating medication treatment) with extended follow-up – Treated subjects in CA209227 Part 1 (updated table 02-Jul-2019 Database lock)

	Nivolumab+ Ipilimumab N=576		**Nivolumab N=391**		**Nivolumab + Chemotherapy N=172**		**Chemotherapy N= 570**	
	any grade	grade 3-4	any grade	grade 3-4	any grade	grade 3-4	any grade	grade 3-4
Myasthenic Syndrome	1	1	0	0	0	0	0	0
Pancreatitis	6	4	0	0	0	0	0	0
Uveitis	2	0	0	0	0	0	0	0
Encephalitis	2	2	0	0	0	0	0	0
Myocarditis	2	2	0	0	1	0	0	0
Myositis	2	1	2	2	1	0	1	0
Rhabdomyolysis	1	1	0	0	0	0	0	0

Late-emergent adverse events

Late-emergent drug-related AEs were defined as drug-related AEs with an onset date > 100 days after the last dose of study therapy. Late-emergent drug-related AEs were reported in 16 (4.1%) subjects in the nivolumab + ipilimumab arm B (PD-L1≥1%) and 11 (5.9%) in arm D (PD-L1 < 1%), 10 (2.6%) subjects in the nivolumab arm (Arm A), 4 (2.3%) subjects in nivolumab+chemotherapy arm (Arm G) and 2 (0.5%) subjects in the chemotherapy arm C (PD-L1≥1%) and 2 (1.1%) in arm F (PD-L1 < 1%).

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2.

Grade 3 or 4 hematologic abnormalities reported in ≥ 5% of subjects were:

- Nivolumab + ipilimumab (Arms B + D): decreased lymphocytes (5.2% Grade 3)
- Nivolumab (Arm A): decreased lymphocytes (6.8% Grade 3)Nivolumab +chemotherapy arm (Arm G): decreased lymphocytes (19.5% Grade 3), decreased absolute neutrophil count (18.3% Grade 3 and 7.7% Grade 4), decreased hemoglobin (17.8% Grade 3), and decreased leukocytes (13.6% Grade 3)
- Chemotherapy arms (Arm C + F): decreased absolute lymphocytes (14.8% Grade 3), decreased haemoglobin (14.2% Grade 3), decreased absolute neutrophil count (11.8% Grade 3 and 6.3% Grade 4) and decreased leukocytes (7.2% Grade 3).

Liver function test

Abnormalities in hepatic parameters are described in the following table. The majority were Grade 1-2.

Table 40: On-treatment laboratory abnormalities in specific liver test (SI units) - Treated subjects in CA209227 Part 1 (updated table 02-Jul-2019 Database lock).

	Nivo + Ipi (Arms B + D) (N=576)	Chemotherapy (Arms C + F) (N=570)
	N = 557	N = 535
ALT OR AST > 3XULN	86 (15.4)	23 (4.3)
ALT OR AST > 5XULN	45 (8.1)	5 (0.9)
ALT OR AST > 10XULN	20 (3.6)	1 (0.2)
ALT OR AST > 20XULN	7 (1.3)	0
	N = 556	N = 534
TOTAL BILIRUBIN > 2XULN	14 (2.5)	1 (0.2)
	N = 556	N = 534
CONCURRENT (WITHIN ONE DAY) ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN	10 (1.8)	0
CONCURRENT (WITHIN 30 DAYS) ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN	10 (1.8)	0

	Nivolumab (Arm A) (N=391)	Nivo + Chemo (Arm G) (N=172)
	N = 368	N = 167
ALT OR AST > 3XULN	45 (12.2)	15 (9.0)
ALT OR AST > 5XULN	23 (6.3)	6 (3.6)
ALT OR AST > 10XULN	6 (1.6)	3 (1.8)
ALT OR AST > 20XULN	1 (0.3)	3 (1.8)
	N = 367	N = 165
TOTAL BILIRUBIN > 2XULN	8 (2.2)	0
	N = 367	N = 165
CONCURRENT (WITHIN ONE DAY) ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN	5 (1.4)	0
CONCURRENT (WITHIN 30 DAYS) ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN	5 (1.4)	0

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Source: Table S.7.6.1.2 (SI), Table S.7.6.2.2 (SI),

Kidney function tests

Most subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment period. The abnormalities in creatinine (increases) were primarily reported as Grade 1 or 2. Grade 3 increased creatinine level were reported in 4 (0.7%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 2 (0.5%) subject in the nivolumab arm (Arm A), and 1 (0.2%) subject in the chemotherapy arms (Arms C + F). Grade 4 increased creatinine level were reported in 1 (0.2%) subject in the nivolumab + ipilimumab arms (Arms B + D), and 2 (0.5%) subject in the nivolumab arm (Arm A) and 1 (0.6%) in the nivolumab+chemotherapy arm (Arm G)

Thyroid function tests

Abnormalities in thyroid function tests are described in table 41

Table 41: On-treatment laboratory abnormalities in specific thyroid tests (SI units) – Treated subjects with at least one on-treatment TSH measurement in CA209227 Part 1 (updated table 02-Jul-2019 Database lock).

	Nivo + Ipi (Arms B + D) N = 463	Chemotherapy (Arms C + F) N = 445
TSH > ULN	139 (30.0)	47 (10.6)
TSH > ULN		
WITH TSH <= ULN AT BASELINE	115 (24.8)	34 (7.6)
TSH > ULN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (a)	77 (16.6)	5 (1.1)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (a)	39 (8.4)	28 (6.3)
WITH FT3/FT4 TEST MISSING (a) (b)	23 (5.0)	14 (3.1)
TSH < LLN	129 (27.9)	78 (17.5)
TSH < LLN		
WITH TSH >= LLN AT BASELINE	116 (25.1)	56 (12.6)
TSH < LLN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (a)	74 (16.0)	7 (1.6)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (a)	36 (7.8)	40 (9.0)
WITH FT3/FT4 TEST MISSING (a) (b)	19 (4.1)	31 (7.0)

	Nivolumab (Arm A) (N=300)	Nivo + Chemo (Arm G) (N=154)
TSH > ULN	71 (23.7)	35 (22.7)
TSH > ULN		
WITH TSH <= ULN AT BASELINE	55 (18.3)	28 (18.2)
TSH > ULN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (a)	38 (12.7)	15 (9.7)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (a)	26 (8.7)	14 (9.1)
WITH FT3/FT4 TEST MISSING (a) (b)	7 (2.3)	6 (3.9)
TSH < LLN	72 (24.0)	47 (30.5)
TSH < LLN		
WITH TSH >= LLN AT BASELINE	58 (19.3)	37 (24.0)
TSH < LLN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (a)	33 (11.0)	13 (8.4)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (a)	32 (10.7)	23 (14.9)
WITH FT3/FT4 TEST MISSING (a) (b)	7 (2.3)	11 (7.1)

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: Table S.7.8.1.2 (SI), Table S.7.8.2.2 (SI)

Pancrease Function Tests

Most subjects had normal amylase and lipase levels during the treatment reporting period. Abnormalities in amylase and lipase during treatment were primarily Grade 1 to 2 in severity.

The following Grade 3 or 4 abnormalities in amylase and lipase were reported in ≥ 5% of treated subjects with on-treatment laboratory results:

- Nivolumab + ipilimumab arms (Arms B + D): amylase (7.2% Grade 3) and lipase (10.0% Grade 3)
- Nivolumab arm (Arm A): lipase (6.7% Grade 3)
- Nivolumab + chemotherapy arm (Arm G): amylase (5.4% Grade 3)

Electrolytes

Most subjects had normal electrolyte levels during the treatment period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity.

