EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 May 2023
EMA/287093/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0117

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
1°	primary
2L+	second line and above
5-FU	5-flourouracil
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
ALB	albumin
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
BBWT	baseline body weight
BIC	Bayesian information criterion
BICR	blinded independent central review
BIPR	blinded independent pathological review
BMS	Bristol-Myers Squibb
Cavg1	time-averaged concentration over the first dosing interval
Cavg1	time-averaged concentration at the first dosing interval
Cavgss	time-averaged serum concentration at steady state
chemo	chemotherapy
chemo	platinum-doublet chemotherapy
chemo	platinum-doublet chemotherapy
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL0	clearance at time 0 (ie, baseline clearance)
CLss	clearance at steady state
Cmax	maximum observed concentration
Cmax1	peak concentration after the first dose
Cmaxss	peak concentration at steady state
CMH	Cochran-Mantel-Haenszel
Cmin1	trough concentration after the first dose
Cminss	trough concentration at steady state
CPH	Cox Proportional Hazards
CRC	colorectal cancer
CRF	case report form
cRR	clinical response rate
CSR	clinical study report
CT	computed tomography

CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CWRES	conditional weighted residuals
DBL	database lock
DC	discontinuation
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DSTG	disease stage
EAC	esophageal adenocarcinoma
ECL	electrochemiluminesence
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EFS2	event-free survival on next line of therapy
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMAX	maximum change in CL
E-R	exposure-response
ESCC	esophageal squamous cell carcinoma
EU	European Union
FA	final analysis
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GC	gastric cancer
GEJC	gastro-esophageal junction cancer
GI	gastrointestinal
GM	geometric mean
Gr2+ IMAEs	Grade ≥2 immune-mediated adverse events
HCC	hepatocellular carcinoma
HCP	healthcare provider
HLGT	High-level Group Term
HR	hazard ratio
IA	interim analysis
IA1	interim analysis 1
IA2	second interim OS analysis
IA3	third interim OS analysis
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
ipi	ipilimumab
IQR	inter-quartile range
irARs	immune-related adverse reactions
IRB	Institutional Review Board

IRT	interactive response technology
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LLN	lower limit of normal
LPLV	last patient last visit
MAP	maximum a-posteriori
MedDRA	Medical Dictionary for Regulatory Activities
mEFS	median event-free survival
mo	months
Mono	nivolumab monotherapy
MPM	malignant pleural mesothelioma
MPR	major pathologic response
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
N, n	number of subjects or observations
NA	not available / not applicable
NADJ	neoadjuvant
NCI	National Cancer Institute
NCT	National Clinical Trial number
NE	not evaluable
nivo	nivolumab
nivo+chemo	nivolumab 360 mg plus platinum-doublet chemotherapy
No.	number
NSCLC	non-small cell lung cancer
NSQ	nonsquamous
OESIs	other events of special interest
OR	odds ratio
OS	overall survival
P05	5th percentile
P95	95th percentile
PBRER	Periodic Benefit-Risk Evaluation Report
pCR	pathologic complete response
pcVPC	prediction-corrected visual predictive check
PD	progressive disease
PD-1	programmed cell death receptor 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS2	progression-free survival on next line of therapy
PK	pharmacokinetic(s)
PP	persistent positive
PPK	population pharmacokinetic(s)
Pr(pCR)	probability of pathologic complete response
PRO	patient reported outcome

PS	performance status
PT	preferred term
Q	volume/time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QxW	every x weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RSE	relative standard error
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCS	summary of clinical safety
SD	stable disease
SI	International System of Units
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	standard of care
SOC	system organ class
SQ	squamous
TMB	tumor mutation burden
TNM	classification of malignant tumors
TNM	classification of malignant tumors
TSH	thyroid-stimulating hormone
TTDM	time to death or distant metastases
tx	treatment
ULN	upper limit of normal
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VC	volume of distribution central compartment
VP	volume of distribution peripheral compartment
wk	week
WT	wild-type

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 7 March 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include OPDIVO in combination with platinum-based chemotherapy for neoadjuvant treatment of adult patients with resectable Stage IB-IIIA non-small cell lung cancer (NSCLC), based on results from study CA209816; a randomised, open-label, phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 27.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0432/2020, P/0237/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0432/2020 was completed and the P/0237/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The Applicant received Scientific Advice on the development of nivolumab for neoadjuvant treatment of patients with resectable stage IB-IIIA NSCLC from the CHMP on 30 January 2020 (EMEA/H/SA/2253/11/2019/II). The Scientific Advice pertained to the following clinical aspects:

- Regarding a randomised, open-label phase 3 study: The characterisation of the patient population; the choice of comparator; the choice of PCR and EFS as dual primary endpoints; the statistical analysis plan.

Questions were related to the suitability of study CA209816 to support a B/R assessment for

nivolumab in the currently claimed indication. CHMP noted that the study enrolment had finalized before the SA final letter was issued so the included recommendations could not be implemented on the clinical development. Multiple limitations of the study design were highlighted, such as the repeated protocol amendments resulting in a heterogeneous patient population, the fact that histology or backbone treatment were not included as stratification factors, the multiple chemotherapy options which were to be selected after randomization or the possibility to receive adjuvant treatment up to the investigator's decision, as reflected in the protocol. CHMP supported the choice of EFS as primary endpoint, which should be associated with a non-detrimental effect on OS, but not the use of pCR as primary endpoint as no correlation with OS/EFS has been established. Also, the timing and excessive number of interim analyses (IA) were questioned.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Carolina Prieto Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	07 March 2022
Start of procedure	26 March 2022
CHMP Rapporteur's preliminary assessment report circulated on	30 May 2022
PRAC Rapporteur's preliminary assessment report circulated on	30 May 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 June 2022
CHMP Rapporteur's updated assessment report circulated on	18 June 2022
Request for supplementary information adopted by the CHMP on	23 June 2022
MAH's responses submitted to the CHMP on	09 August 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	30 September 2022
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	07 October 2022
2nd Request for supplementary information adopted by the CHMP on	13 October 2022
MAH's responses submitted to the CHMP on	19 December 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	13 May 2023
CHMP opinion adopted on	25 May 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH initially applied for the following indication:

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable Stage IB-IIIA non-small cell lung cancer in adults (see section 5.1).

During the procedure the indication was amended. The agreed indication is as follows:

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria).

Proposed Dosage and Administration

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles.

Epidemiology and risk factors, screening tools/prevention

Lung cancer is the leading cause of cancer mortality worldwide (1.8 million, or 18% of all cancer deaths in 2020), with 2.2 million newly diagnosed cases, or 11.4% of all cancers diagnosed, in 2020. In Europe, 477,534 new lung cancer cases and 384,176 deaths due to lung cancer were estimated to occur in the same year (Globocan 2020).

About 87% of lung cancer cases are NSCLC. At initial diagnosis, 26% of patients present with stage I disease, 8.3% with stage II, 27.6% with stage III, and 38.1% with stage IV disease. Enhanced screening techniques and improved diagnosing methods based on imaging have led to more subjects identified with early-stage disease and the number of patients diagnosed during the non-metastatic stages is expected to increase over time. Long-term outcomes for patients with non-metastatic NSCLC remain poor with 5-year survival rates ranging from 82% for patients with clinical stage IA to 19% for patients with clinical stage IIIB.

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths. The risk for lung cancer increases with the number of packs of cigarettes smoked per day and with the number of years spent smoking. Exposed non-smokers also have an increased relative risk of developing lung cancer (NCCN Guidelines v. 3.2022). Other possible risk factors for lung cancer include disease history (i.e., COPD), cancer history, family history of lung cancer, and exposure to other carcinogens. Asbestos is a known carcinogen that increases the risk for lung cancer in people exposed, especially in individuals who smoke.

Clinical presentation, diagnosis and stage/prognosis

Whenever feasible, patients with early-stage NSCLC are treated surgically with curative intent. Approximately 20–25% of the patients are candidates for surgical resection (Datta et al. 2003). However, many patients are at risk of lung cancer recurrence even after complete resection. The 5-year survival rate in resected NSCLC patients has been reported to be over 70% in stage I patients to only 25% in stage IIIA patients (Goldstraw et al. 2016). A high proportion of patients with resected NSCLC die of recurrent NSCLC, suggesting that a good proportion of these patients have micrometastatic disease at the time of surgical resection (Uramoto et al. 2014).

Management

Treatment options for patients with newly-diagnosed non-metastatic NSCLC depend on tumour resectability and patient operability. Key considerations include tumour characteristics and location, extent of nodal involvement, lung function, patient age and comorbidities. Curative resection is intended for 20% to 25% of patients with newly diagnosed NSCLC. Thoracotomy is the open approach used for lung resection while minimally invasive approaches such as video-assisted thoracoscopy or robotic-assisted thoracoscopy are increasingly considered in order to limit post-operative pain and complications (Lim et al. 2021). A complete resection without residual disease (R0) is desired in order to maximize survival. Rates of complete resection range from 70% to 90% in most historical trials (Pisters et al. 2010).

NCCN guidelines recommend that patients with stage IB (T2a, N0) to IIIA (T1-2, N2; T3, N1) disease (per the 8th edition American Joint Committee on Cancer/Union for International Cancer Control [AJCC/UICC] staging criteria) who had complete resection should receive adjuvant chemotherapy. In the case of N2 disease confirmed by mediastinal biopsy, a preferred treatment would be definitive concurrent chemoradiation followed by consolidation with durvalumab, but patients may also receive neoadjuvant chemotherapy with or without radiation followed by surgery in some cases. ESMO guidelines also support adjuvant chemotherapy to be offered for patients with resectable stage III disease. If single-station N2 disease can be demonstrated by preoperative pathological nodal analysis, induction chemo followed by surgery or induction chemoradiotherapy followed by surgery are also options. Preferred treatment for multi-station N2 includes definitive chemoradiation. A two-drug combination regimen with cisplatin is preferable in the adjuvant setting following these guidelines. Local treatment recommendations usually include neoadjuvant chemotherapy for stage IIIA N2 disease potentially resectable as a treatment option according to a multidisciplinary committee (ESMO 2015, NCCN 2023).

There is enough clinical evidence to support the use of platinum doublets for stage IB-III completely resected tumours. A meta-analysis of surgery followed by adjuvant chemotherapy versus surgery alone in resected NSCLC based on 34 trial comparisons demonstrated a hazard ratio for overall survival (OS) of 0.86 (95% confidence interval [CI]: 0.81, 0.92, $p < 0.0001$), with an absolute increase in survival of 4% at 5 years, from 60% to 64%. Recurrence-free survival (RFS) data were available for 18 trial comparisons and also favoured adjuvant chemotherapy with a HR of 0.83 (95% CI: 0.77, 0.90, $p<0.0001$) (Arriaga et al. 2010). Recent trials have shown a postsurgery disease-free survival benefit with adjuvant targeted therapy and immunotherapy, e.g. IMpower 010 study with atezolizumab.

For the neoadjuvant strategy, evidence is less clear, especially for stage IB-II and stage IIIA tumours considered resectable at diagnosis. Analyses of 15 randomized controlled trials showed a significant benefit of neoadjuvant chemotherapy on OS with an HR of 0.87 (95% CI: 0.78, 0.96, $p = 0.007$), showing an absolute survival improvement of 5% at 5 years vs surgery alone, from 40% to 45%. RFS

results also significantly favoured neoadjuvant chemotherapy (HR = 0.85, 95% CI: 0.76, 0.94, p = 0.002) (Lim et al. 2009). Unfortunately, there is little evidence comparing both strategies in cases where both could be an option. An indirect-comparison meta-analysis of 32 randomized trials showed that the relative HRs for OS and disease-free survival (DFS) with adjuvant chemotherapy compared with neoadjuvant chemotherapy were 0.99 (95% CI: 0.81, 1.21; p = 0.91) and 0.96 (95% CI: 0.77, 1.20; p = 0.70), respectively (Arriaga et al. 2010). Furthermore, the Spanish Lung Cancer group conducted a trial comparing neoadjuvant or adjuvant chemotherapy to surgery alone and 5-year DFS and OS were similar between the three arms (Felip et al. 2010). Currently, there are several phase 3 studies where immune checkpoint inhibitors are being administered as neoadjuvant therapy (± adjuvant).

Regarding the chemotherapy combination, there is no clear evidence of a difference in the effect on OS by chemotherapy regimen or scheduling, number of drugs, or platinum agent used (NSCLC Meta-analysis collaborator group, 2014).

2.1.2. About the product

OPDIVO (nivolumab) is a programmed death receptor-1 blocking antibody which binds to the programmed death 1 (PD 1) receptor and blocks its interaction with PD L1 and PD L2. The PD 1 receptor is a negative regulator of T cell activity that has been shown to be involved in the control of T cell immune responses. Engagement of PD 1 with the ligands PD L1 and PD L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab potentiates T cell responses, including anti tumour responses, through blockade of PD 1 binding to PD L1 and PD L2 ligands.. Nivolumab as a single agent has been approved in the European Union (EU), United States (US), and several other countries for the treatment of patients with melanoma, NSCLC, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and oesophageal cancers.

Nivolumab and ipilimumab combination therapy has been approved in the EU, US, and several other countries for the treatment of advanced (unresectable or metastatic) melanoma, intermediate/poor-risk advanced RCC, unresectable malignant pleural mesothelioma, and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC).

Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy has been approved for first-line treatment of metastatic NSCLC.

Nivolumab in combination with cabozantinib has been approved for the treatment of advanced RCC.

Nivolumab in combination with chemotherapy has been approved for gastric cancer, gastroesophageal junction cancer, and oesophageal adenocarcinoma.

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

The nivolumab non-metastatic NSCLC development program includes four phase 3 studies, which investigate the potential role of nivolumab (± ipilimumab, chemotherapy, or chemoradiotherapy) as neoadjuvant, adjuvant, peri-operative, or concurrent chemoradiotherapy (CCRT) add-on treatment options for patients with unmet medical needs across several clinical settings and as part of various multi-modality based regimens (see table below).

Non-Metastatic NSCLC Study Populations and Efficacy Endpoints

	CA209816	CA209427[a]	CA20973L	CA20977T
Type of therapy	Neoadjuvant	Adjuvant	Add to CCRT	Peri-operative
Primary Population	Stage IB (≥ 4 cm) – IIIA NSCLC	Stage IB (≥ 4 cm) - IIIA NSCLC	Locally advanced stage IIIA, IIIB, or IIIC (T1-2 N2-3 M0, T3 N1-3 M0, orT4 N0-3 M0) histologically-confirmed NSCLC	Stage IIA (≥ 4 cm) to IIIB (T3N2 only) NSCLC
Study Status	Fully accrued	Fully accrued	Fully accrued	Fully accrued
Treatment	Nivo + Chemo; Chemo; Nivo + Ipi	Nivo; Observation	Nivo + CCRT then Nivo + Ipi; Nivo + CCRT then Nivo; CCRT then Durva	Nivo + Chemo then Nivo; Chemo + placebo then placebo
Cancer Stage	7th edition	7th edition	8th edition	8th edition
IB (≥ 4 cm)	√	√		
II	√	√		√
IIIA	√	√	√	√
IIIB			√	√
IIIC			√	
Efficacy Endpoints[b]				
OS	√	√ (Primary)	√	√
EFS	√ (Primary)			√ (Primary)
PFS			√ (Primary)	
DFS		√ (Primary)		
TTDM	√		√	√
pCR rate	√ (Primary)			√
MPR rate	√			√
ORR	√[c]		√	√[c]
CR rate			√	
DOR			√	
TTR			√	

[a] ANVIL: A Phase 3 NCI-sponsored research study of registrational intent.
[b] Exploratory endpoints are not included.
[c] Response rate at the tumor assessment prior to surgery
Abbreviations: CCRT - concurrent chemoradiotherapy, chemo - chemotherapy, CR - complete response; DFS - disease-free survival, DOR - duration of response, durva - durvalumab, EFS - event-free survival, ipi - ipilimumab, MPR - major pathological response, NCI - National Cancer Institute, nivo - nivolumab, NSCLC - non-small cell lung cancer, ORR - objective response rate, OS - overall survival, pCR - pathologic complete response, PFS – progression-free survival, TTDM - time to death or distant metastases, TTR-time to response.

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

BMS-936558 (nivolumab) is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, nivolumab is exempt from preparation of an Environmental Risk Assessment under the 1 June 2006 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00). Nivolumab and the product excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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.

Of note, the MAH during a routine inspection readiness activity for the CA209816 study conducted in June 2022, observed deficiencies in their monitoring process at one investigative site in China (Tianjin Medical University Cancer Institute and Hospital, Site 0163, 27 randomized patients). Multiple potential adverse events (AEs, all non-serious) and concomitant medications documented in medical notes across all study arms were not entered into the Electronic Data Capture (EDC) system. Following complete source data review, sites entered the missing data into the EDC and preliminary assessment of the newly entered safety information was performed in July 2022. Due to this GCP finding, the MAH expanded the investigation to all 15 sites in China participating in the study and performed full on-site review of all available source records. Upon complete source review, a second site (Beijing Cancer Hospital, Site 0161, 13 randomized patients) had similar findings with potentially missed AEs (all non-serious AEs). The potential root cause of the issues at Sites 0163 and 0161 appeared to be related to deficiency in the MAH monitoring at those two trial sites (see section 2.5.1).

- Tabular overview of clinical studies

Summary of CA209816 (Resectable NSCLC) - Data Supporting this submission

Trial Identity/ NCT no.	Trial Design	Regimen/ Schedule/ Route for this Application	Key Efficacy Endpoints	Treatment Duration/ Follow-up	No. of subjects enrolled	Study Population	No. of Centers and Countries
CA209816 Pivotal	Phase 3, randomized,	**Nivo+Chemo Arm** Nivolumab (Q3W): Nivo	Primary: EFS and pCR	3 cycles / Follow-up	773[a] (505	Subjects with	111 sites in 14 countries[b]

Summary of CA209816 (Resectable NSCLC) - Data Supporting this submission

Trial Identity/ NCT no.	Trial Design	Regimen/ Schedule/ Route for this Application	Key Efficacy Endpoints	Treatment Duration/ Follow-up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Study/ NCT02998528	open-label study of nivo+chemo vs chemo in subjects with resectable NSCLC	360 mg IV every 3 weeks for up to 3 cycles Chemotherapy: Investigator's choice of cisplatin (75 mg/m^2 on Day 1 of a 3-week cycle for up to 3 cycles) or carboplatin (AUC 5 or 6 on Day 1 of a 3-week cycle for up to 3 cycles) in combination with gemcitabine (1000 mg/m^2 or 1250 mg/m^2 on Days 1 and 8 of a 3-week cycle for up to 3 cycles) for squamous histology, or with pemetrexed (500 mg/m^2 on Day 1 of a 3-week cycle for up to 3 cycles) for non-squamous histology, or carboplatin (AUC 5 or 6 on Day 1 of a 3-week cycle for up to 3 cycles) + paclitaxel (175 or 200 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles) for any histology **Chemo Arm** Investigator's choice of cisplatin (75 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles) or carboplatin (AUC 5 or 6 on Day 1 of a 3-week cycle for up to 3 cycles) in combination with vinorelbine (25 mg/m^2 or 30 mg/m^2 on Days 1 and 8 of a 3-week cycle for up to 3 cycles), docetaxel (60 mg/m^2 or 75 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles), gemcitabine (1000 mg/m^2 or 1250 mg/m^2 on Days 1 and 8 of a 3-week cycle for up to 3 cycles) (for squamous histology only), or pemetrexed (500 mg/m^2 on Day 1 of a 3-week cycle for up to 3 cycles) (for non-squamous histology only); or carboplatin (AUC 5 or 6) + paclitaxel (175 or 200 mg/m^2) on Day 1 of a 3 week cycle for up to 3 cycles)	of nivo+chemo vs chemo. Secondary: OS, TTDM, MPR Exploratory: EFS2	Visit 1 at 30 days, Visit 2 around 100 days, and then every 3 months	subjects randomized, including 358 concurrently randomized to the nivo+chemo [n = 179] and chemo [n = 179] arms)	resectable NSCLC (stage IB [≥ 4 cm], stage II, and stage IIIA)	

[a] The enrolled population contains all subjects who were screened for the trial.

[b] Brazil did not enroll patients under revised protocol 02 and onwards.

Abbreviations from previous page: AUC - area under the plasma drug concentration-time curve; chemo - chemotherapy; cRR - clinical response rate; EFS - event-free survival; EFS2 - event-free survival on second line therapy; ipi - ipilimumab; IV - intravenous; MPR - major pathologic response; NCT - National Clinical Trial number; nivo - nivolumab; NSCLC - non-small cell lung cancer; OS - overall survival; pCR - pathologic complete response; PD-L1 - programmed death ligand 1; PRO - patient-reported outcome; QxW - every X weeks; TNM - classification of malignant tumors; TTDM - time to death or distant metastases.

2.3.2. Pharmacokinetics

Pharmacokinetics in the target population

A previously developed population pharmacokinetic (PPK) model of nivolumab was updated by retaining the Phase 1 dose-ranging studies, and select studies in NSCLC tumour type, and by adding data from the first-line (1L) NSCLC study containing nivolumab monotherapy and nivolumab + chemotherapy arms (Study CA209227). Additionally, data from nivolumab monotherapy studies conducted with Chinese or Japanese subjects in NSCLC or other solid tumours, and data in early-stage NSCLC subjects (Study CA209816) were included.

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

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule	Analysis
MDX1106-03 (CA209003): Phase I, open-label, multicenter, multi-dose, dose-escalation study to evaluate the safety and tolerability of BMS-936558 in subjects with selected advanced or recurrent malignancies *Adult subjects with pathologically verified and advanced or recurrent and progressing colorectal adenocarcinoma, melanoma, NSCLC, castrate resistant prostate adenocarcinoma, and RCC*	Nivo 0.1, 0.3, 1, 3, or 10 mg/kg depending upon tumor type Q2W (60 min infusion) for up to twelve 8-week cycles	338 (290+48 from amendment)	**Pre-Amendment:** C1: EOI and pre-infusion levels on infusion days: D1, D15, D29, and D43 and C2: Single samples were collected **Post-Amendment:** Serial PK samples were collected from all subjects enrolled in 0.1, 0.3 and 1 mg/kg MEL cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts. C1: D1 (after 60-min infusion, 4, 8 h), D2, D3, D5, D8, D15), C2: D1 (pre-infusion), C3: D1 (pre-infusion, after 60-min infusion), and D2, D3, D5, D8, D15) Limited PK samples were collected from subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC. C1: D1 (after 60-min infusion), D3, D8, D15), C2D1 (pre-infusion), C3D1 (pre-infusion, after 60-min infusion), and D3, D8, D15) Each treatment cycle is comprised of 4 doses administered on D1, D15, D29, and D43 of the cycle	Nivo PPK
ONO-4538-01 (CA209005): Phase 1 single-dose study to evaluate of safety, tolerability, and pharmacokinetics in	Nivo 1, 3, 10, and 20 mg/kg Q3W for 1st dose then Q2W (60 min infusion)	24 (up to 6 subjects are each dose level)	**Single-Dose Phase:** D1: 1 h after the start and 2 and 8 hours after EOI, Pre-Day 2, pre-Day 3;	Nivo PPK

subjects with progressive or recurrent solid tumors *Subjects with melanoma and NSCLC*			pre-Day 4; D8, D15, and D22 or study discontinuation **Multiple-Dose Phase:** Before administration on D1; before administration and immediately after the end of administration on D15; and D29 or study discontinuation **Extended-Treatment Phase:** Before administration on D1; before administration on D15 and D29; before administration and immediately after the end of administration on D43 and D57	
CA209017: An open-label, randomized Phase 3 trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) *Squamous NSCLC*	Nivo 3 mg/kg Q2W (60 min infusion)	132 (Nivo treated)	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion and pre-infusion at C2 and C3 and every 8th cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	Nivo PPK
CA209057: An open-label, randomized Phase 3 trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic non-squamous cell non-small cell lung cancer (NSCLC) *NSQ NSCLC*	Nivo 3 mg/kg Q2W (60 min infusion)	287 (Nivo treated)	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion and pre-infusion at C2 and C3 and every 8th cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	Nivo PPK
CA209077: A Phase 1/2, open-label study of nivolumab (BMS-936558) in Chinese subjects with previously treated advanced or recurrent solid tumors *Subjects with multiple solid tumor types*	**Dose Evaluation Phase:** Nivo 3 mg/kg Q2W **Cohort Expansion Phase:** A: Nivo 3 mg/kg Q2W B: Nivo 240 mg Q2W	~14 6-9 (dose evaluation) 12-20 (A: NSCLC or other)	C1: predose, 0.5 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, and 336 h C2: predose	Nivo PPK
	C: Nivo 360 mg Q3W D: Nivo 480 mg Q4W	12 (C: GC or NSCLC or other)	C3: predose, 0.5 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, and 336 h C5, C7: predose Every 2 cycles after C7: predose 2 follow-up samples 30 days and 70 days after last visit 1 cycle = 8 weeks for cohorts A and B; 1 cycle = 3weeks for cohort C; 1 cycle = 4 weeks for cohort D	
CA209078: An open-label randomized multinational Phase 3 trial of nivolumab versus docetaxel in previously treated subjects with advanced or metastatic non-small cell lung cancer *Advanced or metastatic NSCLC*	Nivo 3 mg/kg Q2W	~333	C1, C3, C11, C19, C27, C39 : D1, predose; Every 12th cycles after C39: D1, predose; First 2 Follow-up visits 1 cycle = 2 weeks	Nivo PPK
CA209227: An open-label, randomized Phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in subjects with chemotherapy-naïve Stage IV or recurrent non-small cell lung cancer (NSCLC) [CheckMate 227,	**Part 1a, Arm A:** Nivo 240 mg IV (30 min infusion) Q2W until disease progression (PD-L1 ≥ 1%) **Part 1b, Arm G:** Nivo 360 mg IV (30 min infusion) Q3W + histology-based platinum-doublet chemotherapy, four 3-week cycles (PD-L1 < 1%)	400 subjects in Arm A 180 subjects in Arm G 375 subjects in Arm H	**Arm A:** Blood samples were collected at C1D1, C2D1, C4D1, C10D1, and D1 of every 9th cycle after C10D1 until end of study treatment. First 2 follow-up visits (approximately up to 100 days from the discontinuation of study drug)	Nivo PPK

CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 227] *Chemotherapy-naïve stage IV or recurrent NSCLC*	**Part 2, Arm H**: Nivo 360 mg IV (30 min infusion) Q3W + histology-based platinum-doublet chemotherapy, four 3-week cycles (PD-L1 all comers)		**Arms G and H:** Blood samples were collected at C1D1, C2D1, C5D1, C10D1, and D1 of every 9th cycle after C10D1 until end of study treatment. First 2 follow-up visits (approximately up to 100 days from the discontinuation of study drug)	
CA209816: Randomized, open-label, Phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC (CheckMate 816: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 816) *Histologically confirmed stage IB (≥ 4 cm), II, IIIA (N2) NSCLC (per the 7th International Association for the Study of Lung Cancer) with disease that is considered resectable*	**Arm C:** Nivo 360 mg IV + platinum-doublet chemotherapy Q3W x 3 doses	175	Blood samples were collected at EOI time point on C1D1, and at predose time point on C2D1, C3D1, where each cycle = 3 weeks	Nivo PPK

Abbreviations: C = Cycle; D = Day; EOI = end of infusion; GC = gastric cancer; IV = intravenous; Nivo = nivolumab; NSCLC = non-small cell carcinoma; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; PPK = population pharmacokinetics; MEL = melanoma; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; NSQ = non-squamous; RCC = renal cell carcinoma.

[a] As per protocol.

The nivolumab PPK analysis includes all subjects from the studies listed in Table 1 who were treated with nivolumab monotherapy and/or in combination with chemotherapy for whom nivolumab serum concentration data were available. Subjects for whom no serum concentrations were available or those who had PK samples that could not be associated with clinical data were excluded from the analysis.

A summary of the subjects included in the nivolumab PPK analysis dataset is provided in Table 2.

Table 2: Subjects Included in the Nivolumab Population Pharmacokinetic Analysis Dataset

	Number of Subjects			
Study	**Nivolumab Treated**	**PK Database[a]**	**Flagged[b]**	**Included in the PPK Analysis (% of subjects in PK Database)**
MDX-1106-03	306	310	6	304 (98.1)
ONO-4538-01	17	17	0	17 (100)
CA209017	132	127	2	125 (98.4)
CA209057	287	282	2	280 (99.3)
CA209077	35	35	0	35 (100)
CA209078	337	331	30	301 (90.9)
CA209227[c]	938	880	59	821 (93.3)
CA209816[d]	176	174	0	174 (100)
Total	2228	2156	99	2057 (95.4)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1.1-1.rtf

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

[b] Flag details are provided in Appendix 3.3.1-1.

[c] Part 1: Arms A and G, and Part 2: Arm H

[d] Arm C

Table 3 provides a summary of the PK samples in the nivolumab PPK analysis dataset, indicating the percentage of samples included in the PPK analysis, and the reasons for exclusion of the remaining samples.

Table 3: Samples Included in the Nivolumab Population Pharmacokinetic Analysis Dataset

Study	PK DB[a]	Day 1 Pre-Dose	Missing dose or sample information	Duplicate samples at same time (set up for NCA)	LLOQ[b]	Other[c]	Outliers	Samples included in analysis (%)[d]
MDX-1106-03	3733	331	32	76	74	2	10	3208 (94.3)
ONO-4538-01	285	17	0	0	0	0	0	268 (100.0)
CA209017	585	122	0	0	9	0	1	453 (97.8)
CA209057	1355	267	13	0	15	0	2	1058 (97.2)
CA209077	501	35	0	48	0	0	0	418 (89.7)
CA209078	897	329	0	0	3	0	1	564 (99.3)
CA209227	2969	733	42	0	10	4	4	2176 (97.3)
CA209816	477	0	9	0	1	0	0	467 (97.9)
Total	**10802**	**1834**	**96**	**124**	**112**	**6**	**18**	**8612 (96.0)**

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1.2-1.rtf
Abbreviations: DB = database; LLOQ = lower limit of quantitation; NCA = noncompartmental analysis; PK = pharmacokinetic.

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

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

[c] Samples with nivolumab serum concentration > 2000 μg/mL or samples collected using incorrect kit

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

Table 4 provides summary statistics of the baseline covariates used in the model development. Subjects treated with nivolumab monotherapy and/or in combination with chemotherapy (N = 2057) were used in the main analysis.

Table 4: Summary of Covariates in the Nivolumab Population Pharmacokinetic Analysis Dataset by Tumour Type and Line of Therapy

Covariate	1L NSCLC N = 821	2L+ NSCLC N = 849	NADJ NSCLC N = 174	Others N = 213	Overall N = 2057
Sex N (%)					
Male	572 (69.7)	568 (66.9)	127 (73.0)	148 (69.5)	1415 (68.8)
Female	249 (30.3)	281 (33.1)	47 (27.0)	65 (30.5)	642 (31.2)
Race N (%)					
Missing	0 (0)	2 (0.2)	0 (0)	0 (0)	2 (0.1)
White	619 (75.4)	506 (59.6)	86 (49.4)	165 (77.5)	1376 (66.9)
Black/African American	8 (1.0)	21 (2.5)	4 (2.3)	6 (2.8)	39 (1.9)
Asian	178 (21.7)	309 (36.4)	84 (48.3)	40 (18.8)	611 (29.7)
American Indian/Alaska Native	2 (0.2)	1 (0.1)	0 (0)	0 (0)	3 (0.1)
Others	13 (1.6)	8 (0.9)	0 (0)	2 (0.9)	23 (1.1)
Unknown	1 (0.1)	2 (0.2)	0 (0)	0 (0)	3 (0.1)
Baseline Performance Status N (%)					
0	304 (37.0)	187 (22.0)	120 (69.0)	112 (52.6)	723 (35.1)
1	515 (62.7)	658 (77.5)	54 (31.0)	97 (45.5)	1324 (64.4)
2	2 (0.2)	4 (0.5)	0 (0)	4 (1.9)	10 (0.5)
Tumor Type N (%)					
NSCLC	821 (100.0)	849 (100.0)	174 (100.0)	0 (0)	1844 (89.6)
Others	0 (0)	0 (0)	0 (0)	213 (100.0)	213 (10.4)
Liver Dysfunction Groups N (%)					
Missing	2 (0.2)	3 (0.4)	4 (2.3)	4 (1.9)	13 (0.6)
GROUP A: Normal	752 (91.6)	787 (92.7)	161 (92.5)	181 (85.0)	1881 (91.4)
GROUP B: Mild	67 (8.2)	58 (6.8)	9 (5.2)	28 (13.1)	162 (7.9)
GROUP C: Moderate	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.0)
Nominal Dose of Nivolumab					
0.1 mg/kg	0 (0)	0 (0)	0 (0)	17 (8.0)	17 (0.8)
0.3 mg/kg	0 (0)	0 (0)	0 (0)	18 (8.5)	18 (0.9)
1 mg/kg	0 (0)	34 (4.0)	0 (0)	55 (25.8)	89 (4.3)
3 mg/kg	0 (0)	754 (88.8)	0 (0)	25 (11.7)	779 (37.9)
10 mg/kg	0 (0)	60 (7.1)	0 (0)	76 (35.7)	136 (6.6)
20 mg/kg	0 (0)	0 (0)	0 (0)	3 (1.4)	3 (0.1)
240 mg	328 (40.0)	1 (0.1)	0 (0)	19 (8.9)	348 (16.9)
360 mg	493 (60.0)	0 (0)	174 (100.0)	0 (0)	667 (32.4)
Treatment					
nivo	328 (40.0)	849 (100.0)	0 (0)	213 (100.0)	1390 (67.6)
nivo+chemo	493 (60.0)	0 (0)	174 (100.0)	0 (0)	667 (32.4)

Covariate	1L NSCLC N = 821	2L+ NSCLC N = 849	NADJ NSCLC N = 174	Others N = 213	Overall N = 2057
Line of Therapy N (%)					
Neoadjuvant	0 (0)	0 (0)	174 (100.0)	0 (0)	174 (8.5)
1	821 (100.0)	0 (0)	0 (0)	1 (0.5)	822 (40.0)
> 1	0 (0)	849 (100.0)	0 (0)	212 (99.5)	1061 (51.6)
Best Overall Response					
Missing	0 (0)	5 (0.6)	174 (100.0)	12 (5.6)	191 (9.3)
CR	30 (3.7)	5 (0.6)	0 (0)	2 (0.9)	37 (1.8)
PR	326 (39.7)	98 (11.5)	0 (0)	41 (19.2)	465 (22.6)
SD	319 (38.9)	141 (16.6)	0 (0)	47 (22.1)	507 (24.6)
PD	117 (14.3)	237 (27.9)	0 (0)	70 (32.9)	424 (20.6)
NE	29 (3.5)	35 (4.1)	0 (0)	0 (0)	64 (3.1)
NA	0 (0)	328 (38.6)	0 (0)	41 (19.2)	369 (17.9)
BOR Criteria					
Missing	0 (0)	316 (37.2)	174 (100.0)	37 (17.4)	527 (25.6)
RECIST v1.0	0 (0)	128 (15.1)	0 (0)	176 (82.6)	304 (14.8)
RECIST v1.1	821 (100.0)	405 (47.7)	0 (0)	0 (0)	1226 (59.6)
Age (years)					
Mean (SD)	63 (9.81)	60.8 (9.41)	64.1 (7.56)	58.5 (13.2)	61.7 (10)
Median (Min, Max)	64 (27, 85)	61 (27, 85)	64 (46, 82)	59 (27, 85)	62 (27, 85)
Baseline Body Weight (kg)					
Mean (SD)	70.8 (16)	70.7 (15.3)	71 (15.6)	80.5 (21)	71.8 (16.5)
Median (Min, Max)	68.7 (37.2, 131)	68.5 (41, 158)	68.1 (40.4, 148)	77 (36.2, 153)	69.2 (36.2, 158)
Missing N (%)	2 (0.244)	1 (0.118)	-	-	3 (0.146)
Baseline eGFR (mL/min/1.73 m^2)					
Mean (SD)	91.1 (16.4)	86.6 (19.1)	90.4 (15.1)	83.6 (21.8)	88.4 (18.3)
Median (Min, Max)	93.5 (34.2, 143)	89.1 (31.1, 135)	93.3 (43.8, 138)	87.5 (36.4, 132)	91.3 (31.1, 143)
Missing N (%)	2 (0.244)	3 (0.353)	4 (2.3)	3 (1.41)	12 (0.583)
Baseline Lactate Dehydrogenase (U/L)					
Mean (SD)	304 (248)	309 (253)	234 (108)	321 (441)	302 (269)
Median (Min, Max)	236 (82, 3601)	226 (97, 3085)	202 (95, 842)	196 (74, 3004)	225 (74, 3601)
Missing N (%)	8 (0.974)	6 (0.707)	5 (2.87)	5 (2.35)	24 (1.17)

Covariate	1L NSCLC N = 821	2L+ NSCLC N = 849	NADJ NSCLC N = 174	Others N = 213	Overall N = 2057
Baseline Serum Albumin (g/dL)					
Mean (SD)	3.91 (0.495)	4.02 (0.475)	4.13 (0.423)	4.11 (0.51)	3.99 (0.489)
Median (Min, Max)	4 (1.5, 5.1)	4 (1.9, 5.3)	4.2 (2.9, 5.1)	4.2 (2.5, 5.1)	4 (1.5, 5.3)
Missing N (%)	8 (0.974)	13 (1.53)	4 (2.3)	3 (1.41)	28 (1.36)
Baseline Alanine Aminotransferase (U/L)					
Mean (SD)	23.2 (16.2)	21.6 (12.9)	21.1 (12.8)	24.6 (17.8)	22.5 (14.8)
Median (Min, Max)	18 (5, 121)	18 (4, 108)	18 (5, 99)	19 (2, 118)	18 (2, 121)
Missing N (%)	4 (0.487)	7 (0.824)	4 (2.3)	16 (7.51)	31 (1.51)
Baseline Aspartate Aminotransferase (U/L)					
Mean (SD)	22.4 (10.8)	23.7 (10.4)	20.2 (7.36)	26.7 (15.8)	23.2 (11.1)
Median (Min, Max)	20 (7, 100)	22 (6, 114)	18 (8, 61)	22 (11, 130)	21 (6, 130)
Missing N (%)	2 (0.244)	8 (0.942)	4 (2.3)	16 (7.51)	30 (1.46)
Baseline Serum Alkaline Phosphatase (U/L)					
Mean (SD)	126 (88.5)	108 (73)	130 (142)	126 (140)	119 (94.9)
Median (Min, Max)	94 (29, 925)	90 (30, 1165)	92 (33, 1652)	83 (34, 1414)	92 (29, 1652)
Missing N (%)	4 (0.487)	9 (1.06)	4 (2.3)	17 (7.98)	34 (1.65)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
Program Source: Analysis-Directory/sas/Table3.3.1.5-1.sas
Source: Analysis-Directory/reports/Table3.3.1.5-1.rtf
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; BOR = best overall response; chemo = chemotherapy; CR = complete response; eGFR = estimated glomerular filtration rate; Min = minimum; Max = maximum; NA = missing or not reported; NADJ = neoadjuvant; NE = unevaluable; nivo = nivolumab; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = standard deviation or stable disease (for BOR values).

Model Development

This analysis was primarily to re-estimate the parameters and variability using full models, and to assess the PPK of nivolumab when coadministered with chemotherapy in early-stage NSCLC subjects.

Base model

Base model development consisted of re-estimating parameters of a previously developed full model (tumour type, ipilimumab dosing regimens, ipilimumab coadministration, and ipilimumab + chemotherapy coadministration were removed) with the current analysis dataset.

The base model was a 2-compartment, zero-order IV infusion PK model, with time-varying CL (sigmoidal-Emax function); and a proportional residual error model, with random effects on CL, Q, VC, VP, and EMAX; and correlation of random effect between CL and VC. The variance of random effect was estimated jointly for the two CL parameters (CL, Q) and for the two volume parameters (VC, VP). The base model contained BBWT, sex, race, GFR, PS, and chemotherapy coadministration on CL; BBWT and sex on VC; BBWT on Q; BBWT on VP; and PS on EMAX.

Table 5: Parameter Estimates of the Base Nivolumab Population Pharmacokinetic Model

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed Effects				
CL [L/h]	θ_1	0.0123	3.81E-04 (3.09)	0.0116 - 0.0131
VC [L]	θ_2	4.24	0.0545 (1.29)	4.13 - 4.34
Q [L/h]	θ_3	0.0308	0.00254 (8.25)	0.0258 - 0.0358
VP [L]	θ_4	2.54	0.119 (4.67)	2.31 - 2.77
CL_{BBWT}	θ_7	0.441	0.0451 (10.2)	0.353 - 0.530
CL_{GFR}	θ_8	0.128	0.0352 (27.5)	0.0589 - 0.197
CL_{FEMALE}	θ_9	-0.212	0.0193 (9.08)	-0.250 - -0.175
CL_{PS}	θ_{10}	0.135	0.0213 (15.8)	0.0929 - 0.176
CL_{RAAA}	θ_{11}	0.0519	0.0569 (110)	-0.0597 - 0.163
CL_{RAAS}	θ_{12}	-0.133	0.0186 (14.0)	-0.170 - -0.0965
$V1_{BBWT}$	θ_{13}	0.632	0.0461 (7.30)	0.542 - 0.723
$V1_{FEMALE}$	θ_{14}	-0.164	0.0242 (14.8)	-0.211 - -0.116
CL_{EMAX}	θ_{15}	-0.346	0.0380 (11.0)	-0.420 - -0.271
CL_{T50}	θ_{16}	1.39E+03	73.3 (5.27)	1.25E+03 - 1.53E+03
CL_{HILL}	θ_{17}	2.46	0.383 (15.6)	1.71 - 3.21
CL_{CHEMO}	θ_{18}	-0.153	0.0158 (10.4)	-0.184 - -0.122
$EMAX_{PS}$	θ_{19}	-0.0878	0.0305 (34.7)	-0.147 - -0.0281
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.0919 (0.303)	0.00634 (6.90)	0.0795 - 0.104
ZV1 [-]	$\omega_{2,2}$	0.101 (0.318)	0.0131 (12.9)	0.0755 - 0.127
ZEMAX [h]	$\omega_{4,4}$	0.0444 (0.211)	0.0108 (24.3)	0.0233 - 0.0655
ZCL:ZV1	$\omega_{1,2}$	0.0445 (0.461)	0.00582 (13.1)	0.0331 - 0.0559
Residual Error				
PERR [-]	θ_6	0.209	0.00472 (2.26)	0.199 - 0.218

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final

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

Source: Analysis-Directory/nm/basef/reports/basef_RTF.rtf

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

Note 2: Eta shrinkage (%): ETA_CL: 14.4; ETA_VC: 37.5; ETA_EMAX: 53.1; EPS shrinkage (%): 16.7.

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

Full model

The full model was developed from the base model by incorporating additional covariates representing the effect of tumour type + line of therapy (NADJ NSCLC, 1L NSCLC, and Others [OTHER] versus 2L+ NSCLC) and baseline albumin on nivolumab CL, and chemotherapy combination effect on EMAX.

The full model was as follows:

$$CL0_i = CL0_{REF} \cdot \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \cdot \left(\frac{eGFR_i}{eGFR_{REF}}\right)^{CL_{eGFR}} \cdot \left(\frac{BALB_i}{BALB_{REF}}\right)^{CL_{BALB}} \cdot e^{CL_{CHEMO} \cdot I_{CHEMO}} \cdot e^{CL_{1L\ NSCLC} \cdot I_{1L\ NSCLC}} \cdot e^{CL_{NADJ\ NSCLC} \cdot I_{NADJ\ NSCLC}} \cdot e^{CL_{OTHER} \cdot I_{OTHER}} \cdot e^{CL_{FEMALE} \cdot I_{FEMALE}} \cdot e^{CL_{PS} \cdot I_{PS}} \cdot e^{CL_{RAAA} \cdot I_{RAAA}} \cdot e^{CL_{RAAS} \cdot I_{RAAS}} \cdot e^{\eta_{CL_i}}$$

$$EMAX_i = EMAX_{REF} + EMAX_{PS} \cdot I_{PS} + EMAX_{CHEMO} \cdot I_{CHEMO} + \eta_{EMAX_i}$$

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

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

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

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

where *CL0REF* is the typical value of CL at time 0 (CL0) at the reference values of BBWT, PS, and eGFR, SEX is referenced to male, and race is referenced to white. *VCREF*, *QREF*, and *VPREF* are typical values of VC, Q, and VP at the reference values of BBWT, respectively. *CLBBWT*, *CLeGFR*, *CLFEMALE*, *CLPS*, *CL1L NSCLC*, *CLNADJ NSCLC*, *CLOTHER*, *CLBALB*, *CLCHEMO*, *CLRAAA*, *CLRAAS*, *EMAXPS*, *EMAXCHEMO*, *VCBBWT*, and VCFEMALE are model parameters. CHEMO indicates nivolumab combined with chemotherapy, RAAA indicates race (African American), and RAAS indicates race (Asian). EMAXREF represents the reference value of the maximal change in CL. The T50 parameter represent the time at which the change in CLt,i is 50% of EMAX and HILL represents the sigmoidicity of the relationship with time.

ηCLi, *ηQi*, *ηVCi*, *ηVPi*, and *ηEMAXi* are normally distributed random variables. *IFEMALE*, *IPS*, *IRAAA*, *IRAAS* and *ICHEMO* are the categorical covariate indicator

Parameter estimates for this model are presented in Table 6, and the covariate effects are shown in Figure 1.

Table 6: Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d,e]
Fixed Effects				
CL [L/h]	θ_1	0.0119	3.79E-04 (3.19)	0.0112 - 0.0127
VC [L]	θ_2	4.23	0.0559 (1.32)	4.12 - 4.34
Q [L/h]	θ_3	0.0306	0.00259 (8.49)	0.0254 - 0.0358
VP [L]	θ_4	2.55	0.118 (4.63)	2.31 - 2.81
CL_{BBWT}	θ_7	0.506	0.0423 (8.36)	0.421 - 0.590
CL_{GFR}	θ_9	0.110	0.0337 (30.7)	0.0466 - 0.179
CL_{BALB}	θ_{11}	-0.937	0.0709 (7.57)	-1.07 - -0.787
CL_{FEMALE}	θ_{12}	-0.198	0.0180 (9.13)	-0.233 - -0.163
CL_PS_1	θ_{13}	0.103	0.0211 (20.6)	0.0621 - 0.144
CL_{RAAA}	θ_{14}	0.0501	0.0533 (106)	-0.0616 - 0.152
CL_{RAAS}	θ_{15}	-0.0754	0.0182 (24.2)	-0.112 - -0.0411
$V1_{BBWT}$	θ_{16}	0.641	0.0458 (7.16)	0.548 - 0.724
$V1_{FEMALE}$	θ_{17}	-0.161	0.0243 (15.1)	-0.210 - -0.113
CL_{EMAX}	θ_{18}	-0.328	0.0413 (12.6)	-0.419 - -0.243
CL_{T50}	θ_{19}	1.38E+03	69.9 (5.06)	1.25E+03 - 1.53E+03
CL_{HILL}	θ_{20}	2.51	0.420 (16.8)	1.85 - 3.67
$CL_{NADJ\ NSCLC}$	θ_{21}	-0.0504	0.0391 (77.6)	-0.132 - 0.0227
$CL_{IL\ NSCLC}$	θ_{22}	0.0242	0.0232 (95.9)	-0.0229 - 0.0672
CL_{OTH}	θ_{23}	0.119	0.0296 (24.9)	0.0628 - 0.177
CL_{CHEMO}	θ_{24}	-0.111	0.0282 (25.5)	-0.165 - -0.0574
$EMAX\_PS_1$	θ_{25}	-0.0751	0.0300 (39.9)	-0.136 - -0.0179
$EMAX_{CHEMO}$	θ_{26}	-0.0707	0.0291 (41.1)	-0.128 - -0.0137
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.0776 (0.279)	0.00610 (7.86)	0.0653 - 0.0883
ZV1 [-]	$\omega_{2,2}$	0.102 (0.319)	0.0130 (12.7)	0.0761 - 0.130
ZEMAX [h]	$\omega_{4,4}$	0.0467 (0.216)	0.0102 (21.9)	0.0277 - 0.0712
ZCL:ZV1	$\omega_{1,2}$	0.0361 (0.406)	0.00574 (15.9)	0.0251 - 0.0482
Residual Error				
PERR [-]	θ_6	0.207	0.00466 (2.25)	0.198 - 0.216

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final

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

Source: Analysis-Directory/nm/full816/reports/full816_RTF.rtf

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

Note 2: Eta shrinkage (%): ETA_CL: 16.5; ETA_VC: 38.8; ETA_EMAX: 51.4; EPS shrinkage (%): 16.7.