Grade 3 or 4 abnormalities in electrolytes reported in ≥ 5% of treated subjects with on-treatment laboratory results:

- Nivolumab + ipilimumab (Arms B + D): hyponatremia (10.5% Grade 3)

- Nivolumab (Arms A): hyponatremia (10.5% Grade 3)
- Nivolumab + chemotherapy arm (Arm G): hyponatremia (7.8% Grade 3)
- Chemotherapy (Arms C + F): hyponatremia (5.4% Grade 3)

Immunogenicity

Of the 491 nivolumab ADA evaluable subjects in the nivolumab + ipilimumab arms, 44 (9.0%) subjects were nivolumab ADA positive at baseline and 180 (36.7%) subjects were nivolumab ADA positive after start of treatment.

Of the 483 ipilimumab ADA evaluable subjects in the nivolumab + ipilimumab arms, 20 (4.1%) subjects were ipilimumab ADA positive at baseline and 41 (8.5%) subjects were ipilimumab ADA positive after the start of treatment.

Table 42: ADA assessments based on 16-week definition of persistent positive – nivolumab+ipilimumab and nivolumab treated subjects with baseline and at least one post-baseline assessment in CA209227 Part 1 (updated table 02-Jul-2019 Database lock).

	Number of Subjects (%)			
	Nivo + Ipi (Arms B + D)		Nivolumab (Arm A)	Nivo + Chemo (Arm G)
	Nivolumab ADA N = 491	Ipilimumab ADA N = 483	Nivolumab ADA N = 322	Nivolumab ADA N = 148
BASELINE ADA POSITIVE	44 (9.0)	20 (4.1)	33 (10.2)	6 (4.1)
ADA POSITIVE	180 (36.7)	41 (8.5)	77 (23.9)	12 (8.1)
PERSISTENT POSITIVE	7 (1.4)	3 (0.6)	2 (0.6)	0
NOT PP - LAST SAMPLE POSITIVE	44 (9.0)	13 (2.7)	17 (5.3)	4 (2.7)
OTHER POSITIVE	129 (26.3)	25 (5.2)	58 (18.0)	8 (5.4)
NEUTRALIZING ADA POSITIVE	7 (1.4)	0	5 (1.6)	1 (0.7)
ADA NEGATIVE	311 (63.3)	442 (91.5)	245 (76.1)	136 (91.9)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint; Other Positive: Not PP but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Source: Table S.7.10.1

The effect of immunogenicity on safety was assessed in the nivolumab + ipilimumab (Arms B + D), nivolumab (Arm A), and nivolumab + chemotherapy (Arm G) arms (**Table 43**).

Table 43: Select AEs of hypersensitivity/infusion reaction by ADA status – Treated Subjects with ADA positive or ADA negative in CA209227 Part 1 (updated table 02-Jul-2019 Database lock).

	Nivo + Ipi (Arms B + D)			
	Nivolumab ADA		Ipilimumab ADA	
Preferred Term	Positive N = 180	Negative N = 311	Positive N = 41	Negative N = 442
TOTAL SUBJECTS WITH AN EVENT	10 (5.6)	16 (5.1)	6 (14.6)	19 (4.3)
Anaphylactic reaction	0	2 (0.6)	1 (2.4)	1 (0.2)
Bronchospasm	3 (1.7)	1 (0.3)	1 (2.4)	3 (0.7)
Hypersensitivity	1 (0.6)	2 (0.6)	0	3 (0.7)
Infusion related reaction	6 (3.3)	11 (3.5)	4 (9.8)	12 (2.7)

	Arm A: Nivolumab		Arm G: Nivo + Chemo	
	Nivolumab ADA		Nivolumab ADA	
Preferred Term	Positive N = 77	Negative N = 245	Positive N = 12	Negative N = 136
TOTAL SUBJECTS WITH AN EVENT	3 (3.9)	11 (4.5)	1 (8.3)	4 (2.9)
Anaphylactic reaction	0	1 (0.4)	0	0
Bronchospasm	0	2 (0.8)	0	1 (0.7)
Hypersensitivity	0	2 (0.8)	1 (8.3)	0
Infusion related reaction	3 (3.9)	6 (2.4)	0	3 (2.2)

Source: Table S.7.238
MedDRA Version: 22.0
CTC Version 4.0
Includes events between first dose and within the last dose of therapy + 100 days

Discontinuation due to adverse events

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 190 (33.0%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 94 (24.0%) subjects in the nivolumab arm (Arm A), 42 (24.4%) subjects in the nivolumab + chemotherapy arm (Arm G) and 122 (21.4%) subjects in the chemotherapy arms (Arms C + F).

Grade 3-4 AEs leading to discontinuation were reported in 141 (24.5%) subjects in the nivolumab + ipilimumab arm, 68 (17.4%) subjects in the nivolumab arm, 27 (15.7) subjects in the nivolumab + chemotherapy arm and 72 (12.6%) subjects in the chemotherapy arms.

The most common AEs leading to discontinuation (regardless of causality) were:

- Nivolumab + ipilimumab (Arms B + D): malignant neoplasm progression (9.2%), pneumonitis (3.6%), and diarrhoea (2.1%)
- Nivolumab (Arm A): malignant neoplasm progression (7.7%), pneumonitis (2.6%), pneumonia (1.0%), diarrhoea (1.0%)
- Nivolumab + chemotherapy: malignant neoplasm progression (6.4%), and pneumonitis, colitis, increased blood creatinine, decreased creatinine renal clearance, decreased appetite, and fatigue, (1.2% each)
- Chemotherapy (Arms C + F): malignant neoplasm progression (6.5%), anaemia (1.1%) and fatigue (0.9%).

Any-grade drug-related AEs leading to discontinuation were reported in 104 (18.1%) subjects in the nivolumab + ipilimumab arms (Arms B + D), 48 (12.3%) subjects in the nivolumab arm (Arm A), 22 (12.8%) subjects in the nivolumab + chemotherapy arm (Arm G), and 52 (9.1%) subjects in the chemotherapy arms (Arms C + F).

Grade 3-4 drug-related AEs leading to discontinuation were reported in 71 (12.3%) subjects in the nivolumab + ipilimumab arms, 28 (7.2%) subjects in the nivolumab arm, 13 (7.6%) subjects in the nivolumab + chemotherapy arm and 28 (4.9%) subjects in the chemotherapy arms. The most common drug-related AEs leading to discontinuation were:

- Nivolumab + ipilimumab (Arms B + D): pneumonitis (3.6%), diarrhoea (2.1%), hepatitis (1%) and increased AST and colitis (0.9% each)
- Nivolumab (Arm A): pneumonitis (2.3%), diarrhoea (1.0%), increased amylase and increased ALT (0.8% each)
- Nivolumab + chemotherapy: pneumonitis, colitis, increased blood creatinine, decreased creatinine renal clearance, and decreased appetite, were reported
- Chemotherapy (Arms C + F): fatigue and anaemia (0.9% each), nausea,increased blood creatinine and decreased appetite (0.5% each); all others were reported in ≤ 2 subjects.

Safety in special populations

The safety profile of nivolumab + ipilimumab among subgroups defined by age, gender, and race was generally similar to the all nivolumab + ipilimumab treated population. However, drug-related AEs leading to discontinuation were more common in subjects > 75 years compared with the all nivolumab + ipilimumab treated population (29.3% vs 18.1%).

<u>Safety in subjects with PD-L1 ≥ 1% and PD-L1 < 1%.</u>

The safety of nivolumab + ipilimumab vs chemotherapy was similar in subjects with PD-L1 ≥ 1% (Part 1a) and PD-L1 < 1% (Part 1b).

Table 44: Safety summary of Nivolumab + Ipilimumab vs Chemotherapy in Subjects with PD-L1 ≥ 1% (Part 1a) and PD-L1 (02-Jul-2019 Database lock)

	Number (%) of Subjects			
	PD-L1 ≥ 1% (Part 1a)		PD-L1 < 1% (Part 1b)	
Safety Parameters	Nivolumab + Ipilimumab (Arm B) (N = 391)	Chemotherapy (Arm C) (N = 387)	Nivolumab + Ipilimumab (Arm D) (N = 185)	Chemotherapy (Arm F) (N = 183)
Deaths	254 (65.0)	292 (75.5)	118 (63.8)	153 (83.6)
Disease	210 (53.7)	240 (62.0)	94 (50.8)	124 (67.8)
Due to Study Drug Toxicity[a]	5 (1.3)	5 (1.3)	3 (1.6)	1 (0.5)
Unknown	8 (2.0)	16 (4.1)	6 (3.2)	11 (6.0)
Other	31 (7.9)	31 (8.0)	15 (8.1)	17 (9.3)
	Adverse Event Grades			
	Any Grade / Grade 3-4	Any Grade / Grade 3-4	Any Grade / Grade 3-4	Any Grade / Grade 3-4
All Causality SAEs	247 (63.2) / 179 (45.8)	158 (40.8) / 114 (29.5)	108 (58.4) / 80 (43.2)	70 (38.3) / 50 (27.3)
Drug-related SAEs	96 (24.6) / 76 (19.4)	55 (14.2) / 42 (10.9)	45 (24.3) / 30 (16.2)	24 (13.1) / 19 (10.4)
All Causality AEs leading to DC	126 (32.2) / 92 (23.5)	68 (17.6) / 37 (9.6)	64 (34.6) / 49 (26.5)	54 (29.5) / 35 (19.1)
Drug-Related AEs leading to DC	72 (18.4) / 51 (13.0)	26 (6.7) / 11 (2.8)	32 (17.3) / 20 (10.8)	26 (14.2) / 17 (9.3)
All Causality AEs	387 (99.0) / 253 (64.7)	380 (98.2) / 213 (55.0)	181 (97.8) / 107 (57.8)	174 (95.1) / 98 (53.6)
Drug-Related AEs	302 (77.2) / 139 (35.5)	324 (83.7) / 141 (36.4)	140 (75.7) / 50 (27.0)	143 (78.1) / 64 (35.0)
≥ Drug-Related AEs ≥ 15%				
Rash	73 (18.7) / 9 (2.3)	23 (5.9) / 0	25 (13.5) / 0	7 (3.8) / 0
Diarrhea	70 (17.9) / 6 (1.5)	36 (9.3) / 2 (0.5)	28 (15.1) / 4 (2.2)	19 (10.4) / 2 (1.1)
Pruritus	62 (15.9) / 2 (0.5)	4 (1.0) / 0	20 (10.8) / 1 (0.5)	2 (1.1) / 0
Fatigue	56 (14.3) / 8 (2.0)	74 (19.1) / 4 (1.0)	27 (14.6) / 2 (1.1)	34 (18.6) / 4 (2.2)
Decreased Appetite	53 (13.6) / 4 (1.0)	73 (18.9) / 4 (1.0)	23 (12.4) / 0	39 (21.3) / 3 (1.6)
Nausea	42 (10.7) / 2 (0.5)	145 (37.5) / 7 (1.8)	15 (8.1) / 1 (0.5)	61 (33.3) / 5 (2.7)
Asthenia	38 (9.7) / 5 (1.3)	43 (11.1) / 4 (1.0)	21 (11.4) / 3 (1.6)	29 (15.8) / 1 (0.5)
Constipation	16 (4.1) / 0	55 (14.2) / 0	10 (5.4) / 0	30 (16.4) / 2 (1.1)
Anemia	14 (3.6) / 5 (1.3)	125 (32.3) / 41 (10.6)	8 (4.3) / 3 (1.6)	63 (34.4) / 25 (13.7)
Neutropenia	1 (0.3) / 0	68 (17.6) / 33 (8.5)	0 / 0	30 (16.4) / 21 (11.5)

Safety to support the adverse reactions in the nivolumab and ipilimumab Product Information (PI)

The presentation of adverse drug reactions (ADRs) in Section 4.8 of the current approved OPDIVO SmPC displays two columns in the table, one for nivolumab monotherapy and one for nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg. The nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg pooled dataset includes three studies in melanoma.

In this application, the proposed OPDIVO SmPC, Section 4.8 from the ongoing procedure EMEA/H/C/WS/1278 (RCC) is included as grey shaded. In this ongoing procedure, it is proposed to split the ADR table into two. One ADR table for nivolumab monotherapy and one ADR table for nivolumab in combination with ipilimumab, with two different columns: one for nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg and one for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC.

With the current application, a third column is added to the ADR table for nivolumab in combination with ipilimumab, to present safety data for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in first-line treatment of NSCLC (n = 576 of treated patients).

In the procedure EMEA/H/C/WS/1278, a table was added to Section 4.8 of the nivolumab SmPC to reflect the immune-related ADRs leading to permanent discontinuation or requiring high-dose corticosteroids for nivolumab monotherapy, nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, and nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC. With the current

application, this table is updated with a fourth column to present data for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in first-line treatment of NSCLC.

In the ongoing procedure EMEA/H/C/WS/1278, two additional tables have been added to Section 4.8 in the YERVOY SmPC: one table to reflect the ADRs for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in RCC; and another table to reflect the immune-related ADRs leading to permanent discontinuation or requiring high-dose corticosteroids for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg.

With the current application, a second column to both tables is proposed to present data for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in first-line treatment of NSCLC.

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the United States (US) and in the European Union (EU), and for other indications. Ipilimumab was first approved on 25-Mar-2011 in the US for advanced melanoma, and has since been approved for market use in 60 countries worldwide.

Nivolumab + ipilimumab was first approved on 30-Sep-2015 in the US and on 11-May-2016 in the EU for the treatment of patients with unresectable or metastatic melanoma and has since been approved in multiple countries.

The safety profile of nivolumab and ipilimumab in the postmarketing setting remain favorable and similar to the profile established during clinical trials. To date, no new significant safety concerns have been identified based on global postmarketing reports.

2.5.1. Discussion on clinical safety

The safety profile of the combination of nivolumab 3 mg/kg (Q2W) + ipilimumab 1 mg/kg (Q6W) is based mainly on Part 1 of the open label phase III study CA209227, in which a total of 576 patients received nivolumab+ipilimumab (Arms B + D) for the first line treatment of NSCLC. Additionally, data on 391 patients who received nivolumab monotherapy (Arm A), 172 patients that received nivolumab + chemotherapy (Arm G) and 570 subjects that received platinum-doublet chemotherapy (Arms C+F) have been provided as comparative.