[a] 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 $\sigma_{i,j}$).

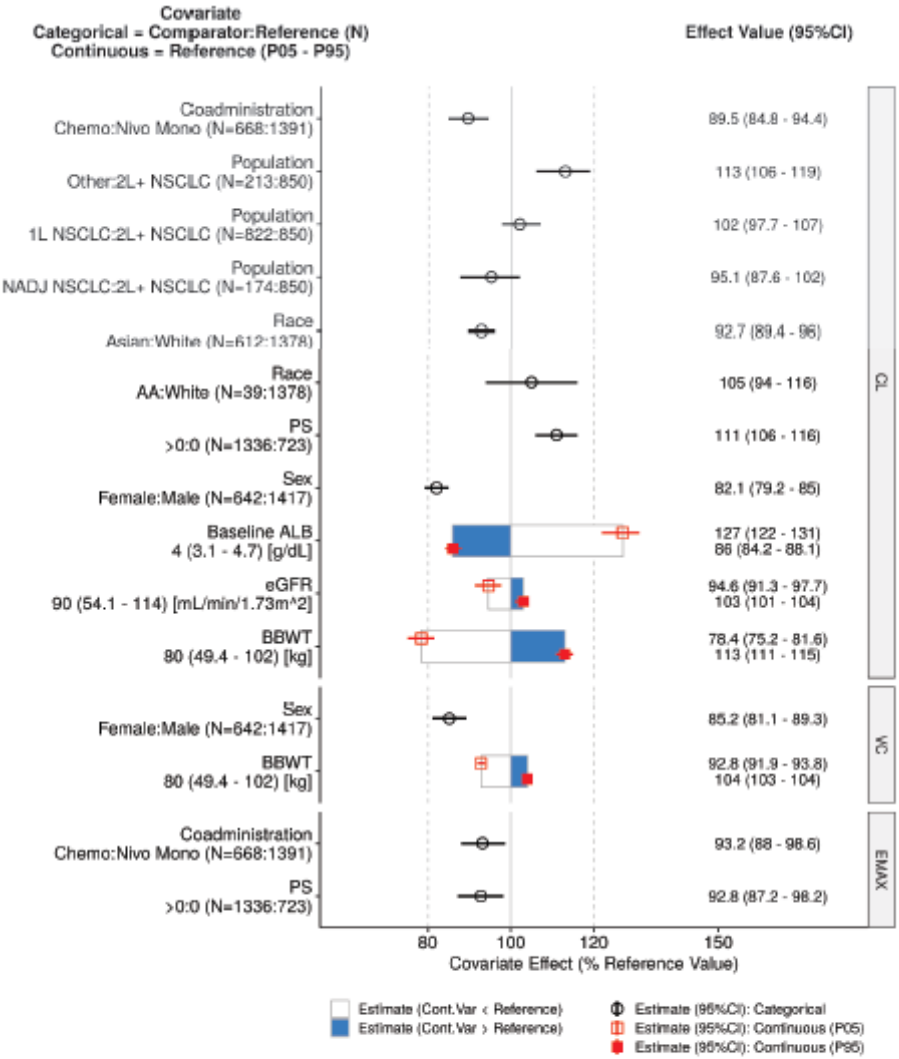
[b] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

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

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

[e] Confidence Interval values are taken from bootstrap calculations (777 successful out of a total of 1000).

Figure 1: Covariate Effects on Nivolumab Pharmacokinetic Model Parameters (Full Nivolumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final

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

Source: Analysis-Directory/R/plots/full-1-ggcoveff-plot.png

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

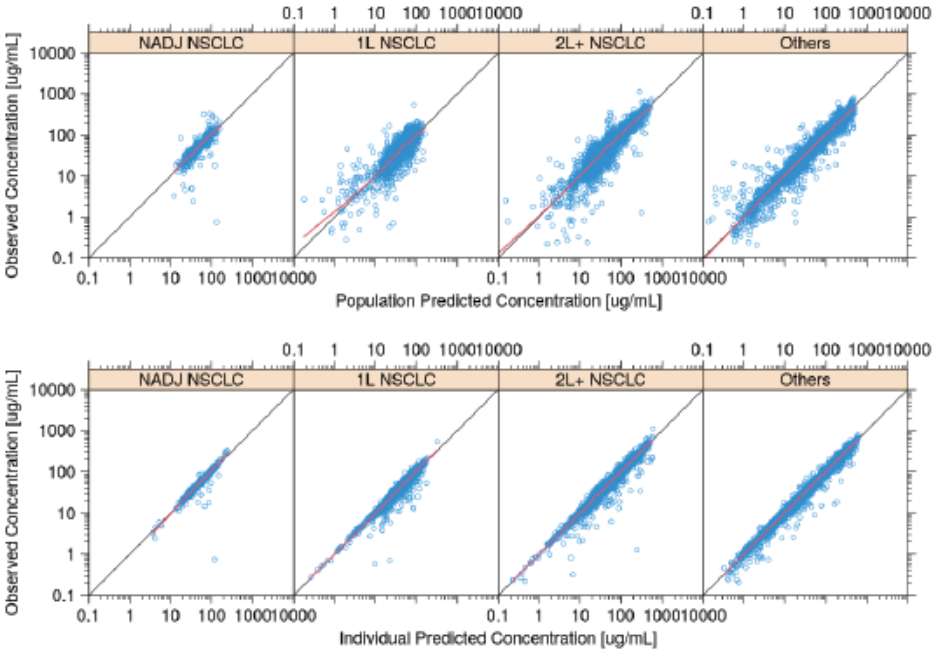
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

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

Note 4: The effect of BBWT was also added on inter-compartment clearance (Q) and volume of distribution of peripheral compartment (VP) and their estimates were fixed to be similar to that CL and VC, respectively.

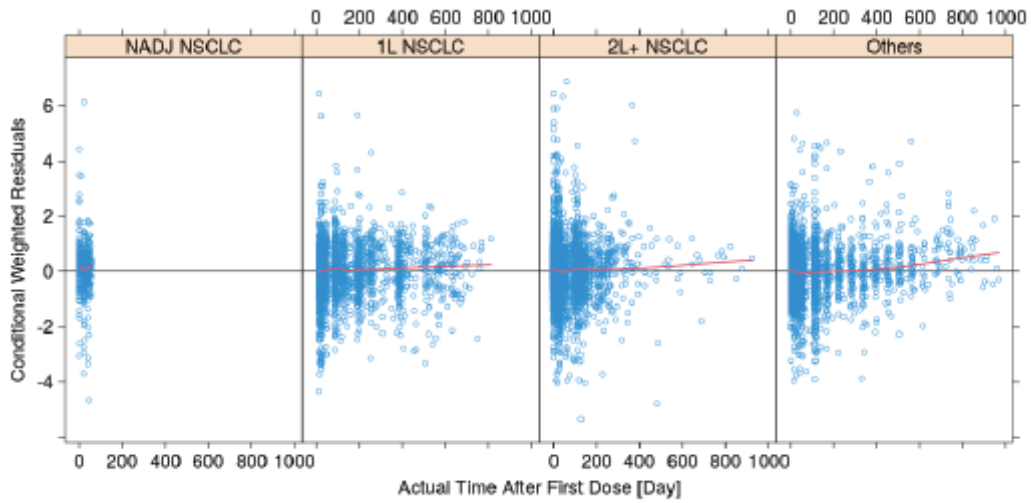
Abbreviations: 1L = first-line therapy; 2L+ = second-line or above therapy; AA = Asian American; ALB = albumin; BBWT = baseline body weight; Chemo = chemotherapy; CI = confidence interval; CL = clearance; Cont. Var = continuous variable; eGFR = estimated glomerular filtration rate; NADJ = neoadjuvant; Nivo Mono = nivolumab monotherapy; NSCLC = non-small cell lung cancer; PS = performance status; P05 = 5th percentile; P95 = 95th percentile; VC = volume of distribution of central compartment.

Figure 2: Observed versus Predicted Population Average and Individual Concentration by Tumour Type and Line of Therapy (Full Nivolumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/obs-pred/full816-obs-pred-pop.png
Source: Analysis-Directory/R/plots/obs-pred/full816-obs-ipred-pop.png
Note: Solid red line represents linear regression line, and solid black line represents line of identity.
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; NADJ = neoadjuvant; NSCLC = non-small cell lung cancer.

Figure 3: CWRES versus Time after First Dose by Tumor Type and Line of Therapy (Full Nivolumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/resid/full816-cwres-atafd-pop.png
Note: Solid red line represents locally weighted smooth line, and solid black line represents line of identity.
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; CWRES = conditional weighted residuals; NADJ = neoadjuvant; NSCLC = non-small cell lung cancer.

Sensitivity Analyses

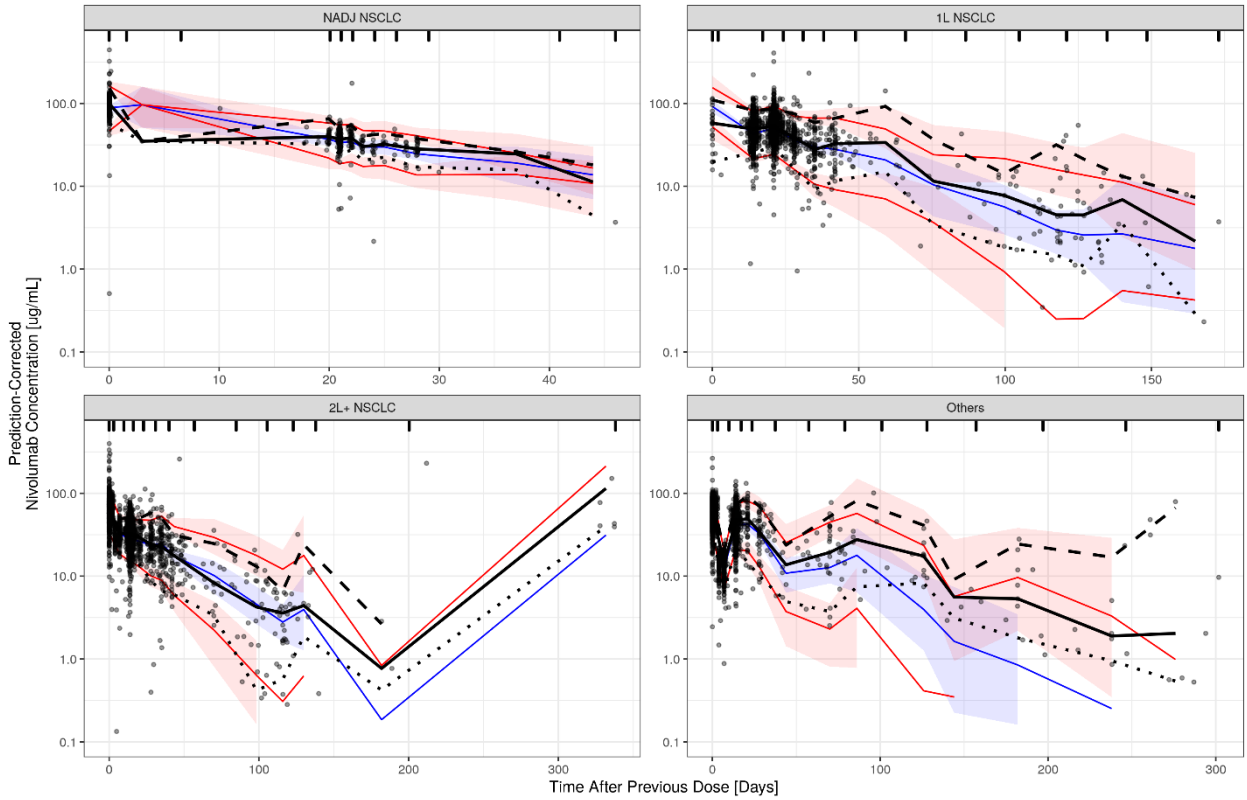
Sensitivity analyses were performed based on the full model. The covariate effect disease stage (DSTG) on nivolumab clearance was evaluated in sensitivity analysis. DSTG was not included as a covariate in

the main analysis as the subjects included in the DSTG group were the same subjects who were categorized as NADJ NSCLC.

Model Evaluation

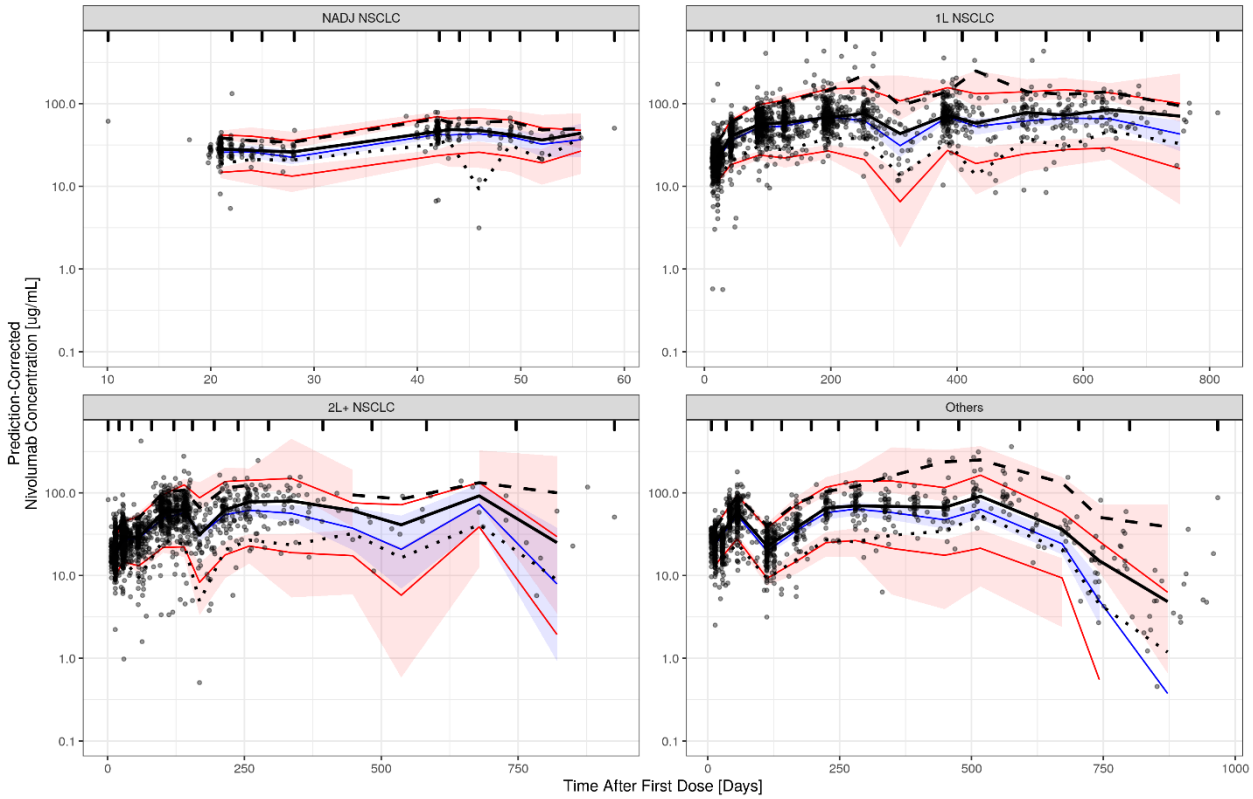
The predictive performance of the full PPK model was determined using pcVPC with stratification by tumor type and line of therapy (NADJ NSCLC, 1L NSCLC, 2L+ NSCLC, and Others).

Figure 4: Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose in Nivolumab Monotherapy and Combination Therapies (Full Nivolumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final3
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full816-1-vpc-all-atapd-bin-jenks.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.
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; NADJ = neoadjuvant; NSCLC = non-small cell lung cancer.

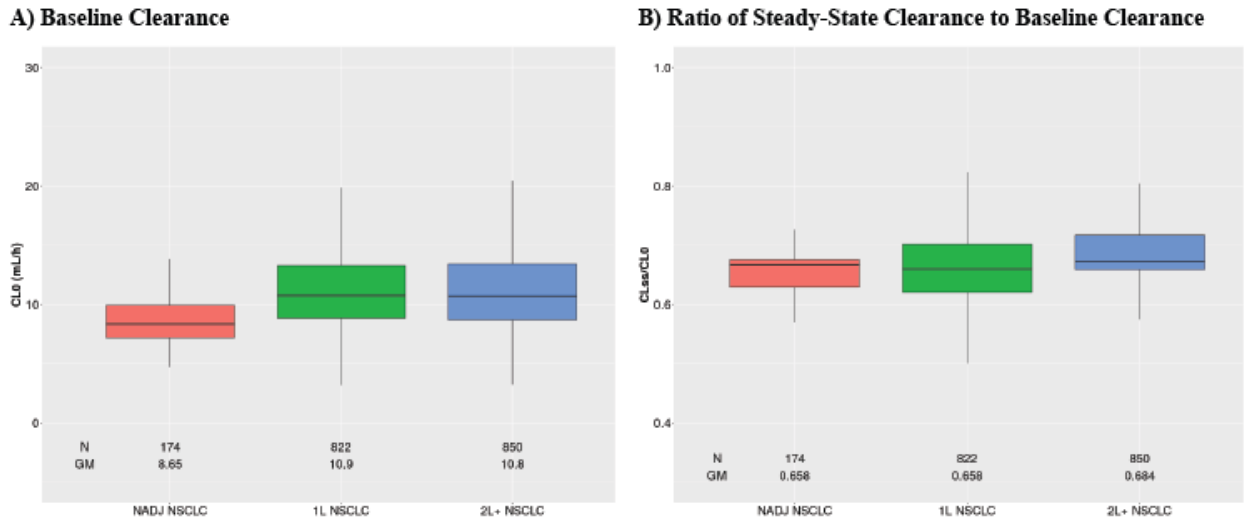
Figure 5: Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose in Nivolumab Monotherapy and Combination Therapies (Full Nivolumab Population Pharmacokinetic Model)



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final3
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full816-1-vpc-trough-atafd-bin-jenks.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.
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; NADJ = neoadjuvant; NSCLC = non-small cell lung cancer.

Model Application

Figure 6: Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by NSCLC Population



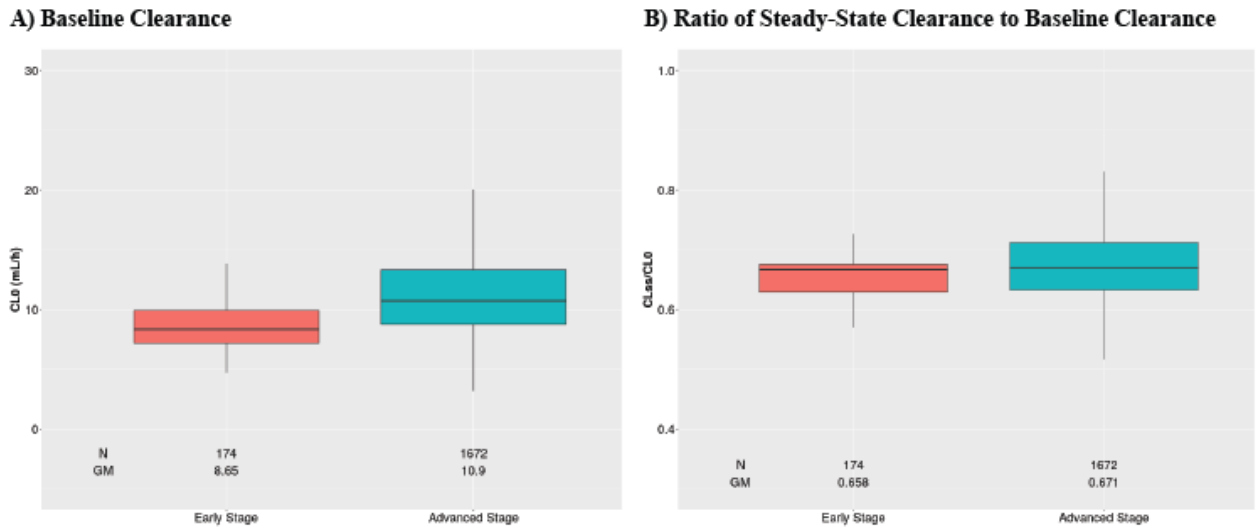
Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/CL0-nsclc.png
Source: Analysis-Directory/R/plots/CL-ratio-nsclc.png
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 1.5 times the inter-quartile range (IQR) beyond the quartiles, or maximum/minimum value, whichever is less.
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; CL0 = baseline clearance; CLss = clearance at steady state; GM = geometric mean; NADJ = neoadjuvant; NSCLC = non-small cell lung cancer.

Table 7: Summary Statistics of Individual Measures of Nivolumab Exposure (Cmax, Cmin, Cavg for Dose 1 and Steady State) in Neoadjuvant NSCLC and 1L and 2L+ NSCLC Subjects after 360 mg Q3W Dosing Regimen

	Geometric Mean (CV%)			Difference of GM (%)	
Exposure (µg/mL)	NADJ NSCLC (N = 174)	2L+ NSCLC (N = 850)	1L NSCLC (N = 822)	NADJ NSCLC vs 2L+ NSCLC	NADJ NSCLC vs 1L NSCLC
Cmax1	102 (29.2)	102 (34.2)	98.2 (23.2)	0	3.87
Cavg1	43.8 (20)	40.1 (24.2)	39.5 (23.1)	9.23	10.9
Cmin1	27 (24.3)	22.2 (31.7)	22.1 (30.6)	21.6	22.2
Cmaxss	199 (25)	171 (32.3)	171 (28.8)	16.4	16.4
Cavgss	126 (26.4)	96.3 (37.3)	100 (36.4)	30.8	26
Cminss	93.6 (30.1)	65.4 (47)	69.6 (45)	43.1	34.5

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-NS.csv
Abbreviations: 1L = first-line therapy; 2L+ = second-line and above therapy; Cavg1 = time-averaged concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Cmax1 = peak concentration after the first dose; Cmaxss = peak concentration at steady state; Cmin1 = trough concentration after the first dose; Cminss = trough concentration at steady state; CV% = coefficient of variation expressed as a percentage; GM = geometric mean; NADJ = neoadjuvant; NSCLC = non-small cell lung cancer.

Figure 7: Distribution of Nivolumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance in NSCLC Subjects with Early and Advanced Disease Stage



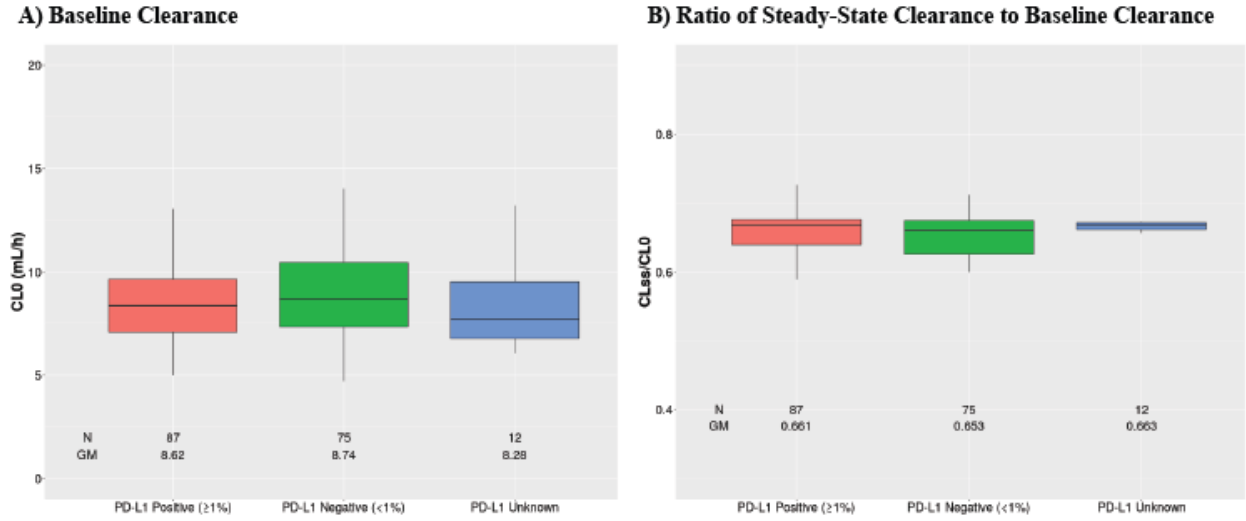
Analysis Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final2
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/CL0-dstg.png
Source: Analysis-Directory/R/plots/CL-ratio-dstg.png
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 1.5 times the inter-quartile range (IQR) beyond the quartiles, or maximum/minimum value, whichever is less.
Abbreviations: Chemo = chemotherapy; CL0 = baseline clearance; CLss = clearance at steady state; GM = geometric mean; Mono =monotherapy; Nivo = nivolumab; NSCLC = non-small cell lung cancer.

Table 8: Predicted Exposure Measures in NSCLC Subjects with Early Disease Stage vs Advanced Disease Stage

Exposure (µg/mL)	Geometric Mean (CV%)		Difference of GM (%)
	Early Stage (N = 174)	Advanced Stage (N = 1672)	Early Stage vs Advanced Stage
Cmax1	102 (29.2)	100 (29.8)	2
Cavg1	43.8 (20)	39.8 (23.7)	10.1
Cmin1	27 (24.3)	22.1 (31.2)	22.2
Cmaxss	199 (25)	171 (30.6)	16.4
Cavgss	126 (26.4)	98.1 (36.9)	28.4
Cminss	93.6 (30.1)	67.5 (46.0)	38.7

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final2
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-ds.csv
Abbreviations: Cavg1 = time-averaged concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Chemo = chemotherapy; Cmax1 = peak concentration after the first dose; Cmin1 = trough concentration after the first dose; Cminss = trough concentration at steady state; CV% = coefficient of variation expressed as a percentage; Mono = monotherapy; NADJ = neoadjuvant; Nivo = nivolumab; NSCLC = non-small cell lung cancer.

Figure 8: Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Baseline PD-L1 Status in Study CA209816



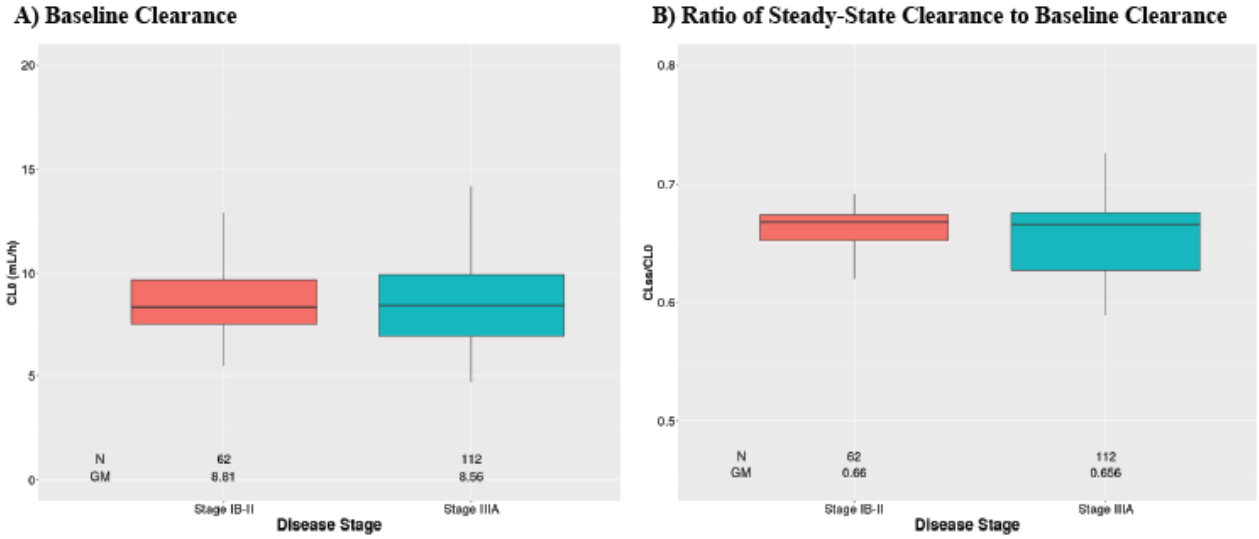
Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/CL0-pd.png
Source: Analysis-Directory/R/plots/CL-ratio-pd.png
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 1.5 times the inter-quartile range (IQR) beyond the quartiles, or maximum/minimum value, whichever is less.
Abbreviations: CL0 = baseline clearance; CLss = clearance at steady state; GM = geometric mean; PD-L1 = programmed death-ligand 1.

Table 9: Summary Statistics of Individual Measures of Nivolumab Exposure (Cmax, Cmin, Cavg for Dose 1 and Steady State) by PD-L1 Status in Study CA209816

Exposure (µg/mL)	Geometric Mean (CV%)			Difference of GM (%)	
	PD-L1 Positive (N = 87)	PD-L1 Negative (N = 75)	PD-L1 Unknown (N = 12)	PD-L1 Positive vs PD-L1 Negative	PD-L1 Positive vs PD-L1 Unknown
Cmax1	103 (25.7)	98.8 (26.7)	118 (47)	4.25	-12.7
Cavg1	43.9 (18.6)	43.2 (21.4)	46.7 (21.4)	1.62	-6
Cmin1	26.8 (24.9)	27 (24.2)	28.5 (22.7)	-0.741	-5.96
Cmaxss	200 (22.9)	195 (25.3)	217 (34.3)	2.56	-7.83
Cavgss	125 (26.9)	125 (26.3)	130 (25.5)	0	-3.85
Cminss	92.4 (31.4)	94.6 (29.2)	96.4 (28.7)	-2.33	-4.15

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-pd.csv
Abbreviations: Cavg1 = time-averaged concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Cmaxss = peak concentration at steady state; CL0 = baseline clearance; CLss = clearance at steady state; CV% = coefficient of variation expressed as a percentage; GM = geometric mean; PD-L1 = programmed death-ligand 1.

Figure 9: Distribution of Nivolumab Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance by Disease Stage in Study CA209816



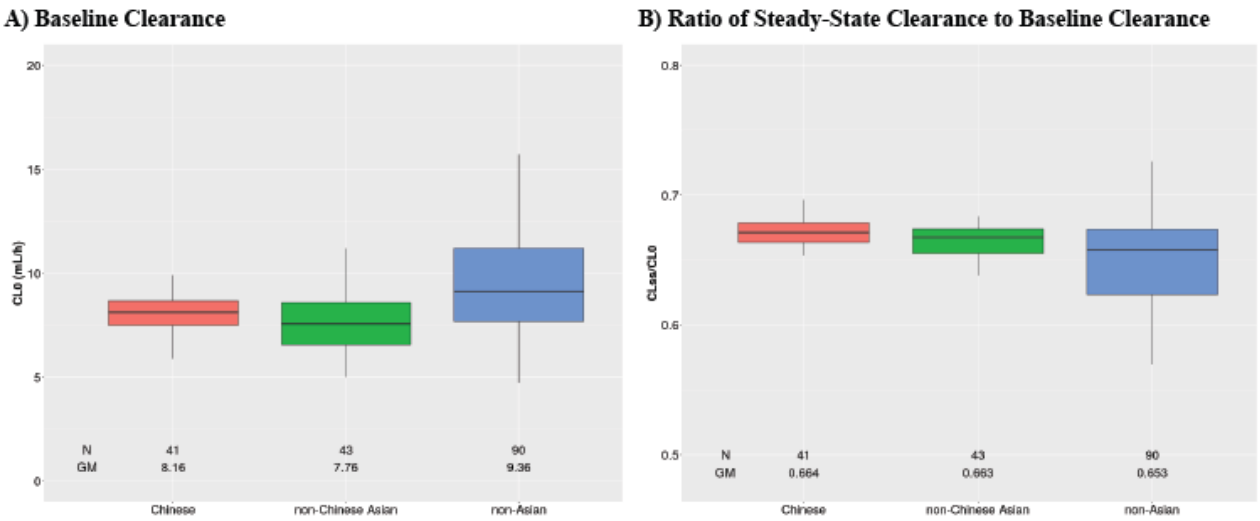
Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/CL0-estg.png
Source: Analysis-Directory/R/plots/CL-ratio-estg.png
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 1.5 times the inter-quartile range (IQR) beyond the quartiles, or maximum/minimum value, whichever is less.
Abbreviations: CL0 = baseline clearance; CLss = clearance at steady state; GM = geometric mean.

Figure 10: Predicted Nivolumab Exposure Measures in NSCLC Subjects by Disease Stage in Study CA209816

Exposure (µg/mL)	Geometric Mean (CV%)		Difference of GM (%)
	Stage IB-II (N = 62)	Stage IIIa (N = 112)	Stage IB-II vs Stage IIIa
Cmax1	101 (27.8)	103 (30)	-1.94
Cavg1	43.1 (19.9)	44.2 (20.2)	-2.49
Cmin1	26.5 (23.7)	27.3 (24.7)	-2.93
Cmaxss	195 (24.2)	201 (25.5)	-2.99
Cavgss	123 (24.5)	127 (27.4)	-3.15
Cminss	91.3 (27.6)	94.9 (31.3)	-3.79

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-es.csv
Abbreviations: Cavg1 = time-averaged concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Chemo = chemotherapy; Cmax1 = peak concentration after the first dose; Cmin1 = trough concentration after the first dose; Cminss = trough concentration at steady state; CV% = coefficient of variation expressed as a percentage; GM = geometric mean; NSCLC = non-small cell lung cancer.

Figure 11: Distribution of Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance in Chinese, Non-Chinese Asian, and Non-Asian Subjects in Study CA209816



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final

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

Source: Analysis-Directory/R/plots/CL0-ethc.png

Source: Analysis-Directory/R/plots/CL-ratio-ethc.png

Note: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 1.5 times the inter-quartile range (IQR) beyond the quartiles, or maximum/minimum value, whichever is less.

Abbreviations: CL0 = baseline clearance; CLss = clearance at steady state; GM = geometric mean.

Table 10: Summary Statistics of Individual Measures of Nivolumab Exposure (Cmax, Cmin, Cavg for Dose 1 and Steady State) in Chinese, Non- Chinese Asian, and Non Asian Subjects in Study CA209816

	Geometric Mean (CV%)			Difference of GM (%)	
Exposure (µg/mL)	Chinese (N = 41)	Non-Chinese Asian (N = 43)	Non-Asian (N = 90)	Chinese vs Non-Chinese Asian	Chinese vs Non-Asian
Cmax1	104 (16.9)	104 (18.5)	99.8 (37.1)	0	4.21
Cavg1	45.4 (13.8)	46.8 (15.8)	41.7 (23.8)	-2.99	8.87
Cmin1	28.7 (16.6)	30.1 (19.3)	25 (28.5)	-4.65	14.8
Cmaxss	206 (17)	212 (19.8)	190 (30.2)	-2.83	8.42
Cavgss	132 (19.1)	139 (22.1)	117 (30.5)	-5.04	12.8
Cminss	100 (22.3)	106 (25)	85.4 (34.7)	-5.66	17.1

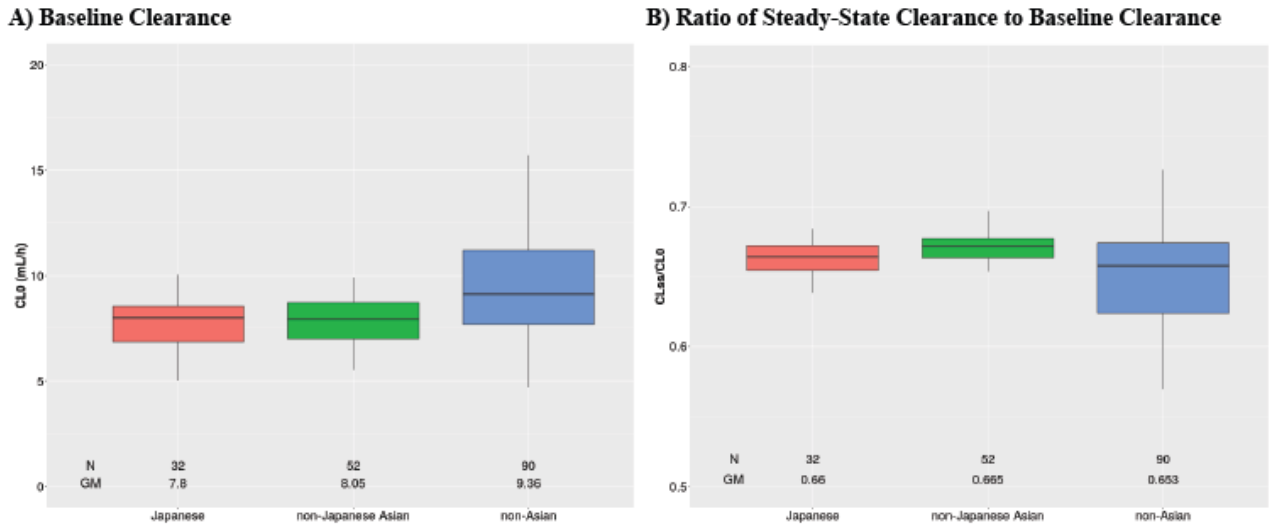
Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final

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

Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-ch.csv

Abbreviations: Cavg1 = time-averaged concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; CL0 = baseline clearance; CLss = clearance at steady state; CV% = coefficient of variation expressed as a percentage; GM = geometric mean; PD-L1 = programmed death-ligand 1.

Figure 12: Distribution of Baseline Clearance and Ratio of Steady State Clearance to Baseline Clearance in Japanese, Non-Japanese Asian, and Non-Asian Subjects in Study CA209816



Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/CL0-ethj.png
Source: Analysis-Directory/R/plots/CL-ratio-ethj.png
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 1.5 times the inter-quartile range (IQR) beyond the quartiles, or maximum/minimum value, whichever is less.
Abbreviations: CL0 = baseline clearance; CLss = clearance at steady state; GM = geometric mean.

Table 11: Summary Statistics of Individual Measures of Nivolumab Exposure (Cmax, Cmin, Cavg for Dose 1 and Steady State) in Japanese, Non- Japanese Asian, and Non Asian Subjects in Study CA209816

	Geometric Mean (CV%)			Difference of GM (%)	
Exposure (µg/mL)	Japanese (N = 32)	Non-Japanese Asian (N = 52)	Non-Asian (N = 90)	Japanese vs Non-Japanese Asian	Japanese vs Non-Asian
Cmax1	104 (14.5)	105 (19.3)	99.8 (37.1)	-0.952	4.21
Cavg1	46.6 (13.4)	45.9 (15.8)	41.7 (23.8)	1.53	11.8
Cmin1	29.9 (17.1)	29.1 (19)	25 (28.5)	2.75	19.6
Cmaxss	211 (16.5)	207 (19.9)	190 (30.2)	1.93	11.1
Cavgss	139 (19.7)	133 (21.7)	117 (30.5)	4.51	18.8
Cminss	107 (22.9)	101 (24.8)	85.4 (34.7)	5.94	25.3

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/ppk/final
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/export/sumstat-exps-bygeomean-jp.csv
Abbreviations: Cavg1 = time-averaged concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; CL0 = baseline clearance; CLss = clearance at steady state; CV% = coefficient of variation expressed as a percentage; GM = geometric mean; PD-L1 = programmed death-ligand 1.

Dose selection

A flat dose of nivolumab 360 mg in combination with platinum-doublet chemotherapy was selected for evaluation in the pivotal Phase 3 study, CA209816. Previously conducted PPK analysis predicted nivolumab exposures following the originally approved dose of 3mg/kg Q2W and flat doses of 240 mg Q2W and 480 mg Q4W in subjects with different tumour types that included NSCLC, and the resultant exposures were similar. The Sponsor also conducted simulations of 360 mg Q3W and 3 mg/kg Q2W using the same nivolumab monotherapy PPK model (Table 12).

Table 12: Summary of Simulated Exposure Measures Following Nivolumab 3 mg/kg Q2W and 360 mg Q3W

Exposure (µg/mL)	Median 3 mg/kg Q2W	Median 360 mg Q3W	Difference, %
Cmax1	57.6	90.6	57
Cavg1	27.6	37.3	35
Cmin1	18.3	22.1	21
Cmaxss	128	158	23
Cavgss	87.6	91.2	4
Cminss	69	64.7	-6

/globalpkms/data/CA/209/dose-optimization/prd/ppk-simulation-tvCL-ppkmega/final/R/export

The analyses indicated that the Cavgss following nivolumab 360 mg Q3W would be similar to that following 3 mg/kg Q2W, while Cminss is predicted to be approximately 6% lower. Following nivolumab 360 mg Q3W, Cmaxss is predicted to be approximately23% higher relative to that following nivolumab 3 mg/kg Q2W.

Immunogenicity

Immunogenicity was not evaluated in pivotal Study CA209816 because the nivolumab anti-drug antibody (ADA) incidence rate with nivo+chemo is expected to be low and similar to nivolumab monotherapy with up to 2 years of treatment in 1L NSCLC (i.e. overall ADA positive subjects < 20% and subjects with neutralizing antibodies < 5%).

In addition, due to the limited nivolumab dosing (up to 3 cycles of 360 mg nivolumab administered Q3W) for neoadjuvant treatment of resectable NSCLC in Study CA209816, the duration of any treatment-emergent ADA positivity would likely be transient.

Table 13: Summary of Nivolumab Antibody Assessments Following Nivolumab 3 mg/kg Q2W or 240 mg Q2W Monotherapy and Nivolumab 360 mg Q3W in Combination with 4 Cycles of Platinum-doublet Chemotherapy in First-line NSCLC

	Number of Subjects (%)					
	Nivolumab 3 mg/kg Q2W or 240 mg Q2W Monotherapy			Nivolumab 360 mg Q3W in Combination with 4 Cycles of Platinum-doublet Chemotherapy		
Study	CA209026 N = 230	CA209227 Part 1 N = 322	Pooled Summary N = 552	CA209227 Part 1 (Arm G) N = 148	CA209227 Part 2 (Arm H) N = 301	Pooled Summary N = 449
Baseline ADA positive	13 (5.7)	33 (10.2)	46 (8.3)	6 (4.1)	19 (6.3)	25 (5.6)
ADA positive	21 (9.1)	77 (23.9)	98 (17.8)	12 (8.1)	48 (15.9)	60 (13.4)
Persistent positive (PP)	1 (0.4)	2 (0.6)	3 (0.5)	0	2 (0.7)	2 (0.4)
Not PP - last sample positive	9 (3.9)	17 (5.3)	26 (4.7)	4 (2.7)	10 (3.3)	14 (3.1)
Other positive	11 (4.8)	58 (18.0)	69 (12.5)	8 (5.4)	36 (12.0)	44 (9.8)
Neutralizing ADA positive	0	5 (1.6)	5 (0.9)	1 (0.7)	14 (4.7)	15 (3.3)
ADA negative	209 (90.9)	245 (76.1)	454 (82.2)	136 (91.9)	253 (84.1)	389 (86.6)

Baseline ADA (anti-drug antibody) 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.

2.3.1. PK/PD modelling

Exposure-efficacy relationship

The E-R efficacy analyses were performed with data from 349 subjects with early-stage NSCLC from study CA209816, which investigated the efficacy and safety of neoadjuvant nivolumab 360 mg Q3W +

3 cycles of platinum-doublet chemotherapy versus 3 cycles of platinum-doublet chemotherapy for early-stage NSCLC.

Exposure-Response Efficacy: pCR

The following variables were included in the E-R of pCR analysis dataset:

-Exposure variable: nivolumab Cavg1, obtained from PPK analyses
-Response variable: pCR based on BIPR assessment
-Baseline demographic variables: age, body weight, sex
-Baseline disease characteristics: PS, tumor size, disease stage (IB, and II vs IIIA, or IB, IIA, and IIB vs IIIA) at initial diagnosis, histology (SQ vs NSQ), smoking status, PD-L1 expression (≥ 1% vs <1%)
-Baseline laboratory values: LDH and serum albumin
-Other: nivolumab (nivo+chemo vs chemo)

The relationship between nivolumab exposure (Cavg1) and the probability of subject *i* achieving pCR was described by a **logistic regression model** and included assessments of the modulatory effect of covariates on the E-R relationship.

Table 14: Parameter Estimates of the Exposure-Response of pCR (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Odds Ratio[c] (95% CI)
Intercept	-4.51	0.668	14.8	0.011 (0.00296, 0.0405)
Nivo Cavg1	0.0557	0.0107	19.2	1.06 (1.04, 1.08)
Sex [Female:Male]	0.274	0.43	157	1.32 (0.566, 3.06)
Age [years]	0.00841	0.0251	298	1.01 (0.96, 1.06)
Histology [SQ:NSQ]	0.526	0.39	74.1	1.69 (0.788, 3.63)
Disease Stage [IB/II:IIIA]	0.433	0.377	87.1	1.54 (0.736, 3.23)
Smoking Status [Non-smoker:Smoker]	-1.47	0.823	56	0.23 (0.046, 1.16)
PD-L1 [≥ 1%:< 1%]	0.714	0.39	54.5	2.04 (0.952, 4.38)
Performance Score [≥1:0]	-0.426	0.421	98.8	0.653 (0.286, 1.49)
Body Weight [kg]	0.00833	0.0131	157	1.01 (0.983, 1.03)
Log(LDH) [xULN]	2.01	0.669	33.3	7.47 (2.01, 27.7)
Albumin [g/L]	0.486	0.49	101	1.63 (0.622, 4.25)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-pcr/final/

Program Source: Analysis-Directory/R/scripts/er-pcr.Rmd

Source: Analysis-Directory/R/exports/pcr-full-param.csv

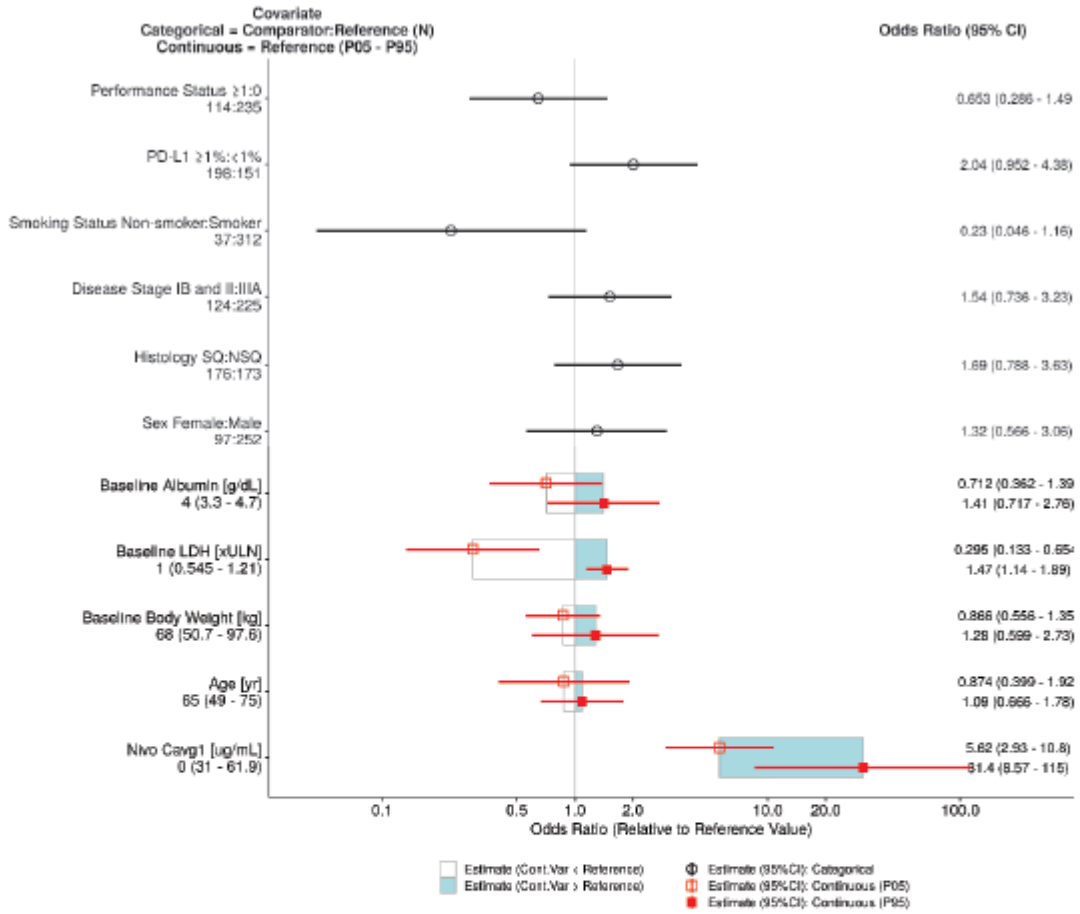
[a] Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference]

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

[c] Increase in odds ratio for every unit increase in continuous predictor variables; for categorical variables, it represents the odds ratio of the comparator group to reference group: Disease Stage IIIA, PS = 0, NSQ NSCLC, smoker, PD-L1 <1%, and male subject.

Figure 13 is a graphical presentation of all the estimated effects in the full model, showing the OR of pCR across the predictor ranges and the associated 95% CIs. The predictor variables with a significant effect on pCR were baseline LDH and nivolumab Cavg1 (95% CI of effect did not include the null value).

Figure 13: Estimated Covariate Effects of the Exposure-Response of pCR (Full Model)



Abbreviations: Cavg1 = time-averaged concentration at the first dosing interval; CI = confidence interval; LDH = lactate dehydrogenase; Nivo = nivolumab; NSQ = non-squamous; pCR = pathological complete response; PD-L1 = programmed death-ligand 1; SQ = squamous; ULN = upper limit of normal.

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-pcr/final/

Program Source: Analysis-Directory/R/er-pcr.Rmd

Source: Analysis-Directory/R/plots/ggcoveff-full-model.png

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

Note: Reference subject: Subject who received chemotherapy in Study CA209816 (Nivo Cavg1=0), and median value of LDH, albumin, body weight, NSQ, male, smoker, PS = 0, PD-L1 <1%, and disease stage IIIA.

Table 15: The Odds Ratio for the Effect of 5th Percentile or 95th Percentile of Cavg1 Relative to Median Cavg1 on the pCR

	Hazard Ratio of Cavg1 Effect	
Parameter	**5th Percentile of Cavg1**	**95th Percentile of Cavg1**
Estimate	0.493	2.76
Lower 95% CI	0.378	1.88
Upper 95% CI	0.643	4.04

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-pcr/final
Program Source: Analysis-Directory/R/scripts/er-pcr-additional.Rmd
Source: Analysis-Directory/R/export/full-pcr-or-cavg1-p5-p95.csv

Exposure-Response Efficacy: EFS

The following variables were included in the E-R of EFS analysis dataset:

- Exposure variable: nivolumab Cavg1, obtained from PPK analyses
- Response variable: EFS based on BICR assessment; EFS was defined as the length of time from randomization to any one of the following events: a) any progression of disease precluding surgery, b) progression or recurrence of disease (based on BICR assessment per Response Evaluation Criteria In Solid Tumors [RECIST] 1.1) after surgery, or c) death due to any cause.
- Baseline demographic variables: age, body weight, sex
- Baseline disease characteristics: PS, tumour size, disease stage (IB, and II vs IIIA, or IB, IIA, and IIB, vs IIIA) at initial diagnosis, histology (SQ vs. NSQ), smoking status, PD-L1 expression (≥ 1% vs. < 1%)
- Baseline laboratory values: LDH and serum albumin
- Other: nivolumab (nivo+chemo vs chemo)

The relationship between nivolumab exposure (Cavg1) and EFS was described by a **Cox Proportional Hazards (CPH) model** and included assessments of the potential modulatory effect of covariates on the E-R relationship.

Table 16: Parameter Estimates of the Exposure-Response of EFS (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Cavg_nivo [µg/mL]	-0.00965	0.003781	39.2	0.9904 (0.9831, 0.9978)
Albumin [g/L]	-0.5475	0.2148	39.22	0.5784 (0.3797, 0.8811)
Age [years]	0.002898	0.01041	359.1	1.003 (0.9827, 1.024)
Body Weight [kg]	-0.0088	0.006508	73.95	0.9912 (0.9787, 1.004)
Log(LDH) [xULN]	-0.1763	0.2948	167.2	0.8383 (0.4704, 1.494)
Sex [Female:Male]	-0.6854	0.2168	31.63	0.5039 (0.3295, 0.7706)
Performance Score [≥1:0]	0.2393	0.1793	74.93	1.27 (0.8939, 1.805)
PD-L1 [≥ 1%:< 1%]	-0.444	0.1695	38.17	0.6415 (0.4602, 0.8942)
Tumor Size [cm]	0.04743	0.03375	71.17	1.049 (0.9814, 1.12)
Smoking Status [Non-smoker:Smoker]	0.8423	0.2499	29.67	2.322 (1.423, 3.789)
Histology [SQ:NSQ]	-0.1104	0.1735	157.2	0.8955 (0.6374, 1.258)
Disease Stage [Stage IB/II:IIIA]	-0.4387	0.1855	42.28	0.6449 (0.4483, 0.9276)

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-efs/final

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

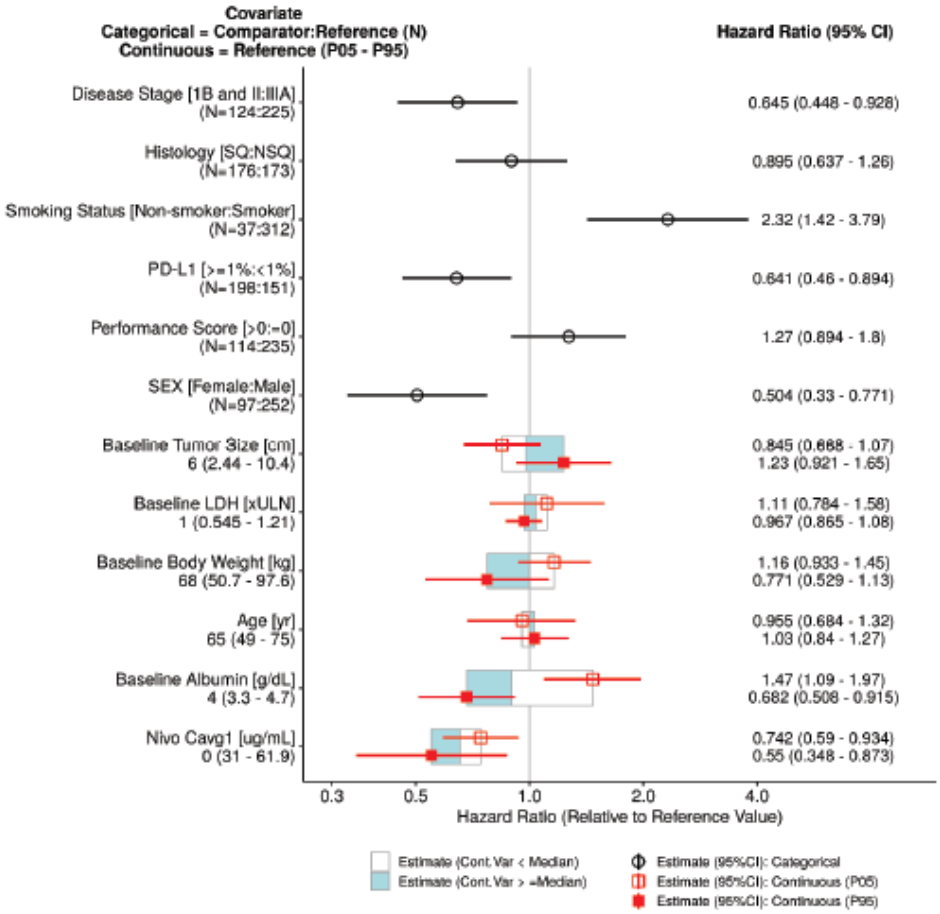
Source: Analysis-Directory/R/export/efs-param-cph-full.csv

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

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

[c] Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group: Disease Stage IIIA, performance status = 0, PD-L1 < 1%, NSQ NSCLC, smoker, and male subject.

Figure 14: Estimated Covariate Effects of the Exposure-Response of EFS (Full Model)



Abbreviations: Cavg1 = time-averaged concentration at the first dosing interval; CI = confidence interval; EFS = event-free survival; LDH = lactate dehydrogenase; Nivo = nivolumab; NSQ = non-squamous; pCR = pathological complete response; PD-L1 = programmed death-ligand 1; SQ = squamous; ULN = upper limit of normal

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-efs/final

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

Source: Analysis-Directory/R/plots/ggcoveff-full-model.png

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

Note: Reference subject: Subject who received chemotherapy in Study CA209816 (nivo Cavg1 = 0), and median value of LDH, albumin, body weight, baseline clearance, baseline tumor size, NSQ, male, smoker, PS = 0, PD-L1 < 1%, and disease stage IIIA.

Table 17: The Hazard Ratio for the Effect of 5th Percentile or 95th Percentile of Cavg1 Relative to Median Cavg1 on the EFS

	Hazard Ratio of Cavg1 Effect	
Parameter	**5th Percentile of Cavg1**	**95th Percentile of Cavg1**
Estimate	1.13	0.84
Lower 95% CI	1.24	0.734
Upper 95% CI	1.03	0.96

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-efs/final

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

Source: Analysis-Directory/final/R/export/full-efs-hr-cavg1-p5-p95.csv

The predictor variables with a significant effect on EFS were nivolumab Cavg1, disease stage, smoking status, PD-L1 status, sex, and baseline albumin (95% CI of effect did not include the null value).

Exposure-safety relationship

The E-R safety analysis was performed with data from 2145 early-stage (stage IIIA or better) and late stage (stage IV) NSCLC subjects from studies CA209816 and CA209227, respectively, who received nivolumab 240 mg Q2W monotherapy in CA209227, or nivolumab 360 mg Q3W + 3 cycles of chemotherapy in CA209816, or nivolumab 360 mg Q3W + 4 cycles of chemotherapy in CA209227, or chemotherapy alone (3 cycles in CA209816 and 4 cycles in CA209227).

The following variables were included in the E-R safety analysis data set:
-Exposure variable: nivolumab Cavg1, obtained from PPK analyses
-Response variable: Gr2+ IMAEs
-Baseline demographic variables: age, body weight, sex
-Baseline disease characteristics: PS, tumour size, disease stage at initial diagnosis, histology (SQ vs NSQ), smoking status, PD-L1 expression (≥ 1% vs < 1%)
-Baseline laboratory values: LDH and serum albumin
-Others: treatment (nivo+chemo, nivo vs. chemo)

The relationship between nivolumab exposure (Cavg1) and time to first occurrence of Gr2+ IMAEs was described by a semi-parametric **CPH model** and included assessments of the modulatory effect of covariates on the E-R relationship.

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

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Log Cavg_nivo [ug/mL] (Nivo+Chemo)	0.2242	0.0253	11.28	1.251 (1.191, 1.315)
Log Cavg_nivo [ug/mL] (Nivo)	0.2354	0.02658	11.29	1.265 (1.201, 1.333)
Age [yr]	0.002162	0.007587	351	1.002 (0.9874, 1.017)
SEX [Female:Male]	-0.1317	0.1686	128	0.8766 (0.6299, 1.22)
Body weight [kg]	0.000118	0.004797	4057	1 (0.9908, 1.01)
Albumin [g/L]	-0.0818	0.1577	192.8	0.9215 (0.6764, 1.255)
Log(LDH) [xULN]	0.03334	0.1858	557.3	1.034 (0.7183, 1.488)
Tumor Size [cm]	-0.00725	0.01638	225.9	0.9928 (0.9614, 1.025)
Performance Score [≥1:0]	-0.2047	0.1441	70.4	0.8149 (0.6144, 1.081)
Disease Stage [IB/II:IV/RECURRENT]	-0.2534	0.4346	171.5	0.7761 (0.3311, 1.819)
Disease Stage [IIIA:IV/RECURRENT]	0.06027	0.3004	498.5	1.062 (0.5894, 1.914)
Histology [SQ:NSQ]	-0.1203	0.1635	135.8	0.8866 (0.6436, 1.221)
Smoking Status [Non-smoker:Smoker]	-0.07248	0.2114	291.6	0.9301 (0.6146, 1.407)
PD-L1 [≥ 1%:< 1%]	0.309	0.1777	57.49	1.362 (0.9616, 1.929)

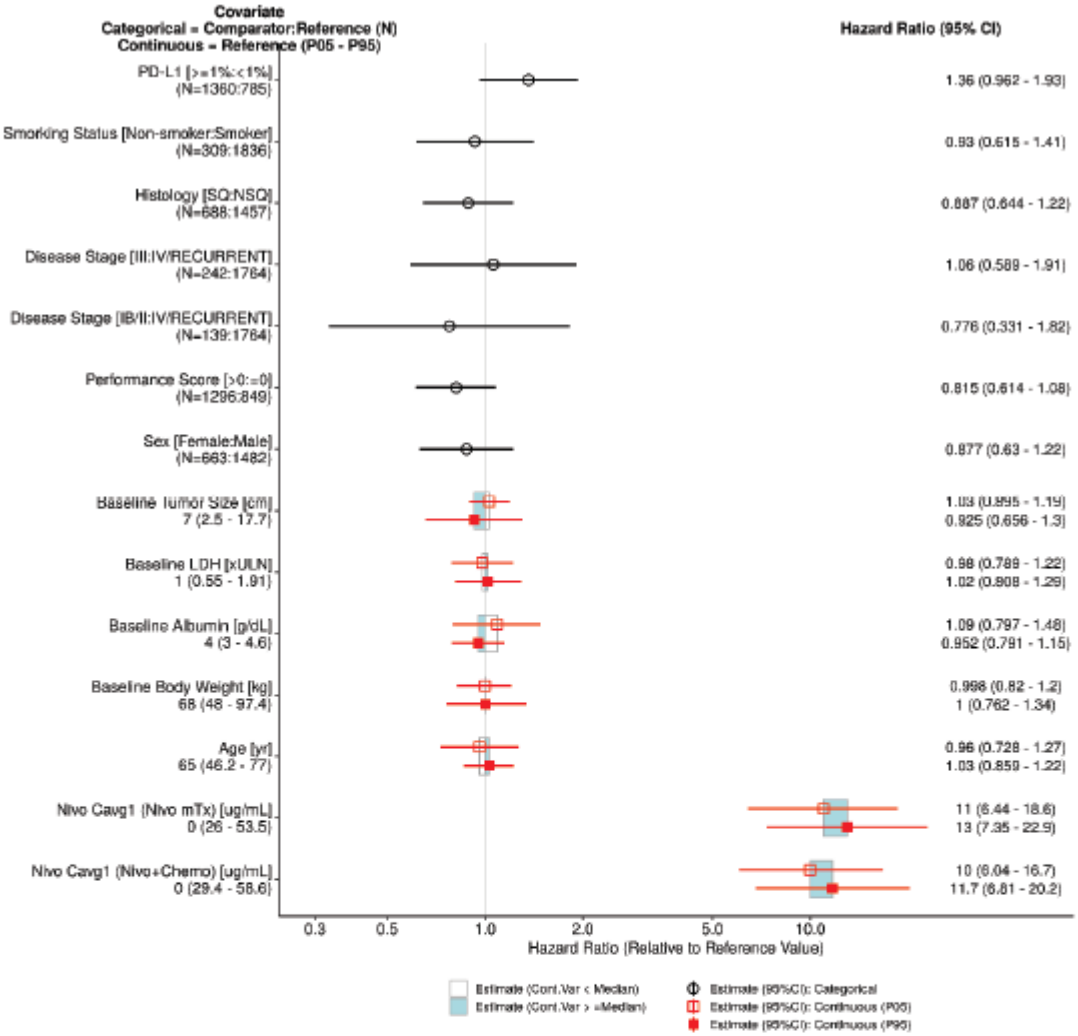
Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-imae/final
Program Source: Analysis-Directory/R/scripts/2-model-imae-dev-app-imae.Rmd
Source: Analysis-Directory/R/export/imae-param-cph-full.csv

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

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

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

Figure 15: Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Full Model)



Abbreviations: Cavg1 = time-averaged concentration at the first dosing interval; CI = confidence interval; EFS = event-free survival; LDH = lactate dehydrogenase; Nivo = nivolumab; NSQ = non-squamous; pCR = pathological complete response; PD-L1 = programmed death-ligand 1; SQ = squamous; ULN = upper limit of normal

Analysis-Directory: /global/pkms/data/CA/209/nsclc-earlystage-816/prd/er-imae/final
Program Source: Analysis-Directory/R/scripts/2-model-imae-dev-app-imae.Rmd
Source: Analysis-Directory/R/plots/ggcoveff-full-imae.png
Note: Continuous covariate effects (95% CI) at, the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.

Note: Reference subject: subject who received chemotherapy (Nivo Cavg1=0) and median value of LDH, albumin, body weight, baseline tumor size, NSQ, male, smoker, performance status = 0, PD-L1 < 1% and IV/recurrent disease stage.

Overall, it shows an increased hazard in nivolumab + chemotherapy combination regimen compared to chemotherapy, as a result of the nivolumab treatment effect. The estimated HR ranged between 10 and 11.7 at the 5th and 95th percentiles of nivolumab Cavg1 from nivolumab + chemotherapy combination regimen compared with chemotherapy, which indicates that while the risk of Gr2+ IMAEs is higher for subjects who receive nivo+chemo relative to chemo alone, the E-R relationship is relatively flat over the range of exposures produced by nivolumab 360 mg Q3W.

2.3.2. Discussion on clinical pharmacology

The population PK analysis was based on a pooled dataset from 8 Studies, which includes data of nivolumab as monotherapy from Phase 1 dose-ranging studies (AA209003 and CA209005 studies) in NSCLC and other cancers, from a Phase 1 /2 study (CA209077) in Chinese subjects with multiple solid tumour types and from Phase 3 trials (CA209017, CA209057 and CA209078 studies) in squamous NSCLC, non squamous NSCLC and advanced or metastatic NSCLC respectively, and data of nivolumab as monotherapy and/or in combination with chemotherapy from Phase 3 trials (CA209227 and CA209816 studies) in chemotherapy-naïve stage IV or recurrent NSCLC and resectable NSCLC.

PK samples of nivolumab below the lower limit of quantification (LLQ) were low (1,3%) and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

The population PK model development of nivolumab includes the re-use of the full nivolumab PPK model previously established as the new base model, with all the significant covariates previously identified excluding the effect of tumour type, ipilimumab dosing regimens and coadministration of ipilimumab and coadministration of ipilimumab+chemotherapy. Subsequently, a full model was developed by incorporating covariates to assess the impact of tumour type and line of therapy and baseline albumin on nivolumab CL, and chemotherapy combination effect on EMAX. Moderate (CV<35%) inter-individual variability has been characterized on several PK parameters (CL, VC and Emax). The updated full popPK model includes only the 12 covariate effects that were statistically significant. According to the pcVPC provided related to the NADJ NSCLC indication, first days after the previous dose are not properly characterised and there is a slight over-prediction of concentrations for the 5^{th}, 50^{th} and 95^{th} percentiles. However, the overall model performance seems adequate to describe most of the experimental evidence.

Immunogenicity was not evaluated in the current study (CA209816), but no clinically relevant immunogenicity effect of nivolumab has been found in previous studies despite the fact that according to the current dosing regimen, higher PK levels (>20%) of nivolumab are predicted in NADJ patients compared to 1L and 2L+ NSCLC patients.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the main PK parameters (CL, VC and Emax) rather than PK exposure metrics (i.e. AUC, Cmax, Cmin), showing that baseline ALB levels equal or lower than 3.1 lead to changes on CL >20%. Although it is not fully clear how changes greater than 20% on CL may be translated into the PK exposure metrics, this change is considered of minor relevance based on the flat and non-significant exposure-response relationship identified so far in patients receiving the combination therapy.

In order to compare the use of the flat dose of 360 mg of nivolumab Q3W with the weight base dosage (3 mg/kg Q2W), the Sponsor conducted simulations of both dosages using the nivolumab monotherapy PPK model. The analyses indicated that Cmaxss1, Cmaxss and Cavg 1 for the flat dose are predicted to be 57%, 23% and 35% higher relative to the weight base dose. Switching from bodyweight-based dosing to flat dosing results in significant differences in exposure parameters, leading to Cavg1 and Cmax1 following 360 mg Q3W 51,4% and 72.3% higher, respectively. Based on the updated exposure-safety analysis, the impact of Cavg or Cmax levels of nivolumab to explain the probability of Gr2+ IMAE is of minor relevance, and additional covariates may have stronger statistical relationship (disease status or PD-L1 expression). The exposure-efficacy analysis was based on patients from study CA209816 with early-stage NSCLC treated with 3 cycles of the combination treatment versus 3 cycles of chemotherapy. Nivolumab Cavg1 derived from the PPK analysis was used as the measure of exposure.

An exposure-efficacy relationship has been established to characterize the probability of pCR by a logistic regression model. The forest plot analysis of the Odds Ratio among the different covariates

suggests that the probability of response was significantly higher in subjects receiving the combination therapy compared to patients who received only the chemotherapy. A proportional hazard model to account for the exposure–efficacy of nivolumab on EFS was also performed. EFS was longer in subjects receiving the combination therapy relative to chemotherapy alone.

The exposure-response safety analysis was performed with data from 2145 early-stage (stage IIIA or better) and late stage (stage IV) NSCLC subjects from studies CA209816 and CA209227. Nivolumab Cavg1 derived from the PPK analysis was used as the measure of exposure. The exposure-safety analysis characterized the probability of Gr2+ imAE in patients who received nivolumab 240 mg Q2W monotherapy or nivolumab 360 mg Q3W + chemotherapy. Nivolumab exposure was associated with Grade2+ imAE. The HR for nivolumab Cavg1 compared to chemotherapy was relatively high. The HR for the combination was similar to the monotherapy treatment.

2.3.3. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab in combination with chemotherapy for neoadjuvant treatment of resectable NSCLC has been characterized using information from the pivotal Phase 3 study CA209816. The characterization of the data is adequate and the rationale for the dose schedule appropriate.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were submitted as part of this application.

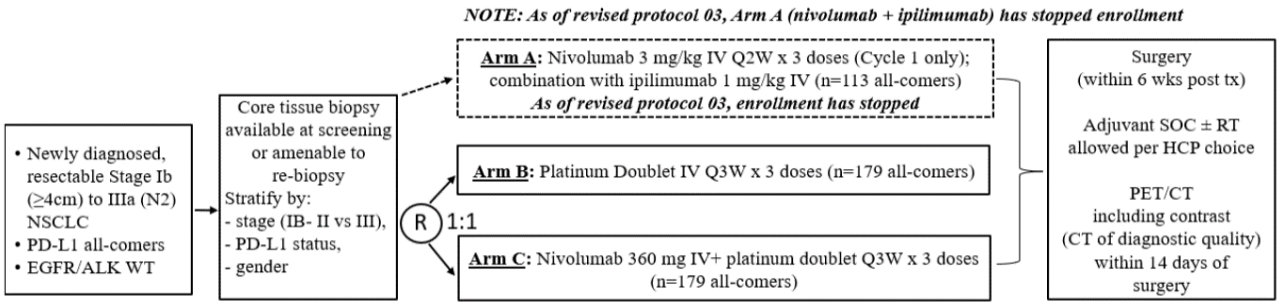
2.4.2. Main study

Study CA209816: A Randomized, Open-label, Phase 3 Trial of Nivolumab plus Ipilimumab or Nivolumab plus Platinum-doublet Chemotherapy in Early Stage NSCLC (CheckMate 816)

Methods

CA209816 is an open-label, randomized Phase 3 study of nivolumab (3 mg/kg every 2 weeks [Q2W]; up to 3 cycles) and a single 1 mg/kg dose of ipilimumab (nivo+ipi), nivolumab 360 mg flat dose plus platinum-doublet chemotherapy (every 3 weeks [Q3W] up to 3 cycles; nivo+chemo), or platinum-doublet chemotherapy (Q3W up to 3 cycles; chemo) as neoadjuvant treatment in subjects with resectable (stage IB [≥4 cm], stage II, and resectable stage IIIA), per AJJCC/UICC TNM 7th edition, non-small cell lung cancer (NSCLC).

Figure 1. Study Design Schematic



Endpoints
Primary: EFS and pCR rate in PD-L1 all-comers
Secondary: MPR, OS, and TTDM in PD-L1 all-comers
Exploratory: cRR in PD-L1 all-comers; pCR rate, EFS, MPR rate, OS, TTDM, and cRR by PD-L1 status. Safety, surgical feasibility, and rate of peri- and post-operative complications; PK, biomarkers, PROs
Post Surgical Assessments: CT /MRI Q12W for 2 yrs; then Q6 mos for 3 years, and every 52 weeks for 5 years thereafter until disease recurrence or PD. Independent review for pathological and radiologic response

Abbreviations: ALK - anaplastic lymphoma kinase; cRR - clinical response rate; CT - computed tomography; EGFR - epidermal growth factor receptor; EFS - event-free survival; EFS2 - event-free survival on second line therapy; HCP - healthcare provider; ipi - ipilimumab; IV - intravenous; MPR - major pathologic response; MRI - magnetic resonance imaging; nivo - nivolumab; NSCLC - non-small cell lung cancer; OS - overall survival; pCR - pathologic complete response; PD-L1 - programmed death-ligand 1; PD - disease progression; PET - positron emission tomography; PK - pharmacokinetic; PRO - patient-reported outcome; QxW - every X weeks; RT - radiotherapy; SOC - standard-of-care; TTDM - time to death or distant metastases; tx - treatment; WT - wild type.

Source: Appendix 1.1 in the CA209816 Primary CSR

Study participants

Inclusion criteria

1. Signed written informed consent.
2. Males and females ≥18 or age of majority.
3. Eastern Cooperative Group (ECOG) Performance Status: 0-1
4. Participants with histologically confirmed Stage IB (≥4 cm), II, IIIA (N2) NSCLC (per the 7th International Association for the Study of Lung Cancer) with disease that is considered resectable.
5. Measurable disease according to RECIST version 1.1
6. Participants must have a tumour tissue sample available for PD-L1 IHC testing performed by a third-party analyzing lab during the screening period.
7. Absence of major associated pathologies that increase the surgery risk to an unacceptable level and pulmonary function capacity (eg, FVC, FEV1, TLC, FRC, and DLco) capable of tolerating the proposed lung resection according to the surgeon.
8. All suspicious mediastinal lymph nodes including those that are pathologically enlarged or FDG avid on PET/CT require further sampling for pathological confirmation if accessible by mediastinoscopy, thoracoscopy, or EBUS.
9. Screening laboratory values must meet the following criteria (using CTCAE v4):
    a. WBC <2000/µL
    b. Neutrophils <1500/µL
    c. Platelets <100 x 10^3/µL
    d. Haemoglobin <9 g/dL

e. Serum creatinine > 1.5 x ULN or calculated creatinine clearance (CrCl) <50 mL/min (Cockcroft-Gault)

f. AST >3 x ULN

g. ALT >3 x ULN

h. Total bilirubin >1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of <3.0 x ULN)

Exclusion criteria

1. Presence of locally advanced unresectable (regardless of stage) or metastatic disease (stage IV).
2. Participants with known EGFR mutations or ALK translocation.
3. Participants with brain metastases are excluded from this study, and all participants with stage II or higher disease and those with suspicion of brain metastases should have MRI or CT of the brain with pre- and post-contrast within 28 days prior to randomization.
4. Participants with Grade ≥2 peripheral neuropathy.
5. Participants with an active, known or suspected autoimmune disease. Participants 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.
6. Participants 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 doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
7. HIV positive
8. Participants with large-cell neuroendocrine carcinoma tumour histology (from Revised Protocol 03)
9. Prior administration of chemotherapy or any other cancer therapy for early stage NSCLC. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PDL-2, or anti-CTLA-4 antibody or any other antibody targeting T cell co-regulatory pathways.
10. Participants with active hepatitis B (positive hepatitis B surface antigen [HBsAg] or hepatitis C virus (HCV) [positive HCV RNA]).
11. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
12. Participants with serious or uncontrolled medical disorders.

AJCC/UICC TNM 7th edition staging was used for the entirety of CA209816 for eligibility, stratification, and reporting of results. External to the study, AJCC officially transitioned to TNM 8th edition in the US on 01-Jan-2018, and sites were instructed to continue using the 7th edition when entering data for the trial. There are some differences between the 7th and 8th editions, mainly related to the T (primary tumor) categories. In CA209816, subjects enrolled with stage IB (≥4cm)–IIIA NSCLC using TNM 7th edition would cover stages IB-IIIB using TNM 8th edition.

Treatments

The treatments administered to subjects concurrently randomized to the nivo+chemo (Arm C) and chemo (Arm B) arms (the primary efficacy analysis population discussed in this report) are summarized below. Selection of a chemotherapy regimen was based on histology and investigator's choice, and was performed after each subject had been randomized.

Nivo+Chemo Arm (Arm C)

- Nivolumab 360 mg IV Q3W for up to 3 cycles
- Chemotherapy: investigator choice of platinum-based doublet chemotherapy IV
    - Cisplatin (75 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles) and one of the following:
        - Gemcitabine (1000 mg/m^2 or 1250 mg/m^2 [per local prescribing information] on Days 1 and 8 of a 3 week cycle for up to 3 cycles) (squamous histology)
        - Pemetrexed (500 mg/m^2 on Day 1 of a 3-week cycle for up to 3 cycles) (non-squamous histology)
    - Carboplatin (AUC 5-6 on Day 1 of a 3-week cycle for up to 3 cycles) and the following:
        - Paclitaxel (175 or 200 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles) (any histology)

Chemo Arm (Arm B)

Investigator choice of platinum-based doublet chemotherapy IV:

- Cisplatin (75 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles) and one of the following:
    - Gemcitabine (1000 mg/m^2 or 1250 mg/m^2 [per local prescribing information] on Days 1 and 8 of a 3-week cycle for up to 3 cycles) (squamous histology)
    - Pemetrexed (500 mg/m^2 on Day 1 of a 3-week cycle for up to 3 cycles) (non-squamous histology)
    - Vinorelbine (25 mg/m^2 or 30 mg/m^2 [per local prescribing information] on Days 1 and 8 of a 3-week cycle for up to 3 cycles)
    - Docetaxel (60 mg/m^2 or 75 mg/m^2 [per local prescribing information] on Day 1 of a 3 week cycle for up to 3 cycles)
- Carboplatin (AUC 5-6 on Day 1 of a 3-week cycle for up to 3 cycles) and the following:
    - Paclitaxel (175 or 200 mg/m^2 on Day 1 of a 3 week cycle for up to 3 cycles)

For subjects unable to tolerate cisplatin, the reasons were documented. If the investigator desired to use a carboplatin containing regimen, the investigator was to obtain approval from the Medical Monitor prior to utilization, except for opting for carboplatin plus paclitaxel.

Two of the chemotherapy options, which were allowed for Arm B (cisplatin+docetaxel and cisplatin+vinorelbine) were not allowed for Arm C. This was because, at the time Arm C was added to the protocol, safety data were not available for nivolumab in combination with those chemotherapy backbones. The remaining chemotherapy options were the same for Arms B and C.

Where multiple doses are noted for docetaxel, gemcitabine, and vinorelbine, the investigator was to use the locally approved/recommended dose, due to regional differences, mostly in Asia.

Objectives

The primary and secondary objectives are as mentioned on Table 19:

Table 19: Study CA209816 Key Efficacy Objectives and Endpoints

Objectives	Endpoints	Included in Interim CSR	Included in Primary CSR
Primary:			
To compare the pCR rate in subjects receiving nivo+chemo vs. subjects receiving chemo in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC	pCR by BIPR	Yes	Yes, no change from the Interim CSR
To compare the EFS by BICR in subjects receiving nivo+chemo vs subjects receiving chemo in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC	EFS by BICR	No	Yes
Secondary:			
To compare the OS of subjects receiving nivo+chemo vs. subjects receiving chemo in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC	OS	No	No
To assess the TTDM of subjects receiving nivo+chemo vs. subjects receiving chemo in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC	TTDM by BICR	No	Yes
To assess the MPR rate by BIPR of subjects receiving nivo+chemo vs. subjects receiving chemo in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC	MPR by BIPR	Yes	Yes, no change from the Interim CSR
Exploratory:			
To assess EFS2 in early-stage NSCLC subjects treated with nivo+chemo compared to those treated with chemo	EFS2	No	Yes

Abbreviations: BICR - blinded independent central review; BIPR - blinded independent pathological review; CSR - clinical study report; chemo - platinum-doublet chemotherapy; EFS - event-free survival; EFS2 - event-free survival on second line therapy; MPR - major pathologic response; nivo - nivolumab; NSCLC - non-small cell lung cancer; OS - overall survival; pCR - pathologic complete response; TTDM - time to death or distant metastases.

Outcomes/endpoints

Primary endpoints

- **EFS (by BICR):** for the primary analyses, EFS was defined as the length of time from randomization to any of the following events: a) any progression of disease precluding surgery, b) progression or recurrence of disease (based on BICR assessment per RECIST 1.1) after surgery, or c) death due to any cause. Subjects who did not undergo surgery for reasons other than progression were considered to have an event at RECIST 1.1 (based on BICR) progression or death. The primary definition accounts for subsequent therapy by censoring at the last evaluable tumour assessment on or prior to the date of subsequent therapy (outside of the protocol specified adjuvant therapy). The secondary definition (EFS2) does not incorporate censoring due to subsequent therapy.
- **pCR (by BIPR):** in the primary analysis, the pCR rate was defined as the number of randomized subjects with an absence of residual tumor in lung resected tissue and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each treatment arm. Randomized subjects who were no longer eligible for surgery, who received alternative anticancer therapy before surgery, who discontinued the study (eg, withdraw consent) before surgery, or who otherwise did not have an evaluable BIPR result available were all counted as non-responders.

Secondary endpoints

- **OS:** was defined as the time between the date of randomization and the date of death due to any cause. OS was censored on the last date a subject was known to be alive.
- **Time to Death or Distant Metastasis (TDDM):** was defined as the time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis. A distant metastasis was defined as any new lesion outside of the thorax using BICR and RECIST 1.1 criteria. Subjects who had not developed distant metastasis or died at the time of the analysis were censored on the date of their last evaluable tumour assessment.
- **Major Pathologic Response (MPR) (by BIPR):** was defined as the number of randomized subjects with ≤10% residual tumour in lung and lymph nodes (per BIPR), divided by the number of randomized subjects for each treatment arm. Viable tumours in situ carcinoma were not included in the MPR calculation.

Exploratory endpoint

- **EFS on next line therapy (EFS2)**: was defined as the time from randomization to objectively documented progression, per investigator assessment, after the next line of therapy or to death from any cause, whichever occurred first. Subjects without documented progression on the next line who started a second next line of subsequent therapy were considered to have an event at the start of second next line of therapy. Subjects who were alive and without progression after the next line of therapy were censored at last known alive date.

Tumour assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression.

Sample size

The original study design (before Revised protocol 02) had two arms, with participants randomized in a 1:1 ratio to either neoadjuvant nivolumab plus ipilimumab or platinum doublet chemotherapy arm. Revised protocol 02 added a new, neoadjuvant nivolumab plus platinum doublet chemotherapy arm. When the third arm opens and as each site receives IRB/EC approval of revised protocol 02, the IRT will switch to a 1:1:1 randomization at the respective site. Starting from that point on, the site will only enrol under revised protocol 02.

Revised protocol 03 withholds randomization into the arm of neoadjuvant nivolumab plus ipilimumab but continues randomizing eligible participants into either neoadjuvant nivolumab plus platinum doublet chemotherapy arm or platinum doublet chemotherapy arm in a 1:1 ratio.

Approximately 350 participants (175 participants per arm) will be randomized between 2 arms neoadjuvant nivolumab plus platinum doublet chemotherapy or platinum doublet chemotherapy from 1:1:1 randomization in revised protocol 02 and 1:1 randomization in revised protocol 03.

Participants already randomized in the original 2-arm part (neoadjuvant nivolumab plus ipilimumab vs. neoadjuvant chemotherapy) and in the arm of neoadjuvant nivolumab plus ipilimumab in 3-arm part defined by revised protocol 02 will remain in trial and continue scheduled trial procedures. It is expected to have around 70 participants randomized in the original 2-arm part and approximately other 75 participants randomized in the arm of neoadjuvant nivolumab plus ipilimumab in the 3-arm part. It is estimated that there will be a total of approximately 500 participants on the study.

The sample size of the study is calculated based on the primary endpoint of EFS and accounts for the multiple primary endpoints comparisons: pCR (per BIPR) and EFS (per BICR) with an initial alpha

allocation of 0.01 and 0.04 respectively. Formal analyses of pCR and EFS may be conducted at different timepoints. The fallback method will be used, i.e. if the pCR comparison between Arm C and Arm B is statistically significant, then 0.01 alpha allocated to pCR will be passed to the EFS comparison for Arm C vs Arm B and the EFS comparison will be conducted at the alpha = 0.05 level. If the pCR comparison between Arm C and Arm B is not statistically significant, then the EFS comparison for Arm C vs Arm B will be conducted at the alpha = 0.04 level. If EFS is significant, the secondary endpoint OS will be tested hierarchically, at the same overall alpha level as EFS, using a separate O'Brien Fleming alpha spending function for OS.

Pathologic Complete Response (pCR)

Assuming an accrual rate of 10 participants (all comers) a month between Arms B and C during 1:1:1 randomization (about 10 months), and 15 participants per month during 1:1 randomization, it is anticipated that the 350 participants will be randomized in approximately 27 months. The pCR endpoint is expected to be analyzed after about 30 months from start of 1:1:1 randomization.

Assuming pCR rate of 10% on Arm B chemotherapy and 30% on Arm C nivolumab plus chemotherapy, respectively, the 350 participants will provide more than 90% power to detect an odds ratio of 3.857 with a 2-sided type I error of 1%.

It is estimated that there will be about 110 subjects randomized to Arm A neoadjuvant nivolumab plus ipilimumab before revised protocol 03 is implemented. Assuming true pCR rate is 15% on this arm, there is 95% probability that the lower bound of 95% exact confidence interval of pCR is above 5%.

Event Free Survival (EFS)

A total of 185 events ensure that an overall 2-sided 5% significance level sequential test procedure with two interim analyses after 148 events (80% of events required for final analysis) and 167 events (90% of events required for final analysis) in 358 randomized participants will have 82% power assuming an HR of 0.65 between the 2 Arms. Considering a piecewise exponential distribution with control hazard rates of 0.028 before 20 months, 0.017 between 20 months and 40 months, 0.014 between 40 and 60 months and 0.008 after 60 months, and a dropout rate of approximately 20%, it is anticipated that the EFS analyses will take place at about 48, 58, and 73 months from start of 1:1:1 randomization. The trigger of the first interim analysis is event driven. The second interim analysis will take place when 167 events are observed or one year after the first interim analysis, whichever occurs first. The final analysis will take place when approximately 185 events are observed or four years after the last subject's randomization (i.e. December 2023). The stopping boundaries at the interim and final EFS analyses will be derived based on the exact number of events using Lan-DeMets alpha spending function with O'Brien- Fleming boundaries. If the interim analyses of EFS are performed at exactly 148 and 167 events, the nominal significance level for EFS superiority will be 0.024 and 0.030, respectively. The nominal significance level for the final look of EFS after 185 events would then be 0.038.

Power Considerations for Overall Survival

A total of 185 events ensure that an overall 2-sided 5% significance level sequential test procedure with 3 interim analyses after approximately 101, 128 and 161 events (55%, 69% and 87% of events required for final analysis) in 358 randomized participants will have 82% power assuming an exponential distribution with the median OS time in the control (Arm B) is 54 months and of 83 months in the nivolumab and platinum doublet chemotherapy (Arm C) (corresponding to a target hazard ratio of 0.65). It is anticipated that the analyses will take place at about 48 (EFS IA1), 58 (EFS IA2), 73 (EFS FA), and 86 months from start of 1:1:1 randomization.

The trigger for these interim analyses timing is based on the EFS number of events. However, in case EFS hits significance earlier than OS, the OS analyses will be triggered by the number of OS events (approximately 128 OS events or 1 year after Interim Analysis 1, whichever occurs first for Interim 2 and 161 OS events or 4 years after last subject's randomization, whichever occurs first for Interim 3). The stopping boundaries at the interim and final OS analyses will be derived based on the exact number of events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. This spending function is specific to OS and accounts for potential interim OS analyses even if they did not actually take place because of EFS nonsignificance.

If the interim analyses of OS is performed at exactly 101, 128 and 161 events, respectively, the nominal significance level for OS superiority are 0.005, 0.013 and 0.028, respectively. The nominal significance level for the final analysis of OS after 185 events would then be 0.039.

Randomisation

Per the initial protocol, subjects meeting the inclusion criteria were centrally randomized (1:1 to Arms A [nivo+ipi] and B [chemo]) by the investigator or designee using an IRT system.

Per revised Protocol 02, subjects meeting the inclusion criteria were centrally randomized (1:1:1 to Arms A [nivo+ipi], B [chemo] and C [nivo+chemo]) by the investigator or designee using an IRT system.

Per revised Protocol 03, all subjects meeting the inclusion criteria were centrally randomized (1:1 to Arms B [chemo] and C [nivo+chemo]) by the investigator or designee using an IRT system.

The randomization was based on randomization lists generated using permutated blocks and stratified according to:

- PD-L1 status (≥1% and <1% or not evaluable/indeterminate)
- disease stage (IB/II vs. IIIA)
- gender

For each randomization period (A:B, A:B:C, B:C) a separate randomization list was generated. As each site received IRB/IEC approval of the revised protocol, the IRT switched to the new randomization list at each respective site. From that point on, the site only enrolled under the revised protocol.

Blinding (masking)

This was an open-label study so blinding procedures between participants and investigators are not applicable. The BIPR and BICR were blinded.

Statistical methods

Type I error control

The sample size of the study is calculated based on the primary endpoint of EFS and accounts for the multiple primary endpoints comparisons: pCR (per BIPR) and EFS (per BICR) with an initial alpha allocation of 0.01 and 0.04 respectively. Formal analyses of pCR and EFS may be conducted at different timepoints. The fallback method will be used, i.e., if the pCR comparison between Arm C and Arm B is statistically significant, then 0.01 alpha allocated to pCR will be passed to the EFS comparison for Arm C vs. Arm B and the EFS comparison will be conducted at the alpha = 0.05 level. If the pCR

comparison between Arm C and Arm B is not statistically significant, then the EFS comparison for Arm C vs. Arm B will be conducted at the alpha = 0.04 level. If EFS is significant, the secondary endpoint OS will be tested hierarchically, at the same overall alpha level as EFS, using a separate O'Brien Fleming alpha spending function for OS.

The overall alpha was to be controlled using the following procedure:

1) The primary endpoint pCR rate was to be tested at 1% alpha.
    a. if pCR rate was not significant, the primary endpoint EFS was to be tested at 4%
    b. if pCR rate was significant, the 1% alpha was to be re-allocated to the EFS primary endpoint which was to be tested at 5% alpha level
2) if EFS is significant, OS will be tested hierarchically at the same level as EFS.

EFS and OS will be tested at planned interim and final analyses. Stopping boundaries are calculated for each endpoint according to the observed number of events by Lan-DeMets alpha spending function with O'Brien-Fleming boundaries corresponding to an overall alpha of 4% or 5%. Given EFS and OS endpoints are tested using group sequential approach, overall hierarchical testing approach will be used where each endpoint will have its own specific Lan DeMets alpha spending function with O'Brien-Fleming boundaries.

Additionally, with this sample size, assuming a pCR rate of 10% in the chemo arm (Arm B) chemotherapy and 30% in the nivo+chemo arm (Arm C), 350 subjects would provide more than 90% power to detect an odds ratio of 3.857 with a 2 sided type I error of 1%.

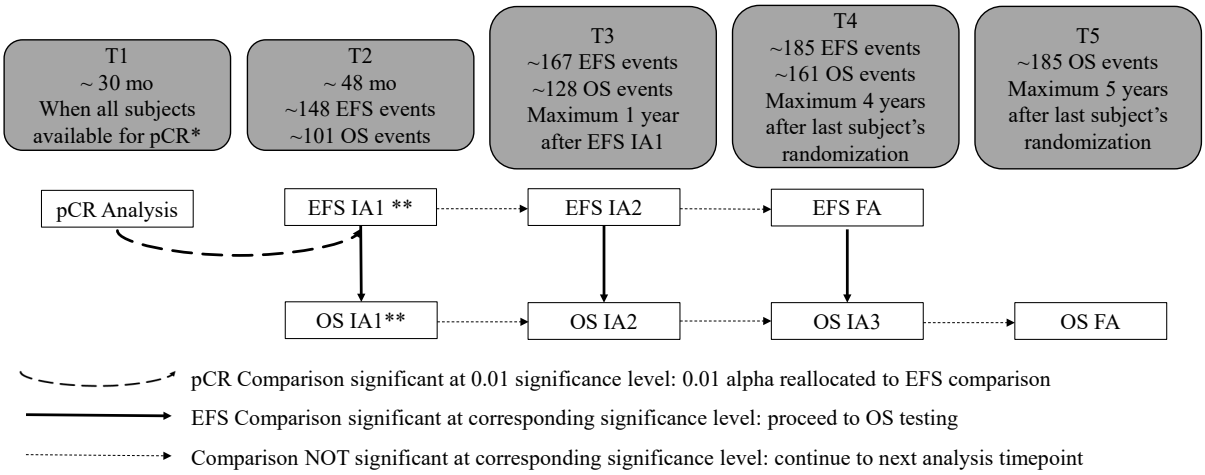
A total of 185 EFS events ensured that an overall 2-sided 5% significance level sequential test procedure with 2 interim analyses after 148 events (80% of events required for final analysis) and 167 events (90% of events required for final analysis) in 358 randomized subjects would have 82% power, assuming an HR of 0.65 between the 2 arms. The trigger of the IA1 of EFS (presented in this CSR) was event driven (at least 148 events; 20 Oct 2021 database lock). The stopping boundaries at the interim and final EFS analyses were to be derived based on the exact number of events using Lan DeMets alpha spending function with O'Brien-Fleming boundaries.

A total of 185 OS events ensures that an overall 2-sided 5% significance level sequential test procedure with 3 interim analyses after approximately 101, 128 and 161 events (55%, 69% and 87% of events required for final analysis) in 358 randomized subjects would have 82% power, assuming an exponential distribution with the median OS time in the chemo arm being 54 months and in the nivo+chemo arm being 83 months (corresponding to a target HR of 0.65). It was anticipated that the analyses would take place at about 48 (EFS IA1), 58 (EFS IA2), 73 (EFS final analysis [FA]), and 86 months (OS FA) from start of 1:1:1 randomization. The trigger for these interim analyses timing is based on the EFS number of events. However, in case EFS hits significance earlier than OS, the formal remaining OS analyses will be triggered by the number of OS events (approximately 128 OS events [69% information fraction] or 1 year after EFS IA1, whichever occurs first for IA2 and 161 OS events or 4 years after last subject's randomization, whichever occurs first for OS IA3).

Given the potential slowdown in event rate that may be observed in the longer term in this setting and that could prevent the analysis being performed in a reasonable time window, if the 185th event has not occurred 5 years after randomization of the last participant, then the final OS analysis will take place at that time. In such case the FA boundary will be re-calculated based on the actual updated final number of events.

A schematic representation of the planned analyses timepoints is provided in Figure 2:

Figure 2. Schematic Representation of Analyses Schedule



EFS and OS tested using each their own O'Brien-Fleming alpha spending function

* Analysis occurred based on 16-Sep-2020 database lock

** Analysis occurred based on 20-Oct-2021 database lock

Abbreviations: EFS - event free survival; FA - final analysis; IA - interim analysis; mo - months; OS - overall survival; pCR - pathologic complete response.

Table 20 summarizes the key parameters of the power calculation for EFS and OS in the concurrently randomized participants from Arms B and C.