The combination of nivolumab+ ipilimumab is already approved for the treatment of advanced melanoma (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) and of renal cell carcinoma [RCC] (nivolumab 3 mg/kg + ipilimumab 1 mg/kg). In both these indications, the combination nivolumab + ipilimumab is to be administered for four doses (Q3W), followed by nivolumab 3 mg/kg (Q2W). The proposed regimen in NSCLC is therefore different from those approved for melanoma and RCC.

In the study CA209227 nivolumab + ipilimumab and nivolumab were administered up to 24 months while chemotherapy was given up to 4 cycles (12 weeks), except in those patients that received pemetrexed maintenance therapy (64.3%). The median duration of treatment was 4.19 months (CI 95%: 3.71-5.09) in the nivolumab+ipilimumab groups (arm B (4.24 mo) and D (3.96 mo)), 4.63 months (CI 95%: 3.75-5.22) in the nivolumab arm (Arm A), 5.82 months (CI95%: 4.90-7.16) in the nivolumab_chemotherapy group (Arm G) and 2.63 months (CI 95%: 2.56-2.79) in chemotherapy groups (Arm C (2.66 mo) and F (2.60 mo)). The duration of treatment was therefore longer in the nivolumab+ipilimumab arm compared to the chemotherapy arm. In the nivolumab+ipilimumab group, approximately 23% of patients were treated >12 months.

It should be noted that the study was open label. This might have affected the reporting of drug related adverse event. Therefore, both the all causality as drug-related AEs were taken into account in

the safety assessment. The drug side effects of immunotherapy are expected to be immune related, while the side effects of chemotherapy are likely related to the bone marrow suppression.

Frequency of AEs and drug-related AEs leading to discontinuation of study therapy was highest and almost doubled in the nivolumab+ipilumumab therapy group (24.5/18.1%) compared to chemotherapy groups (12.6/9.1%). The other treatments groups showed an AE incidence that was also higher compared to chemotherapy (nivolumab monotherapy (24.0/12.3%), nivolumab+chemotherapy (24.4/12.8%)).

The main drug-related AEs leading to discontinuation of nivolumab + ipilimumab treatment were pneumonitis, diarrhoea, hepatitis and increased aspartate aminotransferase (AST). Those reported for chemotherapy were fatigue, anaemia, nausea, increased blood creatinine and decreased appetite.

The overall incidence of AEs was similar between treatment groups (> 97%) . The most commonly reported AEs (regardless of causality and grade) in the nivolumab + ipilimumab group were decreased appetite, diarrhoea, dyspnoea, fatigue, asthenia, rash,nausea and pruritis and differed slightly form those reported in the chemotherapy. In the chemotherapy group the most commonly reported AEs were nausea, anaemia, constipation, decreased appetite and fatigue.
Grade 3-4 AEs (regardless of causality) were more frequent in patients treated with nivolumab + ipilimumab (62.5%) than in those that received chemotherapy (54.6%),nivolumab monotherapy (53.2%), nivolumab+chemotherapy (70.3%).

Drug-related AEs were more frequent with the combination therapy (76.7%) than with the monotherapy (65.5%) although lower than with nivolumab+chemotherapy (92.4%) or chemotherapy (81.9%). In the nivolumab + ipilimumab group (vs. nivolumab vs. nivolumab+chemo), the most frequent drug-related AEs were rash (17.0% vs. 11.0% vs. 15.1%), diarrhoea (17.0% vs. 12.5% vs. 9.9%), pruritus (14.2% vs. 8.2% vs. 8.7%), fatigue (14.4% vs. 11.3% vs. 25.6%), decreased appetite (13.2% vs. 6.6% vs. 22.7) and hypothyroidism (11.6% vs. 7.2% vs. 4.1%) while in the chemotherapy group (vs. nivolumab+chemotherapy) the most frequent drug-related AEs were nausea (36.1% vs. 39.0%), anaemia (33.0% vs. 40.7%), decreased appetite (19.6% vs. 22.7%), fatigue (18.9% vs. 25.0%).. Grade 3-4 drug-related AEs were reported in 32.8% of subjects in the nivolumab+ipilimumab group and36.0% in the chemotherapy group (nivolumab, 19.4% and nivolumab + chemotherapy, 55.8%). In the nivolumab+ipilimumab arm, the most commonly reported drug-related grade 3-4 AEs were lipase increased (4.0%), alanine aminotransferase increased [ALT] (3.3%), AST increased (3.1%),amylase increased (3.0%) and pneumonitis (2.8%). In the chemotherapy arm, the most frequent drug-related grade 3-4 AEs were anaemia (11.6%), neutropenia (9.5%) and neutrophil count decreased (6.3%).The safety profile of nivolumab + ipilimumab is mainly characterised by immune-related adverse events. Adverse events considered of special interest (AEOSIs) include endocrine, gastrointestinal, hepatic, pulmonary, renal and skin AEs as well as hypersensitivity reactions. In general, the incidence of these AEOSIs was higher with the nivolumab+ipilimumab combination therapy than with the nivolumab monotherapy and nivolumab+chemotherapy. An increase compared to thechemotherapy is seen, as expected when comparing an immunotherapy to a non-immunotherapy. Moreover, in general a shorter median time to onset and a longer median time to resolution were reported in the nivolumab + ipilimumab group compared to the nivolumab group. Most of this AEOSIs were within the skin (34.0% nivolumab + ipilimumab vs. 21.2% nivolumab vs. 28.5% nivolumab+chemotherapy) and endocrine (23.8% nivolumab + ipilimumab vs. 13.0% nivolumab vs. 10.5% nivolumab+chemotherapy) SOCs. In the nivolumab+ipilimumab combination arm the majority of the AEOSIs were of grade 1 or 2. Only one fatal event was reported (a grade 5 AE of pneumonitis in the nivolumab arm). Generally, most of the events resolved, except endocrine AEs, were around 55% of subjects remained unresolved.

Frequency of late-emergent AEs, that is drug-related AEs with an onset date >100 days after the last dose of study therapy, was relatively low in all treatment groups. In the nivolumab + ipilimumab group the most late-emergent AEs were reported, with 4.1% of subjects compared to 2.6% subjects in the nivolumab group, 2.3% of subjects in the nivolumab+chemotherapy arm and 0.5% of subjects in the chemotherapy group. In the nivolumab + ipilimumab combination group, there were eight AEs of grade 3 and two AE of grade 4 (immune-mediated hepatitis and type 1 diabetes mellitus); no grade 5 late-emergent AEs were reported.

The majority of deaths reported during study CA209227 Part 1 were due to disease progression. Deaths related to study drug toxicity occurred in 8 (1.4%) patients in the nivolumab+ipilimumab group compared to 2 (0.5%) patients in the nivolumab arm, 4 (2.3%) patients in the nivolumab+chemotherapy arm and 6 (1.1%) patients in the chemotherapy group. In the nivolumab+ipilimumab combination group, there were 46 (8.0%) deaths due to "other" reason. This proportion was comparable to those reported in the nivolumab group (37 [9.5%]), nivolumab+chemotherapy group (11 [6.4%] and the chemotherapy group (48 [8.4%]). In general, no large differences in amount of toxicity-related deaths are observed. Nevertheless, a higher number of deaths in the combination group were related to cardiac events compared to those in the nivolumab and chemotherapy groups. A similar pattern was observed in patients with RCC treated with nivolumab + ipilimumab in Study CA209214. Although the contribution of the combination therapy to those deaths is unclear, the consistency of patterns does raise concerns.