Table 20: **Power calculations for EFS and OS**

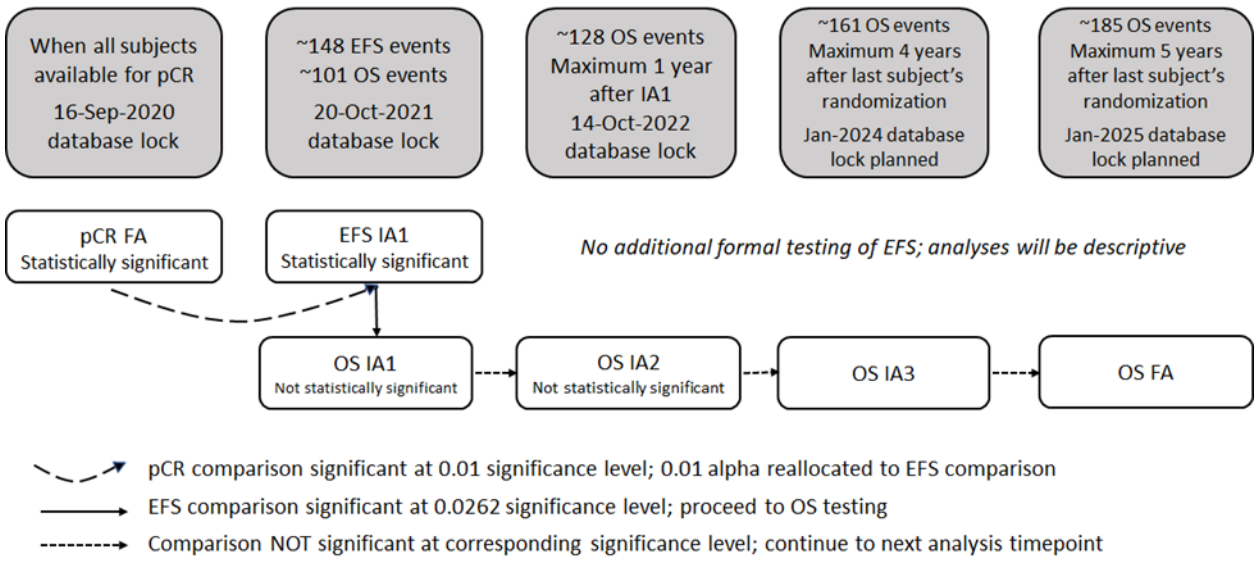
	EFS **Arm C vs Arm B**	**OS** **Arm C vs Arm B**
Accrual	Actual accural 25 months	Actual accural 25 months
Power	82%	82%
Two-sided alpha	0.05	0.05
Hypothesized Median Control vs exp (months)	28 vs 52* Piecewise exponential model	54 vs 83 Exponential model
Hypothesized Hazard ratio	0.65	0.65
Sample size for concurrent comparison	358	358

First interim analysis for EFS (EFS IA1) and OS (OS IA1)	148 events Alpha boundary: 0.024	Triggered by EFS IA1 approx. 101 events Alpha boundary: 0.005
Second interim analysis for EFS (EFS IA2) and OS (OS IA2)	167 events or at maximum 1 year after EFS IA1 Alpha boundary: 0.030	• If EFS IA1 not significant: triggered by EFS IA2. • Else at 128 OS events or at maximum 1 year after OS IA1 Alpha boundary (for 128 events): 0.013
Final EFS (EFS FA) and third OS (OS IA3) interim analysis	185 events or at maximum 4 years after last subject's randomization Alpha boundary: 0.038	• If EFS IA2 not significant: triggered by EFS FA. • Else at 161 OS events or at maximum 4 years after last subject's randomization Alpha boundary (for 161 events): 0.028
Final OS analysis (OS FA)	-	185 events Or at maximum 5 years after last patient's randomization Alpha boundary: 0.039

* Estimated from the piecewise model described in Section 5.2

Following the analyses schedule displayed on figure 2, the OS IA2 was performed with a DBL of 14-Oct-2022, leaving the pending planned analyses as follows (figure 16):

Figure 16: **Schematic Representation of Planned Analyses Schedule (Primary CSR Addendum 01)**



EFS and OS tested using each their own O'Brien-Fleming alpha spending function

Efficacy analyses

Primary Endpoints (EFS and pCR)

The primary analysis of pCR was performed after all randomized subjects in the concurrently randomized (ie, from the start of 1:1:1 randomization) nivo+chemo (Arm C) and chemo (Arm B) arms had an opportunity for surgery. The pCR rate was computed for each treatment arm along with the exact 95% CI using the Clopper-Pearson method. The numerator was based on randomized subjects achieving pCR in both the tumor and lymph nodes, as assessed by BIPR. The denominator was based on all subjects concurrently randomized to the nivo+chemo (Arm C) and chemo (Arm B) arms. Subjects who were no longer eligible for surgery, or who were on alternative anti-cancer therapy before surgery, or who discontinued before surgery, or for whom pCR results were not available, were

all counted as non responders. pCR was compared for concurrently randomized nivo+chemo vs. chemo using the stratified Cochran Mantel-Haenszel (CMH) test with a 2 sided, 1% alpha level. An estimate of the difference and odds ratio and corresponding 99% CI were calculated using CMH methodology adjusting for stratification factors.

The primary analysis of EFS compared the concurrently randomized Arm C (nivo+chemo) and Arm B (chemo) using a stratified log-rank test, with stratification factors per IRT (PD-L1 expression [≥1% or <1%/not evaluable/indeterminate], disease stage [IB/II vs IIIA], and gender/sex) and a 2 sided p-value. A Lan DeMets α-spending function with O'Brien and Fleming type of boundary was used to determine the nominal significance levels for the interim and final analyses. The HR and the corresponding (1 adjusted alpha) CI were estimated for Arm C vs. Arm B using a stratified Cox proportional hazards model with the randomized arm as a single covariate. The EFS curves for each randomized arm were estimated using the Kaplan-Meier (KM) product limit method. The median and 2-sided 95% CI for median EFS in each treatment group was computed using the log-log transformation method. In addition, EFS rates at different timepoints were estimated using KM estimates on the EFS curve for each randomized arm. Associated 2 sided 95% CIs were calculated using the Greenwood formula (using log-log transformation).

Secondary endpoint (TTDM)

The secondary endpoint of TTDM was analyzed descriptively without hypothesis testing. TTDM, based on BICR assessments, was compared between the treatment groups (concurrent Arms C [nivo+chemo] and B [chemo]), using the same methods as those described above for EFS.

Secondary endpoint (OS)

If EFS was significant, the OS secondary endpoint was to be tested hierarchically at the same overall level as EFS.

Exploratory endpoints (EFS2, EFS by pCR/MPR, Biomarker Analyses)

Event-free survival on the next line of therapy (EFS2) was assessed in concurrent Arms B (nivo+chemo) and C (chemo), using the same methods as those described above for EFS, with no hypothesis testing. This analysis was descriptive.

EFS (based on BICR assessments, primary definition) KM curves were generated by pCR status and by MPR status from randomization for all concurrently randomized subjects in Arms C (nivo+chemo) and B (chemo). Median and 95% CI were provided. HR and 95% CIs for concurrently randomized subjects in Arms C (nivo+chemo) and B (chemo) were provided by pCR and by MPR status, as well as HR of pCR/MPR vs. no pCR/MPR by treatment arm.

In addition, these analyses were repeated, landmarked at the time of surgery (ie, time from surgery to progression or death) and limited to subjects with pCR or MPR status available who underwent surgery. Median and 95% CIs were provided. HR and 95% CIs for concurrently randomized subjects in Arms C (nivo+chemo) and B (chemo) were provided by pCR and by MPR status, as well as HR of pCR/MPR vs. no pCR/MPR by treatment arm.

Note that if a subset category had less than 10 subjects per treatment arm, the HR was not computed/displayed.

Regarding biomarker analyses, descriptive analyses were conducted to report the distribution of tumour cell PD-L1 and TMB using continuous values or categories. Association of PD-L1 and TMB with efficacy endpoints (EFS) was explored by running separate analyses for each category of the biomarker.

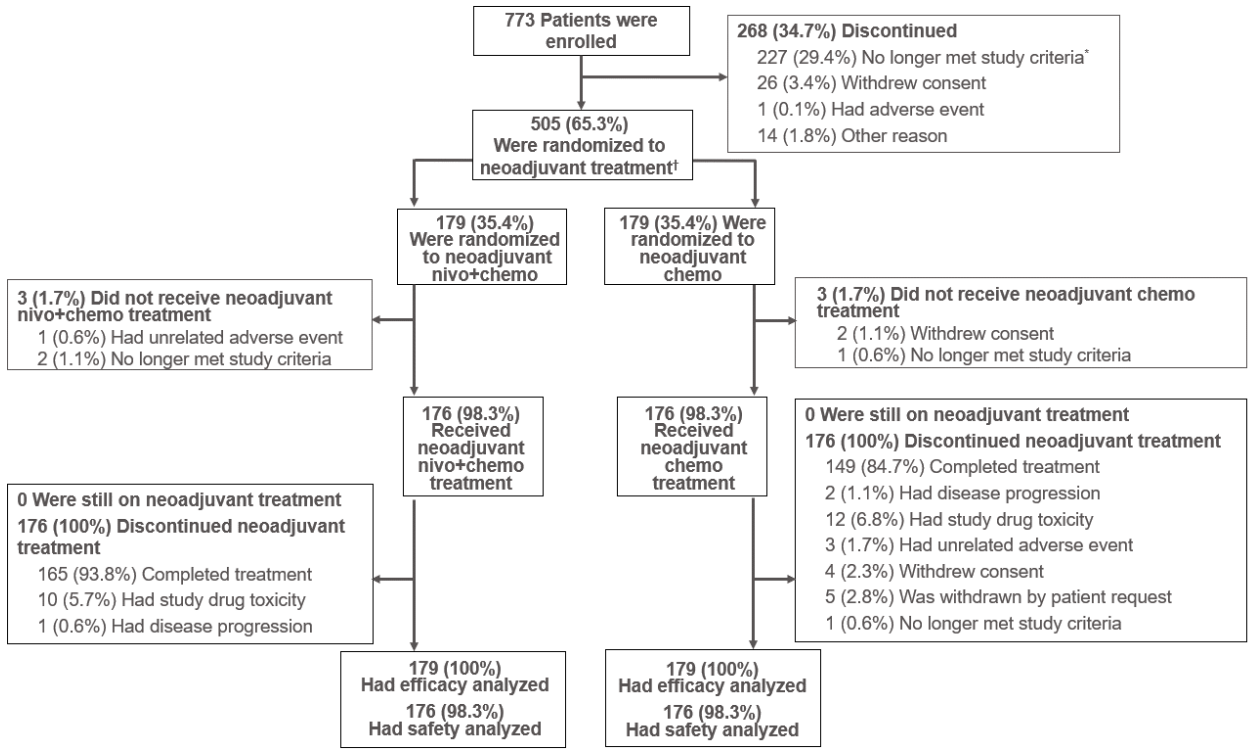
The categories used for PD-L1 were PD-L1 <1%, PD-L1 ≥1%, PD-L1 1-49%, PD-L1 ≥50%, PD-L1 indeterminate/not evaluable. The categories for tumour TMB were < 12.3 mut/Mb, ≥12.3 mut/Mb, and not evaluable/not reported.

In the subjects concurrently randomized to Arms C (nivo+chemo) and B (chemo), a Cox proportional hazards regression model was fitted for EFS with PD-L1 (or TMB), treatment arm and PD-L1 (or TMB) by treatment arm interaction, among all biomarker evaluable subjects and reported a plot of estimated log HR with 95% CI vs. PD-L1 expression (or TMB).

Results

Participant flow

Figure 17: **Participant Flow Chart – Study CA209816**



* Screen failure.

† Includes 113 enrolled patients randomized to an exploratory neoadjuvant nivolumab plus ipilimumab arm for which enrollment was closed early and the arm discontinued, and 34 patients randomized to chemotherapy in the initial protocol (ie, prior to the addition of the nivo+chemo arm) who were not included in the primary analysis population.

At the time of the database lock for the CSR (20-Oct-2021), all treated subjects were off neoadjuvant study treatment for >18 months. Most subjects had completed the course of neoadjuvant therapy (93.8% and 84.7% of treated subjects in the nivo+chemo and chemo arms, respectively). The proportion of subjects not completing the neoadjuvant treatment period due to study drug toxicity was similar in the 2 arms: nivo+chemo (5.7%) and chemo (6.8%).

The reasons for not completing the neoadjuvant treatment period are summarized in Table 21.

Table 21: **End of Neoadjuvant Treatment Period Subject Status - All Treated Subjects**

Status (%)	Arm A: Nivo + Ipi N = 111	Arm C: Nivo + Chemo N = 176	Arm B: Chemo (Concurrent) N = 176	Total N = 495

CONTINUING IN THE NEOADJUVANT TREATMENT PERIOD	0	0	0	0
NOT CONTINUING IN THE NEOADJUVANT TREATMENT PERIOD	111 (100.0)	176 (100.0)	176 (100.0)	495 (100.0)
REASON FOR NOT CONTINUING IN THE NEOADJUVANT TREATMENT PERIOD				
COMPLETED NEOADJUVANT TREATMENT	101 (91.0)	164 (93.2)	149 (84.7)	442 (89.3)
DISEASE PROGRESSION	3 (2.7)	1 (0.6)	2 (1.1)	6 (1.2)
STUDY DRUG TOXICITY	6 (5.4)	10 (5.7)	12 (6.8)	30 (6.1)
DEATH	1 (0.9)	0	0	1 (0.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	1 (0.6)	3 (1.7)	4 (0.8)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	0	5 (2.8)	7 (1.4)
SUBJECT WITHDREW CONSENT	0	0	4 (2.3)	4 (0.8)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	1 (0.6)	1 (0.2)
DISCONTINUED NEOADJUVANT TREATMENT DUE TO COVID-19	0	0	0	0
CONTINUING IN THE STUDY	110 (99.1)	175 (99.4)	172 (97.7)	489 (98.8)
NOT CONTINUING IN THE STUDY	1 (0.9)	1 (0.6)	4 (2.3)	6 (1.2)
REASON FOR NOT CONTINUING IN THE STUDY				
DEATH	1 (0.9)	0	1 (0.6)	2 (0.4)
SUBJECT WITHDREW CONSENT	0	1 (0.6)	3 (1.7)	4 (0.8)
DISCONTINUED STUDY DUE TO COVID-19	0	0	0	0

Percentages based on subjects entering period.
Subjects in Arm B randomized in the initial protocol are included in Total.
Continuing in the study status at the end of neoadjuvant period.
Source: Table S.2.7.1

Recruitment

The enrolment period for the study was from Mar-2017 to Nov-2019. A total of 773 subjects were enrolled at 111 sites in 14 countries (Argentina, Brazil, Canada, China, France, Greece, Italy, Japan, South Korea, Romania, Spain, Taiwan, Turkey, and the United States), and 505 subjects were randomized: 358 concurrently randomized to Arms C (nivo+chemo: 179) and B (chemo: 179). A total of 113 subjects were randomized to Arm A (nivo+ipi).

An addendum to the CSR was provided including exploratory analyses for the key endpoints, with longer follow-up, at the time when the OS IA2 was performed. The key dates and follow-up are included in Table 22 below. Updated results for efficacy endpoints and OS IA2 are included in each section.

Table 22: Key Dates and Follow-up

Last Subject Randomized Date for Concurrent Arms C and B	11-Dec-2019
Last Subject Randomized Date for Arm A	05-Aug-2019
Clinical Cutoff Date (LPLV)	08-Sep-2021
Database Lock	20-Oct-2021
Minimum Follow-up,[a] months	
Concurrently Randomized Arms B (chemo) and C (nivo+chemo)	21.0
Arm A (nivo+ipi)	25.2
Median Follow-up,[b] months	
Concurrently Randomized Arms B (chemo) and C (nivo+chemo)	29.5
Arm A (nivo+ipi)	37.7
Clinical Cutoff Date (LPLV) for Addendum	06-Sep-2022
Database Lock for Addendum	14-Oct-2022
Minimum Follow-up,[c] months	
Concurrently Randomized Arms B (chemo) and C (nivo+chemo)	32.9
Arm A (nivo+ipi)	37.1

Median Follow-up,[d] months	
Concurrently Randomized Arms B (chemo) and C (nivo+chemo)	41.4
Arm A (nivo+ipi)	49.6

[a] Minimum follow-up: time from last subject's randomization to clinical cutoff date (08 Sep 2021) for database lock.
[b] Median follow-up: median of time between randomization date and clinical cutoff date (08 Sep 2021) for database lock for each individual subject.

[c] Minimum follow-up: time from last subject's randomization to clinical cutoff date for database lock.
[d] Median follow-up: median of time between randomization date and clinical cutoff date for database lock for each individual subject.

Abbreviations: chemo - chemotherapy, ipi - ipilimumab, LPLV - last patient last visit, nivo - nivolumab

Conduct of the study

Table 23: Summary of Key Changes to Protocol CA209816

Document/ Date	Summary of Key Changes	Subjects Randomized at time of Protocol Revision
Revised Protocol 01 / 03-Mar-2017	Incorporated changes from Amendment 02 and Administrative Letters 01 and 02. Clarified the use of TNM 7th edition on the study, adjusted dosing details of the chemotherapy regimens to include the dose approved by the local prescribing information and the standard of care infusion time for each country, expanded and split the biomarker objective into 3 more detailed objectives, clarified lymph node samples at screening and definitive surgery, clarified the tissue sample process for calculation of primary endpoint, clarified requirements for PET/CT scans and broadened the window for scans prior to surgery, adjusted hepatitis B virus criteria, added live vaccines and strong cytochrome P450 3A4 (CYP3A4) inhibitors to the prohibited treatments, added caution for concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) with pemetrexed, and added unacceptable methods of contraception.	0
Revised Protocol 02 / 06-Jul-2017	Added the third arm of nivo+chemo (Arm C), increased the sample size to 642 to accommodate the new treatment arm, changed the primary objective to dual primary objectives of pCR and EFS and a secondary objective was changed to MPR based on health authority feedback, increased the pre-screening tissue requirement to 15 slides, updated contrast requirements for brain MRI scans, expanded the window for pulmonary function tests to within 6 weeks of randomization, and included updates to synopsis, rationale/background information, and study personnel.	13
Revised Protocol 03 / 21-Sep-2018	Stopped enrolment in Arm A (nivo+ipi) and made the primary population concurrently randomized subjects on Arms B and C based on external clinical data with PD-1 + chemo, clarified the definition of EFS, excluded subjects with large-cell neuroendocrine carcinoma tumour histology, added an additional platinum-doublet chemotherapy regimen (paclitaxel/carboplatin), updated dose modification for docetaxel, added time to death or distant metastases as a secondary endpoint, clarified tumour assessments for subjects who did not proceed to definitive surgery, updated the SAP, rationale, background information, and trial schematic, clarified pulmonary function parameters, clarified the time relationship between adjuvant radiotherapy and tumour imaging assessments, and clarified the time window of Cycle 1 Day 1 end-of-infusion PK sampling.	170
Revised Protocol 04 / 25-Jun-2019	Updated the collection of serum/plasma-soluble factors post-surgery, added the concomitant administration of substances that were also tuburlarly secreted (e.g., probenecid) and could potentially result in delayed clearance of pemetrexed, added hypothesis testing for OS, clarified the analysis population for pCR, added an exploratory endpoint of EFS on the next line of therapy, added instructions for BICR, and updated AE appendix.	400
Revised Protocol 05 / 18-Sep-2019	Modified the pCR analysis population and projected timelines, updated the surgical approach endpoint, updated the censoring rule of TTDM, removed the optional biopsy at disease progression in China, and updated Management Algorithms to include myocarditis.	456
Revised Protocol 06 / 14-Jul-2020	Clarified that any progression precluding surgery was an EFS event and that RECIST 1.1 progression/recurrence per BICR applied post-surgery or for subjects without surgery, corrected the number of subjects, removed the first of 2 IA of	505

Document/ Date	Summary of Key Changes	Subjects Randomized at time of Protocol Revision
	EFS (60% events) and updated alpha spending on the remaining single interim and final analyses of EFS, and clarified that actual timing of analyses may differ from projected timing.	
Protocol Amendment 07 / 18-Aug-2021	Added an additional interim analysis of EFS and calendar-based rule for the final analysis of EFS, with an additional corresponding OS interim analysis (only if EFS was significant).	505

Abbreviations: BICR - blinded independent central review; CYP3A4 - cytochrome P450 3A4; EFS - event-free survival; HIV - human immunodeficiency virus; MPR - major pathological response; MRI - magnetic resonance imaging; NSAIDs - non-steroidal anti-inflammatory drugs; NSCLC - non-small cell lung cancer; OS - overall survival; pCR - pathologic complete response; PD-1 - programmed cell death protein 1; PD-L1 - programmed death ligand 1; PET/CT - positron emission tomography/computed tomography; PK - pharmacokinetic; RECIST - Response Evaluation Criteria in Solid Tumors; RNA - ribonucleic acid; SNP - single nucleotide polymorphism; TCR - T-cell receptor; TNM - classification of malignant tumors; TTDM - time to death or distant metastases.

Protocol deviations

A summary of important protocol deviations as of the clinical cut-off (8-Sep-2021) is included in Table 7.

Table 24: Summary of Important Protocol Deviations - All Enrolled Subjects

	Nivo + Ipi (Arm A)	Nivo + Chemo (Arm C)	Chemo (Arm B)	Not Randomized	Total
Informed consent and/or ethics (IEC/IRB) deviations					
Failure to obtain written informed consent on the correct approved version and maintain in the study record	5	6	3	4	18
Consistent failure to obtain ICF update from subject	3	3	5	0	11
Failure to report all SAEs in accordance with the time period required by GCP, the protocol, BMS and applicable regulations	2	8	9	3	22
Use of prohibited concomitant medications	1	2	3	0	6
Inclusion or exclusion deviations					
Incorrect disease stage at baseline	1	1	3	0	5
Screening procedure not done or out of window	9	11	11	0	31
Subject enrolled with EGFR positive mutation	0	1	2	0	3
Incorrect dosing or study treatment assignment	3	1	5	0	9
Trial procedures					
Consistent issues with tumour assessments out of window	10	3	6	0	19
Definitive pathology sample not collected per study requirements	2	1	3	0	6
Pre-surgery scan out of window	0	2	1	0	3
Protocol required biomarker labs routinely not drawn.	2	1	3	0	6
Safety labs not done	7	8	5	0	20
ECG not performed within 28 days of randomization	0	0	1	0	1
Other					
Misclassified stratification level [IRT vs Clinical database]	0	1	1	0	2
Follow-up visit documentation missing	1	4	3	0	8
Drug accountability not completed per protocol (receipt of study drug and unassigned kits not accounted for)	0	0	1	0	1

	Nivo + Ipi (Arm A)	Nivo + Chemo (Arm C)	Chemo (Arm B)	Not Randomized	Total
Total	**46**	**53**	**65**	**7**	**171**

Additional sub-categories were added for clarity beyond Appendix 2.1.

Abbreviations: BMS - Bristol Myers Squibb, Chemo - chemotherapy, EGFR - epidermal growth factor receptor, GCP - Good Clinical Practice, ICF - informed consent form, IEC - independent ethics committee, Ipi - ipilimumab; IRB -institutional review board, , Nivo - nivolumab, SAEs - serious adverse events

A total of 3 subjects (1 in the nivo+chemo arm and 2 in the concurrent chemo arm) received concurrent cancer therapy. The subject in the nivo+chemo arm received 2 doses of albumin-based paclitaxel instead of Cremophor-based paclitaxel during the optional adjuvant phase. In the chemo arm, 1 subject received cantharidinate sodium/vitamin B6 injection (dicanth/pyrdx) and the other subject received thymopentin.

Note that 1 subject randomized to Arm A (nivo+ipi) prior to Revised Protocol 02 received the wrong treatment of chemotherapy. This subject is counted in Arm A (nivo+ipi) for baseline and efficacy analyses (analyses based on the randomized population) and is counted in Arm B (chemo) for exposure and safety analyses (based on the treated population). However, since this subject was randomized before implementation of Revised Protocol 02, the subject is not included in the All Treated Subjects from the Concurrently Randomized Arms C (nivo+chemo) and B (chemo) population.

Relevant protocol deviations were defined in the SAP.

Table 25: **Relevant Protocol Deviations**

	Number of Subjects (%)			
Status (%)	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179	Total N = 505
SUBJECTS WITH AT LEAST ONE DEVIATION	2 (1.8)	2 (1.1)	4 (2.2)	10 (2.0)
AT ENTRANCE				
SUBJECTS WITH INADEQUATE DISEASE STAGE	0	1 (0.6)	2 (1.1)	5 (1.0)
SUBJECTS WITH BASELINE ECOG PS > 1	1 (0.9)	0	0	1 (0.2)
ON-TREATMENT DEVIATIONS				
SUBJECTS RECEIVING CONCURRENT CANCER THERAPY	0	1 (0.6)	2 (1.1)	3 (0.6)
SUBJECTS TREATED DIFFERENTLY THAN AS RANDOMIZED	1 (0.9)	0	0	1 (0.2)

Subjects in Arm B randomized in the initial protocol are included in Total.

Baseline data

Demographics and baseline disease characteristics

Table 26: **Demographic Characteristics - All Randomized Subjects**

	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179	Total N = 505
AGE (YEARS)				
N	113	179	179	505
MEAN	63.1	64.1	63.6	63.7
MEDIAN	64.0	64.0	65.0	64.0
MIN , MAX	34 , 83	41 , 82	34 , 84	34 , 86
Q1 , Q3	58.0 , 70.0	58.0 , 70.0	59.0 , 70.0	59.0 , 70.0
SD	9.4	7.8	8.9	8.6
AGE CATEGORIZATION 1 (%)				

< 65	62 (54.9)	93 (52.0)	83 (46.4)	254 (50.3)
>= 65	51 (45.1)	86 (48.0)	96 (53.6)	251 (49.7)
>= 65 AND < 75	40 (35.4)	75 (41.9)	83 (46.4)	211 (41.8)
>= 75 AND < 85	11 (9.7)	11 (6.1)	13 (7.3)	39 (7.7)
>= 85	0	0	0	1 (0.2)
SEX (%)				
MALE	73 (64.6)	128 (71.5)	127 (70.9)	349 (69.1)
FEMALE	40 (35.4)	51 (28.5)	52 (29.1)	156 (30.9)
RACE (%)				
WHITE	64 (56.6)	89 (49.7)	80 (44.7)	261 (51.7)
BLACK OR AFRICAN AMERICAN	4 (3.5)	4 (2.2)	3 (1.7)	13 (2.6)
ASIAN	41 (36.3)	86 (48.0)	93 (52.0)	223 (44.2)
ASIAN INDIAN	0	1 (0.6)	0	1 (0.2)
CHINESE	20 (17.7)	44 (24.6)	53 (29.6)	118 (23.4)
JAPANESE	16 (14.2)	33 (18.4)	35 (19.6)	86 (17.0)
ASIAN OTHER	5 (4.4)	8 (4.5)	5 (2.8)	18 (3.6)
OTHER	4 (3.5)	0	3 (1.7)	8 (1.6)
GEOGRAPHIC REGION (%)				
NORTH AMERICA	46 (40.7)	41 (22.9)	50 (27.9)	157 (31.1)
EUROPE	15 (13.3)	41 (22.9)	25 (14.0)	90 (17.8)
ASIA	41 (36.3)	85 (47.5)	92 (51.4)	220 (43.6)
REST OF THE WORLD	11 (9.7)	12 (6.7)	12 (6.7)	38 (7.5)

Subjects in Arm B randomized in the initial protocol (and not included in the concurrently randomized Arm B; N = 34) are included in Total.

Geographic Regions: **North America** (Canada, United States), **Europe** (France, Greece, Italy, Romania, Spain), **Asia** (China, Japan, Korea, Taiwan), **Rest of World** (Argentina, Brazil)

Table 27: **Demographic Characteristics in the ITT Population and in Subjects with Baseline Disease Stage II-IIIA and PD-L1 Expression ≥ 1% - All Concurrently Randomized Subjects in the Nivo+Chemo (Arm C) and Chemo (Arm B) Arms of Study CA209816 (14-Oct-2022 Database Lock)**

	ITT		Stage II-IIIA Disease and PD-L1 Expression >= 1%	
	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179	Arm C: Nivo + Chemo N = 81	Arm B: Chemo (Concurrent) N = 86
AGE (YEARS)				
N	179	179	81	86
MEAN	64.1	63.6	64.1	63.6
MEDIAN	64.0	65.0	64.0	65.5
MIN , MAX	41 , 82	34 , 84	47 , 82	41 , 84
Q1 , Q3	58.0 , 70.0	59.0 , 70.0	58.0 , 70.0	59.0 , 70.0
SD	7.8	8.9	7.3	8.7
AGE CATEGORIZATION (%)				
< 65	93 (52.0)	83 (46.4)	44 (54.3)	40 (46.5)
>= 65	86 (48.0)	96 (53.6)	37 (45.7)	46 (53.5)
>= 65 AND < 75	75 (41.9)	83 (46.4)	32 (39.5)	42 (48.8)
>= 75 AND < 85	11 (6.1)	13 (7.3)	5 (6.2)	4 (4.7)
>= 85	0	0	0	0
SEX (%)				
MALE	128 (71.5)	127 (70.9)	62 (76.5)	62 (72.1)
FEMALE	51 (28.5)	52 (29.1)	19 (23.5)	24 (27.9)
RACE (%)				
WHITE	89 (49.7)	80 (44.7)	35 (43.2)	36 (41.9)
BLACK OR AFRICAN AMERICAN	4 (2.2)	3 (1.7)	1 (1.2)	1 (1.2)
ASIAN	86 (48.0)	93 (52.0)	45 (55.6)	49 (57.0)
ASIAN INDIAN	1 (0.6)	0	1 (1.2)	0
CHINESE	44 (24.6)	53 (29.6)	25 (30.9)	28 (32.6)
JAPANESE	33 (18.4)	35 (19.6)	16 (19.8)	20 (23.3)
ASIAN OTHER	8 (4.5)	5 (2.8)	3 (3.7)	1 (1.2)
OTHER	0	3 (1.7)	0	0
GEOGRAPHIC REGION (%)				
NORTH AMERICA	41 (22.9)	50 (27.9)	14 (17.3)	21 (24.4)
EUROPE	41 (22.9)	25 (14.0)	18 (22.2)	11 (12.8)
ASIA	85 (47.5)	92 (51.4)	45 (55.6)	49 (57.0)
REST OF THE WORLD	12 (6.7)	12 (6.7)	4 (4.9)	5 (5.8)

Subpopulation based on baseline PD-L1 expression level recorded on clinical database and disease stage at study entry per CRF

Source: **ITT**: refer to Table S.3.2.1 of Addendum 01 to the Primary CSR[2]; **Subjects with Stage II-IIIA Disease and PD-L1 ≥ 1% (New Output)**: Table S.3.102 of Appendix 2

Table 28: **Baseline Disease Characteristics - All Randomized Subjects**

	Number of Subjects (%)			
	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179	Total N = 505

DISEASE STAGE AT STUDY ENTRY (CRF) (A)				
STAGE IA	0	0	1 (0.6)	1 (0.2)
STAGE IB	6 (5.3)	10 (5.6)	8 (4.5)	27 (5.3)
STAGE IIA	18 (15.9)	30 (16.8)	32 (17.9)	89 (17.6)
STAGE IIB	18 (15.9)	25 (14.0)	22 (12.3)	69 (13.7)
STAGE IIIA	71 (62.8)	113 (63.1)	115 (64.2)	316 (62.6)
STAGE IIIB	0	0	0	1 (0.2)
STAGE IV	0	1 (0.6)	1 (0.6)	2 (0.4)
CELL TYPE AT STUDY ENTRY				
SQUAMOUS CELL CARCINOMA	55 (48.7)	87 (48.6)	95 (53.1)	253 (50.1)
NON-SQUAMOUS CELL CARCINOMA	58 (51.3)	92 (51.4)	84 (46.9)	252 (49.9)
ADENOCARCINOMA	58 (51.3)	86 (48.0)	84 (46.9)	245 (48.5)
LARGE CELL CARCINOMA	0	2 (1.1)	0	3 (0.6)
OTHER	0	4 (2.2)	0	4 (0.8)
TOBACCO USE				
NEVER SMOKER	14 (12.4)	19 (10.6)	20 (11.2)	56 (11.1)
CURRENT/FORMER	99 (87.6)	160 (89.4)	158 (88.3)	448 (88.7)
UNKNOWN	0	0	1 (0.6)	1 (0.2)
BASELINE ECOG PS				
0	73 (64.6)	124 (69.3)	117 (65.4)	332 (65.7)
1	39 (34.5)	55 (30.7)	62 (34.6)	172 (34.1)
> 1	1 (0.9)	0	0	1 (0.2)
BASELINE WEIGHT (KG)				
N	113	179	179	505
MEAN	72.83	71.21	68.55	71.03
MEDIAN	69.00	68.10	67.20	68.50
MIN, MAX	45.0 , 168.5	40.4 , 147.9	35.7 , 114.6	35.7 , 168.5
SD	17.42	15.80	13.94	15.80
TIME FROM CURRENT DIAGNOSIS TO RANDOMIZATION (MONTHS)				
N	113	179	179	505
MEAN	1.41	1.27	1.24	1.32
MEDIAN	1.25	1.05	1.08	1.12
MIN, MAX	0.0 , 4.9	0.0 , 9.1	0.0 , 3.7	0.0 , 9.1
SD	0.81	0.89	0.72	0.84
TIME FROM CURRENT DIAGNOSIS TO RANDOMIZATION (%)				
< 1 MONTHS	40 (35.4)	85 (47.5)	82 (45.8)	217 (43.0)
1 - < 2 MONTHS	49 (43.4)	68 (38.0)	72 (40.2)	202 (40.0)
2 - < 3 MONTHS	19 (16.8)	23 (12.8)	18 (10.1)	69 (13.7)
3 - < 4 MONTHS	4 (3.5)	2 (1.1)	7 (3.9)	14 (2.8)
4 - < 5 MONTHS	1 (0.9)	0	0	1 (0.2)
>= 5 MONTHS	0	1 (0.6)	0	2 (0.4)
PD-L1 (CLINICAL DATABASE)				
< 1%	49 (43.4)	78 (43.6)	77 (43.0)	215 (42.6)
>= 1%	60 (53.1)	89 (49.7)	89 (49.7)	259 (51.3)
1-49%	37 (32.7)	51 (28.5)	47 (26.3)	153 (30.3)
>= 50%	23 (20.4)	38 (21.2)	42 (23.5)	106 (21.0)
NOT EVALUABLE	4 (3.5)	12 (6.7)	13 (7.3)	31 (6.1)
TUMOR TISSUE TMB				
>=12.3 MUT/MB	25 (22.1)	39 (21.8)	37 (20.7)	105 (20.8)
< 12.3 MUT/MB	35 (31.0)	49 (27.4)	53 (29.6)	145 (28.7)
NOT EVALUABLE	7 (6.2)	13 (7.3)	8 (4.5)	33 (6.5)
NOT REPORTED (B)	46 (40.7)	78 (43.6)	81 (45.3)	222 (44.0)

(A) TNM 7th edition used for classification.

(B) TMB was not analyzed from subjects in China, and these subjects are included in the Not Reported category.

Subjects in Arm B randomized in the initial protocol (and not included in the concurrently randomized Arm B; N = 34) are included in Total.

Table 29: **Baseline Disease Characteristics in the ITT Population and in Subjects with Baseline Disease Stage II IIIA and PD L1 Expression ≥1% - All Concurrently Randomized Subjects in the Nivo+Chemo (Arm C) and Chemo (Arm B) Arms of Study CA209816 (14-Oct-2022 Database Lock)**

	Number of Subjects (%)			
	ITT		Stage II-IIIA Disease and PD-L1 Expression >= 1%	
	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179	Arm C: Nivo + Chemo N = 81	Arm B: Chemo (Concurrent) N = 86
DISEASE STAGE AT STUDY ENTRY (CRF)				
STAGE IA	0	1 (0.6)	0	0
STAGE IB	10 (5.6)	8 (4.5)	0	0
STAGE IIA	30 (16.8)	32 (17.9)	13 (16.0)	19 (22.1)
STAGE IIB	25 (14.0)	21 (11.7)	12 (14.8)	11 (12.8)
STAGE IIIA	113 (63.1)	116 (64.8)	56 (69.1)	56 (65.1)
STAGE IIIB	0	0	0	0
STAGE IV	1 (0.6)	1 (0.6)	0	0
CELL TYPE AT STUDY ENTRY				
SQUAMOUS CELL CARCINOMA	87 (48.6)	95 (53.1)	42 (51.9)	47 (54.7)
NON-SQUAMOUS CELL CARCINOMA	92 (51.4)	84 (46.9)	39 (48.1)	39 (45.3)
ADENOCARCINOMA	86 (48.0)	84 (46.9)	37 (45.7)	39 (45.3)
LARGE CELL CARCINOMA	2 (1.1)	0	0	0
OTHER	4 (2.2)	0	2 (2.5)	0
TOBACCO USE				
NEVER SMOKER	19 (10.6)	20 (11.2)	9 (11.1)	8 (9.3)
CURRENT/FORMER	160 (89.4)	158 (88.3)	72 (88.9)	77 (89.5)
UNKNOWN	0	1 (0.6)	0	1 (1.2)
BASELINE ECOG PS				
0	124 (69.3)	117 (65.4)	59 (72.8)	62 (72.1)
1	55 (30.7)	62 (34.6)	22 (27.2)	24 (27.9)
> 1	0	0	0	0
BASELINE WEIGHT (KG)				
N	179	179	81	86
MEAN	71.21	68.55	69.98	67.23
MEDIAN	68.10	67.20	68.50	65.45
MIN, MAX	40.4 , 147.9	35.7 , 114.6	40.4 , 126.3	44.6 , 114.6
SD	15.80	13.94	15.04	13.30
TIME FROM CURRENT DIAGNOSIS TO RANDOMIZATION (MONTHS)				
N	179	179	81	86
MEAN	1.27	1.24	1.33	1.23
MEDIAN	1.05	1.08	0.99	1.12
MIN, MAX	0.0 , 9.1	0.0 , 3.7	0.1 , 9.1	0.2 , 3.4
SD	0.89	0.72	1.13	0.69
TIME FROM CURRENT DIAGNOSIS TO RANDOMIZATION (%)				
< 1 MONTHS	85 (47.5)	82 (45.8)	42 (51.9)	41 (47.7)
1 - < 2 MONTHS	68 (38.0)	72 (40.2)	26 (32.1)	34 (39.5)
2 - < 3 MONTHS	23 (12.8)	18 (10.1)	11 (13.6)	9 (10.5)
3 - < 4 MONTHS	2 (1.1)	7 (3.9)	1 (1.2)	2 (2.3)
4 - < 5 MONTHS	0	0	0	0
>= 5 MONTHS	1 (0.6)	0	1 (1.2)	0
PD-L1 (CLINICAL DATABASE)				
< 1%	78 (43.6)	77 (43.0)	0	0
>= 1%	89 (49.7)	89 (49.7)	81 (100.0)	86 (100.0)
1-49%	51 (28.5)	47 (26.3)	46 (56.8)	46 (53.5)
>= 50%	38 (21.2)	42 (23.5)	35 (43.2)	40 (46.5)
NOT EVALUABLE	12 (6.7)	13 (7.3)	0	0
TUMOR TISSUE TMB				
>=12.3 MUT/MB	39 (21.8)	37 (20.7)	18 (22.2)	24 (27.9)
< 12.3 MUT/MB	49 (27.4)	53 (29.6)	25 (30.9)	22 (25.6)
NOT EVALUABLE	13 (7.3)	8 (4.5)	4 (4.9)	4 (4.7)
NOT REPORTED	78 (43.6)	81 (45.3)	34 (42.0)	36 (41.9)

Subpopulation based on baseline PD-L1 expression level recorded on clinical database and disease stage at study entry per CRF.

Source: **ITT** : refer to Table S.3.2.7 of Addendum 01 to the Primary CSR[2]; **Subjects with Stage II-IIIA Disease and PD-L1 ≥ 1% (New Output)**: Table S.3.103 of Appendix 2

Baseline PD-L1 tumour cell expression

All subjects provided a tumour sample (archival or current FFPE tumour tissue) to the central laboratory for PD-L1 (Dako 28-8 IHC) testing at baseline. Subjects were randomized regardless of PD-L1 status.

Table 30: **Frequency of PD-L1 Tumour Cell Expression Status - All Randomized PD-L1 Quantifiable Subjects in Arm A (Nivo+Ipi) and Concurrent Arms B (Chemo) and C (Nivo+Chemo)**

Population PD-L1 Expression Category	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179	Total N = 505

SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	109 (96.5)	167 (93.3)	166 (92.7)	474 (93.9)
PD-L1 EXPRESSION (%)				
MEAN	23.1	21.9	22.9	22.1
MEDIAN	2.0	1.0	1.0	1.0
MIN , MAX	0 , 100	0 , 100	0 , 100	0 , 100
Q1 , Q3	0.0 , 30.0	0.0 , 40.0	0.0 , 50.0	0.0 , 40.0
STANDARD DEVIATION	32.7	32.4	33.4	32.2
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	60/109 (55.0)	89/167 (53.3)	89/166 (53.6)	259/474 (54.6)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	49/109 (45.0)	78/167 (46.7)	77/166 (46.4)	215/474 (45.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 50%	23/109 (21.1)	38/167 (22.8)	42/166 (25.3)	106/474 (22.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 50%	86/109 (78.9)	129/167 (77.2)	124/166 (74.7)	368/474 (77.6)
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	4 (3.5)	12 (6.7)	13 (7.3)	31 (6.1)

Subjects in Arm B randomized in the initial protocol (N = 34) are included in Total.

Definitive surgery following neoadjuvant treatment

Table 31: **Definitive Surgery - All Randomized Subjects in Arm A (Nivo+Ipi) & Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)**

	Number of Subjects (%)		
	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: (Concurrent) N = 179
SUBJECTS WITH CLINICAL DOWNSTAGING (1) (%)	22 (19.5)	55 (30.7)	42 (23.5)
SUBJECTS WITH DEFINITIVE SURGERY (%)	83 (73.5)	149 (83.2)	135 (75.4)
SUBJECTS WITH DEFINITIVE SURGERY NOT REPORTED (%)	1 (0.9)	2 (1.1)	7 (3.9)
SUBJECTS WITH CANCELED DEFINITIVE SURGERY (%)	29 (25.7)	28 (15.6)	37 (20.7)
REASON FOR CANCELED SURGERY (2)			
ADVERSE EVENT	3 (10.3)	2 (7.1)	1 (2.7)
DISEASE PROGRESSION	18 (62.1)	12 (42.9)	17 (45.9)
OTHER	8 (27.6)	14 (50.0)	19 (51.4)
SUBJECTS WITH DELAYED SURGERY (3) (6) (%)	5 (6.0)	31 (20.8)	24 (17.8)
REASON FOR DELAYED SURGERY (3) (4)			
ADVERSE EVENT	3 (60.0)	6 (19.4)	9 (37.5)
ADMINISTRATIVE REASON	0	17 (54.8)	8 (33.3)
OTHER	2 (40.0)	8 (25.8)	7 (29.2)
LENGTH OF DELAY (WEEKS)			
N	5	31	24
MEAN	2.9	3.0	3.6
MEDIAN	2.1	2.0	2.4
MIN, MAX	1, 6	0, 26	0, 20
Q1, Q3	1.9, 3.4	0.6, 3.0	1.0, 3.7
SD	2.1	4.7	4.4
LENGTH OF DELAY (4)			
<= 2 WEEKS	2 (40.0)	17 (54.8)	11 (45.8)
> 2 AND <= 4 WEEKS	2 (40.0)	8 (25.8)	8 (33.3)
> 4 AND <= 6 WEEKS	0	3 (9.7)	2 (8.3)
> 6 WEEKS	1 (20.0)	3 (9.7)	3 (12.5)
DURATION OF SURGERY (MINUTES)			
N	70	122	120
MEAN	226.2	203.9	221.3
MEDIAN	212.0	185.0	213.5
MIN, MAX	85, 525	25, 560	46, 486
Q1, Q3	152.0, 273.0	133.0, 260.0	150.0, 283.0
SD	94.3	95.9	94.4
LENGTH OF HOSPITAL STAY (DAYS)			
N	80	142	127
MEAN	12.8	11.6	12.8

MEDIAN	10.0	10.0	10.0
MIN, MAX	1, 51	1, 51	1, 67
Q1, Q3	6.0, 16.0	7.0, 14.0	7.0, 15.0
SD	9.9	8.3	10.1
METHOD OF SURGERY (6) (%)			
MINIMALLY INVASIVE-THORACOSCOPIC/ROBOTIC	22 (26.5)	44 (29.5)	29 (21.5)
THORACOTOMY	51 (61.4)	88 (59.1)	85 (63.0)
MINIMALLY INVASIVE TO THORACOTOMY	10 (12.0)	17 (11.4)	21 (15.6)
TYPE OF SURGERY (5) (6) (%)			
PNEUMONECTOMY	9 (10.8)	25 (16.8)	34 (25.2)
LOBECTOMY	55 (66.3)	115 (77.2)	82 (60.7)
SLEEVE LOBECTOMY	4 (4.8)	2 (1.3)	10 (7.4)
BILOBECTOMY	6 (7.2)	3 (2.0)	4 (3.0)
OTHER	22 (26.5)	24 (16.1)	21 (15.6)
SURGERY OUTCOME (6) (%)			
R0 (negative margin)	66 (79.5)	124 (83.2)	105 (77.8)
R1 (microscopic positive margin)	12 (14.5)	16 (10.7)	21 (15.6)
R2 (macroscopic positive margin)	3 (3.6)	5 (3.4)	4 (3.0)
UNKNOWN	2 (2.4)	4 (2.7)	5 (3.7)

(1) Subjects with clinical downstaging have lower disease stage prior to surgery vs. baseline.
(2) Denominator based on number of subjects with cancelled surgery.
(3) Time from last neoadjuvant dose to surgery > 6 weeks
(4) Denominator based on number of subjects with delayed surgery.
(5) Subjects may have more than one surgery type.
(6) Denominator based on number of subjects with surgery

Adjuvant therapy

Optional adjuvant chemo or radiotherapy was allowed after surgery per protocol (per the investigator's judgment).

Table 32: **Adjuvant Therapy Treatment - All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)**

	Arm A: Nivo + Ipi N = 111	Arm C: Nivo + Chemo N = 176	Arm B: Chemo (Concurrent) N = 176	Total N = 463
SUBJECTS RECEIVING ADJUVANT SYSTEMIC THERAPY	37 (33.3)	26 (14.8)	44 (25.0)	107 (23.1)
SUBJECTS RECEIVING ADJUVANT RADIOTHERAPY	3 (2.7)	14 (8.0)	17 (9.7)	34 (7.3)
SUBJECTS RECEIVING ADJUVANT RADIOTHERAPY WITHOUT SYSTEMIC ADJUVANT	1 (0.9)	9 (5.1)	12 (6.8)	22 (4.8)
SUBJECTS RECEIVING ANY ADJUVANT THERAPY	38 (34.2)	35 (19.9)	56 (31.8)	129 (27.9)

Table 33: **Adjuvant Systemic Therapy Dose Information Summary - All Subjects with Adjuvant Systemic Treatment Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)**

	Nivo + Chemo (N = 26)						
	Carboplatin N = 11	Cisplatin N = 15	Docetaxel N = 1	Gemcitabine N = 6	Paclitaxel N = 6	Pemetrexed N = 10	Vinorelbine N = 2
SUBJECTS RECEIVING ADJUVANT SYSTEMIC THERAPY	11 (42.3)	15 (57.7)	1 (3.8)	6 (23.1)	6 (23.1)	10 (38.5)	2 (7.7)
NUMBER OF DOSES RECEIVED							
1	3 (27.3)	5 (33.3)	1 (100.0)	0	1 (16.7)	4 (40.0)	0
2	3 (27.3)	4 (26.7)	0	2 (33.3)	3 (50.0)	2 (20.0)	0
3	2 (18.2)	4 (26.7)	0	0	1 (16.7)	3 (30.0)	0
4	3 (27.3)	2 (13.3)	0	2 (33.3)	1 (16.7)	1 (10.0)	0
> 4	0	0	0	2 (33.3)	0	0	2 (100.0)

	Chemo (Concurrent) (N = 44)						
	Carboplatin	Cisplatin	Docetaxel	Gemcitabine	Paclitaxel	Pemetrexed	Vinorelbine
	N = 13	N = 32	N = 10	N = 7	N = 8	N = 14	N = 5
SUBJECTS RECEIVING ADJUVANT SYSTEMIC THERAPY	13 (29.5)	32 (72.7)	10 (22.7)	7 (15.9)	8 (18.2)	14 (31.8)	5 (11.4)
NUMBER OF DOSES RECEIVED							
1	3 (23.1)	12 (37.5)	2 (20.0)	1 (14.3)	3 (37.5)	3 (21.4)	2 (40.0)
2	4 (30.8)	9 (28.1)	2 (20.0)	3 (42.9)	3 (37.5)	6 (42.9)	0
3	4 (30.8)	8 (25.0)	5 (50.0)	0	1 (12.5)	2 (14.3)	0
4	2 (15.4)	3 (9.4)	1 (10.0)	1 (14.3)	1 (12.5)	3 (21.4)	1 (20.0)
> 4	0	0	0	2 (28.6)	0	0	2 (40.0)

Subsequent cancer therapy

Subsequent therapies are defined as cancer therapies that were started on or after the first study drug dose (started on or after the date of randomization, if not treated), outside of the on-protocol adjuvant study therapy (systemic and radiotherapy).

Table 34: **Subsequent Cancer Therapy - All Randomized Subjects in Arm A (Nivo+Ipi) and Concurrent Arms C (Nivo+Chemo) and B (Chemo) (14-Oct-2022 DBL)**

	Number of Subjects (%)		
	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%)	36 (31.9)	49 (27.4)	87 (48.6)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	13 (11.5)	25 (14.0)	44 (24.6)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	7 (6.2)	5 (2.8)	8 (4.5)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	34 (30.1)	41 (22.9)	75 (41.9)
IMMUNOTHERAPY	12 (10.6)	15 (8.4)	47 (26.3)
ANTI-PD1	7 (6.2)	11 (6.1)	36 (20.1)
ANTI PD 1	0	0	1 (0.6)
NIVOLUMAB	2 (1.8)	3 (1.7)	9 (5.0)
PEMBROLIZUMAB	5 (4.4)	6 (3.4)	25 (14.0)
SINTILIMAB	0	0	1 (0.6)
TISLELIZUMAB	0	2 (1.1)	0
TORIPALIMAB	0	0	1 (0.6)
ANTI-PDL1	6 (5.3)	4 (2.2)	14 (7.8)
ATEZOLIZUMAB	3 (2.7)	2 (1.1)	8 (4.5)
DURVALUMAB	3 (2.7)	2 (1.1)	6 (3.4)
ANTI-CTLA4	1 (0.9)	1 (0.6)	0
IPILIMUMAB	1 (0.9)	1 (0.6)	0
OTHER IMMUNOTHERAPY	0	0	1 (0.6)
TERELIZUMAB	0	0	1 (0.6)
TARGETED THERAPY	8 (7.1)	15 (8.4)	27 (15.1)
ALK/EGFR TYROSINE KINASE INHIBITORS	5 (4.4)	5 (2.8)	11 (6.1)
AFATINIB	0	0	1 (0.6)
ALECTINIB	0	0	2 (1.1)
BRIGATINIB	0	1 (0.6)	0
CRIZOTINIB	1 (0.9)	1 (0.6)	1 (0.6)
ERLOTINIB	0	1 (0.6)	0
GEFITINIB	1 (0.9)	0	3 (1.7)
ICOTINIB	1 (0.9)	1 (0.6)	0
LORLATINIB	0	0	1 (0.6)
OSIMERTINIB	3 (2.7)	2 (1.1)	6 (3.4)

	Number of Subjects (%)		
	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179

VEGFR INHIBITORS	3 (2.7)	11 (6.1)	15 (8.4)
BEVACIZUMAB	2 (1.8)	2 (1.1)	6 (3.4)
CATEQUENTINIB	0	3 (1.7)	6 (3.4)
ENDOSTAR	0	1 (0.6)	0
ENDOSTATIN	0	1 (0.6)	4 (2.2)
RAMUCIRUMAB	2 (1.8)	4 (2.2)	2 (1.1)
OTHER TARGETED THERAPY	1 (0.9)	0	4 (2.2)
AMIVANTAMAB	0	0	1 (0.6)
CAPMATINIB	0	0	1 (0.6)
ENTRECTINIB	0	0	1 (0.6)
PRALSETINIB	0	0	1 (0.6)
REGORAFENIB	0	0	1 (0.6)
TEMSIROLIMUS	1 (0.9)	0	0
OTHER SYSTEMIC CANCER THERAPY - CHEMOTHERAPY	28 (24.8)	37 (20.7)	47 (26.3)
CARBOPLATIN	20 (17.7)	19 (10.6)	23 (12.8)
CARPLA/PEMB/TAXOL	0	0	1 (0.6)
CISPLATIN	9 (8.0)	8 (4.5)	11 (6.1)
DOCETAXEL	7 (6.2)	9 (5.0)	9 (5.0)
ETOPOSIDE	1 (0.9)	4 (2.2)	1 (0.6)
GEMCITABINE	3 (2.7)	6 (3.4)	5 (2.8)
GIMER/OTERA/TEGFUR	0	1 (0.6)	1 (0.6)
LOBAPLATIN	0	1 (0.6)	0
NEDAPLATIN	1 (0.9)	1 (0.6)	3 (1.7)
PACLITAXEL	11 (9.7)	18 (10.1)	20 (11.2)
PEMETREXED	13 (11.5)	5 (2.8)	10 (5.6)
TAXANE	1 (0.9)	0	0
TEGAFUR	1 (0.9)	0	3 (1.7)
VINORELBINE	5 (4.4)	6 (3.4)	5 (2.8)
OTHER SYSTEMIC CANCER THERAPY	1 (0.9)	1 (0.6)	7 (3.9)
ELEMENE	0	1 (0.6)	0
HERBS	0	0	5 (2.8)
MLN0128	1 (0.9)	0	0
PAMIDRONATE	0	0	1 (0.6)
SPLEEN EXTRACT	0	0	1 (0.6)
TELISOTUZUMAB	0	0	1 (0.6)

Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated), outside of the protocol-specified adjuvant therapy.
Source: Table S.6.23

Numbers analysed

The primary population for efficacy analyses was All Concurrently Randomized Subjects in Arms B and C. The primary population for safety analyses was All Treated Subjects from Concurrently Randomized Arms B and C.

Table 35: Analysis Populations

Population	Nivo+Ipi (Arm A)	Nivo+Chemo (Arm C)	Chemo (Arm B)	Total
Enrolled Subjects: All subjects who signed an ICF and were registered into the IRT.				773
Randomized Subjects: All subjects who were randomized to any treatment group in the study**.**	113	179	213	505
Treated Subjects: All randomized subjects who received at least one dose of study drug. This is the population for the safety and dosing evaluation.	111	176	208	495
All Concurrently Randomized Subjects in Arms B and C: All subjects concurrently randomized on Arms B and C under and after Revised Protocol 02). **This is the primary analysis population for efficacy.**	--	179	179	358
All Concurrently Randomized Subjects in Arms A and B: All subjects concurrently randomized on Arms A and B before and under Revised Protocol 02. This is the population used to describe key measures of efficacy for Arm A.	113	--	108	221
All Treated Subjects from the Concurrently Randomized Arms B and C: All subjects concurrently randomized on Arms B and C under and after Revised Protocol 02 who received at least one dose of any study medication in the neoadjuvant setting. This is the primary analysis population for drug exposure and safety for Arms B and C.	--	176	176	352
PD-L1 Evaluable Subjects: All randomized subjects with baseline evaluable PD-L1 (non-missing numeric).	109	167	166[a]	474[b]
Tumor Tissue TMB Evaluable Subjects: All randomized subjects with baseline evaluable tumor tissue TMB (non-missing numeric). TMB data were not available for subjects in China.	60	88	90[a]	250[b]
ctDNA Clearance Evaluable Subjects: All randomized subjects who are ctDNA clearance evaluable (ctDNA status present at Cycle 1 Day 1 and sample with status absent or present at Cycle 3 Day 1 or ctDNA status absent at Cycle 1 Day 1 sample and status present at Cycle 3 Day 1).	36	43	43[a]	122[c]

[a] Concurrently randomized with the nivo+chemo arm (Arm C)
[b] This total includes all subjects randomized to Arm B in the initial protocol.
[c] This total excludes subjects randomized to Arm B who were not concurrently randomized to Arm C.

Abbreviations: ctDNA - circulating tumor deoxyribonucleic acid; EQ-5D-3L - EuroQol-5 Dimension-3 Level; ICF - informed consent form; IRT - Interactive Response Technology; ipi - ipilimumab; nivo - nivolumab; PD-L1 - programmed death ligand 1; TMB - tumor mutational burden.

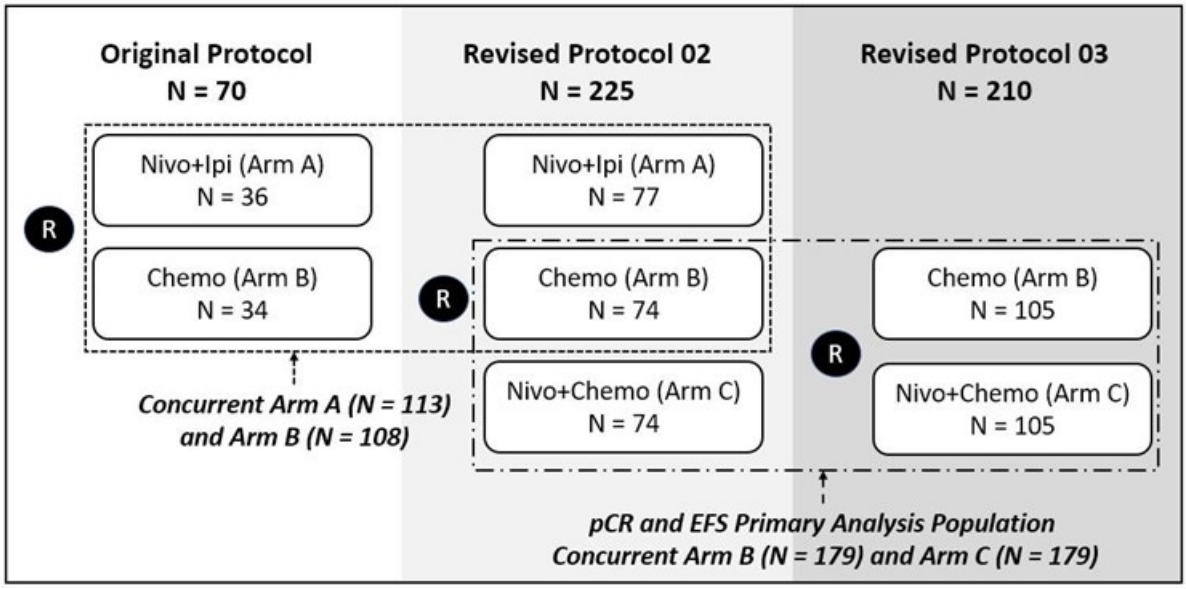
A summary of the populations by randomization period is provided in Table 36 and Figure 18.

Table 36: Populations by Randomization Period

Randomization Period	Number of Randomized Subjects		
	Arm A Nivo + Ipi	Arm B Chemo	Arm C Nivo + Chemo
Before Revised Protocol 02	36	34	N.A.
Under Revised Protocol 02	77	74	74
As of Revised Protocol 03	N.A.	105	105
Concurrent A and B Population	113	108	N.A.
Concurrent B and C Population (Primary)	N.A.	179	179

Abbreviations: chemo - chemotherapy; ipi - ipilimumab; NA - not applicable; nivo – nivolumab

Figure 18: Randomization Scheme Modifications per Protocol Revisions in Study CA209816



Abbreviations: EFS - event-free survival, pCR - pathologic complete response

Outcomes and estimation

For the analysis of EFS and pCR, the minimum follow-up (time between last subject randomized [11-Dec-2019] and last subject last visit [08-Sep-2021]) was 21.0 months and median follow-up was 29.5 months in the concurrently randomized nivo+chemo and chemo arms.

Updated exploratory analyses for some of the key endpoints were performed at the time of the OS IA2 (DBL 14-Oct-2022). As of 14-Oct-2022, in the concurrently randomized nivo+chemo and chemo arms, the minimum follow-up was 32.9 months and the median follow-up was 41.4 months. These analyses results are included in the corresponding endpoint sections.

A summary of the main efficacy results in the ITT population and in the subset of patients corresponding to the finally agreed indication (subjects with baseline disease stage II-IIIA and PD-L1 expression ≥ 1%) is included below in Table 37.

Table 37: Summary of Efficacy in the ITT Population and in Subjects with Baseline Disease Stage II-IIIA and PD-L1 Expression ≥ 1% - All Concurrently Randomized Subjects in the Nivo+Chemo (Arm C) and Chemo (Arm B) Arms of Study CA209816

	ITT		Stage II-IIIA Disease and PD-L1 Expression ≥ 1%	
	Nivo+Chemo N = 179	Chemo N = 179	Nivo+Chemo N = 81	Chemo N = 86
EFS per BICR (Primary Definition) (20-Oct-2021 Database Lock)				
Events, n (%)	64 (35.8)	87 (48.6)	20 (24.7)	40 (46.5)
Median (95% CI), mo.	31.57 (30.16, NA)	20.80 (14.03, 26.71)	Not reached (NA, NA)	21.06 (11.47, NA)
HR (97.38% CI), stratified log-rank p value	0.63 (0.43, 0.91), p = 0.0052[a]		-	
HR (95% CI)	0.63 (0.45, 0.87)[a]		0.44 (0.26, 0.76)[d]	

	ITT		Stage II-IIIA Disease and PD-L1 Expression ≥ 1%	
	Nivo+Chemo N = 179	**Chemo N = 179**	**Nivo+Chemo N = 81**	**Chemo N = 86**
EFS per BICR (Primary Definition) (14-Oct-2022 Database Lock)				
Events, n (%)	69 (38.5)	88 (49.2)	22 (27.2)	39 (45.3)
Median (95% CI), mo.	Not reached (31.57, NA)	21.06 (14.75, 42.09)	Not reached (44.42, NA)	26.71 (13.40, NA)
HR (95% CI)	0.68 (0.49, 0.93)[a]		0.49 (0.29, 0.83)[d]	
pCR per BIPR (16-Sep-2020 Database Lock)				
Responses, n	43	4	26	2
pCR (95% CI), %	24.0 (18.0, 31.0)	2.2 (0.6, 5.6)	32.1 (22.2, 43.4)	2.3 (0.3, 8.1)
Difference (99% CI), %	21.6 (13.0, 30.3)[b]		-	
Difference (95% CI), %	21.6 (15.1, 28.2)[b]		29.8 (19.0, 40.7)[c]	
Estimate of odds ratio (99% CI), stratified CMH p value	13.94 (3.49, 55.75), p < 0.0001[e]		-	
TTDM per BICR (14-Oct-2022 Database Lock)				
Events, n (%)	53 (29.6)	82 (45.8)	16 (19.8)	35 (40.7)
Median (95% CI), mo.	Not reached (48.59, NA)	34.27 (23.56, NA)	Not reached (44.42, NA)	Not reached (18.83, NA)
HR (95% CI)	0.55 (0.39, 0.78)[a]		0.40 (0.22, 0.72)[d]	
EFS2 per Investigator (14-Oct-2022 Database Lock)				
Events, n (%)	53 (29.6)	75 (41.9)	16 (19.8)	34 (39.5)
Median (95% CI), mo.	Not reached (NA, NA)	Not reached (37.52, NA)	Not reached (NA, NA)	Not reached (29.08, NA)
HR (95% CI)	0.64 (0.45, 0.91)[a]		0.45 (0.25, 0.81)[d]	
OS (14-Oct-2022 Database Lock)				
Events, n (%)	44 (24.6)	67 (37.4)	13 (16.0)	29 (33.7)
Median (95% CI), mo.	Not reached (NA, NA)	Not reached (46.78, NA)	Not reached (NA, NA)	Not reached (NA, NA)
HR (99.34% CI), stratified log-rank p value	0.62 (0.36, 1.05), p = 0.0124[a]		-	
HR (95% CI)	0.62 (0.42, 0.90)[a]		0.43 (0.22, 0.83)[d]	

[a] Statistical model for hazard ratio: Stratified Cox proportional hazard model
[b] pCR ITT: Strata adjusted difference (Arm C - Concurrent Arm B) based on Cochran-Mantel Haenszel (CMH) method of weighting
[c] Two-sided 95% confidence interval for un-weighted was calculated using Newcombe method.
[d] Statistical model for hazard ratio: unstratified Cox proportional hazard model
[e] Strata adjusted odds ratio (Arm C over Concurrent Arm B) using Mantel-Haenszel method.

Subpopulation based on baseline PD-L1 expression level recorded on clinical database and disease stage at study entry per CRF.

Database locks: 16-Sep-2020 for pCR, 20-Oct-2021 (IA1) for EFS, and 14-Oct-2022 (IA2) for EFS, OS, TTDM, and EFS2

Primary endpoints

Pathologic Complete Response (pCR) based on 16-Sep-2020 DBL

In concurrently randomized subjects, nivo+chemo demonstrated a statistically significant and clinically meaningful improvement in pCR rate per BIPR compared with chemo: 43/179 (24.0%, 95% CI: 18.0, 31.0) vs 4/179 (2.2%, 95% CI: 0.6, 5.6); odds ratio 13.94 (99% CI: 3.49, 55.75); Stratified CMH test p-value <0.0001.

Table 38: Summary of Complete Pathological Response per BIPR - All Response Evaluable Subjects in Concurrently Randomized Arm C (Nivo + Chemo) vs Arm B (Chemo)

	Number of Subjects (%)	
	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179
TUMOR REGION:		
COMPLETE PATHOLOGIC RESPONSE		
YES	46 (25.7)	5 (2.8)
NO	95 (53.1)	122 (68.2)
NOT EVALUABLE	6 (3.4)	5 (2.8)
NO SAMPLE AVAILABLE	32 (17.9)	47 (26.3)
%PRIMARY TUMOR AREA WITH VIABLE TUMOR		
N	141	128
MEAN	34.4	62.1
MEDIAN	10.0	74.0
MIN, MAX	0, 100	0, 100
Q1, Q3	0.0, 80.0	40.0, 91.5
STANDARD DEVIATION	39.1	34.4
LYMPH NODES REGION:		
COMPLETE PATHOLOGIC RESPONSE (1)		
YES	96 (53.6)	56 (31.3)
NO	45 (25.1)	71 (39.7)
NOT APPLICABLE	1 (0.6)	1 (0.6)
NOT EVALUABLE	5 (2.8)	4 (2.2)
NO SAMPLE AVAILABLE	32 (17.9)	47 (26.3)
%TUMOR AREA WITH VIABLE TUMOR CELLS		
N	68	76
MEAN	48.1	76.6
MEDIAN	40.0	95.0
MIN, MAX	0, 100	0, 100
Q1, Q3	0.0, 100.0	60.5, 100.0
STANDARD DEVIATION	44.5	33.4
OVERALL:		
COMPLETE PATHOLOGIC RESPONSE (PCR)	43/179 (24.0)	4/179 (2.2)
(95% CI) (2)	(18.0, 31.0)	(0.6, 5.6)
DIFFERENCE OF PCR (3, 4)	21.6	
(99% CI)	(13.0, 30.3)	
(95% CI)	(15.1, 28.2)	
ESTIMATE OF ODDS RATIO OF PCR (4, 5)	13.94	
(99% CI)	(3.49, 55.75)	
(95% CI)	(4.86, 40.02)	
P-VALUE (6)	<0.0001	

(1) Subjects without nodal disease at baseline and assessed as absence of disease in lymph node resection are also included as Yes.
(2) Confidence interval based on the Clopper and Pearson method.
(3) Strata adjusted difference (Arm C - Concurrent Arm B) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
(4) Stratified by PD-L1 (>=1% vs <1%/unevaluable/indeterminate), disease stage (IIB/II vs. IIIA), sex (male vs female) as entered into the IRT.
(5) Strata adjusted odds ratio (Arm C over Concurrent Arm B) using Mantel-Haenszel method.
(6) Two-sided p-value from stratified CMH Test.

- Of the 179 randomized subjects in the nivo+chemo arm, 32 (17.9%) did not provide primary tumour samples for central pathology review (primarily because surgery did not occur), and 6 (3.4%) samples were deemed not evaluable. Of the 179 concurrently randomized subjects in the chemo arm, 47 (26.3%) did not provide primary tumour samples for central pathology

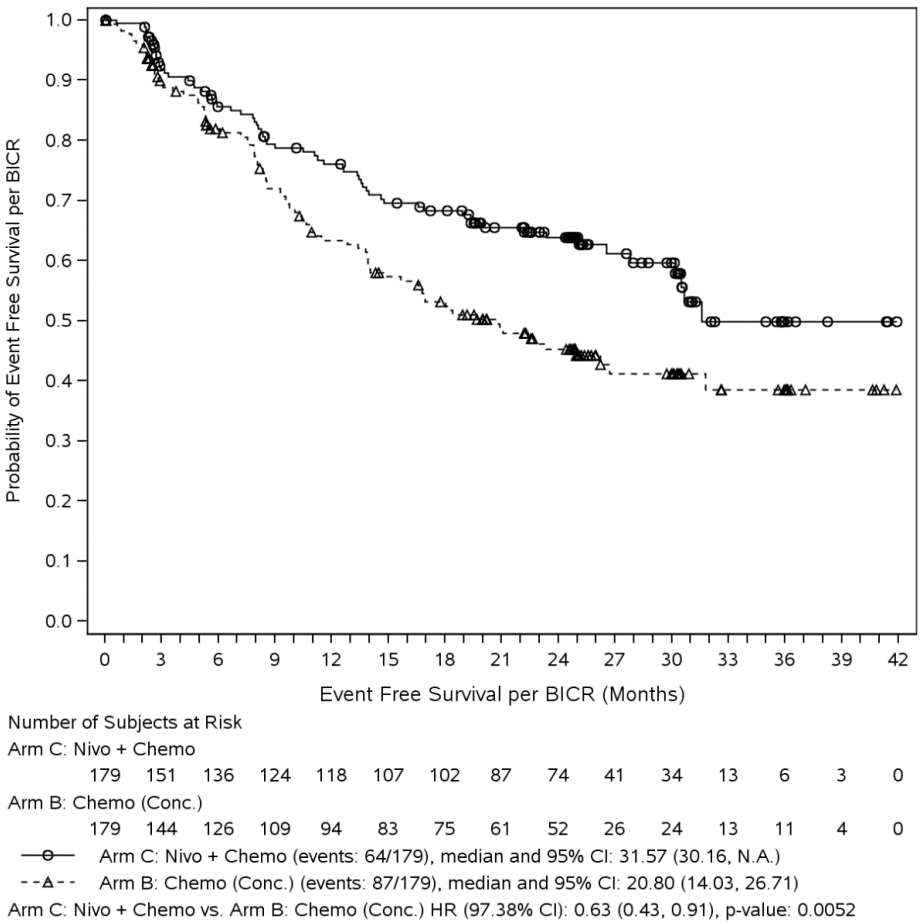
review (primarily because surgery did not occur), and 5 (2.8%) primary tumour samples were deemed not evaluable.

- A sensitivity analysis of pCR per BIPR in all response evaluable subjects was consistent with the primary analysis and favoured nivo+chemo: 30.5% (43/141; 95% CI: 23.0, 38.8) with nivo+chemo vs 4/126 (3.2%, 95% CI: 0.9, 7.9) with chemo; odds ratio: 13.81 (99% CI: 3.34, 57.04); strata-adjusted difference based on CMH method: 27.1% (99% CI: 16.5, 37.7).
- pCR rates were generally consistent for subjects randomized under Revised Protocol 02 (27.0% [20/74] with nivo+chemo and 4.1% [3/74] with chemo) and after Revised Protocol 02 (21.9% [23/105] with nivo+chemo and 1.0% [1/105] with chemo).
- A lower median percentage of viable tumour was observed with nivo+chemo (10.0%) compared with chemo (74%) in concurrently randomized subjects who underwent surgery.

The pCR by BIPR results in subjects with baseline disease stage II-IIIA and PD-L1 expression ≥ 1% (exploratory subgroup analysis) are included in Table 37 above.

Event-Free Survival (EFS)

Figure 19: **Event-Free Survival per BICR, Primary Definition - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (20-Oct-2021 Database Lock)**



Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test.

Symbols represent censored observations.

Abbreviations: BICR - Blinded Independent Central Review; Chemo - chemotherapy; CI - confidence interval; HR - hazard ratio; Nivo - nivolumab.

Table 39: **Type of Event and Reason for Censoring, Event-Free Survival per BICR, Primary Definition - All Randomized Subjects in Concurrent Arms C (Nivo+Chemo) and B (Chemo)**

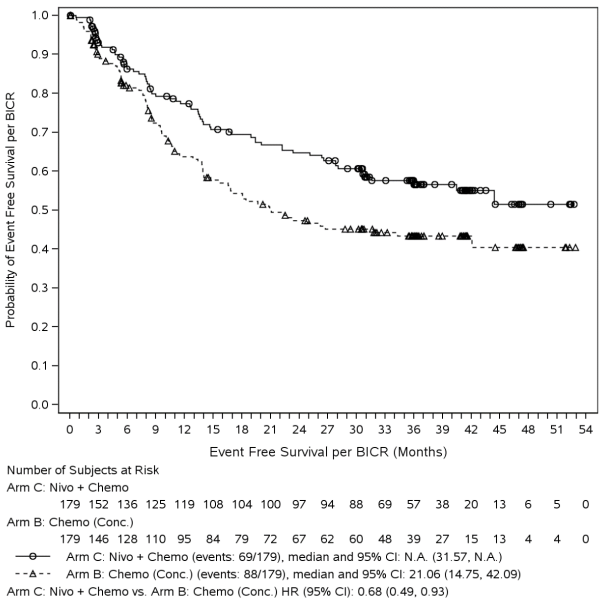
	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179
NUMBER OF EVENTS (%)	64 (35.8)	87 (48.6)
TYPE OF EVENTS (%)		
PROGRESSION PRECLUDING SURGERY (1)	12 (6.7)	16 (8.9)
PROGRESSION/RECURRENCE AFTER SURGERY (2)	39 (21.8)	56 (31.3)
LOCOREGIONAL	24 (13.4)	28 (15.6)
DISTANT	14 (7.8)	25 (14.0)
BOTH LOCOREGIONAL AND DISTANT	1 (0.6)	3 (1.7)
PROGRESSION FOR SUBJECTS WITHOUT SURGERY (2)	2 (1.1)	3 (1.7)
LOCOREGIONAL	2 (1.1)	1 (0.6)
DISTANT	0	1 (0.6)
BOTH LOCOREGIONAL AND DISTANT	0	1 (0.6)
DEATH	11 (6.1)	12 (6.7)
NUMBER OF SUBJECTS CENSORED (%)	115 (64.2)	92 (51.4)
CENSORED ON DATE OF RANDOMIZATION	3 (1.7)	6 (3.4)
NO BASELINE TUMOR ASSESSMENT	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (3)	2 (1.1)	4 (2.2)
NEVER TREATED	2 (1.1)	3 (1.7)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	0	0
OTHER	0	1 (0.6)
NO ON-STUDY TUMOR ASSESSMENT NOR EVENT PRIOR TO SUBSEQUENT THERAPY	1 (0.6)	2 (1.1)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI-CANCER THERAPY	112 (62.6)	86 (48.0)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (4)	12 (6.7)	18 (10.1)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	6 (3.4)	9 (5.0)
RECEIVED SUBSEQUENT RADIOTHERAPY (5)	5 (2.8)	9 (5.0)
RECEIVED SUBSEQUENT SURGERY (6)	1 (0.6)	0
ON STUDY	97 (54.2)	66 (36.9)
STILL ON-NEOADJUVANT TREATMENT	0	0
STILL ON-ADJUVANT TREATMENT	0	0
IN FOLLOW-UP	97 (54.2)	66 (36.9)
OFF STUDY	3 (1.7)	2 (1.1)
LOST TO FOLLOW-UP	1 (0.6)	0
SUBJECT WITHDREW CONSENT	2 (1.1)	2 (1.1)
OTHER	0	0

(1) Progression not necessarily reaching the RECIST 1.1
(2) Progression/ recurrence per RECIST 1.1
(3) Death occurring after start of subsequent anti-cancer therapy are not considered.
(4) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy (outside of protocol-specified adjuvant therapy) without a prior reported EFS event. Those subjects were censored at the last tumor assessment prior to/on start date of subsequent anti-cancer therapy.
(5) Radiotherapy other than protocol defined adjuvant radiotherapy.
(6) Surgeries other than definitive surgery

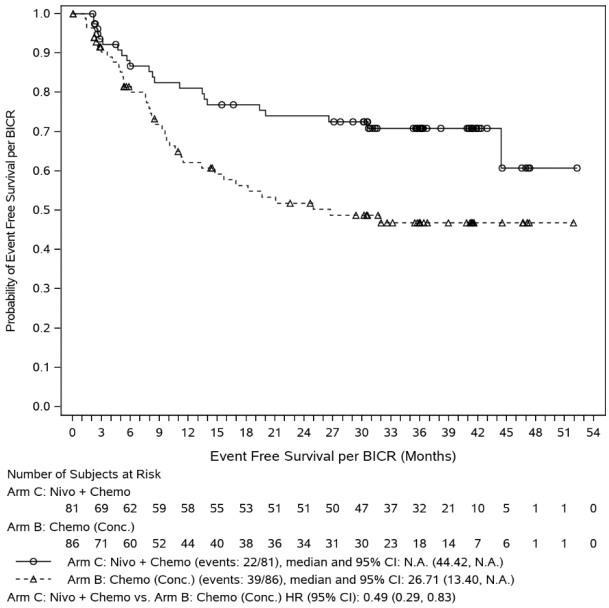
The updated results for EFS based on the 14-Oct-2022 DBL including 12 months additional follow-up were consistent with the results of the primary analysis (see Figure 20).

Figure 20: Event-Free Survival per BICR, Primary Definition in the ITT Population and in Subjects with Baseline Disease Stage II-IIIA and PD-L1 Expression ⩾ 1%- All Concurrently Randomized Subjects in the Nivo + Chemo (Arm C) and Chemo (Arm B) Arms of Study CA209816 (14-Oct-2022 Database Lock)

ITT



Stage II-IIIA Disease and PD-L1 Expression ≥ 1%



Statistical model for hazard ratio: stratified Cox proportional hazard model (ITT) and unstratified Cox proportional hazard model (Stage II-IIIA disease and PD-L1 ≥ 1%).
Symbols represent censored observations.

Secondary endpoints

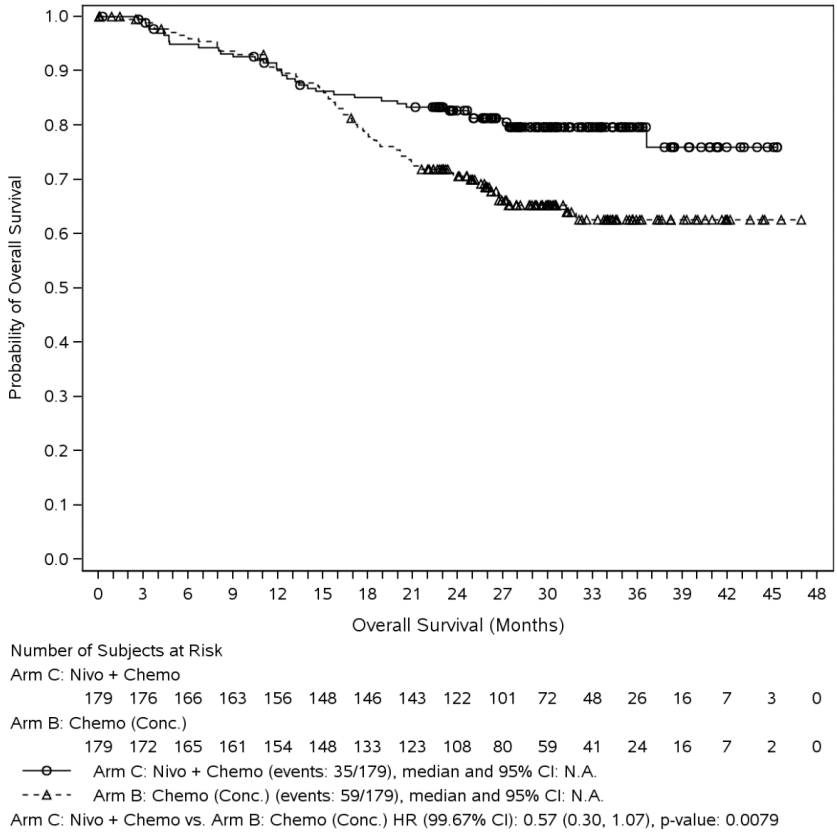
Overall Survival (OS)

OS IA1 (DBL 20-Oct-2021)

In an early OS analysis of concurrently randomized subjects at the planned IA1 (performed at 94 events, 50.8% information fraction), nivo+chemo demonstrated an encouraging trend in OS compared with chemo: HR=0.57 (99.67% CI: 0.30, 1.07); stratified log-rank test p-value = 0.0079 (p <0.0033 needed for statistical significance). Median OS was not reached in either arm (Figure 21).

At database lock, 80.4% and 67.0% of randomized subjects in the nivo+chemo and chemo arms, respectively, were censored for OS.

Figure 21: **Overall Survival - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**



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

Table 40: **Overall Survival Rates - All Randomized Subjects in Arm A (Nivo+Ipi) and Concurrent Arms C (Nivo+Chemo) and B (Chemo)**

Overall Survival Rate (95% CI)	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179
6-MONTH	92.0 (85.1, 95.7)	94.9 (90.4, 97.3)	95.9 (91.7, 98.0)
12-MONTH	88.4 (80.8, 93.1)	90.3 (84.8, 93.8)	90.1 (84.6, 93.7)
18-MONTH	86.6 (78.7, 91.7)	85.1 (78.8, 89.6)	78.4 (71.4, 83.8)
24-MONTH	81.9 (73.4, 87.9)	82.7 (76.2, 87.6)	70.6 (63.1, 76.8)

Based on Kaplan-Meier Estimates
Source: Table S.5.23.4

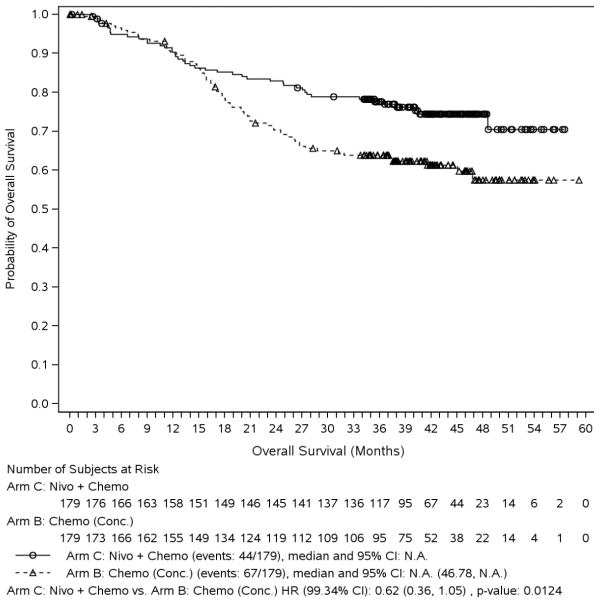
OS IA2 (DBL 14-Oct-2022)

In an OS analysis of concurrently randomized subjects at the planned IA2 (1 year after IA1, 60.0% information fraction), nivo+chemo continued to demonstrate an favourable trend in OS compared with chemo: HR = 0.62 (99.34% CI: 0.36, 1.05; 95% CI: 0.42, 0.90); stratified log-rank test p-value = 0.0124 ($p < 0.0066$ needed for statistical significance. Median OS was not reached in either arm.

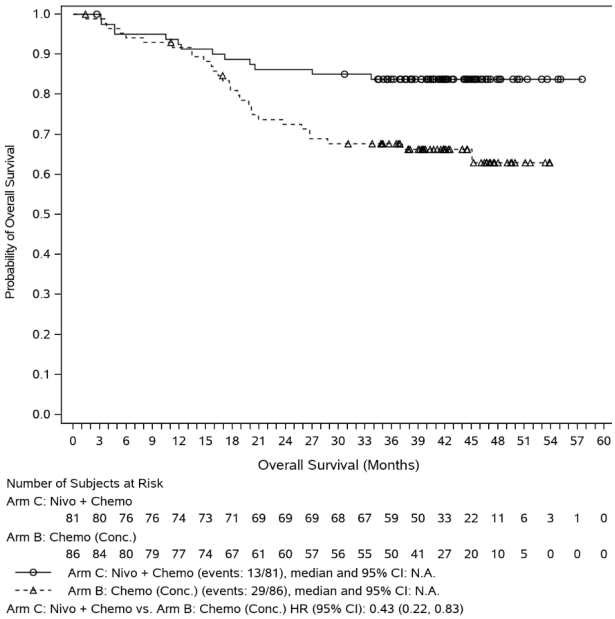
There were only 17 additional OS events since IA1, which were distributed relatively equally across the arms (9 nivo+chemo and 8 chemo). 75.4% and 62.6% of subjects in the nivo+chemo and chemo arms, respectively, were censored for OS (70.4% and 54.2% were in follow-up).

Figure 22: Overall Survival in the ITT Population and in Subjects with Baseline Disease Stage II-IIIA and PD-L1 Expression ≥ 1% - All Concurrently Randomized Subjects in the Nivo + Chemo (Arm C) and Chemo (Arm B) Arms of Study CA209816 (14-Oct-2022 Database Lock)

ITT



Stage II-IIIA Disease and PD-L1 Expression ≥ 1%



Statistical model for hazard ratio: stratified Cox proportional hazard model (ITT) and unstratified Cox proportional hazard model (Stage II-IIIA disease and PD-L1 ≥ 1%).
Symbols represent censored observations.

Table 41: **Overall Survival Rates at IA2 - All Randomized Subjects in Arm A (Nivo+Ipi) and Concurrent Arms C (Nivo+Chemo) and B (Chemo)**

Overall Survival Rate 95% CI)	Arm A: Nivo + Ipi N = 113	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179
6-MONTH	92.0 (85.1, 95.7)	94.9 (90.4, 97.3)	96.0 (91.7, 98.1)
12-MONTH	88.4 (80.8, 93.1)	90.3 (84.9, 93.9)	90.2 (84.7, 93.8)
18-MONTH	86.6 (78.7, 91.7)	85.2 (79.0, 89.6)	78.5 (71.6, 83.9)
24-MONTH	82.0 (73.5, 88.0)	82.9 (76.4, 87.7)	70.3 (62.8, 76.5)
36-MONTH	72.7 (63.3, 80.0)	77.6 (70.7, 83.1)	63.8 (56.1, 70.5)

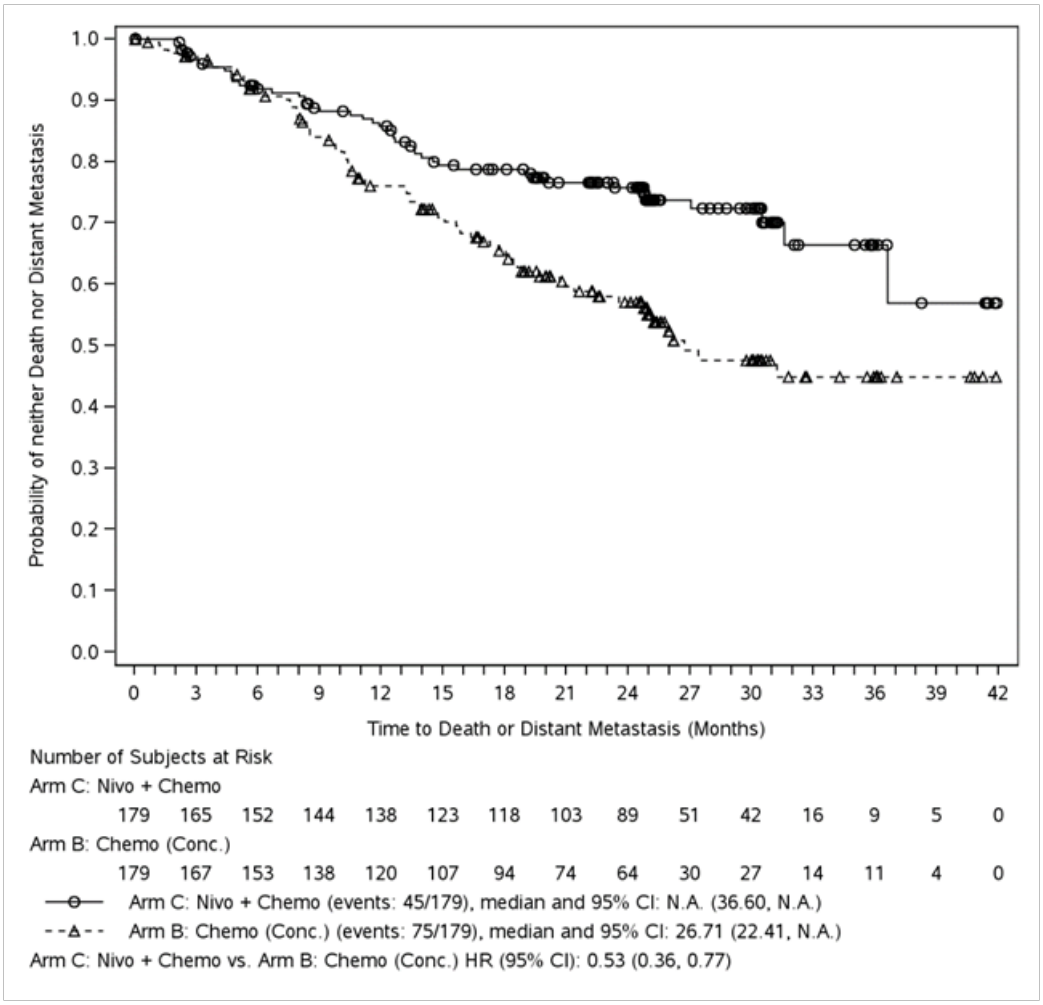
Based on Kaplan-Meier Estimates

Time to Death or Distant Metastases (TTDM)

In concurrently randomized subjects, median TTDM per BICR was longer with nivo+chemo compared with chemo (median: not reached vs. 26.71 months; HR = 0.53 [95% CI: 0.36, 0.77]). TTDM rates were higher with nivo+chemo compared with chemo: 85.7% vs. 76.0% at 12 months and 75.8% vs. 57.1% at 24 months, respectively (Table 17, figure 16).

Investigators were not required to continue trial imaging for TTDM if a subject experienced a BICR-verified locoregional recurrence without any distant metastases; these subjects were censored at their last available tumour assessment or counted as an event if they died.

Figure 23: **Time to Death or Distant Metastasis by BICR - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**



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

Based on the 14-Oct-2022 DBL, with additional 12 months follow-up, median TTDM per BICR was not reached in the nivo+chemo arm and was 34.27 months in the chemo arm. The HR was similar to the Primary CSR and continued to favour nivo+chemo over chemo: HR = 0.55 (95% CI: 0.39, 0.78).

Major Pathologic Response (MPR) based on 16-Sep-2020 DBL

Table 42: **Summary of Major Pathologic Response per BIPR - All Response Evaluable Subjects in Concurrently Randomized Arm C (Nivo + Chemo) and Arm B (Chemo)**

	Number of Subjects (%)	
	Arm C: Nivo + Chemo N = 179	Arm B: Chemo (Concurrent) N = 179
TUMOR REGION:		
MAJOR PATHOLOGIC RESPONSE		
YES	72 (40.2)	22 (12.3)
NO	69 (38.5)	105 (58.7)
NOT EVALUABLE	6 (3.4)	5 (2.8)
NO SAMPLE AVAILABLE	32 (17.9)	47 (26.3)
LYMPH NODES REGION:		
MAJOR PATHOLOGIC RESPONSE (1)		
YES	99 (55.3)	59 (33.0)
NO	42 (23.5)	68 (38.0)

NOT APPLICABLE	1 (0.6)	1 (0.6)
NOT EVALUABLE	5 (2.8)	4 (2.2)
NO SAMPLE AVAILABLE	32 (17.9)	47 (26.3)

OVERALL:

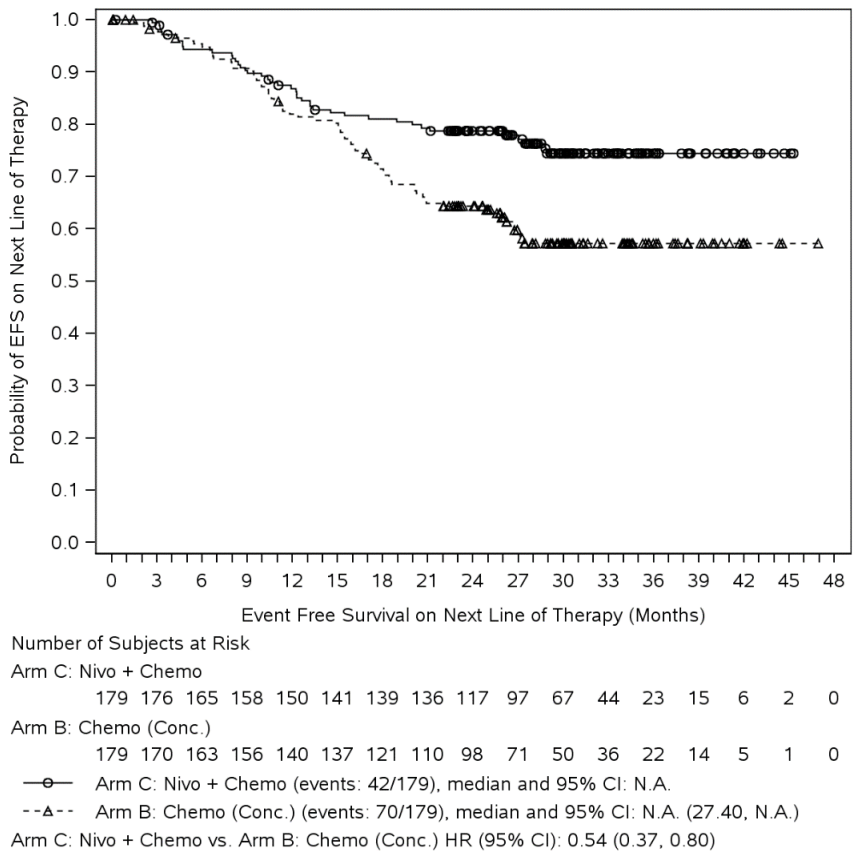
MAJOR PATHOLOGIC RESPONSE (MPR) (95% CI) (2)	66/179 (36.9) (29.8, 44.4)	16/179 (8.9) (5.2, 14.1)
DIFFERENCE OF MPR (3, 4) (95% CI)	27.9 (19.6, 36.1)	
ESTIMATE OF ODDS RATIO OF MPR (4, 5) (95% CI)	5.70 (3.16, 10.26)	

(1) Subjects without nodal disease at baseline and assessed as absence of disease in lymph node resection are also included as Yes.
(2) Confidence interval based on the Clopper and Pearson method.
(3) Strata adjusted difference (Arm C - Concurrent Arm B) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
(4) Stratified by PD-L1 (>=1% vs <1%/unevaluable/indeterminate), disease stage (IIB/II vs. IIIA), sex (male vs female) as entered into the IRT.
(5) Strata adjusted odds ratio (Arm C over Concurrent Arm B) using Mantel-Haenszel method.

Exploratory endpoint

Event-Free Survival on Next Line of Therapy (EFS2)

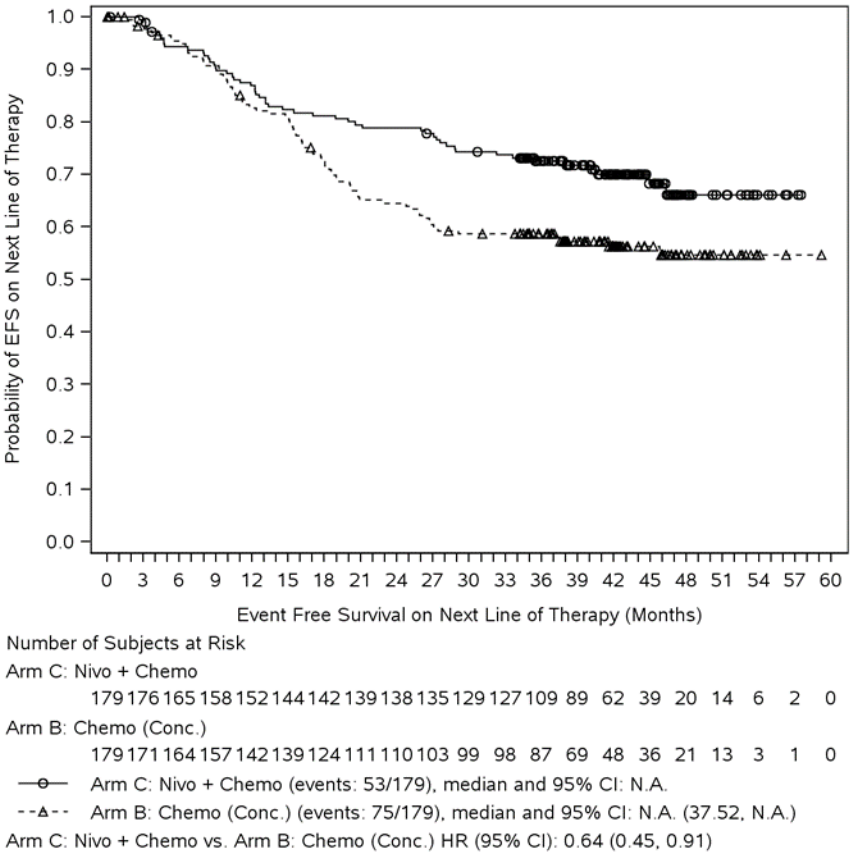
Figure 24: Event-Free Survival on Next Line of Therapy (EFS2) - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)



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

With additional 12 months of follow-up, the median EFS2 per investigator was not reached in either the nivo+chemo arm. The HR increased from the primary analysis: HR = 0.64 (95% CI: 0.45, 0.91).