The incidence of SAEs and drug-related SAEs was higher in the nivolumab+ipilimumab group (61.6%/24.5%) than in the chemotherapy groups (40.0%/13.9%). The other two groups also show frequencies higher frequencies compared to chemotherapy (nivolumab monotherapy (52.9%/11.3%), nivolumab+chemotherapy (52.9%/20.9%)).Pneumonitis, diarrhoea, adrenal insufficiency, colitis, hepatitis and hypophysitis were the most commonly reported drug-related SAEs in the nivolumab + ipilimumab arm while in the chemotherapy group the most commonly reported drug-related SAEs were anaemia, febrile neutropenia and vomiting

The analysis of the safety profile of nivolumab + ipilimumab according to age (<65 years, 65-74 years, 75-84 years and > 85 years) shows higher rates of drug-related AEs of Grade 3-4 in patients between 75 to 84 years [75-84: 43.9%; <65: 32.0%; 65-74: 31.2%]. Discontinuations due to drug-related AEs (29.8% vs. 17.0% vs. 16.5%) were also higher in this subgroup of very elderly patients. Overall, nivolumab+ipilimumab could be less well tolerated in very elderly patients (≥75 years). Considering that the median age of the NSCLC population is 71 years, this data may suggest the safety profile in clinical practice will be worse compared with the data observed in the clinical study.

Additionally, frequencies of all-causality and drug-related grade 3-4 AEs have been provided according to gender, race and region. In Asian patients (n=125) a higher incidence of drug-related AEs and Grade 3-4 AEs were reported compared to White patients (n=435) [all severity drug-related: 86.4% vs. 74.3%; G3-4 drug-related: 40.8% vs. 30.3%, respectively]. Differences between Asian and White patients in terms of drug-related Grade 3-4 AEs were mainly driven by the SOCs of endocrine (7.2% vs. 2.5%, respectively) and metabolism (9.6% vs. 2.3%) disorders with no major differences in any particular AE.

The immunogenicity of nivolumab appears to increase when combined with ipilimumab. The presence of antibodies against nivolumab does not seem to impact on the safety. However, a higher incidence of AEs was observed in patients with ipilimumab ADA-positive compared to those ADA-negative (6 [14.6%] vs. 19 [4.3%], respectively). In contrast, in study CA209568 Part 1, only 1 (3.3%) ipilimumab ADA-positive subject had an event compared to 17 (7.6%) of the ADA-negative subjects. Having said that and considering the low number of subjects with ipilimumab ADA-positive, drawing conclusions about this finding results difficult.

The safety profile of nivolumab + ipilimumab seems similar in subjects with PD-L1 ≥ 1% or and PD-L1 < 1%. Drug-related AEs leading to DC were seen in 18.4% of subjects in PD-L1 ≥ 1% and 17.3% of subjects with PD-L1 < 1%. Also Grade 3-4 drug-related AEs and SAEs showed similar results, with 35.5%/19.4% in PD-L1 ≥ 1% and 27.0%/16.2% in PD-L1 < 1%.

Also the safety profile of the chemotherapy seems similar in subjects with PD-L1 ≥ 1% or and PD-L1 < 1%. Although a differences in drug-related AEs leading to DC can be observed: 6.7% of subjects in PD-L1 ≥ 1% and 14.2% of subjects with PD-L1 < 1%, this was not consistently seen. The Grade 3-4 drug-related AEs and SAEs showed similar results, with 36.4%/10.9% in PD-L1 ≥ 1% and 35.0%/10.4% in PD-L1 < 1%.

For the specific AE categories, a small numerical difference could be observed between low and high PD-L1 expressers, but the differences did not show a trend towards one of the two subgroups specifically.Considering the other two treatments arms (nivolumab+chemotherapy and nivolumab monotherapy), it can be seen that drug-related AEs were more frequent with the nivolumab+chemotherapy (92.4%) combination (compared to the nivolumab+ipilimumab combination (76.7%)). The incidence of drug-related SAEs (N+C 20.9%; N+I 24.5%) and discontinuation due to AEs (N+C 24.4%; N+I 24.5%) was in the same order of magnitude comparing both combination therapies. Overall, both nivolumab+ipilimab as nivolumab+chemotherapy showed a worse safety profile compared to the nivolumab monotherapy or chemotherapy alone. This indicates both the additional treatments with ipilimumab or with chemotherapy add toxicity to nivolumab treatment.

Overall, the type of AEs of nivolumab + ipilimumab in the first line treatment of patients with NSCLC is in line with the known safety profile of the combination in other types of tumours (melanoma and RCC). Additionally, the incidence of all grades and Grade 3-4 drug-related AEs as well as SAEs appears lower in the NSCLC population. The safety profile for nivolumab + ipilimumab is similar in patients with high (≥1%) or low (<1%) PD-L1 expression.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of the combination of nivolumab 3 mg/kg (Q2W) + ipilimumab 1 mg/kg (Q6W) in the first line treatment of subjects with metastatic NSCLC is in line with the known safety profile of the combination in other tumours and no new safety concerns have been identified. The safety profile for nivolumab + ipilimumab seems similar in patients with high (≥1%) or low (<1%) PD-L1 expression.

The safety of the combination therapy is characterised by the immunological effects, while the safety of chemotherapy is characterised by its bone marrow suppression.

Adding ipilimumab to nivolumab therapy involved an increase in toxicity, according to the higher rates of drug-related AEs, Grade 3-4 AEs, SAEs and discontinuation due to AEs reported with nivolumab + ipilimumab compared to nivolumab monotherapy. Overall, the combination treatment appears to be less well tolerated than chemotherapy as the grade 3-4 AEs, (grade 3-4) SAE, and AEs leading to discontinuation (regardless of causality) were consistently higher reported with the nivolumab+ipilimumab combination treatment compared to chemotherapy.

The combination of ipi + nivo treatment might be even worse tolerated in patients aged ≥ 74. Considering that the median age of the NSCLC population is 71 years, this data may suggest the safety profile in clinical practice will be worse compared with the data presented in the clinical study report.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

OPDIVO RMP version 14.1: The changes to the RMP are acceptable.

YERVOY RMP version 24.0: The changes to the RMP are acceptable.

See PRAC AR for further information.

2.7. Update of the Product information

As a consequence of this new indication to include the combination of nivolumab and ipilimumab for the first-line treatment of metastatic NSCLC in adults with TMB≥ 10 mut/Mb sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Opdivo® and Yervoy® SmPCs have been updated. The Package Leaflet has been updated accordingly.

In view on the major objections remaining in the 2nd RSI, it is premature to recommend any conditions for marketing authorisation and to propose changes in the product information (SPC, PL, labelling).

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 changes do not involve a relevant impact on the PIL.

3. Benefit-Risk Balance

Initially, the MAH was seeking a new indication of nivolumab in combination with ipilimumab for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have tumour mutational burden (TMB) ≥10 mutations per megabase (mut/Mb), regardless of programmed death-ligand 1 (PD-L1) expression. However, after the full and final data of CA209227 Part 1, an updated, all comer indication is being submitted: "OPDIVO in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations (see sections 4.4 and 5.1)."

3.1. Therapeutic Context

3.1.1. 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. NSCLC represents approximately 85% of all lung cancers and includes SQ cell carcinoma and NSQ cell carcinoma, which encompasses a variety of histological subtypes including adenocarcinoma, large cell carcinoma, and less common subtypes. At the time of diagnosis, approximately 45% of patients have Stage IV disease.

3.1.2. Available therapies and unmet medical need

With the exception of small subgroups of patients with NSCLC tumours harbouring known driver mutations (e.g., epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK]), chemotherapy doublets (mostly platinum based), immunotherapy in monotherapy or in combination

with chemotherapy are the recommended standard of care for initial treatment of metastatic NSCLC (National Comprehensive Cancer Network guidelines and ESMO guidelines). This recommendation is based on prolongation of OS.

The combination of nivolumab + ipilimumab will be the first applied immuno-therapy for the whole 1L NSCLC population. Although the PD-L1 pembrolizumab therapy is approved for patients with PD-L1 ≥ 50%, platinum based double chemotherapy is still the backbone of treatment in the 1L of NSCLC for the majority of patients.

3.1.3. Main clinical studies

The primary efficacy and safety data in support of this application come from Part 1 of the Phase 3 Study CA209227 and are supported also by data from Phase 2 Study CA209568 (nivolumab + ipilimumab).

CA209227 is a single pivotal open-label, randomized, Phase 3 study of nivolumab monotherapy, nivolumab plus ipilimumab, nivolumab plus platinum-doublet chemotherapy, or platinum-doublet chemotherapy alone in subjects with previously untreated recurrent or metastatic NSCLC. The nivolumab + ipilimumab (Arms B and D) and histology-based chemotherapy (Arms C and F) treatment regimens were identical in Parts 1a (patients with PD-L1 >≥ 1%) and 1b (patients with PD-L1 <1%), respectively.

Subjects were first assessed for PD-L1 expression, using a 1% cut-off, and categorized into 2 separate groups (PD-L1 expressing and PD-L1 non-expressing). Subjects within each group were to be stratified by histology (squamous [SQ] vs non-squamous [NSQ]). Subjects with PD-L1 ≥1% tumours were randomized in a 1:1:1 ratio to Arms A, B, and C. Subjects with PD-L1 < 1% tumours were initially randomized to Arms D, F and G in a 1:1:1 ratio.

The 2 co-primary primary endpoints of Part 1 were:

1) To compare OS of nivolumab in combination with ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C) in subjects with ≥ 1% PD-L1 tumours in Part 1a

2) To compare PFS (BICR-assessed, primary definition) of nivolumab in combination with ipilimumab (Arms B + D) to platinum-doublet chemotherapy (Arms C + F) in subjects with baseline TMB ≥ 10 mut/Mb regardless of PD-L1 expression level in Part 1.

3.2. Favourable effects

1) On 02-Feb-2018, the independent Data Monitoring Committee (DMC) reviewed the data from the 24-Jan-2018 database lock (405 OS events in Part 1a [nivolumab + ipilimumab and chemotherapy arms] and 193 PFS events in Part 1 [TMB ≥10 mut/Mb; nivolumab + ipilimumab and chemotherapy arms]). The final analysis of the co-primary endpoint of PFS with nivolumab + ipilimumab vs chemotherapy in subjects with TMB ≥ 10 mut/Mb based on the database lock of 24-Jan-2018 was statistically significant (HR = 0.58; 97.5% CI: 0.41, 0.81 nivolumab + ipilimumab (Arms B + D) compared with chemotherapy (Arms C + F), i.e. nivo+ipi yielded a median PFS (95% CI) of 7.2 months (5.52-13.21) by BIRC, compared to chemotherapy 5.45 months (4.40-5.78); the difference is a 1.75 months improvement of median PFS.

On the other hand, in the complementary subgroup of patients (those with TMB < 10 mut/Mb) the HR does not seem to point out a benefit for the combination of immunotherapy (HR 1.07 CI 0.81-1.40).

PD-L1 ≥ 1%

2) Based on a database lock of 02-Jul-2019, the pre-specified final analysis for the co-primary endpoint of OS for nivolumab + ipilimumab (Arm B) versus chemotherapy (Arm C) in subjects with PD-L1 ≥ 1% met statistical significance (OS HR = 0.79 [97.72% CI: 0.65, 0.96]; p = 0.0066). This result was below the threshold for hierarchical testing with alfa protection established as < 0.0228. In terms of median OS, there was a gain of roughly 2 months (i,e, 17.08 (14.95, 20.07) vs 14.88 (12.71, 16.72) nivolumab + ipilimumab and chemotherapy, respectively).

Results for sensitivity analyses using a 2-sided unstratified log-rank test were consistent with the primary OS analysis (HR 0.80; 95% CI 0.66, 0.97, p value 0.0100).

Secondary endpoints seem to support the benefit of the combination over chemotherapy. PFS per BICR (HR = 0.82 [97.5% CI: 0.67, 0.99]), ORR per BICR (35.9% vs 30.0%), CR rate (5.8% vs 1.8%), and median DoR (23.16 vs 6.24 months).

PD-L1 <1%

The study included a total or n=187 patients randomised to nivo+ ipi, n= randomised to nivo+chemo and n= 186 randomised to chemotherapy.

After a total of 275/373 (76%) of events, the median OS (95% CI) in the nivolumab + ipilimumab arm is 17.15 (95% CI 12.85, 22.05) months and 12.19 months (95 9.17, 14.32) months for the chemotherapy arm, resulting in an OS gain of about 4.96 months, HR 0.62 (97.5% 0.47, 0.81). The KM curves of OS showed a direct separation favouring the nivo + ipi combination.

3.3. Uncertainties and limitations about favourable effects

- There are concerns that some of the amendments have been data driven:

  The last subject was randomized on 06-Jan-2017, there was an interim analysis of ORR for Part 1a in January 2017 (which also included PFS data), the TMB analyses were performed in April- July 2017 and the protocol amendment was on 19 October 2017. Another interim analysis (OS) was carried out in Jan 2018. Although the amendment was before database lock, considering that the PFS is 4-7 months it could not be excluded that the amendment was influenced on the clinical data, especially due to the fact that results from these interim analyses were distributed to members of the MAH (see below). Furthermore, the decision to amend the trial protocol to include a primary hypothesis for testing the treatment effect on PFS in the TMB≥10 mut/mb population was made during the conduct of this open-label trial and subsequent to interim analyses.

- In order to address the uncertainties related to these changes in the design of the clinical study during the conduct of the trial a triggered GCP inspection was requested.

  A GCP inspection was conducted at Sponsor site Bristol-Myers Squibb ([BMS], Lawrenceville, NJ, US; from 07-May-2019 to 10-May-2019) and at two vendors (one CRO responsible for some data management activities, from 02-Apr-2019 to 04-Apr-2019 and another CRO, responsible for preparation of the statistical outputs, from 08-Apr-2019 to 11-Apr-2019). The inspectors shared the integrated inspection report GCP/2018/040 dated 14-Jun-19 with the rapporteurs and the Committee for Medicinal Products for Human Use (CHMP).

  Regarding the interim analyses of Jan 2017, in the clinical overview, the applicant only reported that the ORR was disclosed. However, it appeared that during the interim analyses also the PFS, including PD-L1 ≥1% has been analysed. This aspect of the interim analyses was neither clearly mentioned nor clearly presented. Upon inspection, it became also clear that the

results were also disseminated to BMS personal likely being involved in strategic decision makings.

The inspection team concluded that the sponsor and the CRO processes were having weaknesses on their systems that led to the departures on ICH GCP observed (lack of solid measures to prevent dissemination of information to authorised/non authorised personnel within a non-robust and immature risk management system). Overall, the MAH was not able to demonstrate that the addition of the TMB endpoint was not informed by the interim analysis.