Figure 25: **Event-Free Survival on Next Line of Therapy (EFS2) - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (DBL 14-Oct-2022)**



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

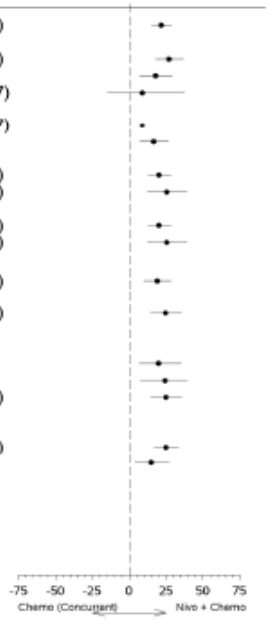
Ancillary analyses

pCR by subgroups

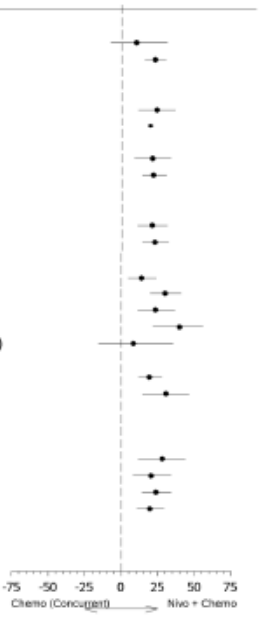
In concurrently randomized subjects, differences in pCR per BIPR favoured (95% CI for the difference >0) nivo+chemo vs. chemo for most subgroups.

Figure 26: **Forest Plot of Treatment Effect on pCR by BIPR in Pre-Defined Subsets - All Concurrently Randomized Subjects in Arm C (Nivo + Chemo) and Arm B (Chemo)**

	N	Arm C: Nivo + Chemo N of responses (N of subjects)	Arm C: Nivo + Chemo pCR (95% Exact CI)	Arm B: Chemo (Concurrent) N of responses (N of subjects)	Arm B: Chemo (Concurrent) pCR (95% Exact CI)	Unweighted pCR Difference (95% CI)
Overall	358	43(179)	24.0% (18.0, 31.0)	4(179)	2.2% (0.6, 5.6)	21.8% (15.2, 28.7)
Age Categorization						
< 65	176	25(93)	26.9% (18.2, 37.1)	0(83)	0.0% (0.0, 4.3)	26.9% (17.8, 36.7)
>= 65 and < 75	158	17(75)	22.7% (13.8, 33.8)	4(83)	4.8% (1.3, 11.9)	17.8% (7.3, 28.9)
>= 75 and < 85	24	1(11)	9.1% (0.2, 41.3)	0(13)	0.0% (0.0, 24.7)	9.1% (-14.9, 37.7)
>= 85	0	0(0)	N.A.	0(0)	N.A.	
>= 75	24	1(11)	9.1% (0.2, 41.3)	0(13)	0.0% (0.0, 24.7)	9.1% (-14.9, 37.7)
>= 65	182	18(86)	20.9% (12.9, 31.0)	4(96)	4.2% (1.1, 10.3)	16.8% (7.3, 26.8)
Sex (IRT)						
Male	255	29(128)	22.7% (15.7, 30.9)	3(127)	2.4% (0.5, 6.7)	20.3% (12.6, 28.4)
Female	103	14(51)	27.5% (15.9, 41.7)	1(52)	1.9% (<0.1, 10.3)	25.5% (12.3, 39.1)
Sex (CRF)						
Male	255	29(128)	22.7% (15.7, 30.9)	3(127)	2.4% (0.5, 6.7)	20.3% (12.6, 28.4)
Female	103	14(51)	27.5% (15.9, 41.7)	1(52)	1.9% (<0.1, 10.3)	25.5% (12.3, 39.1)
Race						
White	169	18(89)	20.2% (12.4, 30.1)	1(80)	1.3% (<0.1, 6.8)	19.0% (10.1, 28.5)
Black or African American	7	1(4)	25.0% (0.6, 80.6)	0(3)	0.0% (0.0, 70.8)	
Asian	179	24(86)	27.9% (18.8, 38.6)	3(93)	3.2% (0.7, 9.1)	24.7% (14.5, 35.2)
Other	3	0(0)	N.A.	0(3)	0.0% (0.0, 70.8)	
Region						
North America	91	9(41)	22.0% (10.6, 37.6)	1(50)	2.0% (<0.1, 10.6)	20.0% (6.9, 34.8)
Europe	66	10(41)	24.4% (12.4, 40.3)	0(25)	0.0% (0.0, 13.7)	24.4% (7.4, 39.3)
Asia	177	24(85)	28.2% (19.0, 39.0)	3(92)	3.3% (0.7, 9.2)	25.0% (14.7, 35.5)
Rest of the World	24	0(12)	0.0% (0.0, 26.5)	0(12)	0.0% (0.0, 26.5)	N.A.
Baseline ECOG Performance Status						
0	241	33(124)	26.6% (19.1, 35.3)	2(117)	1.7% (0.2, 6.0)	24.9% (16.7, 33.4)
1	117	10(55)	18.2% (9.1, 30.9)	2(62)	3.2% (0.4, 11.2)	15.0% (3.8, 27.3)
>1	0	0(0)	N.A.	0(0)	N.A.	



	N	Arm C: Nivo + Chemo N of responses (N of subjects)	Arm C: Nivo + Chemo pCR (95% Exact CI)	Arm B: Chemo (Concurrent) N of responses (N of subjects)	Arm B: Chemo (Concurrent) pCR (95% Exact CI)	Unweighted pCR Difference (95% CI)
Tobacco Use						
Never Smoked	39	2(19)	10.5% (1.3, 33.1)	0(20)	0.0% (0.0, 16.8)	10.5% (-7.3, 31.4)
Current/Former	318	41(160)	25.6% (19.1, 33.1)	4(158)	2.5% (0.7, 6.4)	23.1% (15.9, 30.5)
Unknown	1	0(0)	N.A.	0(1)	0.0% (0.0, 97.5)	
Disease Stage at Study Entry (IRT)						
Stage IB/II	135	21(69)	30.4% (19.9, 42.7)	4(66)	6.1% (1.7, 14.8)	24.4% (11.6, 36.6)
Stage IIIA	223	22(110)	20.0% (13.0, 28.7)	0(113)	0.0% (0.0, 3.2)	20.0% (12.8, 28.4)
Disease Stage at Study Entry (CRF)						
Stage IB/II	128	17(65)	26.2% (16.0, 38.5)	3(63)	4.8% (1.0, 13.3)	21.4% (9.0, 33.6)
Stage IIIA	228	26(113)	23.0% (15.6, 31.9)	1(115)	0.9% (<0.1, 4.7)	22.1% (14.3, 30.7)
Other	2	0(1)	0.0% (0.0, 97.5)	0(1)	0.0% (0.0, 97.5)	
Cell Type at Study Entry						
Squamous Cell Carcinoma	182	22(87)	25.3% (16.6, 35.7)	4(95)	4.2% (1.2, 10.4)	21.1% (11.0, 31.4)
Non-Squamous	176	21(92)	22.8% (14.7, 32.8)	0(84)	0.0% (0.0, 4.3)	22.8% (14.2, 32.4)
PD-L1 Status (Clinical Database)						
< 1%	155	13(78)	16.7% (9.2, 26.8)	2(77)	2.6% (0.3, 9.1)	14.1% (4.8, 24.0)
>= 1%	178	29(89)	32.6% (23.0, 43.3)	2(89)	2.2% (0.3, 7.9)	30.3% (19.9, 40.7)
1-49%	98	12(51)	23.5% (12.8, 37.5)	0(47)	0.0% (0.0, 7.5)	23.5% (11.4, 36.8)
>= 50%	80	17(38)	44.7% (28.6, 61.7)	2(42)	4.8% (0.6, 16.2)	40.0% (21.7, 55.9)
Indeterminate/Not Evaluable	25	1(12)	8.3% (0.2, 38.5)	0(13)	0.0% (0.0, 24.7)	8.3% (-15.5, 35.4)
Type of Platinum Therapy						
Cisplatin	258	27(124)	21.8% (14.9, 30.1)	3(134)	2.2% (0.5, 6.4)	19.5% (12.0, 27.7)
Carboplatin	72	12(39)	30.8% (17.0, 47.6)	0(33)	0.0% (0.0, 10.6)	30.8% (14.7, 46.4)
Switching from Cis. to Carbo.	21	4(12)	33.3% (9.9, 65.1)	1(9)	11.1% (0.3, 48.2)	
Not Reported	7	0(4)	0.0% (0.0, 60.2)	0(3)	0.0% (0.0, 70.8)	
Tumor Tissue TMB						
>= 12.3 Mut/Mb	76	12(39)	30.8% (17.0, 47.6)	1(37)	2.7% (<0.1, 14.2)	28.1% (11.6, 43.9)
< 12.3 Mut/Mb	102	11(49)	22.4% (11.8, 36.6)	1(53)	1.9% (<0.1, 10.1)	20.6% (8.2, 34.1)
Overall Evaluable	178	23(88)	26.1% (17.3, 36.6)	2(90)	2.2% (0.3, 7.8)	23.9% (14.2, 34.1)
Not Evaluable/Not Reported	180	20(91)	22.0% (14.0, 31.9)	2(89)	2.2% (0.3, 7.9)	19.7% (10.6, 29.4)

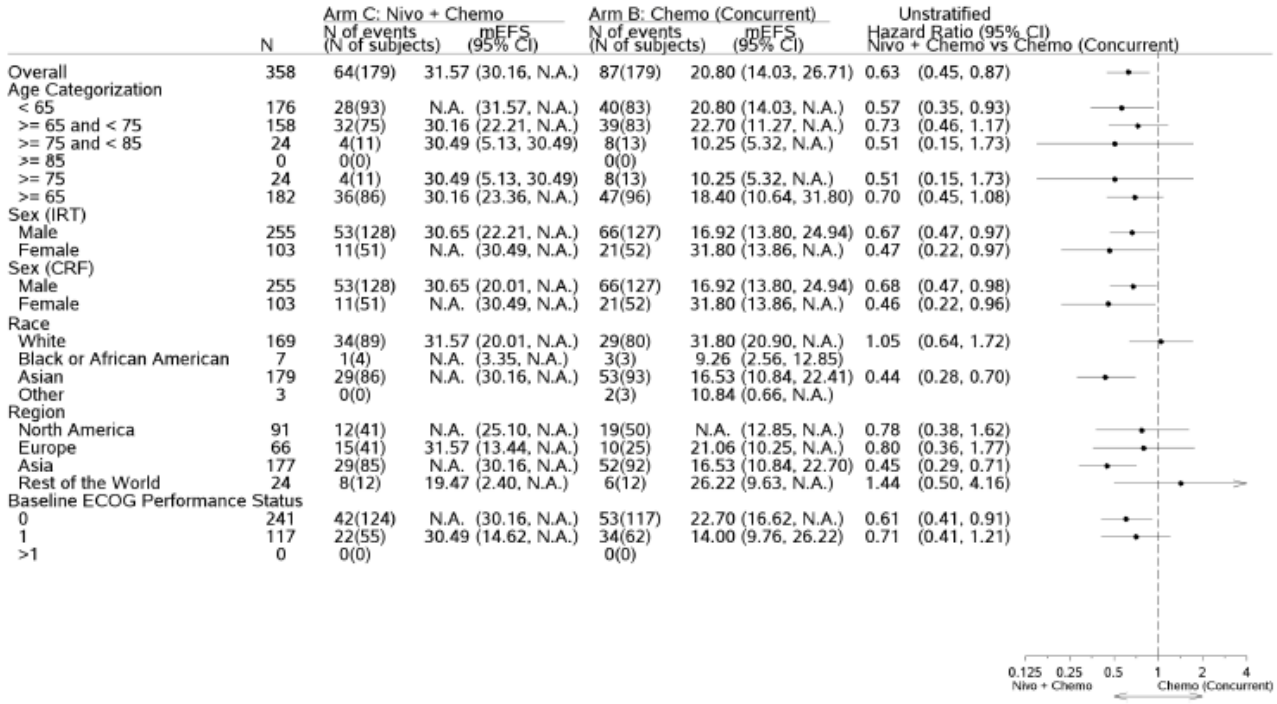


Two-sided 95% confidence interval for un-weighted difference was calculated using Newcombe method.
pCR difference is not computed for subset with less than 10 subjects per treatment group.
TMB was not analyzed from subjects in China, and these subjects are included in the Not Reported category.
Source: Figure S.5.12.1

EFS by subgroups

In a subgroup analysis for all concurrently randomized subjects, EFS HRs for most subgroups favoured (HR point estimate <1) nivo+chemo vs chemo (Figure 27).

Figure 27: **Treatment Effect on Event-Free Survival per BICR, Primary Definition in Pre-Defined Subsets - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**



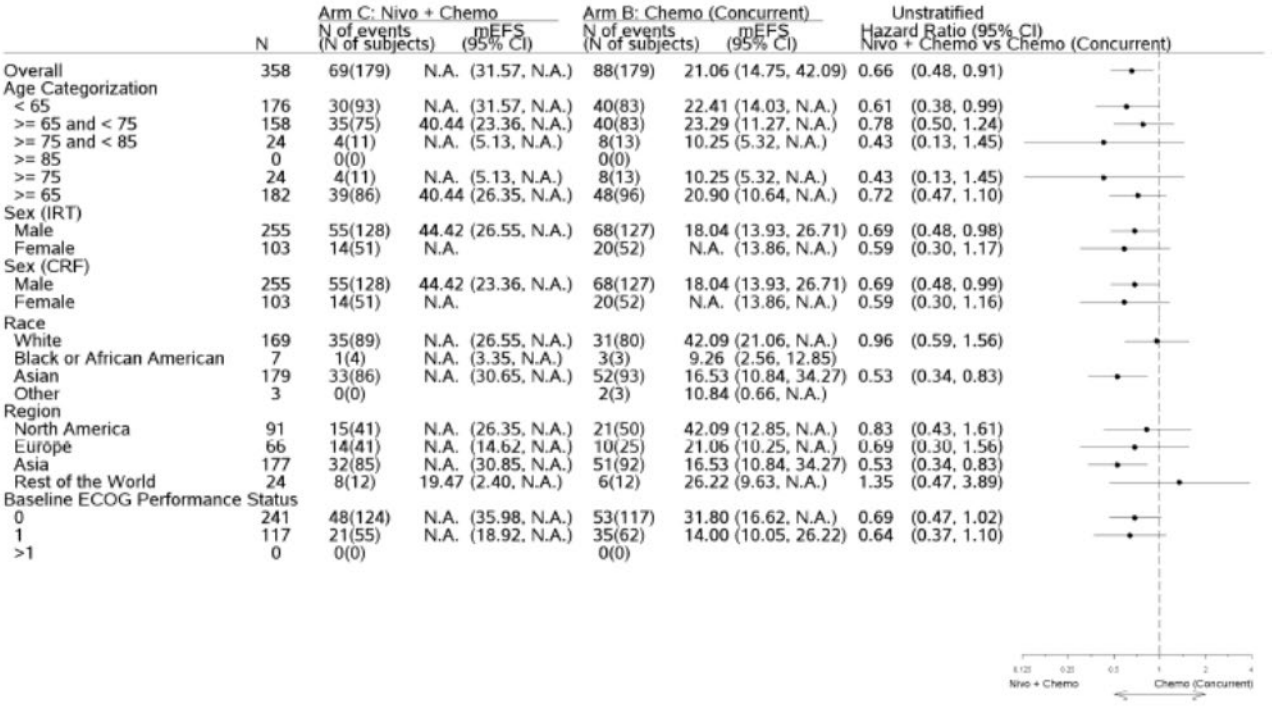
	N	Arm C: Nivo + Chemo N of events (N of subjects)	Arm C: Nivo + Chemo mEFS (95% CI)	Arm B: Chemo (Concurrent) N of events (N of subjects)	Arm B: Chemo (Concurrent) mEFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs Chemo (Concurrent)
Overall	358	64(179)	31.57 (30.16, N.A.)	87(179)	20.80 (14.03, 26.71)	0.63 (0.45, 0.87)
Age Categorization						
< 65	176	28(93)	N.A. (31.57, N.A.)	40(83)	20.80 (14.03, N.A.)	0.57 (0.35, 0.93)
>= 65 and < 75	158	32(75)	30.16 (22.21, N.A.)	39(83)	22.70 (11.27, N.A.)	0.73 (0.46, 1.17)
>= 75 and < 85	24	4(11)	30.49 (5.13, 30.49)	8(13)	10.25 (5.32, N.A.)	0.51 (0.15, 1.73)
>= 85	0	0(0)		0(0)		
>= 75	24	4(11)	30.49 (5.13, 30.49)	8(13)	10.25 (5.32, N.A.)	0.51 (0.15, 1.73)
>= 65	182	36(86)	30.16 (23.36, N.A.)	47(96)	18.40 (10.64, 31.80)	0.70 (0.45, 1.08)
Sex (IRT)						
Male	255	53(128)	30.65 (22.21, N.A.)	66(127)	16.92 (13.80, 24.94)	0.67 (0.47, 0.97)
Female	103	11(51)	N.A. (30.49, N.A.)	21(52)	31.80 (13.86, N.A.)	0.47 (0.22, 0.97)
Sex (CRF)						
Male	255	53(128)	30.65 (20.01, N.A.)	66(127)	16.92 (13.80, 24.94)	0.68 (0.47, 0.98)
Female	103	11(51)	N.A. (30.49, N.A.)	21(52)	31.80 (13.86, N.A.)	0.46 (0.22, 0.96)
Race						
White	169	34(89)	31.57 (20.01, N.A.)	29(80)	31.80 (20.90, N.A.)	1.05 (0.64, 1.72)
Black or African American	7	1(4)	N.A. (3.35, N.A.)	3(3)	9.26 (2.56, 12.85)	
Asian	179	29(86)	N.A. (30.16, N.A.)	53(93)	16.53 (10.84, 22.41)	0.44 (0.28, 0.70)
Other	3	0(0)		2(3)	10.84 (0.66, N.A.)	
Region						
North America	91	12(41)	N.A. (25.10, N.A.)	19(50)	N.A. (12.85, N.A.)	0.78 (0.38, 1.62)
Europe	66	15(41)	31.57 (13.44, N.A.)	10(25)	21.06 (10.25, N.A.)	0.80 (0.36, 1.77)
Asia	177	29(85)	N.A. (30.16, N.A.)	52(92)	16.53 (10.84, 22.70)	0.45 (0.29, 0.71)
Rest of the World	24	8(12)	19.47 (2.40, N.A.)	6(12)	26.22 (9.63, N.A.)	1.44 (0.50, 4.16)
Baseline ECOG Performance Status						
0	241	42(124)	N.A. (30.16, N.A.)	53(117)	22.70 (16.62, N.A.)	0.61 (0.41, 0.91)
1	117	22(55)	30.49 (14.62, N.A.)	34(62)	14.00 (9.76, 26.22)	0.71 (0.41, 1.21)
>1	0	0(0)		0(0)		
Tobacco Use						
Never Smoked	39	6(19)	N.A. (5.65, N.A.)	15(20)	10.41 (7.66, 20.80)	0.33 (0.13, 0.87)
Current/Former	318	58(160)	31.57 (30.16, N.A.)	72(158)	22.41 (15.67, N.A.)	0.68 (0.48, 0.96)
Unknown	1	0(0)		0(1)	N.A.	
Disease Stage at Study Entry (IRT)						
Stage IB/II	135	24(69)	N.A. (27.79, N.A.)	26(66)	N.A. (16.79, N.A.)	0.88 (0.50, 1.53)
Stage IIIA	223	40(110)	31.57 (26.55, N.A.)	61(113)	15.67 (10.84, 22.70)	0.52 (0.35, 0.78)
Disease Stage at Study Entry (CRF)						
Stage IB/II	127	21(65)	N.A. (27.79, N.A.)	24(62)	N.A. (16.79, N.A.)	0.87 (0.48, 1.56)
Stage IIIA	228	43(113)	31.57 (26.55, N.A.)	62(115)	15.67 (10.84, 22.70)	0.54 (0.37, 0.80)
Other	3	0(1)	N.A.	1(2)	1.64 (N.A., N.A.)	
Cell Type at Study Entry						
Squamous Cell Carcinoma	182	33(87)	30.65 (20.01, N.A.)	43(95)	22.70 (11.47, N.A.)	0.77 (0.49, 1.22)
Non-Squamous	176	31(92)	N.A. (27.79, N.A.)	44(84)	19.65 (13.80, 26.22)	0.50 (0.32, 0.79)
PD-L1 Status (Clinical Database)						
< 1%	155	37(78)	25.10 (14.62, N.A.)	41(77)	18.40 (13.86, 26.22)	0.85 (0.54, 1.32)
>= 1%	178	21(89)	N.A.	41(89)	21.06 (11.47, N.A.)	0.41 (0.24, 0.70)
1-49%	98	15(51)	N.A. (27.79, N.A.)	21(47)	26.71 (11.47, N.A.)	0.58 (0.30, 1.12)
>= 50%	80	6(38)	N.A.	20(42)	19.65 (8.18, N.A.)	0.24 (0.10, 0.61)
Indeterminate/Not Evaluable	25	6(12)	22.21 (7.20, 31.57)	5(13)	13.93 (5.32, N.A.)	0.92 (0.26, 3.17)
Tumor Tissue TMB						
>= 12.3 Mut/Mb	76	12(39)	N.A. (14.75, N.A.)	16(37)	22.41 (13.40, N.A.)	0.69 (0.33, 1.46)
< 12.3 Mut/Mb	102	19(49)	30.49 (19.38, N.A.)	24(53)	26.71 (16.62, N.A.)	0.86 (0.47, 1.57)
Overall Evaluable	178	31(88)	N.A. (26.55, N.A.)	40(90)	26.71 (16.92, N.A.)	0.77 (0.48, 1.23)
Not Evaluable/Not Reported	180	33(91)	31.57 (25.10, N.A.)	47(89)	14.03 (10.05, 22.70)	0.49 (0.31, 0.77)
Type of Platinum Therapy						
Cisplatin	258	49(124)	N.A. (25.10, N.A.)	65(134)	20.90 (15.67, N.A.)	0.71 (0.49, 1.03)
Carboplatin	72	11(39)	N.A. (30.49, N.A.)	19(33)	10.64 (7.56, 26.71)	0.31 (0.14, 0.67)
Switching from Cis. to Carbo.	21	4(12)	30.65 (5.13, 30.65)	3(9)	N.A. (5.29, N.A.)	
Not Reported	7	0(4)	N.A.	0(3)	N.A.	

HR is not computed for subset category with less than 10 subjects per treatment group.

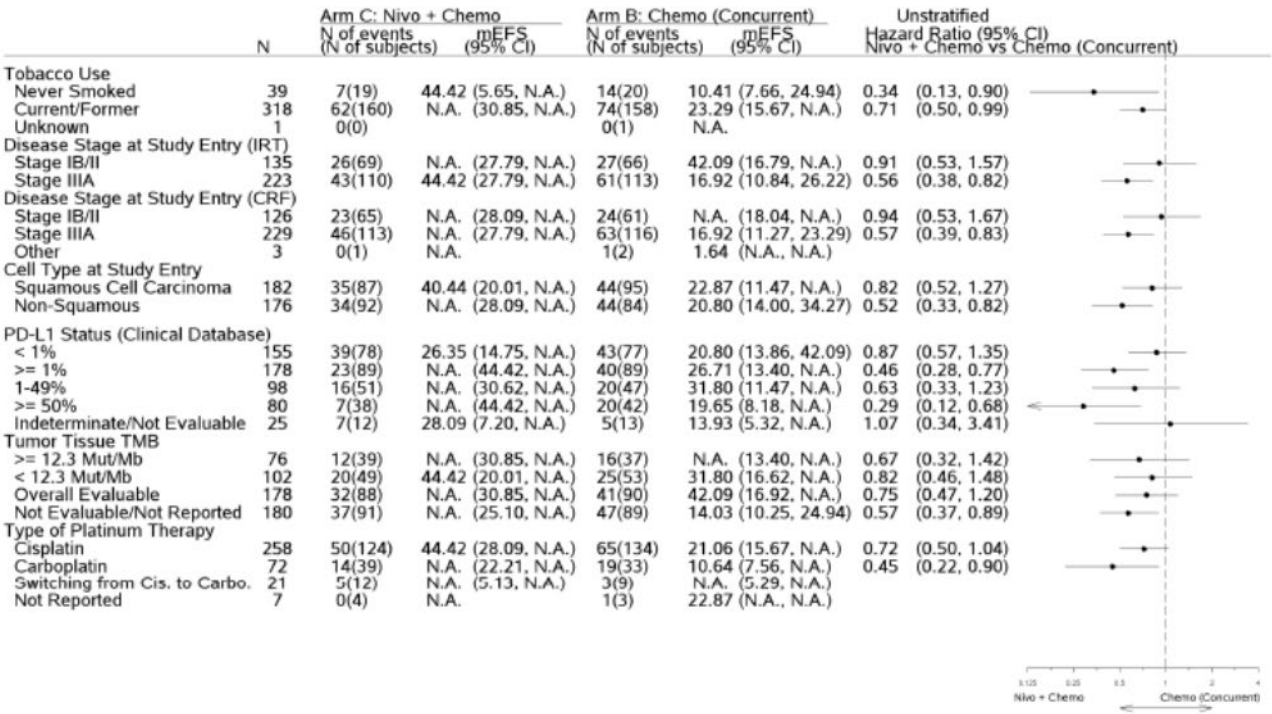
Source: Figure S.5.31.1

Updated subgroup analyses of EFS were performed based on the 14-Oct-2022 DBL (Figure 28)

Figure 28: **Treatment Effect on Event-Free Survival per BICR, Primary Definition in Pre-Defined Subsets - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (DBL 14-Oct-2022)**



	N	Arm C: Nivo + Chemo N of events (N of subjects)	Arm C: Nivo + Chemo mEFS (95% CI)	Arm B: Chemo (Concurrent) N of events (N of subjects)	Arm B: Chemo (Concurrent) mEFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs Chemo (Concurrent)
Overall	358	69(179)	N.A. (31.57, N.A.)	88(179)	21.06 (14.75, 42.09)	0.66 (0.48, 0.91)
Age Categorization						
< 65	176	30(93)	N.A. (31.57, N.A.)	40(83)	22.41 (14.03, N.A.)	0.61 (0.38, 0.99)
>= 65 and < 75	158	35(75)	40.44 (23.36, N.A.)	40(83)	23.29 (11.27, N.A.)	0.78 (0.50, 1.24)
>= 75 and < 85	24	4(11)	N.A. (5.13, N.A.)	8(13)	10.25 (5.32, N.A.)	0.43 (0.13, 1.45)
>= 85	0	0(0)		0(0)		
>= 75	24	4(11)	N.A. (5.13, N.A.)	8(13)	10.25 (5.32, N.A.)	0.43 (0.13, 1.45)
>= 65	182	39(86)	40.44 (26.35, N.A.)	48(96)	20.90 (10.64, N.A.)	0.72 (0.47, 1.10)
Sex (IRT)						
Male	255	55(128)	44.42 (26.55, N.A.)	68(127)	18.04 (13.93, 26.71)	0.69 (0.48, 0.98)
Female	103	14(51)	N.A.	20(52)	N.A. (13.86, N.A.)	0.59 (0.30, 1.17)
Sex (CRF)						
Male	255	55(128)	44.42 (23.36, N.A.)	68(127)	18.04 (13.93, 26.71)	0.69 (0.48, 0.99)
Female	103	14(51)	N.A.	20(52)	N.A. (13.86, N.A.)	0.59 (0.30, 1.16)
Race						
White	169	35(89)	N.A. (26.55, N.A.)	31(80)	42.09 (21.06, N.A.)	0.96 (0.59, 1.56)
Black or African American	7	1(4)	N.A. (3.35, N.A.)	3(3)	9.26 (2.56, 12.85)	
Asian	179	33(86)	N.A. (30.65, N.A.)	52(93)	16.53 (10.84, 34.27)	0.53 (0.34, 0.83)
Other	3	0(0)		2(3)	10.84 (0.66, N.A.)	
Region						
North America	91	15(41)	N.A. (26.35, N.A.)	21(50)	42.09 (12.85, N.A.)	0.83 (0.43, 1.61)
Europe	66	14(41)	N.A. (14.62, N.A.)	10(25)	21.06 (10.25, N.A.)	0.69 (0.30, 1.56)
Asia	177	32(85)	N.A. (30.85, N.A.)	51(92)	16.53 (10.84, 34.27)	0.53 (0.34, 0.83)
Rest of the World	24	8(12)	19.47 (2.40, N.A.)	6(12)	26.22 (9.63, N.A.)	1.35 (0.47, 3.89)
Baseline ECOG Performance Status						
0	241	48(124)	N.A. (35.98, N.A.)	53(117)	31.80 (16.62, N.A.)	0.69 (0.47, 1.02)
1	117	21(55)	N.A. (18.92, N.A.)	35(62)	14.00 (10.05, 26.22)	0.64 (0.37, 1.10)
>1	0	0(0)		0(0)		



	N	Arm C: Nivo + Chemo N of events (N of subjects)	Arm C: Nivo + Chemo mEFS (95% CI)	Arm B: Chemo (Concurrent) N of events (N of subjects)	Arm B: Chemo (Concurrent) mEFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs Chemo (Concurrent)
Tobacco Use						
Never Smoked	39	7(19)	44.42 (5.65, N.A.)	14(20)	10.41 (7.66, 24.94)	0.34 (0.13, 0.90)
Current/Former	318	62(160)	N.A. (30.85, N.A.)	74(158)	23.29 (15.67, N.A.)	0.71 (0.50, 0.99)
Unknown	1	0(0)		0(1)	N.A.	
Disease Stage at Study Entry (IRT)						
Stage IB/II	135	26(69)	N.A. (27.79, N.A.)	27(66)	42.09 (16.79, N.A.)	0.91 (0.53, 1.57)
Stage IIIA	223	43(110)	44.42 (27.79, N.A.)	61(113)	16.92 (10.84, 26.22)	0.56 (0.38, 0.82)
Disease Stage at Study Entry (CRF)						
Stage IB/II	126	23(65)	N.A. (28.09, N.A.)	24(61)	N.A. (18.04, N.A.)	0.94 (0.53, 1.67)
Stage IIIA	229	46(113)	N.A. (27.79, N.A.)	63(116)	16.92 (11.27, 23.29)	0.57 (0.39, 0.83)
Other	3	0(1)	N.A.	1(2)	1.64 (N.A., N.A.)	
Cell Type at Study Entry						
Squamous Cell Carcinoma	182	35(87)	40.44 (20.01, N.A.)	44(95)	22.87 (11.47, N.A.)	0.82 (0.52, 1.27)
Non-Squamous	176	34(92)	N.A. (28.09, N.A.)	44(84)	20.80 (14.00, 34.27)	0.52 (0.33, 0.82)
PD-L1 Status (Clinical Database)						
< 1%	155	39(78)	26.35 (14.75, N.A.)	43(77)	20.80 (13.86, 42.09)	0.87 (0.57, 1.35)
>= 1%	178	23(89)	N.A. (44.42, N.A.)	40(89)	26.71 (13.40, N.A.)	0.46 (0.28, 0.77)
1-49%	98	16(51)	N.A. (30.62, N.A.)	20(47)	31.80 (11.47, N.A.)	0.63 (0.33, 1.23)
>= 50%	80	7(38)	N.A. (44.42, N.A.)	20(42)	19.65 (8.18, N.A.)	0.29 (0.12, 0.68)
Indeterminate/Not Evaluable	25	7(12)	28.09 (7.20, N.A.)	5(13)	13.93 (5.32, N.A.)	1.07 (0.34, 3.41)
Tumor Tissue TMB						
>= 12.3 Mut/Mb	76	12(39)	N.A. (30.85, N.A.)	16(37)	N.A. (13.40, N.A.)	0.67 (0.32, 1.42)
< 12.3 Mut/Mb	102	20(49)	44.42 (20.01, N.A.)	25(53)	31.80 (16.62, N.A.)	0.82 (0.46, 1.48)
Overall Evaluable	178	32(88)	N.A. (30.85, N.A.)	41(90)	42.09 (16.92, N.A.)	0.75 (0.47, 1.20)
Not Evaluable/Not Reported	180	37(91)	N.A. (25.10, N.A.)	47(89)	14.03 (10.25, 24.94)	0.57 (0.37, 0.89)
Type of Platinum Therapy						
Cisplatin	258	50(124)	44.42 (28.09, N.A.)	65(134)	21.06 (15.67, N.A.)	0.72 (0.50, 1.04)
Carboplatin	72	14(39)	N.A. (22.21, N.A.)	19(33)	10.64 (7.56, N.A.)	0.45 (0.22, 0.90)
Switching from Cis. to Carbo.	21	5(12)	N.A. (5.13, N.A.)	3(9)	N.A. (5.29, N.A.)	
Not Reported	7	0(4)	N.A.	1(3)	22.87 (N.A., N.A.)	

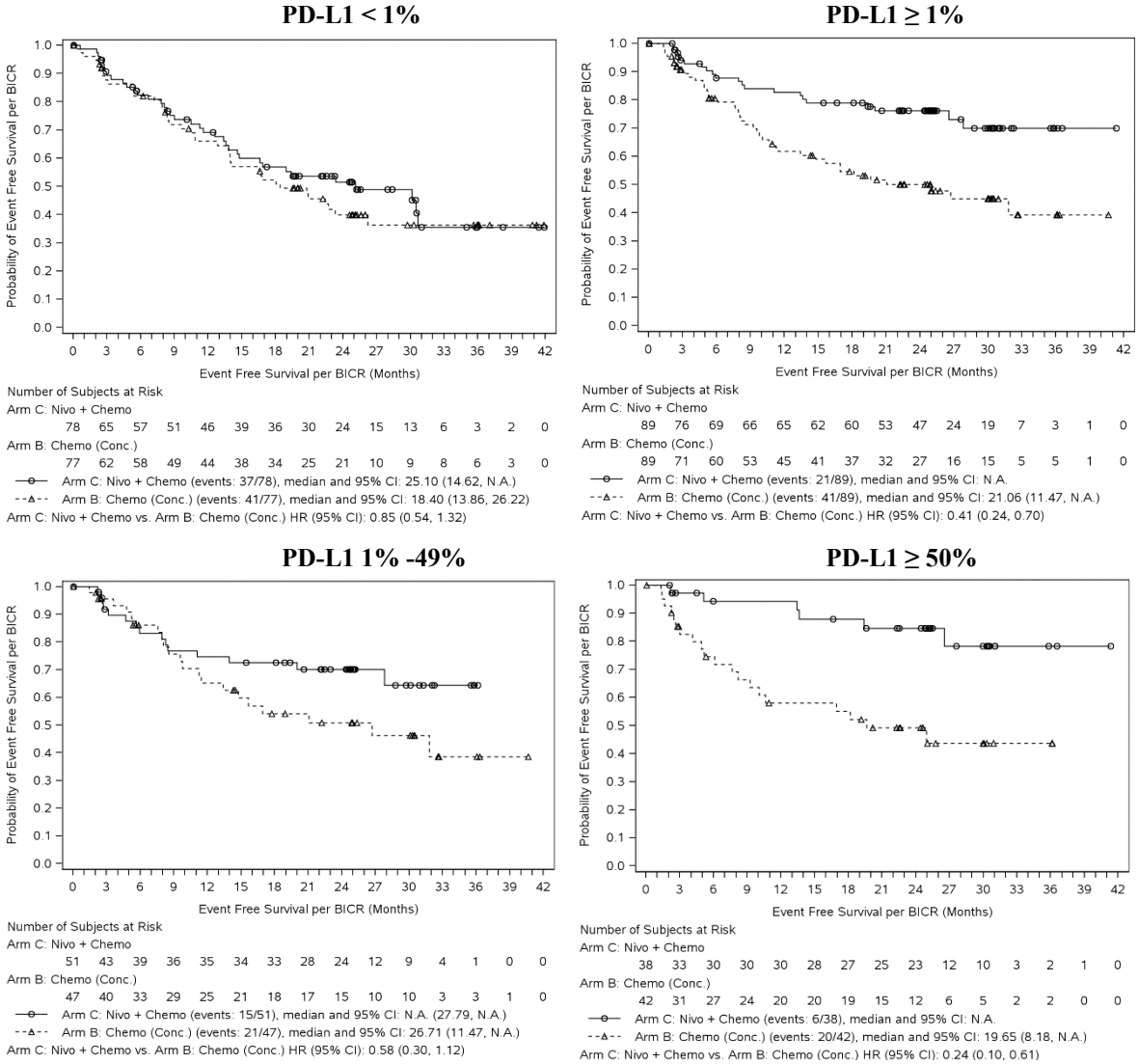
The HR is not computed for subset category with less than 10 subjects per treatment group.

<u>EFS by stratification factor subgroups</u>

PD-L1 Status (< 1%, ≥1%, 1-49%, ≥50%)

The benefit of nivo+chemo vs. chemo was observed across subgroups by PD-L1 expression.

Figure 29: **Event Free Survival per BICR, Primary Definition - by Baseline PD L1 - All Concurrently Randomized Subjects in Arms B and C**



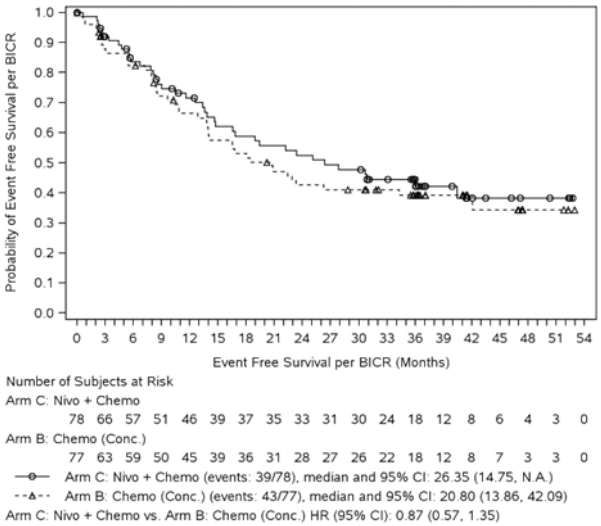
Statistical model for hazard ratio: Unstratified Cox proportional hazard model.

Note: Symbols represent censored observations. Source: Figure S.5.40.1

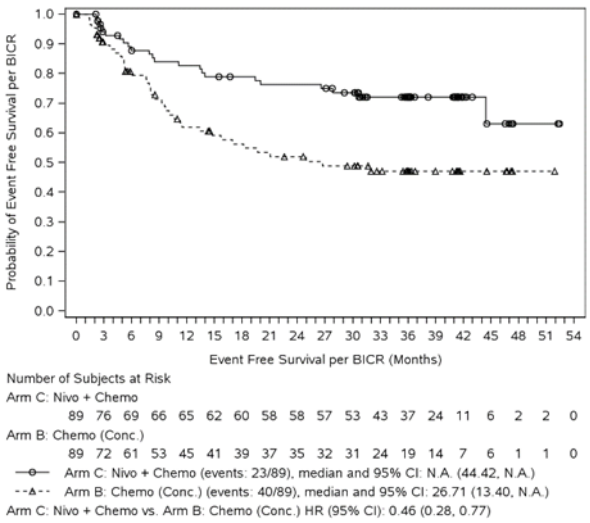
Based on the 14-Oct-2022 DBL, exploratory updated analysis of EFS by PD-L1 expression were performed. Obtained results seem consistent with the primary analysis and are included below:

Figure 30: **Event-Free Survival per BICR, Primary Definition - by Baseline PD L1 - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (DBL 14-Oct-2022)**

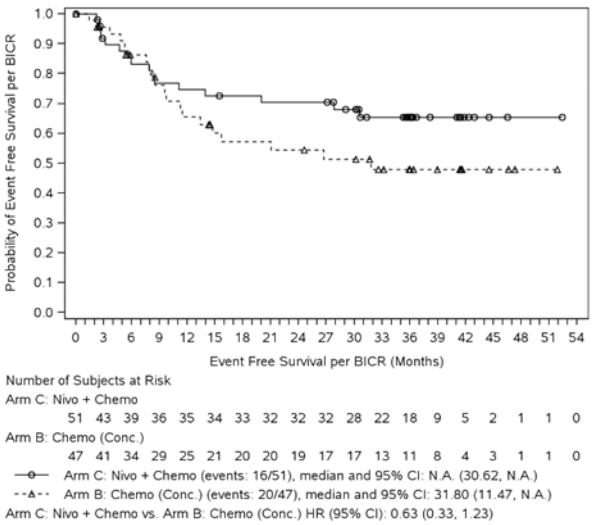
PD-L1 < 1%



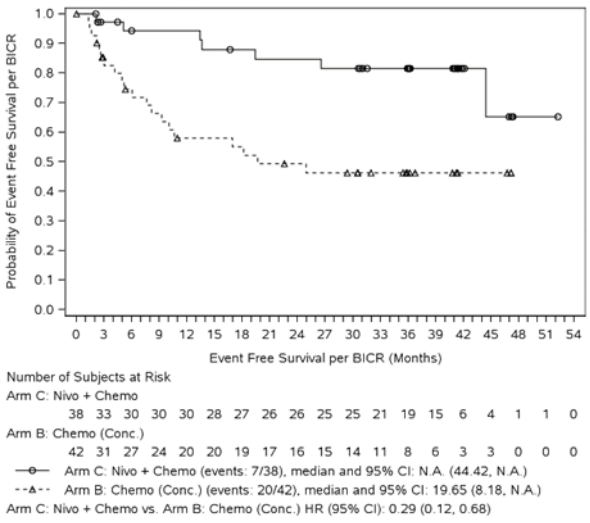
PD-L1 ≥ 1%



PD-L1 1%-49%



PD-L1 ≥ 50%



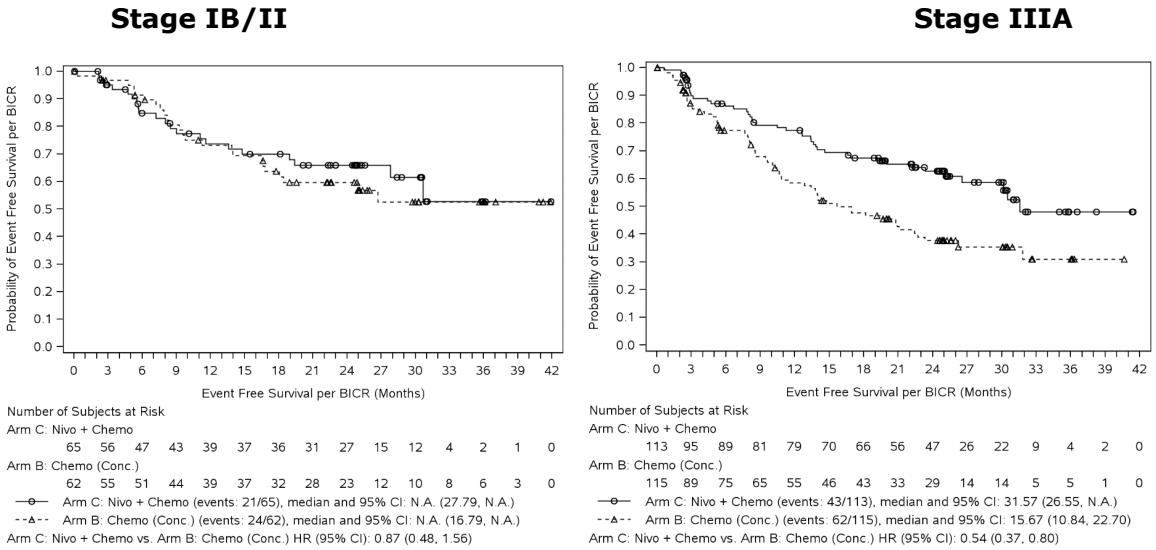
Statistical model for hazard ratio: Unstratified Cox proportional hazard model.

Note: Symbols represent censored observations. Subgroups defined based on baseline PD-L1 expression level recorded in the clinical database.

Disease Stage at Study Entry

The benefit of nivo+chemo vs. chemo was observed across subgroups by disease stage (IIIA vs IB/II).

Figure 31: **Event Free Survival per BICR, Primary Definition - by Disease Stage at Study Entry - All Concurrently Randomized Subjects in Arms B and C**



Statistical model for hazard ratio: Unstratified Cox proportional hazard model.

Note: Symbols represent censored observations.

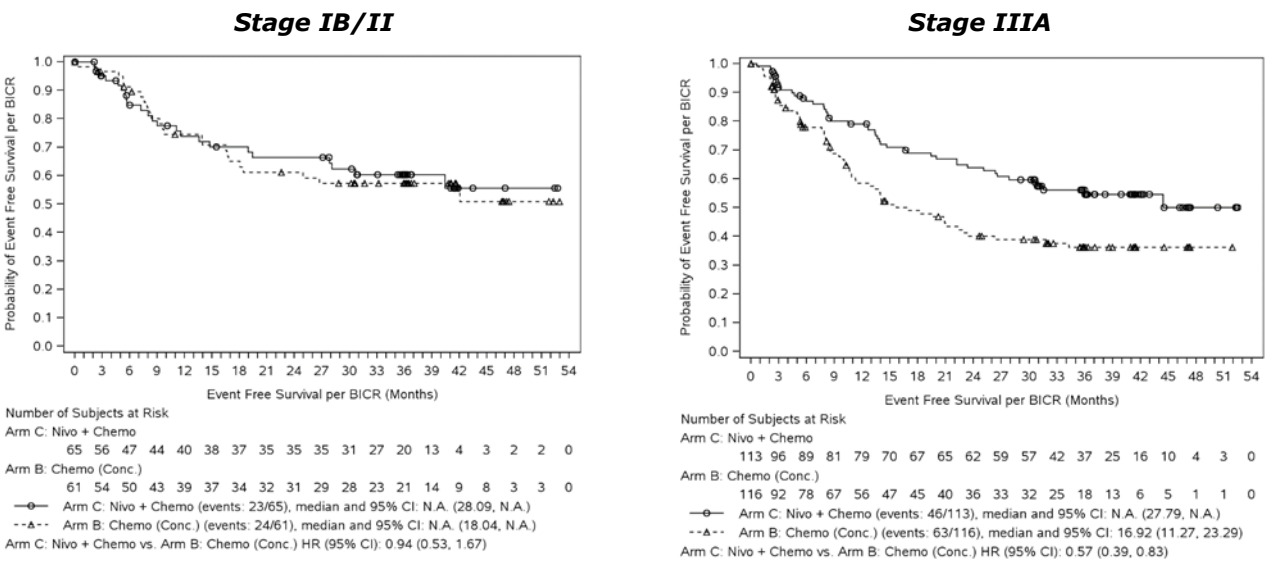
Subgroups defined based on disease stage at study entry per CRF. Subjects with disease stage other than IB, II, IIIA were excluded

For the updated analysis, HR point estimates for EFS by disease stage were as follows:

- IB/II per CRF: HR = 0.91 (95% CI: 0.53, 1.57)
- IIIA per CRF: HR = 0.56 (95% CI: 0.38, 0.82)

Please note, since the CA209816 Primary CSR there was an update in baseline disease stage for one subject from disease stage IIB to stage IIIA upon further review of source documentation.

Figure 32: **Event-Free Survival per BICR, Primary Definition - by Disease Stage at Study Entry - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (DBL 14-Oct-2022)**



Disease Stage at Study Entry and PD-L1 status

In an exploratory post-hoc analysis of EFS by both stage and PD-L1, the benefit of nivo+chemo over chemo was observed in early-stage subjects (stage IB/IIA) with PD-L1 ≥1% and in later stage subjects (stage IIIA) with PD-L1 ≥1% and PD-L1 <1% (Table 21).

Table 43: **EFS by Stage (IB/II and IIIA) and PD-L1 (< 1% and ≥1%) - All Concurrently Randomized subjects in Arms C (Nivo+Chemo) and B (Chemo)**

	PD-L1 < 1%		PD-L1 ≥ 1%	
	Nivo+Chemo	**Chemo**	**Nivo+Chemo**	**Chemo**
Stage IB/II	**N = 28**	**N = 28**	**N = 32**	**N = 33**
Events, n (%)	12 (42.9)	12 (42.9)	7 (21.9)	11 (33.3)
Median (95% CI), mo.	30.65 (11.56, NA)	NA (16.53, NA)	NA (27.79, NA)	NA (11.27, NA)
HR (95% CI)	1.15 (0.52, 2.57)		0.63 (0.24, 1.62)	
Stage IIIA	**N = 50**	**N = 49**	**N = 56**	**N = 55**
Events, n (%)	25 (50.0)	29 (59.2)	14 (25.0)	29 (52.7)
Median (95% CI), mo.	25.10 (13.37, NA)	14.00 (10.41, 22.70)	NA	16.92 (10.05, NA)
HR (95% CI)	0.69 (0.40, 1.19)		0.34 (0.18, 0.65)	

Sex/gender

The benefit of nivo+chemo vs. chemo was observed in both male and female subjects.