- The inspection team considers that as a result of the departures from GCP noted, the inspectors cannot confirm that the full trial data is reliable with adequate quality to be used in support of the Marketing Authorisation Application submitted to the Agency, due to the weaknesses on the processes used for handling this data. Even though this conclusion was made in the context of the TMB application, the outcome of the triggered inspection is applicable to the whole clinical study.
- Confirming the accuracy of the patient data was not within the scope of the GCP inspection. Nevertheless, the accuracy of the patient level data is not questioned since the OS is not prone to that. Its acknowledged that source data as captured in the eCRF should be reliable as OS is a hard endpoint. Also, the type of statistical analyses used by the company to calculate the OS benefit is not questioned.

Clinical data

PD-L1 ≥ 1%

- In the Part 1A of the study (PD-L1>1%), further analyses showed a larger effect on the OS, PFS, ORR and DOR in the predefined subgroup (though not selected for confirmatory testing) PD-L1 ≥ 50% compared with the exploratory subgroup of patients with PDL1-49%.
- The subgroup showed overall larger responses for the SQ population compared with the NSQ population, even though benefit in the latter could still be observed Likewise, in never smokers and in presence of liver metastases, the point estimate is close to unity or even crossing the unity favouring chemotherapy.
- The Kaplan-Meier curves for the OS and PFS are indicating that a subgroup of patients is at risk for an earlier disease progression/death. Apparently, using an age cut-off at 65 years showed a signal that the combinations of age and having pretreatment Grade ⩾ 3 or not could be important to predict for which patients chemotherapy would be advised instead of nivolumab+ipilimumab to prevent early death. Kaplan-Meier curves for the corresponding subgroups should be provided, or, at least, the group "<65 year and baseline Grade ⩾ 3 events" versus the rest should be provided. To further investigate the sensitivity of this interaction, the estimates of a model using an age cut-off at 75 years should be provided
- Regarding the contribution of the monocomponents, The data shows that for the overall group, the ORR, DOR show numerical improvement with the combination nivolumab + ipilimumab therapy compared to the monotherapy nivolumab. These improvements show the contributive effect of ipilimumab.

The lack of beneficial effect over chemotherapy in the PD-L1 1-49% (n=396) is hard to understand considering the observed benefit in the PD-L1 ⩾ 50% (n=397) and the apparent observed OS benefit in the PD-L1 < 1% (n=373).

PD-L1 < 1%

- This analysis was not part of the hierarchical testing strategy and there was not adjustment for multiplicity.
- No replication of the results of this exploratory trial could be obtained from the phase II studies because of the lack of comparison with chemotherapy.
- The combination is also approved for the immunogenic tumours like melanoma and renal cell carcinoma. However, NSCLC is non-immunogenic and this hampers the extrapolation.

TMB population

- Updated efficacy results by TMB (10 mut/Mb cutoff) in CA209227 Part 1 based on the 02-Jul-2019 database lock were consistent with those previously reported in the responses to the first Request for Supplementary Information (RSI 1) dated 26-Jul-2018 based on the 09-Jul-2018 database lock.

  Nivolumab + ipilimumab demonstrated a clinically meaningful improvement in OS compared with chemotherapy in subjects with TMB $\geq$ 10 mut/Mb (HR = 0.68 [97.5% CI: 0.49, 0.95]; unstratified log-rank test descriptive p value = 0.0091) and in subjects with TMB < 10 mut/Mb (HR = 0.75 [97.5% CI: 0.57, 0.97]), with similar HRs. So, these analyses seem to demonstrate that unlike prior results based on PFS and ORR, TMB at a cutoff of 10 mut/Mb did not appear to be predictive of OS benefit

3.4. Unfavourable effects

Adverse events most likely related to the tolerability of treatment are the (drug-related) grade 3-4 AEs, SAEs, grade 3-4 SAEs, AEs leading to discontinuation, and death due to drug toxicity. As the study concerns an open-label design, the collection of AEs (and attributability to the drug) might be biased. Therefore, the all causality data are also considered to provide important information.

Drug-related AEs were reported in 76.7% of patients in the nivolumab + ipilimumab group compared to 65.5% in the nivolumab arm, 92.4% in the nivolumab+chemotherapy arm and 81.9% in the chemotherapy group. The most commonly drug-related AEs reported in the nivolumab + ipilimumab group were rash (17.0%), diarrhoea (17.0%), pruritus (14.2%), fatigue (14.4%), decreased appetite (13.2%) and hypothyroidism (11.6%), and were nausea (36.1%), anaemia (33.0%), decreased appetite (19.6%) and fatigue (18.9%) in the chemotherapy group.

Grade 3-4 AEs and drug-related AEs were reported in 62.5%/32.8% of subjects in the nivolumab+ipilimumab group, 54.6%/36.0% in the chemotherapy group (and 53.2%/19.4% in the nivolumab monotherapy group and 70.3%/55.8% in the nivolumab+chemotherapy group).

Late-emergent AEs were reported in 4.1% of patients in the nivolumab+ipilimumab group, 2.6% of patients in the nivolumab group, 2.3% of patients in the nivolumab+chemotherapy group and 0.5% in the chemotherapy group. In the nivolumab+chemotherapy combination group, there were eight AEs of grade 3 and two AE of grade 4 (immune-mediated hepatitis and type 1 diabetes mellitus); no grade 5 late-emergent AEs were reported.

Regarding adverse events of special interest (AEOSIs), the most frequently reported in the nivolumab + ipilimumab group were within the SOCs of skin (34.0% nivolumab+ipilimumab vs. 21.2% nivolumab vs. 28.5% nivolumab+chemotherapy) and endocrine (23.8% nivolumab+ipilimumab vs. 13.0% nivolumab vs. 10.5% nivolumab+chemotherapy). The majority of the AEOSIs were of grade 1 or 2 with only one fatal event reported (a grade 5 AE of pneumonitis).

Deaths related to study drug toxicity occurred in 8 (1.4%) patients in the nivolumab+ipilimumab group compared to 2 (0.5%) patients in the nivolumab arm, 4 (2.3%) patients in the nivolumab+chemotherapy arm and 6 (1.1%) patients in the chemotherapy group.

SAEs and drug-related SAEs were reported in 61.6%/24.5% of patients in the nivolumab+ipilimumab combination group compared to 40.0%/13.9% in the chemotherapy group. (nivolumab monotherapy (52.9%/11.3%), nivolumab+chemotherapy (52.9%/20.9%)

Pneumonitis, diarrhoea, adrenal insufficiency, colitis, hepatitis and hypophysitis were the most commonly reported drug-related SAEs in the nivolumab+ipilimumab arm and anaemia, febrile neutropenia and vomiting in the chemotherapy arm.

AEs and drug-related AEs leading to discontinuation of study therapy were reported 24.5%/18.1% of patients in the nivolumab + ipilimumab group and 12.6%/9.1% in the chemotherapy group (nivolumab monotherapy (24.0/12.3%), nivolumab+chemotherapy (24.4/12.8%).

The aged group ≥ 74 years treated with nivolumab + ipilimumab showed a higher number of drug-related Grade 3-4 AEs compared to younger age groups ([75-84: 43.9%; <65: 32.0%; 65-74: 31.2%]%) and discontinuations due to drug-related AEs (29.8% vs. 17.0% vs. 16.5%).

When comparing patients with low and high PD-L1 expression, drug-related AEs leading to drug discontinuation were seen in 18.4% of subjects in PD-L1 ≥ 1% and 17.3% of subjects with PD-L1 < 1%. Grade 3-4 drug-related AEs and SAEs were seen in 35.5%/19.4% of subjects in PD-L1 ≥ 1% and 27.0%/16.2% of subjects in PD-L1 < 1%.

For the chemotherapy, drug-related AEs leading to DC were observed in 6.7% of subjects in PD-L1 ≥ 1% and 14.2% of subjects with PD-L1 < 1%. Grade 3-4 drug-related AEs and SAEswere seen in 36.4%/10.9% of subjects in PD-L1 ≥ 1% and 35.0%/10.4% of subjects in PD-L1 < 1%.

The toxicity profile of the combination of ipilimumab + nivolumab is well known. No new treatment emergent adverse events were observed. Overall, the number of these AEs were consistently higher in the nivolumab + ipilimumab arm compared to the chemotherapy arm.

3.1. Uncertainties and limitations about unfavourable effects

A higher number of deaths related to cardiac events were reported in the nivolumab + ipilimumab group compared to the other treatment groups. A similar pattern was observed in patients with RCC treated with nivolumab + ipilimumab in Study CA209214.

That combo of nivolumab+ipilimumab is less well tolerated in very elderly patients (≥75 years). The median age in NSCLC is 71 years, while the investigated population was younger (median age 64 years). This might indicate the safety profile in clinical practice might be worse compared with the safety profile presented in the clinical study report.

Hypersensitivity reactions occurred more frequently in the ipilimumab ADA-positive than in ipilimumab ADA-negative patients.

3.1. Effects Table

Table 45: Efficacy Effects Table for OPDIVO® + YERVOY® vs. chemotherapy for the first-line NSCLC with PD-l1 ≥ 1 % (updated table 02-Jul-2019 Database lock)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Overall Survival N+I vs Chemo		HR (95% CI) p-value	0.79 (0.65, 0.96) 0.0066		Pre-planned in the hierarchical testing strategy.	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					p Value Threshold <0.0228	
PFS per BICR N+I vs Chemo		HR (95% CI)	0.82 (0.69, 0.97)		No multiplicity control	
ORR per BICR (CR + PR)		(%)	Nivo+Ipi: 36%	Chemo: 30%	No multiplicity control	

Table 46: Efficacy Effects Table for OPDIVO® + YERVOY® vs. chemotherapy for the first-line NSCLC with PD-l1 <1–% -(updated table 02-Jul-2019 Database lock)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS Nivo+Chemo vs chemo		HR (95% CI) p-value	0.0070		Pre-planned in the hierarchical testing strategy. p Value Threshold <0.0228	
OS Nivo+Chemo vs chemo		HR (95% CI) p-value	0.0352		Pre-planned in the hierarchical testing strategy. p Value Threshold <0.0228	
Overall Survival N+I vs Chemo		HR (95% CI)	0.62 (0.48, 0.78)		No multiplicity control	
PFS per BICR N+I vs Chemo		HR (95% CI)	0.75 (0.59, 0.96)		No multiplicity control	
ORR per BICR (CR + PR)		(%)	Nivo+Ipi: 27.3%	Chemo: 23.1%	No multiplicity control	

Table 47: Safety Effects Table for OPDIVO® + YERVOY® vs. chemotherapy for the first-line NSCLC (updated table 02-Jul-2019 Database lock)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
			N=576	N=570		
Grade 3-4 AEs	All Causality Grade 3-4 AEs	%	62.5	54.6	open label study, collection of AEs (and attributability to the drug) might be biased.	
	Drug-related Grade 3-4 AEs	%	32.8	36.0		
SAEs	All Causality SAEs	%	61.6	40.0		
	Drug-related SAEs	%	24.5	13.9		
Grade 3-4 SAEs	All Causality Grade 3-4	%	45	28.8		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	SAEs					
	Drug-related Grade 3-4 SAEs	%	18.4	10.7		
AEs leading to DC	All causality AEs leading to DC	%	33.0	21.4		
	Drug-related AEs leading to DC	%	18.1	9.1		
Deaths	Deaths due to study drug toxicity	%	1.4	1.1		

Abbreviations: AE (adverse event), AEOSI (adverse event of special interest), BICR (blinded independent central review); CI (confidence interval), HR (hazard ratio)

3.2. Benefit-risk assessment and discussion

3.2.1. Importance of favourable and unfavourable effects

The currently proposed indication applies for an all comers' indication for the treatment of 1L NSCLC. Up till 2015, platinum doublet therapy was the backbone therapy in the treatment of 1L NSLC. Since then, immunotherapy is approved for patient with PD-L1 ≥ 50 % and in combination with chemotherapy for the overall population. The current application will be the first application that applies for an immune therapy in the 1L NSCLC, without the need of additional chemotherapy. As such, it will provide an additional treatment option in NSCLC.

The first line treatment of NSCLC affects a large patient group. Currently, many treatments are available, and the recently approved therapies have improved the prognosis, although this is still dismal for stage IV NSCLC patients.

There is a biological rational for the combination therapy of nivo+ ipi, which is supported the additive effects in vitro and in vivo. The clinical data to support the application are obtained in a single pivotal, open label phase III trial.

The study contained two sub-studies, one concerning patients with PD-L1 > 1% (part 1A) and one involving patents PD-L1 < 1% (part 1B).

For patients with PD-L1 ⩾ 1%, the trial shows a modest improvement in OS with the combination nivo+ ipilimumab vs chemotherapy , i.e. 2.2 months. However, about 43 % of the included chemotherapy group received second line immunotherapy, a treatment which has improved OS in NSCLC in recent years and is likely to have affected the OS results. As such, the observed improvement can be regarded as clinically relevant. The pre-specified (though not alpha-controlled) subgroup analyses showed that effect was driven by the patients with PD-L1 ⩾ 50%. For patients with PD-L1 < 1% , the exploratory analyses for the nivo+ipi vs chemo indicated a clinically relevant improvement with OS (> 4 months) compared with chemotherapy.

The combination therapy was generally less well tolerated compared to chemotherapy.

The study was subject to a triggered inspection. The GCP findings from this inspection are related to a generalised problem of integrity of the data handling. Concerns have been raised regarding the data handling, which may seriously affect the internal validity and the quality of the obtained data. Although

confirming accuracy of the patient data was not within the scope of the GCP inspection, the accuracy of the patient level data is not questioned since the OS is not prone to that. Its acknowledged that source data as captured in the eCRF should be reliable as OS is a hard endpoint. Also, the type of statistical analyses used by the company to calculate the OS benefit is not questioned.

Furthermore, solid measures were lacking to prevent dissemination of information to authorised/non authorised personnel within a non-robust and immature risk management system. Therefore, it is questioned the data quality obtained in this single pivotal trial is sufficient to support the overall application.

Based on these concerns the B/R is negative for the all comer population as efficacy has not been shown as the data is not reliable.

3.2.2. Balance of benefits and risks

Based on these updated results (final CSR based on July-2019), the company is seeking an all comers indication, "OPDIVO in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations (see sections 4.4 and 5.1)". However, the validity of the data is called into question due to triggered GCP inspection findings.

The pivotal clinical study design was extensively modified by means of several amendments changing the primary analysis population and the primary objectives. The lack of integrity of the study converts any judgement and conclusion in unreliable and therefore the benefit of this combination cannot be deemed substantiated. The problems with integrity of the data are considered an unsolvable hurdle.

3.3. Conclusions

The overall B/R of nivolumab in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults with no EGFR or ALK positive tumour mutations is negative.