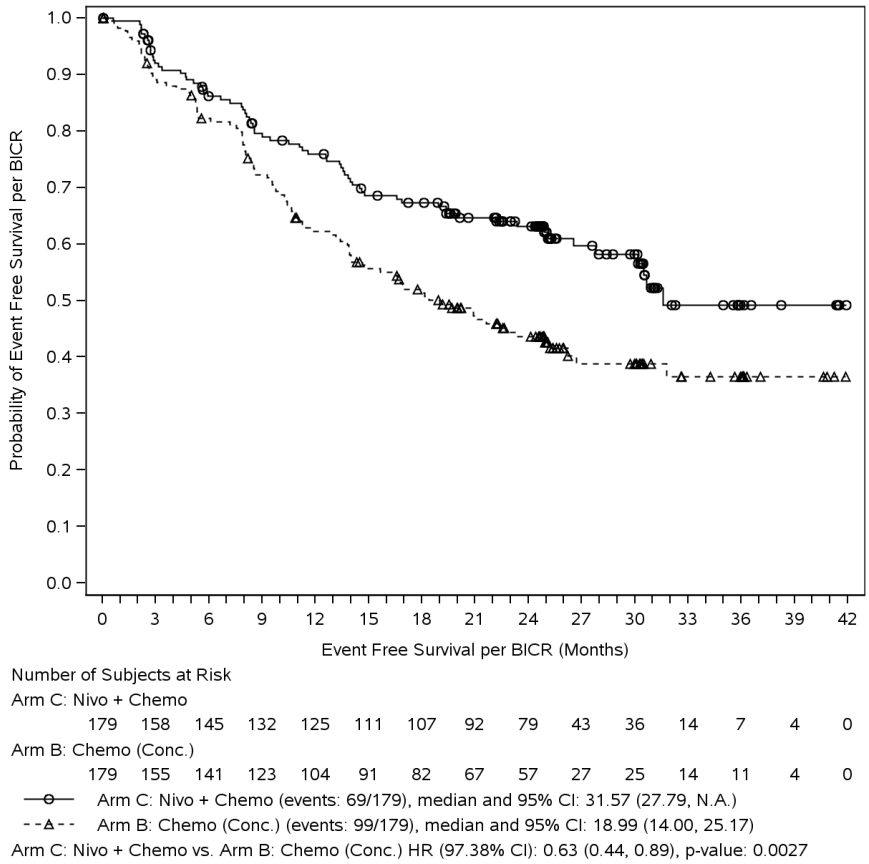
- Male per IRT: HR = 0.67 (95% CI: 0.47, 0.97)
- Female per IRT: HR = 0.47 (95% CI: 0.22, 0.97)

Sensitivity Analyses for the primary endpoint (EFS)

EFS by BICR (Secondary definition)

Analysis of EFS per BICR using the secondary EFS definition, which does not apply censoring at subsequent anti-cancer therapy usage: HR=0.63; (97.38% CI: 0.44, 0.89); this analysis was consistent with the analysis using the primary EFS definition.

Figure 33: **Event-Free Survival per BICR, Secondary Definition - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**



Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test.

Symbols represent censored observations. Source: Figure S.5.30.3

The updated analysis of EFS per BICR using the secondary EFS definition had a similar HR to the EFS analysis using the primary definition: HR=0.66 (95% CI: 0.49, 0.89).

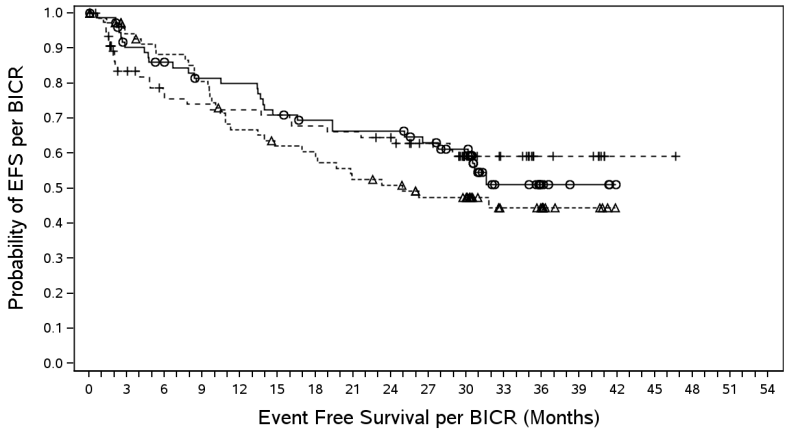
EFS by Investigator

EFS per investigator assessment (primary definition) showed a result consistent with the BICR primary analysis (median EFS 41.56 vs 20.67 months; HR=0.53 [95% CI: 0.38, 0.74]). In concurrently randomized subjects, concordance between BICR and investigator-assessed EFS was high (95.7%).

EFS by Randomization Period

EFS results for nivo+chemo vs chemo were consistent by randomization period including under Revised Protocol 02 (HR=0.67; 95% CI: 0.40, 1.10) and after Revised Protocol 02 (HR=0.61; 95% CI: 0.39, 0.94). KM curves have been provided and are included below (Figure 34[under Revised Protocol 02], and Figure 35 [after Revised Protocol 02, including both before and after Arm A closed]).

Figure 34: **Consistency of EFS Analysis by Randomization Period – KM Plot of EFS per BICR, Primary Definition – Subjects Randomized Under Revised Protocol 02**



Number of Subjects at Risk

Arm A: Nivo + Ipi

77 56 48 47 46 45 43 42 40 34 21 15 8 7 1 1 0 0 0

Arm C: Nivo + Chemo

74 63 58 54 53 47 44 42 42 38 34 13 6 3 0 0 0 0 0

Arm B: Chemo

74 63 58 53 43 39 38 33 31 26 24 13 11 4 0 0 0 0 0

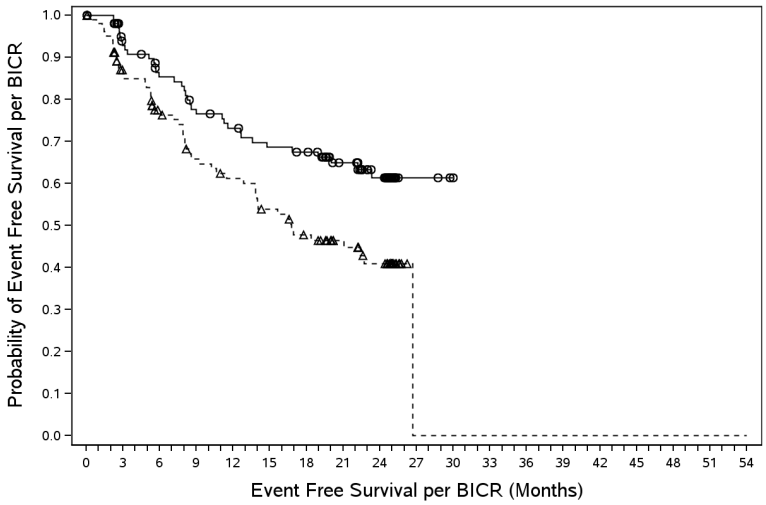
Arm A: Nivo + Ipi (events: 27/77), median and 95% CI: N.A. (28.68, N.A.)

Arm C: Nivo + Chemo (events: 30/74), median and 95% CI: N.A. (27.79, N.A.)

Arm B: Chemo (events: 35/74), median and 95% CI: 24.94 (14.75, N.A.)

Arm C: Nivo + Chemo vs. Arm B: Chemo HR (95% CI): 0.67 (0.40, 1.10)

Figure 35: **Consistency of EFS Analysis by Randomization Period – KM Plot of EFS per BICR, Primary Definition – Subjects Randomized After Revised Protocol 02**



Number of Subjects at Risk

Arm C: Nivo + Chemo

105 88 78 70 65 60 58 45 32 3 0 0 0 0 0 0 0 0 0

Arm B: Chemo

105 81 68 56 51 44 37 28 21 0 0 0 0 0 0 0 0 0 0

Arm C: Nivo + Chemo (events: 34/105), median and 95% CI: N.A.

Arm B: Chemo (events: 52/105), median and 95% CI: 16.79 (12.85, 26.71)

Arm C: Nivo + Chemo vs. Arm B: Chemo HR (95% CI): 0.61 (0.39, 0.94)

Other sensitivity analyses for EFS

Results for the following sensitivity analyses of EFS per BICR were consistent with the primary analysis:

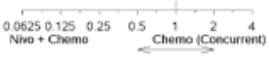
- Analysis using baseline stratification factors per CRF (rather than IRT): HR=0.64 (95% CI: 0.46, 0.89)
- Analysis accounting for missing tumour assessments prior to the EFS event; for subjects with 2 or more missed visits prior to the EFS event, EFS was censored at the last tumour assessment prior to the EFS event: HR=0.66 (95% CI: 0.47, 0.92).
- Analysis using an unstratified Cox model: HR =0.63 (95% CI: 0.45, 0.87).
- The analysis of EFS accounting for BICR progression prior to surgery was consistent with the primary analysis (HR=0.62 [95% CI: 0.45, 0.86]).
- Two chemo regimens were allowed in the chemo arm, but not in the nivo+chemo arm. As a sensitivity analysis, EFS was evaluated comparing the nivo+chemo arm (n = 179) to subjects in the chemo arm (n=134) who received the chemo regimens available to both arms. The results were consistent with the primary analysis (adjusted HR=0.57; 95% CI: 0.41, 0.81).
- Per-protocol adjuvant systemic chemo was optional and was received by 26 (14.8%) subjects in the nivo+chemo arm and 44 (25.0%) subjects in the chemo arm. Results for the EFS per BICR (primary definition) analysis adjusted by receiving systemic adjuvant chemo (as a time dependent covariate), favored nivo+chemo over chemo (adjusted HR=0.65; 95% CI: 0.47, 0.90).

<u>OS by subgroups</u>

The first interim analysis of OS between concurrently randomized subjects in the nivo+chemo and chemo arms was performed with a relatively small number of death events (94 of the 185 events for the final analysis of OS; 50.8% information fraction).

Figure 36: Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)

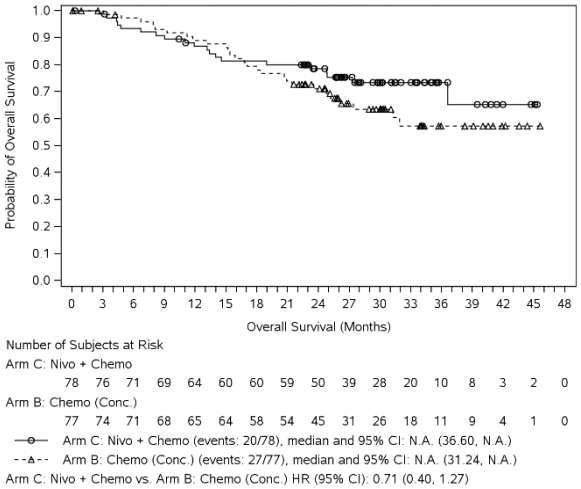
	N	Arm C: Nivo + Chemo N of events (N of subjects)	Arm C: Nivo + Chemo mOS (95% CI)	Arm B: Chemo (Concurrent) N of events (N of subjects)	Arm B: Chemo (Concurrent) mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs Chemo (Concurrent)
Overall	358	35(179)	N.A.	59(179)	N.A.	0.56 (0.37, 0.85)
Sex (CRF)						
Male	255	30(128)	N.A.	46(127)	N.A. (31.24, N.A.)	0.62 (0.39, 0.97)
Female	103	5(51)	N.A.	13(52)	N.A.	0.37 (0.13, 1.03)
Race						
White	169	21(89)	N.A.	23(80)	N.A.	0.80 (0.44, 1.45)
Black or African American	7	2(4)	N.A. (3.35, N.A.)	2(3)	20.93 (20.67, N.A.)	
Asian	179	12(86)	N.A.	33(93)	N.A. (31.24, N.A.)	0.34 (0.17, 0.66)
Other	3	0(0)		1(3)	N.A. (31.90, N.A.)	
Region						
North America	91	9(41)	N.A.	12(50)	N.A.	1.02 (0.43, 2.42)
Europe	66	8(41)	N.A.	10(25)	N.A. (18.40, N.A.)	0.45 (0.18, 1.15)
Asia	177	12(85)	N.A.	32(92)	N.A. (31.24, N.A.)	0.35 (0.18, 0.68)
Rest of the World	24	6(12)	27.04 (8.02, N.A.)	5(12)	N.A. (13.40, N.A.)	1.35 (0.41, 4.42)
Disease Stage at Study Entry (CRF)						
Stage IB/II	127	12(65)	N.A.	19(62)	N.A.	0.60 (0.29, 1.23)
Stage IIIA	228	23(113)	N.A.	39(115)	N.A.	0.56 (0.33, 0.93)
Other	3	0(1)	N.A.	1(2)	12.39 (N.A., N.A.)	
Cell Type at Study Entry						
Squamous Cell Carcinoma	182	24(87)	N.A. (36.60, N.A.)	33(95)	N.A.	0.74 (0.44, 1.25)
Non-Squamous	176	11(92)	N.A.	26(84)	N.A.	0.37 (0.18, 0.76)
PD-L1 Status (Clinical Database)						
< 1%	155	20(78)	N.A. (36.60, N.A.)	27(77)	N.A. (31.24, N.A.)	0.71 (0.40, 1.27)
>= 1%	178	12(89)	N.A.	28(89)	N.A.	0.39 (0.20, 0.77)
1-49%	98	11(51)	N.A.	15(47)	N.A.	0.65 (0.30, 1.42)
>= 50%	80	1(38)	N.A.	13(42)	N.A.	0.07 (<0.01, 0.55)
Indeterminate/Not Evaluable	25	3(12)	N.A. (12.29, N.A.)	4(13)	N.A. (14.65, N.A.)	0.86 (0.19, 3.84)



HR is not computed for subset category with less than 10 subjects per treatment group.
Source: Figure S.5.31.3

Figure 37: **Kaplan-Meier Plot of Overall Survival by Baseline PD-L1 - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**

PD-L1 < 1%

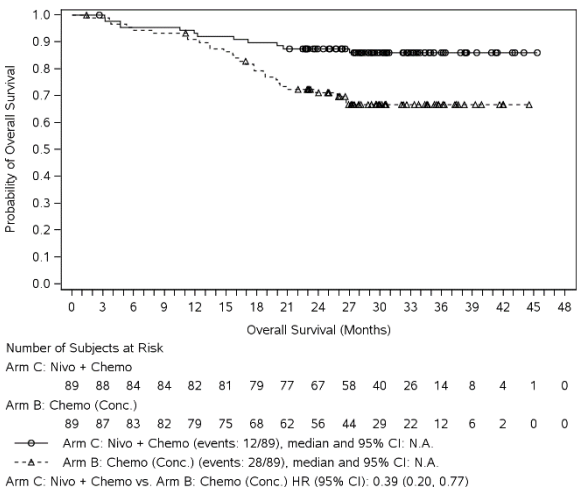


Number of Subjects at Risk

Arm C: Nivo + Chemo	78	76	71	69	64	60	60	59	50	39	28	20	10	8	3	2	0
Arm B: Chemo (Conc.)	77	74	71	68	65	64	58	54	45	31	26	18	11	9	4	1	0

Arm C: Nivo + Chemo (events: 20/78), median and 95% CI: N.A. (36.60, N.A.)
Arm B: Chemo (Conc.) (events: 27/77), median and 95% CI: N.A. (31.24, N.A.)
Arm C: Nivo + Chemo vs. Arm B: Chemo (Conc.) HR (95% CI): 0.71 (0.40, 1.27)

PD-L1 ≥ 1%

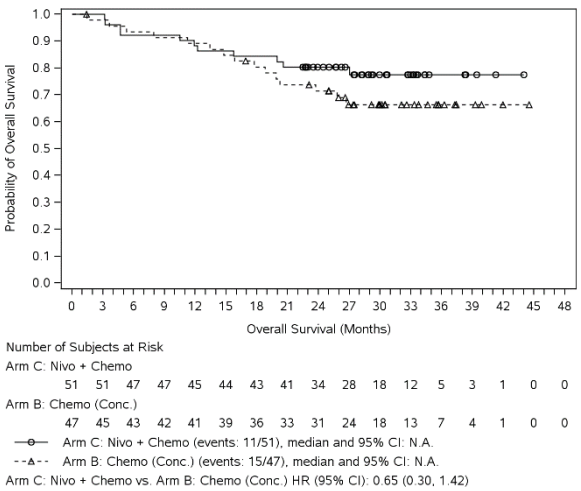


Number of Subjects at Risk

Arm C: Nivo + Chemo	89	88	84	84	82	81	79	77	67	58	40	26	14	8	4	1	0
Arm B: Chemo (Conc.)	89	87	83	82	79	75	68	62	56	44	29	22	12	6	2	0	0

Arm C: Nivo + Chemo (events: 12/89), median and 95% CI: N.A.
Arm B: Chemo (Conc.) (events: 28/89), median and 95% CI: N.A.
Arm C: Nivo + Chemo vs. Arm B: Chemo (Conc.) HR (95% CI): 0.39 (0.20, 0.77)

PD-L1 1-49%

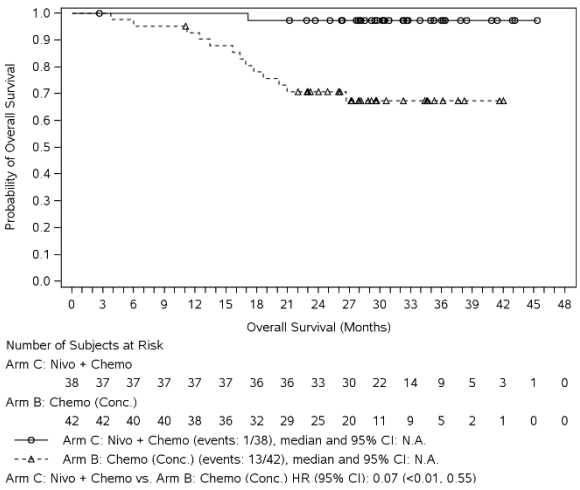


Number of Subjects at Risk

Arm C: Nivo + Chemo	51	51	47	47	45	44	43	41	34	28	18	12	5	3	1	0	0
Arm B: Chemo (Conc.)	47	45	43	42	41	39	36	33	31	24	18	13	7	4	1	0	0

Arm C: Nivo + Chemo (events: 11/51), median and 95% CI: N.A.
Arm B: Chemo (Conc.) (events: 15/47), median and 95% CI: N.A.
Arm C: Nivo + Chemo vs. Arm B: Chemo (Conc.) HR (95% CI): 0.65 (0.30, 1.42)

PD-L1 ≥ 50%



Number of Subjects at Risk

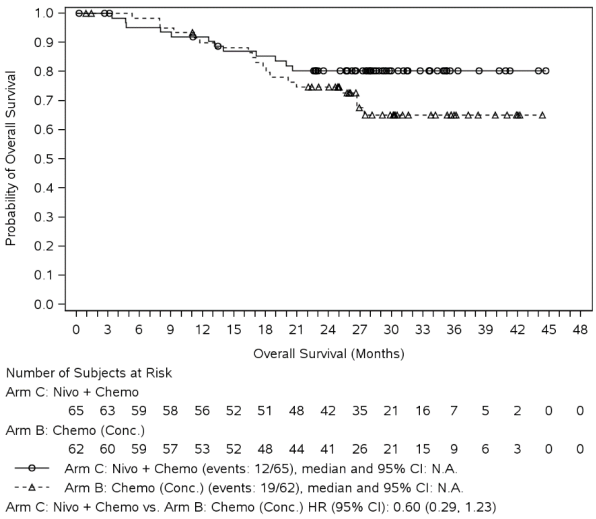
Arm C: Nivo + Chemo	38	37	37	37	37	37	36	36	33	30	22	14	9	5	3	1	0
Arm B: Chemo (Conc.)	42	42	40	40	38	36	32	29	25	20	11	9	5	2	1	0	0

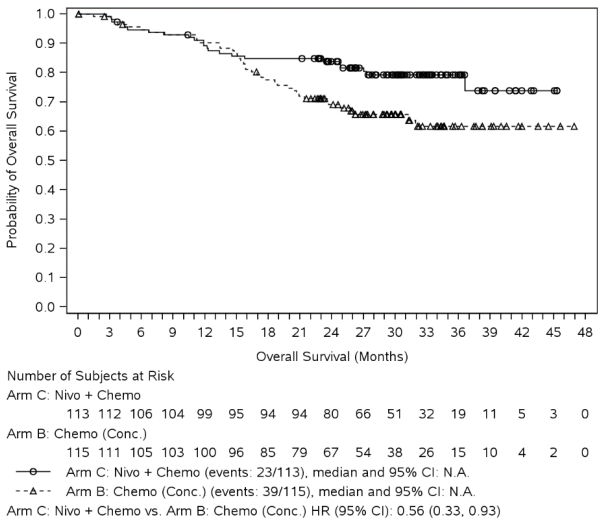
Arm C: Nivo + Chemo (events: 1/38), median and 95% CI: N.A.
Arm B: Chemo (Conc.) (events: 13/42), median and 95% CI: N.A.
Arm C: Nivo + Chemo vs. Arm B: Chemo (Conc.) HR (95% CI): 0.07 (<0.01, 0.55)

Statistical model for hazard ratio: Unstratified Cox proportional hazard model. Symbols represent censored observations. Subgroups defined based on baseline PD-L1 expression level recorded on clinical database.

Figure 38: **Kaplan-Meier Plot of Overall Survival by Disease Stage at Study Entry - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**

Stage IB/II ***Stage IIIA***



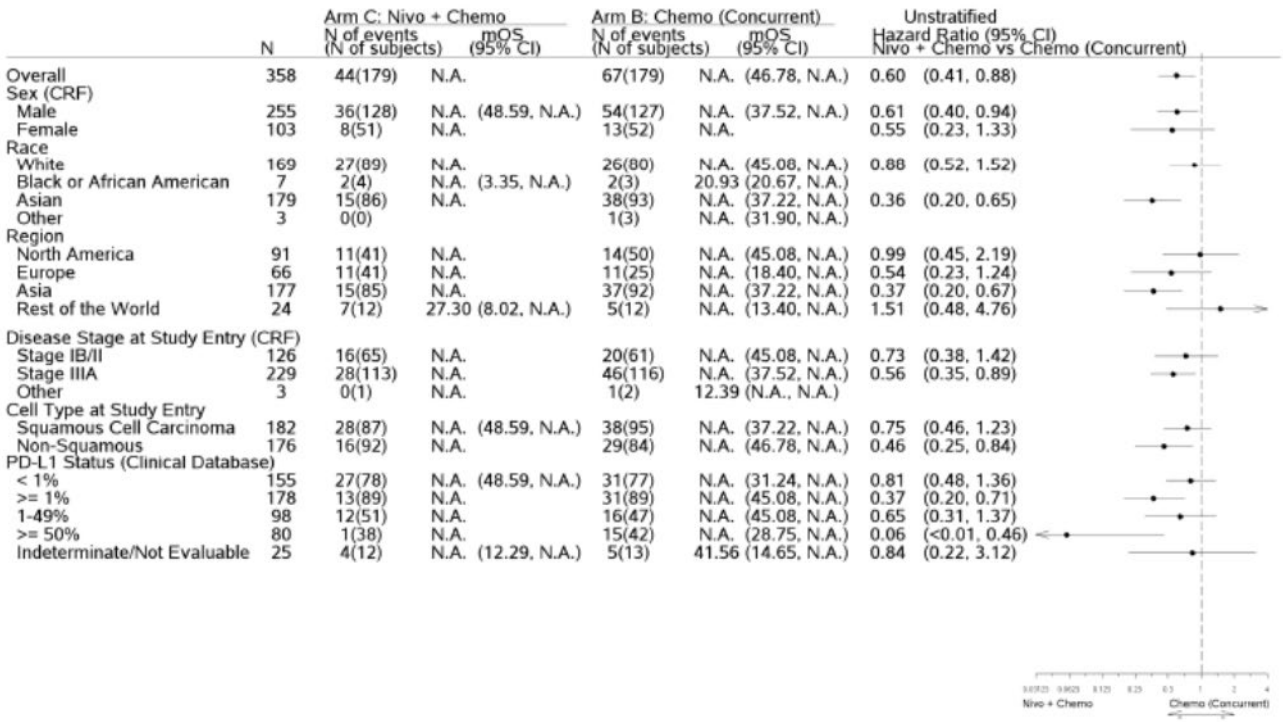


Statistical model for hazard ratio: Unstratified Cox proportional hazard model.
Symbols represent censored observations.
Subgroups defined based on disease stage at study entry per CRF. Subjects with disease stage other than IB, II, IIIA are excluded

Given the delayed separation of the curves leading to non-proportional hazards, an ad hoc sensitivity restricted mean survival time (RMST) analysis was performed. The difference (95% CI) at 12 months between the nivo+chemo arm (RMST [95% CI]: 11.48 [11.19, 11.76]) and chemo arm (RMST [95% CI]: 11.54 [11.27, 11.80]) was -0.06 (-0.45, 0.33). At 24 months, the difference (95% CI) between the nivo+chemo arm (RMST [95% CI]: 21.71 [20.87, 22.54]) and chemo arm (RMST [95% CI]: 21.09 [20.26, 21.91]) was 0.62 (-0.56, 1.80), and at the maximum timepoint (45.3 months), the difference (95% CI) between the nivo+chemo arm (RMST [95% CI]: 38.41 [36.29, 40.53]) and chemo arm (RMST [95% CI]: 34.73 [32.48, 36.98]) was 3.68 (0.59, 6.77), showing an increase in the difference between the 2 arms over time. RMST analyses by disease stage, PD-L1, and histology subgroups have been provided.

As expected, the second interim analysis of OS (DBL 14-Oct-2022) between concurrently randomized subjects in the nivo+chemo and chemo arms was performed with a relatively small number of death events (111 of the 185 events for the final analysis of OS; 60.0% information fraction). Analyses of subgroups were then further limited by even smaller numbers of events. Nevertheless, key subgroups were summarized for OS (Figure 39).

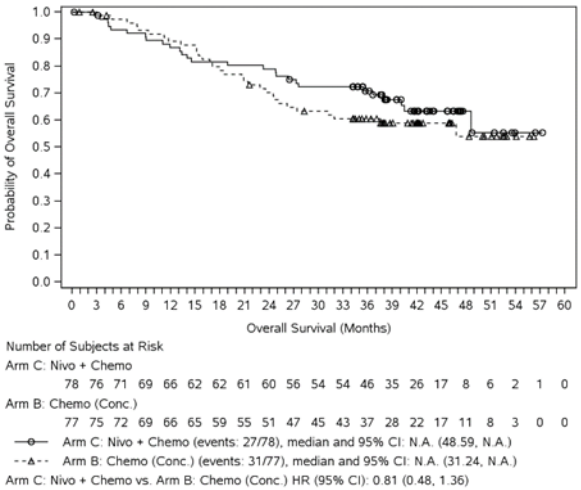
Figure 39: **Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (DBL 14-Oct-2022)**



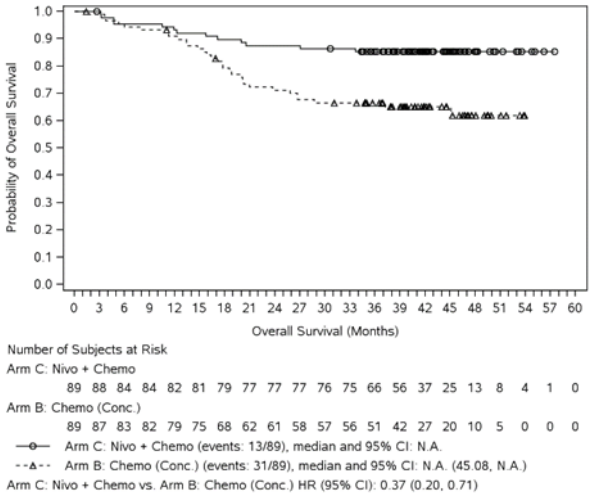
HR is not computed for subset category with less than 10 subjects per treatment group.

Figure 40: **Kaplan-Meier Plot of Overall Survival by Baseline PD-L1 - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo) (DBL 14-Oct-2022)**

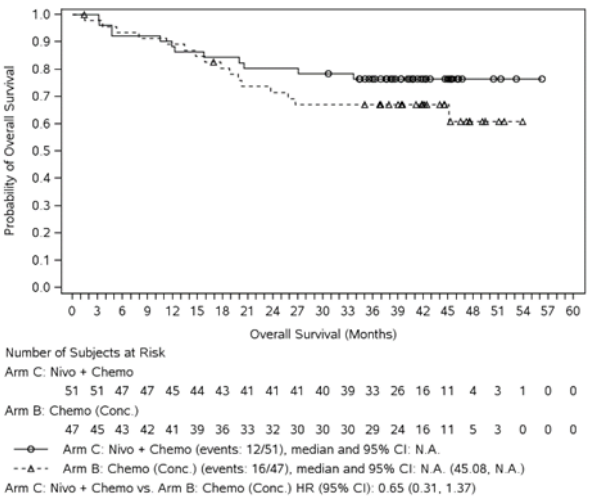
PD-L1 < 1%



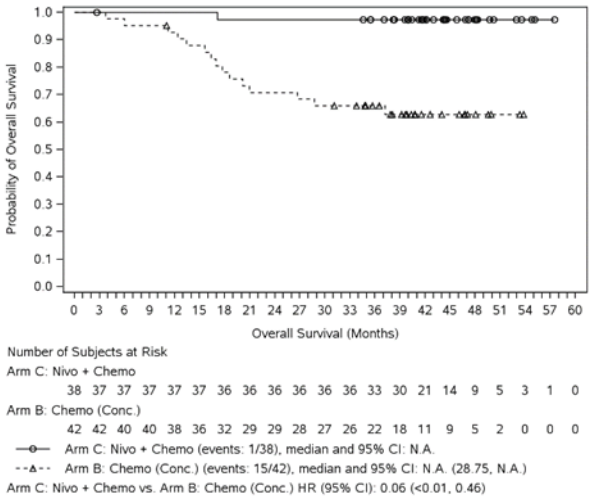
PD-L1 ≥ 1%



PD-L1 1-49%



PD-L1 ≥ 50%



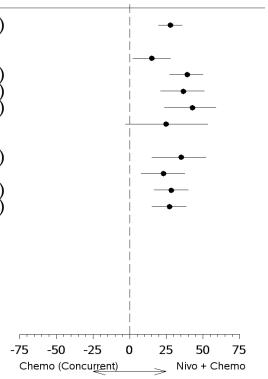
Statistical model for hazard ratio: Unstratified Cox proportional hazard model.
Symbols represent censored observations.
Subgroups defined based on baseline PD-L1 expression level recorded in the clinical database.

MPR by PD-L1

In concurrently randomized subjects, differences in MPR per BIPR favored (95% CI for the difference > 0) nivo+chemo vs chemo for all PD-L1 and TMB expression levels, with the exception of the PD-L1 indeterminate/NE (n = 25) for which the confidence interval crosses 0 but the point estimate favours nivo+chemo (Figure 41).

Figure 41: **Forest Plot of Treatment Effect on MPR by BIPR by PD-L1 and TMB - All Concurrently Randomized Subjects in Arm C (Nivo + Chemo) and Arm B (Chemo)**

	N	Arm C: Nivo + Chemo N of responses (N of subjects)	mPR (95% Exact CI)	Arm B: Chemo (Concurrent) N of responses (N of subjects)	mPR (95% Exact CI)	Unweighted mPR Difference (95% CI)
Overall	358	66(179)	36.9% (29.8, 44.4)	16(179)	8.9% (5.2, 14.1)	27.9% (19.5, 35.9)
PD-L1 Status (Clinical Database)						
< 1%	155	23(78)	29.5% (19.7, 40.9)	11(77)	14.3% (7.4, 24.1)	15.2% (2.1, 27.7)
>= 1%	178	40(89)	44.9% (34.4, 55.9)	5(89)	5.6% (1.8, 12.6)	39.3% (27.3, 50.1)
1-49%	98	21(51)	41.2% (27.6, 55.8)	2(47)	4.3% (0.5, 14.5)	36.9% (21.0, 50.9)
>= 50%	80	19(38)	50.0% (33.4, 66.6)	3(42)	7.1% (1.5, 19.5)	42.9% (23.6, 58.7)
Indeterminate/Not Evaluable	25	3(12)	25.0% (5.5, 57.2)	0(13)	0.0% (0.0, 24.7)	25.0% (-2.9, 53.2)
Tumor Tissue TMB						
>= 12.3 Mut/Mb	76	18(39)	46.2% (30.1, 62.8)	4(37)	10.8% (3.0, 25.4)	35.3% (15.2, 52.0)
< 12.3 Mut/Mb	102	15(49)	30.6% (18.3, 45.4)	4(53)	7.5% (2.1, 18.2)	23.1% (7.9, 37.7)
Overall Evaluable	178	33(88)	37.5% (27.4, 48.5)	8(90)	8.9% (3.9, 16.8)	28.6% (16.5, 39.9)
Not Evaluable/Not Reported	180	33(91)	36.3% (26.4, 47.0)	8(89)	9.0% (4.0, 16.9)	27.3% (15.3, 38.4)



(1) Two-sided 95% confidence interval for un-weighted difference was calculated using Newcombe method.

(2) MPR difference is not computed for subset with less than 10 subjects per treatment group.

EFS by pCR and MPR Status

pCR and MPR results were unchanged at the current 20 Oct 2021 database lock compared with the earlier database lock (16-Sep-2020). In both the nivo+chemo and chemo arms, subjects with a pCR and MPR had longer EFS than subjects without a pCR/MPR.

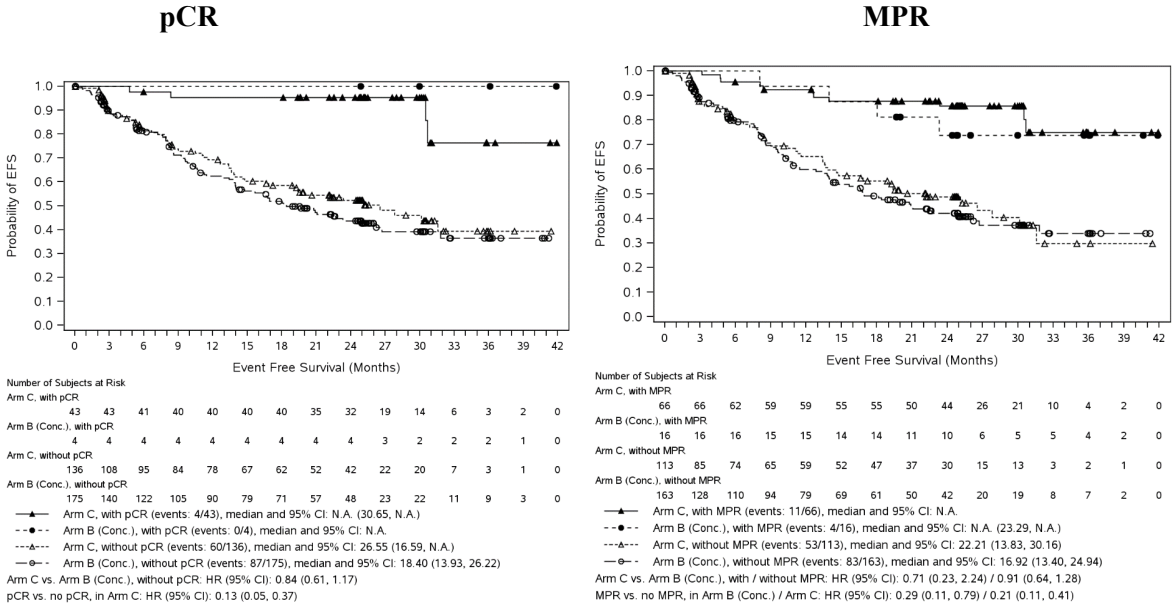
EFS by pCR

- In the nivo+chemo arm, the EFS HR for pCR vs. no pCR was 0.13 (95% CI: 0.05, 0.37). In the chemo arm, no HR was computed due to the small number of subjects achieving a pCR (n=4).
- A highly significant improvement in pCR rate was observed with nivo+chemo vs. chemo alone (24.0% [43/179] vs. 2.2% [4/179]; strata-adjusted difference based on CMH method: 21.6% [99% CI: 13.0, 30.3]).
- Among subjects without a pCR, the median EFS was 26.55 (nivo+chemo) vs .18.40 months (chemo) (HR=0.84 [95% CI: 0.61, 1.17]). In subjects with a pCR, median EFS was not reached in both the nivo+chemo and chemo arms (Figure 19).

EFS by MPR

- In the nivo+chemo arm, the EFS HR for MPR vs. no MPR was 0.21 (95% CI: 0.11, 0.41). In the chemo arm, the EFS HR for MPR vs. no MPR was 0.29 (0.11, 0.79).
- The MPR rate per BIPR for nivo+chemo vs. chemo was 36.9% (95% CI: 29.8, 44.4) vs 8.9% (95% CI: 5.2, 14.1); odds ratio = 5.70 (95% CI: 3.16, 10.26).
- Among subjects with a MPR, the HR for nivo+chemo vs. chemo was 0.71 (95% CI: 0.23, 2.24) and among subjects without a MPR, the HR for nivo+chemo vs. chemo was 0.91 (95% CI: 0.64, 1.28). In subjects with a MPR, median EFS was not reached in both the nivo+chemo and chemo arms (Figure 42).

Figure 42: **EFS per BICR, Primary Definition From Randomization by pCR and MPR Status - All Concurrently Randomized Subjects in Arm C (Nivo+Chemo) and Arm B (Chemo)**



Statistical model for hazard ratio: Cox proportional hazards model. HR involving pCR subjects in Arm Concurrent B are not provided due to small sample size.

Abbreviations: BICR - Blinded Independent Central Review; Chemo - chemotherapy; CI - confidence interval; EFS - event-free survival; HR - hazard ratio; MPR - major pathologic response; NA - not available; Nivo - nivolumab; pCR - pathologic complete response.

Efficacy by disease stages IB, IIA, IIB and IIIA

Efficacy results for individual disease stages are summarized in the following table:

Table 44: **Efficacy by NSCLC Disease Stages – All Concurrently Randomized Subjects in the Nivo + Chemo (Arm C) and Chemo (Arm B) Arms – CA209816**

	Stage IB		Stage IIA		Stage IIB		Stage IIIA	
	Nivo+Chemo N = 10	Chemo N = 8	Nivo+Chemo N = 30	Chemo N = 32	Nivo+Chemo N = 25	Chemo N = 22	Nivo+Chemo N = 113	Chemo N = 115
EFS per BICR (Primary Definition)								
Events, n	1	4	10	7	10	13	43	62
Median, mo.	Not reached	18.40	Not reached	Not reached	30.65	16.53	31.57	15.67
(95% CI)	(27.79, NA)	(0.30, NA)	(14.75, NA)	(NA, NA)	(9.00, NA)	(7.56, NA)	(26.55, NA)	(10.84, 22.70)
HR (95% CI)	0.11 (0.01, 1.06)		2.05 (0.78, 5.42)		0.64 (0.28, 1.46)		0.54 (0.37, 0.80)	
pCR per BIPR								
pCR, %	40.0	0	23.3	3.1	24.0	9.1	23.0	0.9
(95% CI)	(12.2, 73.8)	(0, 36.9)	(9.9, 42.3)	(< 0.1, 16.2)	(9.4, 45.1)	(1.1, 29.2)	(15.6, 31.9)	(< 0.1, 4.7)
Difference (95% CI)	40.0 (0.1, 68.7)		20.2 (3.1, 38.0)		14.9 (-7.6, 35.4)		22.1% (14.3, 30.7)	
MPR per BIPR								
MPR, %	40.0	0	30.0	6.3	28.0	13.6	40.7	9.6
(95% CI)	(12.2, 73.8)	(0, 36.9)	(14.7, 49.4)	(0.8, 20.8)	(12.1, 49.4)	(2.9, 34.9)	(31.6, 50.4)	(4.9, 16.5)
Difference (95% CI)	40.0 (0.1, 68.7)		23.8 (4.5, 42.2)		14.4 (-9.6, 35.9)		31.1 (20.2, 41.2)	
OS								
Events, n	0	2	6	6	6	11	23	39
Median, mo.	Not reached	Not reached	Not reached	Not reached	Not reached	26.71	Not reached	Not reached
(95% CI)	(NA, NA)	(11.24, NA)	(NA, NA)	(NA, NA)	(NA, NA)	(16.36, NA)	(NA, NA)	(NA, NA)
HR (95% CI)	NA		1.30 (0.42, 4.03)		0.41 (0.15, 1.10)		0.56 (0.33, 0.93)	

Database lock of 20-Oct-2021 is used for all values in the table.

Abbreviations: BICR - blinded independent central review; BIPR - blinded independent pathologic review; chemo - chemotherapy; CI - confidence interval; DBL - database lock; EFS - event-free survival; HR - hazard ratio; mo - months; MPR - major pathologic response; NA - not available/not reached; nivo - nivolumab; OS - overall survival; pCR - pathologic complete response.

Kaplan-Meier plots of EFS and OS by individual disease stages have also been submitted but they are not included in this report due to their difficult interpretation considering the low number of subjects and events in the individual stages IB, IIA and IIB subgroups.

Summary of main study

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

Table 45: **Summary of Efficacy for trial CA209816**

Title: Randomized, Open-Label, Phase 3 Trial of Nivolumab plus Ipilimumab or Nivolumab plus Platinum Doublet Chemotherapy versus Platinum-Doublet Chemotherapy in Early Stage NSCLC (CheckMate 816: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 816)			
Study identifier	CA209816		
Design	CA209816 is an open-label, randomized Phase 3 study of nivolumab (3 mg/kg every 2 weeks [Q2W]; up to 3 cycles) and a single 1 mg/kg dose of ipilimumab (nivo+ipi), nivolumab 360 mg flat dose plus platinum-doublet chemotherapy (every 3 weeks [Q3W] up to 3 cycles; nivo+chemo), or platinum-doublet chemotherapy (Q3W up to 3 cycles; chemo) as neoadjuvant treatment in subjects with resectable (Stage IB [≥4 cm], Stage II, and resectable Stage IIIA) non-small cell lung cancer (NSCLC). The 2 primary endpoints are to compare pathologic complete response (pCR) by blinded independent pathological review (BIPR) and event-free survival (EFS) by blinded independent central review (BICR) in subjects in subjects concurrently randomized to nivo+chemo or chemo (population for the primary analysis).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		From 09-Mar-2017 (FPFV) to 08-Sep-2021 (LPLV). Clinical DBL for the primary CSR: 20-Oct-2021 not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Arm A (nivo+ipi)		nivo (3 mg/kg Q2W up to 3 cycles) and a single 1 mg/kg dose of ipi (nivo+ipi) N=113
	Arm B (chemo)		Chemo, different regimens (Q3W up to 3 cycles) N=179
	Arm C (nivo+chemo)		nivo 360 mg flat dose plus chemo (Q3W up to 3 cycles) N=179
Endpoints and definitions	Primary endpoint	pCR by BIPR	Number of randomized subjects with an absence of residual tumour in lung resected tissue and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each treatment arm. Randomized subjects who were no longer eligible for surgery, who received alternative anticancer therapy before surgery, who discontinued the study (e.g. withdraw consent) before surgery, or who otherwise did not have an evaluable BIPR result available were all counted as non responders.

	Primary endpoint	EFS by BICR	Time from randomization to any of the following events: a) any progression of disease precluding surgery, b) progression or recurrence of disease (based on BICR assessment per Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) after surgery, or c) death due to any cause. Subjects who did not undergo surgery for reasons other than progression were considered to have an event at RECIST 1.1 (based on BICR) progression or death. The primary definition accounts for subsequent therapy by censoring at the last evaluable tumour assessment on or prior to the date of subsequent therapy (outside of the protocol specified adjuvant therapy). The secondary definition does not incorporate censoring due to subsequent therapy.
	Secondary endpoint	OS	Time between the date of randomization and the date of death due to any cause. OS was censored on the last date a subject was known to be alive.
	Secondary endpoint	TTDM	Time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis. A distant metastasis was defined as any new lesion outside of the thorax using BICR and RECIST 1.1 criteria. Subjects who had not developed distant metastasis or died at the time of the analysis were censored on the date of their last evaluable tumour assessment.
Database lock	Interim CSR (based on a 16-Sep-2020 DBL) summarized results of the pre-specified final analysis of pCR. Primary CSR based on a 20-Oct-2021 DBL (clinical cut off: 08-Sep-2021) summarizes results for nivo+chemo vs chemo from the pre-specified EFS first interim analysis.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The final EFS analysis was conducted in 358 subjects concurrently randomized to Arms C (nivo+chemo: 179) and B (chemo: 179). Results reported below correspond to subjects with baseline disease stage II-IIIA and PD-L1 tumour cell expression ≥1%		
Descriptive statistics and estimate variability	Treatment group	Nivo+chemo	chemo
	Number of subjects	81	86
	pCR per BIPR[a] responders (%)	26 (32.1)	2 (2.3)
	95% CI	(22.2, 43.4)	(0.3, 8.1)
	EFS by BICR[b] (median, months)	Not reached	21.06
	95% CI	(NA, NA)	(11.47, NA)
	TTDM per BICR[c] (median, months)	Not reached	Not reached
	95% CI	(44.42, NA)	(18.83, NA)
Effect estimate per comparison	Primary endpoint pCR per BIPR[a]	Comparison groups	Nivo+chemo vs. chemo
		Difference, %	29.8
		95% CI	(19.0, 40.7)[d]
	Primary endpoint EFS by BICR[b]	Comparison groups	Nivo+chemo vs. chemo
		Hazard ratio (HR)	0.44
		95% CI	(0.26, 0.76)[e]
	Secondary endpoint TTDM per BICR[c]	Comparison groups	Nivo+chemo vs. chemo
		Hazard ratio (HR)	0.40
		95% CI	(0.22, 0.72)[e]
Notes	Planned OS IA2[c] nivo+chemo vs. chemo: HR=0.43(95% CI: 0.22, 0.83)[e]		

[a] 16-Sep-2020 Database Lock
[b] 20-Oct-2021 Database Lock
[c] 14-Oct-2022 Database Lock
[d] Two-sided 95% confidence interval for un-weighted was calculated using Newcombe method.

[e] Statistical model for hazard ratio: unstratified Cox proportional hazard model

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

Not applicable

Clinical studies in special populations

Table 46: Summary of Subject Disposition by Age Category - All Randomized Subjects - By Treatment Arm and Total for Study CA209816

	Age 65-74 (Older subjects number /total number)				***Age 75-84 (Older subjects number /total number)***				***Age 85+ (Older subjects number /total number)***			
	Nivo + Ipi	**Nivo + Chemo**	**Chemo (Concurrent)**	**Total**	**Nivo + Ipi**	**Nivo + Chemo**	**Chemo (Concurrent)**	**Total**	**Nivo + Ipi**	**Nivo + Chemo**	**Chemo (Concurrent)**	**Total**
Controlled Trials	40/113 (35.4)	75/179 (41.9)	83/179 (46.4)	211/505 (41.8)	11/113 (9.7)	11/179 (6.1)	13/179 (7.3)	39/505 (7.7)	0	0	0	1/505 (0.2)
Non Controlled trials	Not applicable				Not applicable				Not applicable			

2.4.3. Discussion on clinical efficacy

With the current application the MAH applied for an extension of the indication for OPDIVO, in combination with platinum-based chemotherapy, to be used as a neoadjuvant treatment of resectable non-small cell lung cancer. To support this application, results from study CA209816 (CheckMate 816) were submitted.

Design and conduct of clinical studies

CA209816 is an open-label, randomized, phase 3 study of nivolumab combined with different platinum-based chemotherapy regimens for the treatment of stage IB-IIIA NSCLC in the neoadjuvant setting. The study was originally designed to assess the efficacy and safety of nivolumab+ipilimumab compared to chemotherapy but an additional nivolumab+chemotherapy treatment arm was later included. The latter was chosen as the experimental treatment for the main analysis, based on emerging external data that suggested that the combination of nivolumab+ipilimumab was not appropriate for this neoadjuvant setting and positive results of nivolumab+chemotherapy from different studies such as phase 2 study NADIM. Enrolment in the nivolumab+ipilimumab arm was later closed but subjects previously randomized continued in the study and received treatment as planned.

Although blinding would have been preferred, the multiple chemotherapy regimens allowed added difficulties to a possible blinded design. The primary endpoints assessments were done by independent committees (BIPR and BICR), which is reassuring in the context of the open-label design.

The inclusion and exclusion criteria are generally endorsed and are in line with other chemo-immunotherapy studies. Patients could be enrolled having a histologically confirmed Stage IB (≥4 cm), II, IIIA (N2) NSCLC (per the 7th AJCC TNM edition) with disease that was considered resectable. During the conduct of this study, TNM staging system transitioned to the 8th edition which carries some differences that apply to the enrolled population, and which is the one currently used for patients

staging in clinical practice. This could be confusing as, based on the updated TNM (8th), only tumours of 4 cm remain as stage IB and T3-T4N2 are now stage IIIB, both of them being part of the enrolled population in this study. Details of staging criteria / characteristics of the included patients are included in section 5.1 of the SmPC. Further details about patients staging at study entry were provided, including specific recommendations for suspicious mediastinal lymph nodes. Brain MRI or head CT was required during screening for all subjects with stage II-III disease or any subject with suspicion of brain metastasis. However, a small risk of staging discrepancies always remains and could be a source of heterogeneity among the enrolled population.

Patients were included in the study regardless of PD-L1 expression. However, tumour tissue was required for PD-L1 expression determination by a central lab during screening period. Participants with 'known' EGFR mutations or ALK translocation were excluded from the study per protocol.

Stratification factors were disease stage (IB-II vs. III based on 7th TNM edition), PD-L1 status (<1% vs. ≥1%) and gender. Histology could have also been an adequate stratification factor because of the different prognosis squamous and non-squamous NSCLC presents. Although both histologies were balanced in the overall population, some differences were identified across arms, adding some heterogeneity to the comparison.

The chemotherapy schemes allowed both in the experimental and comparator arm seem adequate as they are the regimens commonly used in either the adjuvant or neoadjuvant setting. The decision was up to the investigator, based on histology (squamous or non-squamous), preference and other factors like tolerance to cisplatin. The fact that the choice of chemotherapy regimen, for both treatment arms, was performed after randomization represents a limitation of the study design, as it could have led to biased decisions. Another important limitation of this study was the different chemotherapy regimens available in the experimental arm in comparison with the chemotherapy arm which adds certain grade of heterogeneity to the analyses. The MAH has justified that no safety information was available for the combination of nivolumab plus vinorelbine or docetaxel at the time when the nivo+chemo arm was added. This is somehow unfortunate as the combinations used in this study do not completely reflect the usual clinical practice, where, for example, cisplatin + vinorelbine would be the preferred choice for non-squamous histology in this setting, and not cisplatin + pemetrexed. The currently available information about these schemes that were not allowed in the experimental arm is still limited, especially for the use of nivolumab in combination with cisplatin and vinorelbine. Chemotherapy components dosing could be decided following local recommendations within a protocol-guided dose range, being the highest allowed doses the most commonly used in our practice. The use of 3 cycles is in line with guidelines recommendations.

The MAH conducted a number of relevant changes with regards to the study design and consequently, the sample size estimation was affected considerably. Initially, the sample size was calculated based on two arms (A and B) with MPR in PD-L1≥1% as primary endpoint. Afterwards, at the time of the revised protocol 02 and based on emerging external data, an additional arm was incorporated (Arm C) and the primary endpoint was changed into pCR and EFS. Consequently, the sample size was updated with these relevant changes by considering at this point 642 subjects. At the time of the Revised protocol 03, the arm A was dropped and the sample size was updated accordingly by considering only a total of 358 patients.

The sample size of the study was calculated based on the multiple primary endpoint comparisons: pCR and EFS with an initial alpha allocation of 0.01 and 0.04 respectively. To obtain a power of 90% in pCR, 350 patients were considered needed with an expected pCR rate of 10% on Arm B and 30% on Arm C with an alpha of 1%. On the other hand, to achieve 82% power in EFS assuming an HR of 0.65 between the two Arms, 185 events were considered needed with an overall alpha of 5%.

Additionally, the MAH performed a number of changes with regards to the interim analyses planned for EFS. The current results are presented based on the pre-planned first interim analysis conducted when 151 EFS events were accrued (i.e. 82% of the 185 events calculated for the final EFS analysis).

Overall, the final assumptions and the calculations performed for the sample size are followed and they can be considered agreeable. Also, the strategy of recycling the value of alpha through different endpoints when certain endpoints are statistically significant can be also endorsed from a methodological perspective.

As outlined above, the study protocol was subject to multiple amendments and the design, objectives, endpoints, population of analysis and statistical methods were completely changed during the conduct of the study. The sponsor used an independent DMC and multiple external vendors to ensure correct data management. Further, several additional sensitivity analyses, including according to different protocol versions, have been performed showing consistent results (see further details below). Overall, it seems that integrity of the data was maintained during study conduct and data can be considered reliable to support the proposed extension of the indication.

The original primary endpoint, MPR, was later substituted by dual primary endpoints of pCR and EFS, by BIPR and BICR, respectively. This change seems appropriate. EFS is an adequate endpoint in this setting since it includes events pre- and post-surgery, but it needs to be supported at least by a non-detrimental effect in OS, as the proposed neoadjuvant treatment is given in a potential curative setting. Subjects who did not undergo surgery for reasons other than progression were considered to have an event. The main analyses of EFS use the primary definition, censoring for subsequent therapy. A sensitivity analysis of EFS (secondary definition) not incorporating censoring due to subsequent therapy (EMA preferred) has also been performed. pCR has not been validated as a surrogate endpoint of survival but results on this endpoint provides information about treatment's antitumour activity and are considered supportive. Secondary endpoints are OS, TTDM and MPR. The exploratory endpoint of EFS on next line therapy (EFS2) has also been analysed.

Efficacy data and additional analyses

A total of 773 patients were enrolled in the study, of whom 505 were randomized to receive either nivo+ipi (n=113), chemo (n=213) or nivo+chemo (n=179). The primary population for the efficacy analyses (n=358) is comprised by all subjects concurrently randomized to the nivo+chemo and chemo arm (n=179 each). From the 268 not randomized subjects, 227 (29.4%) no longer met study criteria, 26 (3.4%) withdrew consent, one (0.1%) subject reported an adverse event and 14 (1.8) were not randomized due to "other" reasons. One hundred seventy-six subjects were treated in both nivo+chemo and chemo arms, 165 (93%) subjects in the nivo+chemo arm and 149 (84.7%) in the chemo arm completed the three cycles of neoadjuvant treatment. Apart from the subjects who did not complete neoadjuvant treatment due to disease progression (one and two in the nivo+chemo and chemo arm, respectively) and the ones that discontinued treatment due to study drug toxicity (5.7% vs. 6.8%), 13 subjects discontinued treatment due to other reasons (AE unrelated, subject request, withdrew consent and no longer meeting study criteria) and all of them were from the chemo arm. These discontinuations were further analysed and a possible relation to the open-label design cannot be discarded. Overall, having all discontinuations due to other reasons in the control arm and considering that the combination is an "add-on" treatment, these data should not affect the benefit-risk assessment. At the time of the DBL, all treated subjects were off neoadjuvant treatment for >18 months.

A low number of deviations were reported and are not expected to have impacted the study results.

Baseline patient characteristics were balanced between treatment arms. For baseline disease characteristics, squamous and non-squamous histologies were equally balanced in the overall population but there were some imbalances between arms. The reported imbalances are limited and are not expected to have any clinically relevant impact on the outcomes.

Disease stage at study entrance (IRT) was a stratification factor (IB-II vs. IIIA) and therefore balanced between arms, but also a similar number of subjects from each stage was included in both treatment arms. The overall number of stage III patients included (62.6%) was higher than initially predicted but this is somehow expected, as neoadjuvant treatment for NSCLC is only recommended in the majority of guidelines and local protocols for stage III patients that present a resectable tumour considered not operable, at first, by a multidisciplinary team. Even though most patients randomized were stage III (by TNM 7th edition), 36.6% of subjects were stage IB and II, with a considerably better prognosis and many of them being cured after resection, that could lead to better overall results than the ones observed with only stage III patients. Of note the number of stage IB patients is very limited in the study (n=18). Predefined subgroups analyses by stratification factors and requested efficacy analyses by individual stages have been provided and are discussed below. Discrepancies between IRT and CRF recorded stages (stratification subgroups) have been identified. Although they did not reach the pre-established 10% threshold, a sensitivity analysis of EFS by disease stage (CRF) was submitted. For PD-L1 tumour cell expression, 155 (43.3%) subjects presented <1% expression and 178 (49.7%) subjects presented tumour cell expression ≥1%. Demographic and baseline disease characteristics have also been provided for the subset of patients corresponding to the finally agreed indication, i.e. subjects with baseline disease stage II-IIIA and tumour PD-L1 expression ≥1%. No relevant differences have been identified between them and those of the ITT population.

After neoadjuvant treatment, 83.2% subjects from the nivo+chemo arm and 75.4% from the concurrently randomized patients to the chemo arm underwent definitive surgery. From the subjects whose surgeries were not performed, a 42.9% of subjects in the nivo+chemo arm and 45.9% in the chemo arm did not undergo surgery due to confirmed disease progression. Around 50% subjects from each arm had their surgery cancelled due to "other" reasons such as being unsuitable for surgery, refusing surgery, etc. The post-surgical disease status is considered to be a key risk factor for recurrence. There were not relevant differences between patients who did not have surgery due to disease progression in both arms but there were more R0 resections in the nivo+chemo arm (83.2% vs. 77.8%) for the overall population.

Adjuvant therapy was allowed per protocol. From the treated population (n=176 in each arm), 14.8% subjects from the nivo+chemo arm and 25% from the chemo arm received adjuvant systemic therapy. This is considered another source of heterogeneity in this study as this treatment could have an impact on the "time to event" endpoints, although it should reflect the current clinical practice in this setting. When comparing demographics and disease characteristics at study entry between patients who received adjuvant therapy and the overall randomized population, some slight imbalances were identified but they are not considered clinically relevant, even more when this is a small subgroup of patients. It is acknowledged that there are several studies and treatment developments in the neoadjuvant setting that include further adjuvant therapy.

Up to the DCO, 38 (21.2%) subjects in the nivo+chemo arm and 78 (43.6%) in the chemo arm received subsequent systemic therapy. The most commonly received therapy was chemotherapy (15.1% in the nivo+chemo arm and 22.3% of subjects in the chemo arm). A certain number of patients received subsequent immunotherapy (5.6% vs. 23.5%), and, as expected, higher number was observed in the chemo arm. It is noted that some patients received subsequent ALK/EGFR TKIs (4 and 9 subjects in the nivo+chemo and chemo arms, respectively), while known presence of these genetic alterations was an exclusion criterion, but testing was not mandatory at diagnosis or

enrolment. Further information about these patients was requested to confirm if a biopsy performed upon progression resulted in a positive EGFR or ALK tumour result. A region-specific amendment was implemented (Oct 2018) to include EGFR testing for non-squamous tumours at enrolment in China, Taiwan and Korea due to the higher prevalence of EGFR mutations in that area. However, some patients presenting mutations could have been randomized before this amendment or in other regions, as testing for these mutations it is not yet widely implemented in early-stage NSCLC. Also, some patients in the chemo arm received other subsequent targeted therapy such as capmatinib, entrectinib and regorafenib. In order to provide additional data on patients who received targeted therapy after the study treatment, the MAH performed a sensitivity analysis by excluding patients receiving anti-EGFR, anti-ALK TKIs and other TKIs indicated in oncogene-driven tumours. The result of this analysis, excluding 15 subjects, was consistent with the primary analysis of EFS. With longer follow-up, it is expected to have more information about the sequence of posterior therapies for NSCLC in these patients.

Within this procedure, for the **primary endpoints**, the final pCR per BIPR (DBL: 16-Sep-2020) analysis and the first IA of EFS per BICR (DBL: 20 Oct 2021) have been submitted, with a minimum follow-up of 21 months and median follow-up of 29.5 months.

Nivo+chemo demonstrated a statistically significant improvement in **pCR rate per BIPR** compared with chemo in concurrently randomized subjects who provided primary tumour samples: 24.0% (43/179; 95% CI: 18.0, 31.0) vs. 2.2% (4/179; 95% CI: 0.6, 5.6), which was not changed up to the later DBL. A sensitivity analysis of pCR per BIPR in all response evaluable subjects was consistent with the primary analysis. The subgroup analyses of pCR were also consistent with the primary.

In the first IA of **EFS by BICR**, nivo+chemo also showed a statistically significant improvement compared with chemo in concurrently randomized subjects: median EFS was 31.57 vs. 20.80 months; HR=0.63 (97.38% CI: 0.43, 0.91); stratified log-rank test p value=0.0052. There were 115/179 (64.2%) subjects in the nivo+chemo arm and 92/179 (51.4%) subjects in the chemo arm censored in this analysis. This IA, although performed at 82% (151 events) needed for the final EFS analysis (planned at 185 events), is considered to be a bit premature, with a high percentage of censored subjects. The sensitivity analysis of EFS by BICR not censoring at subsequent therapy (secondary definition, EMA preferred) showed consistent results with the primary analysis: HR=0.63; (97.38% CI: 0.44, 0.89), median EFS 31.57 (27.79, NA) months and 18.99 (14, 25.17) months for the nivo+chemo and chemo arm, respectively. Results from the subgroup analyses were generally consistent with the main analysis. An exploratory EFS analysis was performed based on a 14-Oct-2022 DBL (32.9 months minimum follow-up). It must be noted that only a few of new events were reported since IA1 (6 EFS events and 17 OS events) making the possibility of observing a different treatment effect very unlikely. Based on this later DBL, nivo+chemo continued to show an increased efficacy, in comparison with chemotherapy, in terms of EFS, with a median EFS not reached (95% CI: 31.57, NA) vs 21.06 months (95% CI: 14.75, 42.09) and a HR = 0.68 (95% CI: 0.49, 0.93).

For disease stage (by stratification subgroups), a clear benefit of nivo+chemo was shown for stage IIIA (7th edition) subjects: HR=0.54 (95% CI: 0.37, 0.80) while for stage IB/II the HR was 0.87 (95% CI: 0.48, 1.56), although this was a smaller subgroup. Indeed, concerns were raised about the low representation of patients with stage IB tumours (per the 7th AJCC TNM ed) as only 18 patients (10 and 8 subjects in the nivo+chemo and chemo treatment arm, respectively) were randomized. Whether homogeneity of response could be assumed for stage IB tumours, in whom based on the low numbers treatment efficacy could not be directly inferred, was discussed. According to current clinical guidelines, these patients are generally not candidates to neoadjuvant treatment, since a complete resection would be achieved for most of them if they proceeded directly to surgery. Treatment guidelines usually recommend to make the decision of treating these patients on an individual basis

and this is one of the reasons why the inclusion of these patients in trials in the NSCLC (neo)adjuvant setting has been controversial and may explain the low number of subjects with these early stage tumours enrolled in study CA209816. Exposing these patients to the added toxicity of nivolumab and potentially risking the success of a surgery which may prove curative for most of them, does not seem reasonable in the absence of confirmed benefit of the combination, so the inclusion of patients with stage IB tumours (7th edition TNM staging system) in the therapeutic indication was not considered justified.

In relation to tumour PD-L1 expression, the benefit of the combination of nivo+chemo for NSCLC neoadjuvant treatment is greater for subjects with a PD-L1 tumour expression ≥1%, in comparison with tumours presenting a PD-L1 expression <1%. When comparing main efficacy endpoints results between the subgroup of patients with a tumour PD-L1 expression ≥1% and <1%, all show better results for the PD-L1 ≥1% population, where differences between arms are bigger. The reported pCR rate for the nivo+chemo arm was 16.7% (95% CI: 9.2, 26.8) in the PD-L1 <1% subgroup and 32.6% (95% CI: 23.0, 43.3) in the PD-L1 ≥1% patients, while for the chemo arm, the pCR rate was of 2.6% and 2.2%, respectively. For EFS by BICR, a HR point estimate of 0.85 (95% CI: 0.54, 1.32) was obtained for the PD-L1 <1% population while the HR was 0.41 (95% CI: 0.24, 0.70) for the PD-L1 ≥1% subjects. Updated EFS subgroup analyses (DBL 14-Oct-2022) confirmed this trend: HR point estimate was 0.87 (95% CI: 0.57, 1.35) for the PD-L1 <1% subgroup and 0.46 (95% CI: 0.28, 0.77) for the PD-L1 ≥1% patients.

Regarding other EFS subgroup analyses, some differences were found but results were not conclusive.

As pointed out before, although the multiple protocol amendments and changes over study design seemed to be driven by external data, performing such changes during the conduct of the study could entail putting the study integrity at risk. A sensitivity analysis of EFS by randomization period was provided and results appeared consistent between all randomization periods.

Another source of heterogeneity, as mentioned, is the fact that different chemotherapy regimens were allowed, partly based on histology, in both arms. As an additional sensitivity analysis, EFS was evaluated comparing the nivo+chemo arm (n = 179) to subjects in the chemo arm (n=134) who received the chemo regimens available to both arms. The results were consistent with the primary analysis (adjusted HR=0.57; 95% CI: 0.41, 0.81), but this analysis, adjusted only by removing randomized patients, is of very limited value. Further, as adjuvant treatment was allowed per protocol, a sensitivity analysis of EFS adjusted by receiving systemic adjuvant chemo (as a time dependent covariate) was provided (adjusted HR=0.65; 95% CI: 0.47, 0.90).

In addition, both arms display early censorings and the reasons may differ between arms, also as a result of the open-label design. Some sensitivity analyses were performed, in line with a treatment-policy estimand (EMA/CHMP/27994/2008/Rev.1; Appendix 1 to the Guideline on the evaluation of anticancer medicinal products in man) and results were consistent with the main analyses.

Regarding secondary endpoints, **TTDM per BICR** was longer with nivo+chemo than chemo both for the primary analysis (median not reached vs. 26.71 months; HR=0.53; 95% CI: 0.36, 0.77) and the updated one (HR = 0.55 (95% CI 0.39, 0.78). Also, as reported in the interim CSR (DBL Sep-2020), **MPR rate per BIPR** was higher with nivo+chemo compared with chemo: 36.9% (95% CI: 29.8, 44.4) vs. 8.9% (95% CI: 5.2, 14.1). EFS2 was reported, as an exploratory endpoint, and the results also favoured the nivo+chemo arm although data were still immature at the time of the primary analysis. For the later DBL of 14-Oct-2022, a HR point estimate of 0.64 (95% CI: 0.45, 0.91) was observed and median EFS2 was not reached in either arm.

A **first IA of OS** (secondary endpoint) was planned at approximately 101 events but it was performed with 94 events (50.8% information fraction). A positive trend in OS was observed: HR=0.57 (99.67%

CI: 0.30, 1.07); stratified log-rank test p-value = 0.0079 (p <0.0033 needed for statistical significance) and median OS not reached in either arm. Although a high number of subjects were censored: 80.4% and 67.0% in the nivo+chemo and chemo arm, respectively, and data are indeed immature, the reported results appear promising. Some imbalances in the reported benefit are observed in the submitted subgroup analyses, for example for race or region but the low number of events in each subgroup prevents any conclusion. By PD-L1 tumour expression, the OS HR was 0.71 (95% CI; 0.40, 1.27) in the PD-L1 <1% and 0.39 (95% CI: 0.20, 0.77) in the PD-L1 ≥1% subgroup. According to disease stage, results appear consistent, with a HR of 0.60 (95% CI: 0.29, 1.23) and of 0.56 (95% CI: 0.33, 0.93) for stage IB/II and for stage IIIA, respectively, but, as said, immature with few events, high degree of censoring and wide CIs. Results from **OS IA2** (performed at 60.0% information fraction) also showed a positive trend although they did not reach statistical significance (p <0.0066 needed). HR point estimate was 0.62 (99.34% CI: 0.36, 1.05; 95% CI: 0.42, 0.90); stratified log-rank test p-value = 0.0124. Subgroup analyses were provided and they were consistent with the previous ones.

The Final OS analysis from study CA209816 should be provided by June 2025 (see an Annex II condition) as a post authorisation efficacy study (PAES) imposed in accordance with the Commission Delegated Regulation (EU) No 357/2014 to provide further data on the impact of nivolumab on OS in the intended indication.

Based on the available data, it is confirmed that the benefit of the nivo+chemo combination for NSCLC neoadjuvant treatment is greater for subjects with a PD-L1 tumour expression ≥1%, in comparison with tumours presenting a PD-L1 expression <1%. It is acknowledged that study CA209816 was only powered to show statistical significance of EFS and pCR between nivo+chemo and chemo in the overall population, with the study not adequately sized to draw definitive conclusions on specific subgroups. NSCLC neoadjuvant setting is an unexplored setting regarding the correlation between PD-L1 expression and the (long-term) efficacy of an anti-PD(L)1 product but there is no reason to believe it might be different from the adjuvant and advanced/metastatic settings. Even though decisions based on subgroup analyses can be controversial, the efficacy of the proposed combination in the ITT population is driven by the efficacy in patients with PD-L1 expression ≥1% and uncertainty remains regarding treatment benefit in patients with PD-L1 expression <1% that prevents granting an indication in a PD-L1 unselected patient population in this setting.

Wording of the indication

An indication wording referring to (high) risk of recurrence of patients with resectable NSCLC is considered more appropriate to guide prescribers in the proposed neoadjuvant NSCLC setting, in view of the complexity of issuing an indication statement based on staging considering the revisions of the AJJCC/UICC TNM system (i.e. change from 7th to 8th edition), and also in line with previous decisions made by CHMP for similar (combination) treatments in the (neo)-adjuvant NSCLC setting. A cross-reference to section 5.1 is included where specific selection criteria corresponding to the patient population included in the clinical trial and deriving benefit from the proposed neoadjuvant treatment are detailed. As homogeneity of response cannot be assumed across disease stages and very limited evidence is available in subjects with disease stage IB, hampering any sound decision with regards to benefit of the proposed combination, these patients were excluded from the indication. In addition, as discussed, a broad indication regardless of PD-L1 expression is not justified. For these reasons, the finally granted indication for the proposed combination is restricted to subjects with disease stage II-IIIA and PD-L1 tumour cell expression ≥1%.

Participants with 'known' EGFR mutations or ALK translocation were excluded from the study per protocol. However, information on EGFR or ALK testing was not centrally collected and, therefore, the actual number of patients with a negative result for tested EGFR mutations or ALK rearrangements and

the number of subjects who were never tested is unknown. Overall data on the response of oncogene-addicted tumours to PD1/PD-L1 targeting agents are limited, and the extent to which drivers like EGFR or ALK impact response is not well characterised. Although testing for certain oncogene biomarkers is considered standard-of-care in the advanced NSCLC setting, it is presently not routine clinical practice to test patients with early-stage operable disease for these biomarkers (e.g. 2021 ESMO early-stage NSCLC guidelines eUpdate; Lovely et al. N Engl J Med. 2022). Consequently, there has not been a consensus regarding mandatory testing for these and other oncogene drivers before recruitment in trials in this early-stage setting, and, in many cases, patients have been included regardless their tumour's mutational status.

In study CA209816 the treatment effect cannot be explored/isolated in patients harbouring these mutations, as the number of subjects with oncogene-addicted tumours enrolled is not known. Considering all the above, and despite uncertainty regarding the treatment effect in patients with these actionable mutations (as well as others for which no specific exclusion criteria were part of the protocol), it is considered a reasonable approach not to exclude them from the therapeutic indication (section 4.1 of the SmPC), but rather to reflect the relevant inclusion/exclusion criteria in section 5.1, in the absence of dedicated studies.

2.4.4. Conclusions on the clinical efficacy

The results from a pre-planned interim analysis of study CA209816 showed a statistically significant improvement in both pCR and EFS primary endpoints for nivo+chemo compared to chemotherapy as neoadjuvant treatment of NSCLC. Updated efficacy results, with longer follow-up, confirmed the previously obtained results. A positive trend in OS has also been observed, in the two interim analyses conducted, which is considered encouraging albeit results are still immature. Updated OS data are expected post approval (Annex II). A highly heterogeneous population was enrolled in this (small) study, including patients with stage IB/II tumours with a better disease prognosis and who according to current clinical guidelines are generally not candidates to neoadjuvant treatment. This is a limitation of the trial. The reported benefit appears higher in patients with stage IIIA disease, while the stage IB population is so poorly represented that efficacy cannot be inferred from the results of this study. In addition, an EFS benefit is not established in the subgroup of patients with PD-L1 expression <1%, since the positive results for EFS, OS and the other relevant endpoints reported with the combination appear to be mainly driven by the subgroup of patients with PD-L1 tumour expression ≥1%, questioning whether the proposed neoadjuvant treatment with nivolumab will lead to long term benefit in the PD-L1 <1% population.
Based on all these observations, the finally granted indication for the proposed combination is restricted to subjects with disease stage II-IIIA and PD-L1 tumour cell expression ≥1%.

The following measures are considered necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES): In order to further characterize the efficacy of nivolumab as neoadjuvant treatment of adults with non-small cell lung cancer, the MAH should submit the OS data from the final OS analysis of the Phase 3 study CA209816.

2.5. Clinical safety

Introduction

Safety assessment is based on safety data from all 352 treated subjects receiving at least one dose of

study drug who were concurrently randomized to nivo+chemo (N = 176; Arm C) and chemo (N = 176; Arm B) in the pivotal study, CA209816.

These data are from the 20-Oct-2021 database lock (DBL) for the CA209816 Primary CSR. Safety data from the nivo+ipi arm (Arm A) do not support the proposed indication and therefore is not included in this safety assessment.

Patient exposure

Table 47: **Key Dates and Follow-up - Study CA209816**

Last subject randomized date for concurrent Arms C (nivo+chemo) and B (chemo)	11-Dec-2019
Clinical cutoff date (LPLV)	08-Sep-2021
DBL	20-Oct-2021
Minimum follow-up,[a] months	
Concurrently randomized Arms B (chemo) and C (nivo+chemo)	21.0
Median follow-up,[b] months	
Concurrently randomized Arms B (chemo) and C (nivo+chemo)	29.5

[a] Minimum follow-up: time from last subject's randomization to clinical cutoff date (08-Sep-2021) for DBL.

[b] Median follow-up: median time between randomization date and clinical cutoff date (08-Sep-2021) for DBL for each individual subject.

Abbreviations: chemo - chemotherapy, DBL - database lock; LPLV - last patient last visit, nivo - nivolumab

Table 48: Subject Disposition - All Randomized and Treated Subjects – Concurrently Randomized to Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

Status (%)	Arm C: Nivo + Chemo	Arm B: Chemo (Concurrent)
RANDOMIZED	179	179
TREATED[a]	176 (98.3)	176 (98.3)
NOT TREATED[a]	3 (1.7)	3 (1.7)
REASON FOR NOT TREATED		
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.6)	0
SUBJECT WITHDREW CONSENT	0	2 (1.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (1.1)	1 (0.6)

Status (%)[b]	Arm C: Nivo + Chemo N = 176	Arm B: Chemo (Concurrent) N = 176
CONTINUING IN THE NEOADJUVANT TREATMENT PERIOD	0	0
NOT CONTINUING IN THE NEOADJUVANT TREATMENT PERIOD	176 (100.0)	176 (100.0)
REASON FOR NOT CONTINUING IN THE NEOADJUVANT TREATMENT PERIOD		
COMPLETED NEOADJUVANT TREATMENT	165 (93.8)	149 (84.7)
DISEASE PROGRESSION	1 (0.6)	2 (1.1)
STUDY DRUG TOXICITY	10 (5.7)	12 (6.8)
DEATH	0	0
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	3 (1.7)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	5 (2.8)
SUBJECT WITHDREW CONSENT	0	4 (2.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.6)
DISCONTINUED NEOADJUVANT TREATMENT DUE TO COVID-19[b]	0	0

[a] Percentages based on subjects randomized

[b] Percentages based on subjects entering period
Source: Refer to Table 5.1-1 and Table 5.1-2 of the CA209816 Primary CSR

Table 49: **Cumulative Dose and Relative Dose Intensity in the Neoadjuvant Period - All Treated Subjects in the Concurrently Randomized Nivo + Chemo Arm (Arm C) - Study CA209816**

	Nivo + Chemo (N = 176)		
	Nivolumab (N = 176)	Carboplatin (N = 51)	Cisplatin (N = 136)
NUMBER OF DOSES RECEIVED			
1	4 (2.3)	4 (7.8)	10 (7.4)
2	8 (4.5)	11 (21.6)	11 (8.1)
3	164 (93.2)	36 (70.6)	115 (84.6)
CUMULATIVE DOSE (UNIT) (1)			
MEAN (SD)	1047.273 (129.215)	12.936 (3.499)	203.283 (42.625)
MEDIAN (MIN - MAX)	1080.000 (360.00-1080.00)	14.166 (4.68-18.36)	223.404 (74.47-231.51)
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	3 (5.9)	0
90% TO < 110%	154 (87.5)	28 (54.9)	99 (72.8)
70% TO < 90%	19 (10.8)	18 (35.3)	33 (24.3)
50% TO < 70%	3 (1.7)	1 (2.0)	4 (2.9)
< 50%	0	0	0
NOT REPORTED	0	1 (2.0)	0
	Gemcitabine (N = 65)	Paclitaxel (N = 28)	Pemetrexed (N = 83)
NUMBER OF DOSES RECEIVED			
1	0	2 (7.1)	0
2	1 (1.5)	2 (7.1)	6 (7.2)
3	2 (3.1)	24 (85.7)	77 (92.8)
4	4 (6.2)	0	0
5	11 (16.9)	0	0
> 5	47 (72.3)	0	0
CUMULATIVE DOSE (UNIT) (1)			
MEAN (SD)	5731.083 (1096.287)	460.428 (122.828)	1459.145 (132.539)
MEDIAN (MIN - MAX)	5986.772 (2457.70-7636.31)	518.875 (11.65-558.86)	1500.000 (964.47-1591.65)
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	0	0
90% TO < 110%	30 (46.2)	17 (60.7)	71 (85.5)
70% TO < 90%	28 (43.1)	9 (32.1)	12 (14.5)
50% TO < 70%	5 (7.7)	1 (3.6)	0
< 50%	2 (3.1)	1 (3.6)	0
NOT REPORTED	0	0	0

(1) Dose units: Nivolumab in mg (Arm C); Vinorelbine, Cisplatin, Docetaxel, Gemcitabine, Pemetrexed, and Paclitaxel, in mg/ m^2, Carboplatin in AUC.

Source: Refer to Table 6.1-1 of the CA209816 Primary CSR

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

Dose delays (all agents) and dose reductions (chemo-agents only) were observed across treatment arms for treated subjects concurrently randomized to the nivo+chemo and chemo arms. Infusions interruptions or infusion rate reductions were infrequent. There was a higher proportion of dose omissions with gemcitabine and vinorelbine, which are administered twice per cycle.

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

- Nivo+chemo: 25.0% for nivolumab, 13.7% for carboplatin, 22.8% for cisplatin, 42.4% for gemcitabine, 17.9% for paclitaxel, and 18.1% for pemetrexed
- Chemo: 16.7% for carboplatin, 30.8% for cisplatin, 20.7% for docetaxel, 44.9% for gemcitabine, 9.1% for paclitaxel, 30.2% for pemetrexed, and 71.4% for vinorelbine

In both the concurrently randomized nivo+chemo and chemo arms, the most common cause of dose delay for nivolumab and chemotherapy was AE, and the most frequent AEs leading to dose delay tended to be known toxicities of chemotherapy.

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

- Nivo+chemo: 21.6% for carboplatin, 10.3% for cisplatin, 18.2% for gemcitabine, 14.3% for

paclitaxel, and 1.2% for pemetrexed
- Chemo: 31.0% for carboplatin, 11.9% for cisplatin, 17.2% for docetaxel, 16.3% for gemcitabine, 31.8% for paclitaxel, 4.8% for pemetrexed, and 7.1% for vinorelbine

Among all treated subjects in concurrently randomized nivo+chemo and chemo arms, the most frequently reported drug-related AEs of any grade leading to dose delay or reduction were as follows:

- Nivo+chemo: neutrophil count decreased (9.1%), neutropenia (6.8%), anemia (4.5%)
- Chemo: neutrophil count decreased (12.5%), neutropenia (8.5%), anemia (4.5%)

Infusion interruptions:

- Nivo+chemo: 2.8% for nivolumab, 0% for carboplatin, 0.7% for cisplatin, 1.5% for gemcitabine, 14.3% for paclitaxel, and 0% for pemetrexed
- Chemo: 2.4% for carboplatin, 0.7% for cisplatin, 3.4% for docetaxel, 2.0% for gemcitabine, 18.2% for paclitaxel, 0% for pemetrexed, and 0% for vinorelbine

Infusion rate reductions were reported as follows:

- Nivo+chemo: 1.7% for nivolumab, 3.0% for gemcitabine, 1.5% for cisplatin, and 0% for carboplatin, paclitaxel, and pemetrexed
- Chemo: 1.4% for cisplatin, 4.1% for gemcitabine, 7.1% for vinorelbine, and 0% for carboplatin, docetaxel, paclitaxel, and pemetrexed

Dose omissions of study drug (proportion of subjects with at least 1 dose omission):

- Nivo+chemo: 2.8% for nivolumab, 2.0% for carboplatin, 3.7% for cisplatin, 27.3% for gemcitabine, 3.6% for paclitaxel, and 2.4% for pemetrexed
- Chemo: 2.4% for carboplatin, 4.2% for cisplatin, 0% for docetaxel, 16.3% for gemcitabine, 0% for paclitaxel, 4.8% for pemetrexed, and 50.0% for vinorelbine

Adverse events

The data presented are from the 20-Oct-2021 database lock (DBL) for the CA209816 Primary CSR. During the procedure, the MAH submitted Addendum 01 to the CA209816 Primary CSR (14-Oct-2022 IA2 database lock) containing updated safety data.

The safety percentages presented throughout the report and in the discussion refer to the safety data from the 20-Oct-2021 DBL as no relevant changes have been identified with the updated data.

Table 50: CA209816 Summary of Safety - All Treated Subjects in Concurrently Randomized Nivo + Chemo (Arm C) and Chemo (Arm B) Arms

	Number of Subjects (%)			
	Primary CSR (20-Oct-2021 Database Lock)		Addendum 01 (14-Oct-2022 Database Lock)	
	Nivo+Chemo (Arm C) N = 176	Chemo (Arm B) N = 176	Nivo+Chemo (Arm C) N = 176	Chemo (Arm B) N = 176
Deaths	35 (19.9)	59 (33.5)	44 (25.0)	66 (37.5)
Primary Reason for Death				
Disease	24 (13.6)	45 (25.6)	29 (16.5)	53 (30.1)
Study Drug Toxicity [a]	0	3 (1.7)	0	3 (1.7)
Unknown	2 (1.1)	5 (2.8)	5 (2.8)	3 (1.7)
Other [b]	9 (5.1)	6 (3.4)	10 (5.7)	7 (4.0)

	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
≥ 1% of Subjects in Any Arm, by PT								
Febrile neutropenia	2 (1.1)	2 (1.1)	5 (2.8)	5 (2.8)	2 (1.1)	2 (1.1)	5 (2.8)	5 (2.8)
Vomiting	4 (2.3)	2 (1.1)	0	0	4 (2.3)	2 (1.1)	0	0
Pneumonia	4 (2.3)	1 (0.6)	3 (1.7)	2 (1.1)	4 (2.3)	1 (0.6)	3 (1.7)	2 (1.1)
Embolism	2 (1.1)	1 (0.6)	0	0	2 (1.1)	1 (0.6)	0	0
Neutropenia	0	0	2 (1.1)	2 (1.1)	0	0	2 (1.1)	2 (1.1)
Diarrhea	0	0	2 (1.1)	2 (1.1)	0	0	2 (1.1)	2 (1.1)
Drug-related SAEs	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
≥ 1% of Subjects in Any Arm, by PT								
Febrile neutropenia	2 (1.1)	2 (1.1)	5 (2.8)	5 (2.8)	2 (1.1)	2 (1.1)	5 (2.8)	5 (2.8)
Vomiting	4 (2.3)	2 (1.1)	0	0	4 (2.3)	2 (1.1)	0	0
Pneumonia	0	0	2 (1.1)	1 (0.6)	0	0	2 (1.1)	1 (0.6)
Neutropenia	0	0	2 (1.1)	2 (1.1)	0	0	2 (1.1)	2 (1.1)
Diarrhea	0	0	2 (1.1)	2 (1.1)	0	0	2 (1.1)	2 (1.1)
All-causality AEs leading to DC	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
≥ 1% of Subjects in Any Arm, by PT								
Neutropenia	1 (0.6)	0	4 (2.3)	3 (1.7)	1 (0.6)	0	4 (2.3)	3 (1.7)
Anaphylactic reaction	3 (1.7)	3 (1.7)	0	0	3 (1.7)	3 (1.7)	0	0
Neutrophil count decreased	2 (1.1)	2 (1.1)	2 (1.1)	0	2 (1.1)	2 (1.1)	2 (1.1)	0
Blood creatinine increased	1 (0.6)	0	2 (1.1)	0	1 (0.6)	0	2 (1.1)	0
Fatigue	2 (1.1)	1 (0.6)	0	0	2 (1.1)	1 (0.6)	0	0
Pneumonia	0	0	2 (1.1)	1 (0.6)	0	0	2 (1.1)	1 (0.6)
Drug-Related AEs leading to DC	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
≥ 1% of Subjects in Any Arm, by PT								
Neutropenia	1 (0.6)	0	4 (2.3)	3 (1.7)	1 (0.6)	0	4 (2.3)	3 (1.7)
Anaphylactic reaction	3 (1.7)	3 (1.7)	0	0	3 (1.7)	3 (1.7)	0	0
Neutrophil count decreased	2 (1.1)	2 (1.1)	2 (1.1)	0	2 (1.1)	2 (1.1)	2 (1.1)	0
Blood creatinine increased	1 (0.6)	0	2 (1.1)	0	1 (0.6)	0	2 (1.1)	0
Fatigue	2 (1.1)	1 (0.6)	0	0	2 (1.1)	1 (0.6)	0	0
All-causality AEs	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)	165 (93.8)	76 (43.2)	173 (98.3)	79 (44.9)
≥ 20% of Subjects in Any Arm, by PT								
Nausea	67 (38.1)	1 (0.6)	79 (44.9)	2 (1.1)	67 (38.1)	1 (0.6)	80 (45.5)	2 (1.1)
Constipation	59 (33.5)	0	57 (32.4)	2 (1.1)	59 (33.5)	0	57 (32.4)	2 (1.1)
Anemia	51 (29.0)	7 (4.0)	47 (26.7)	9 (5.1)	51 (29.0)	7 (4.0)	49 (27.8)	9 (5.1)
Decreased appetite	36 (20.5)	2 (1.1)	41 (23.3)	4 (2.3)	37 (21.0)	2 (1.1)	41 (23.3)	4 (2.3)
Neutrophil count decreased	26 (14.8)	13 (7.4)	37 (21.0)	19 (10.8)	26 (14.8)	13 (7.4)	38 (21.6)	19 (10.8)

	Number of Subjects (%)							
	Primary CSR (20-Oct-2021 Database Lock)				Addendum 01 (14-Oct-2022 Database Lock)			
	Nivo+Chemo (Arm C) N = 176		Chemo (Arm B) N = 176		Nivo+Chemo (Arm C) N = 176		Chemo (Arm B) N = 176	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Drug-related AEs	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)	147 (83.5)	63 (35.8)	159 (90.3)	67 (38.1)
≥ 15% of Subjects in Any Arm, by PT								
Nausea	58 (33.0)	1 (0.6)	73 (41.5)	1 (0.6)	58 (33.0)	1 (0.6)	74 (42.0)	1 (0.6)
Anaemia	42 (23.9)	5 (2.8)	40 (22.7)	6 (3.4)	41 (23.3)	5 (2.8)	42 (23.9)	6 (3.4)
Constipation	37 (21.0)	0	36 (20.5)	2 (1.1)	37 (21.0)	0	36 (20.5)	2 (1.1)
Decreased appetite	29 (16.5)	2 (1.1)	38 (21.6)	4 (2.3)	30 (17.0)	2 (1.1)	38 (21.6)	4 (2.3)
Neutropenia	28 (15.9)	15 (8.5)	29 (16.5)	21 (11.9)	30 (17.0)	19 (10.8)	30 (17.0)	23 (13.1)
Neutrophil count decreased	26 (14.8)	13 (7.4)	37 (21.0)	19 (10.8)	26 (14.8)	13 (7.4)	38 (21.6)	19 (10.8)
All-causality Select AEs, by Category								
Endocrine	11 (6.3)	0	0	0	11 (6.3)	0	0	0
Gastrointestinal	16 (9.1)	1 (0.6)	25 (14.2)	4 (2.3)	16 (9.1)	1 (0.6)	25 (14.2)	4 (2.3)
Hepatic	15 (8.5)	1 (0.6)	22 (12.5)	4 (2.3)	16 (9.1)	2 (1.1)	23 (13.1)	4 (2.3)
Pulmonary	2 (1.1)	0	0	0	2 (1.1)	0	0	0
Renal	16 (9.1)	1 (0.6)	21 (11.9)	0	17 (9.7)	1 (0.6)	21 (11.9)	0
Skin	43 (24.4)	4 (2.3)	20 (11.4)	1 (0.6)	43 (24.4)	4 (2.3)	20 (11.4)	1 (0.6)
Hypersensitivity/Infusion Reactions	12 (6.8)	4 (2.3)	6 (3.4)	2 (1.1)	12 (6.8)	4 (2.3)	6 (3.4)	2 (1.1)
Drug-related Select AEs, by Category								
Endocrine	10 (5.7)	0	0	0	10 (5.7)	0	0	0
Gastrointestinal	10 (5.7)	1 (0.6)	21 (11.9)	4 (2.3)	10 (5.7)	1 (0.6)	21 (11.9)	4 (2.3)
Hepatic	13 (7.4)	0	19 (10.8)	4 (2.3)	14 (8.0)	1 (0.6)	20 (11.4)	4 (2.3)
Pulmonary	2 (1.1)	0	0	0	2 (1.1)	0	0	0
Renal	13 (7.4)	1 (0.6)	18 (10.2)	0	13 (7.4)	1 (0.6)	18 (10.2)	0
All-causality IMAEs within 100 Days of Last Dose, by Category								
Treated with IMM								
Diarrhea/Colitis	0	0	0	0	0	0	0	0
Hepatitis	0	0	0	0	0	0	0	0
Pneumonitis	2 (1.1)	0	1 (0.6)	1 (0.6)	2 (1.1)	0	1 (0.6)	1 (0.6)
Nephritis/Renal Dysfunction	0	0	0	0	0	0	0	0
Rash	15 (8.5)	3 (1.7)	1 (0.6)	0	15 (8.5)	3 (1.7)	1 (0.6)	0
Hypersensitivity/Infusion Reactions	2 (1.1)	0	0	0	1 (0.6)	0	0	0
All-causality Endocrine IMAEs within 100 Days of Last Dose, by Category								
Treated With or Without IMM								
Adrenal Insufficiency	2 (1.1)	2 (1.1)	0	0	2 (1.1)	2 (1.1)	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0	0
Hypothyroidism/Thyroiditis	4 (2.3)	0	0	0	5 (2.8)	0	1 (0.6)	0
Hyperthyroidism	7 (4.0)	0	0	0	7 (4.0)	0	0	0
Diabetes Mellitus	2 (1.1)	0	0	0	2 (1.1)	0	0	0

[a] The causes of death per investigator in the **chemotherapy arm** were as follows: pancytopenia, diarrhoea, and acute kidney injury (all 3 reported in one subject), enterocolitis infection, and lung infection/pneumonia.

[b] The verbatim terms reported for the "other" reasons for death in the chemo arm were as follows: COVID-19 and acute hypoxemic respiratory failure, pneumonia, hemoptysis, radiation pneumonitis, cough up phlegm suffocation, natural death, and disease progression. The verbatim terms reported for the "other" reasons for death in the nivo+chemo arm were as follows: chronic congestive heart failure, lung cancer, non-obstructive artery disease (all 3 reported in 1 subject), intraoperative hemorrhage, respiratory failure, esophageal perforation, pneumonia (3 subjects), cardiopulmonary arrest due to pulmonary embolism, surgical complication and aortic rupture (in 1 subject), and respiratory bleeding.

MedDRA version 24.0 for Primary CSR and 25.0 for Addendum 01; CTCAE version 4.0.

All events are within 30 days of the last dose of neoadjuvant study therapy, unless otherwise indicated. Subjects may have received adjuvant therapy during the 100 day follow-up.

AEs/SAEs Identified as Surgical Complications:

Among all treated concurrently randomized subjects with definitive surgery,

- The frequencies of AEs identified as surgical complications by the investigator were similar between the nivo+chemo and chemo arms (41.6% vs 46.7%), with the exception of pain, which was lower

with nivo+chemo than chemo (7.4% vs 15.6%).

- The frequencies of SAEs identified as surgical complications by the investigator were similar between the nivo+chemo and chemo arms (11.4% vs 10.4%).

Table 51: AEs Identified as Surgical Complications - All Treated Subjects with Definitive Surgery in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

	No. of Subjects (%)			
	Nivo + Chemo (Arm C) N = 149		Chemo (Arm B) N = 135	
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality AEs identified as surgical complications	62 (41.6)	17 (11.4)	63 (46.7)	20 (14.8)
≥ 5% of subjects in any treatment arm, by PT				
Anaemia	18 (12.1)	3 (2.0)	17 (12.6)	3 (2.2)
Pain	11 (7.4)	1 (0.7)	21 (15.6)	0
Wound Complication	11 (7.4)	1 (0.7)	8 (5.9)	0
Procedural Pain	9 (6.0)	0	6 (4.4)	0
Pneumonia	8 (5.4)	3 (2.0)	8 (5.9)	4 (3.0)
All-causality SAEs identified as surgical complications	17 (11.4)	11 (7.4)	14 (10.4)	11 (8.1)
≥ 1% of subjects in any treatment arm, by PT				
Pneumonia	2 (1.3)	2 (1.3)	4 (3.0)	3 (2.2)
Pulmonary Embolism	2 (1.3)	1 (0.7)	0	0
Post-procedural Complication	2 (1.3)	1 (0.7)	0	0
Pulmonary Fistula	1 (0.7)	0	2 (1.5)	2 (1.5)
Wound infection	0	0	2 (1.5)	2 (1.5)

Two surgical complications were Grade 5 AEs/SAEs (AEs that led to death within 24 hours) in the nivo+chemo arm (pulmonary embolism and aortic rupture); these AEs/SAEs were not related to study drug per the investigator (Appendix 6.1.4). The causes of death for these subjects were categorized as "other reasons".

MedDRA version 24.0; CTCAE version 4.0. Surgical complications are within 90 days of surgery.

Common adverse events

Adverse Events (Regardless of Causality)

Any-grade AEs (all-causality) were reported in 163 (92.6%) and 171 (97.2%) treated subjects who were concurrently randomized in the nivo+chemo and chemo arms, respectively.

The most frequently reported AEs (all-causality) were as follows:

- Nivo+chemo: nausea (38.1%), constipation (33.5%), anemia (29.0%), decreased appetite (20.5%), fatigue and neutropenia (16.5% each)
- Chemo: nausea (44.9%), constipation (32.4%), anemia (26.7%), decreased appetite (23.3%), and neutrophil count decreased (21.0%)

Grade 3-4 AEs (all-causality) were reported in 72 (40.9%) and 77 (43.8%) subjects in the concurrently randomized nivo+chemo and chemo arms, respectively.
The most frequently reported Grade 3-4 AEs (all-causality) were as follows:

- Nivo+chemo: neutropenia (9.1%), neutrophil count decreased (7.4%), anemia (4.0%), platelet count decreased (2.3%), and white blood cell count decreased (1.7%)
- Chemo: neutropenia (11.9%), neutrophil count decreased (10.8%), anemia (5.1%), white blood cell count decreased (3.4%), decreased appetite and diarrhea (2.3% each)

Drug-Related Adverse Events

Any-grade drug-related AEs were reported in 145 (82.4%) and 156 (88.6%) subjects in the concurrently randomized nivo+chemo and chemo arms, respectively.

The most frequently reported drug-related AEs were:

- Nivo+chemo: nausea (33.0%), anemia (23.9%), constipation (21.0%), decreased appetite (16.5%), and neutropenia (15.9%)
- Chemo: nausea (41.5%), anemia (22.7%), decreased appetite (21.6%), neutrophil count decreased (21.0%), constipation (20.5%), and neutropenia (16.5%)

Grade 3-4 drug-related AEs were reported in 59 (33.5%) and 65 (36.9%) subjects in the concurrently randomized nivo+chemo and chemo arms, respectively.

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

- Nivo+chemo: neutropenia (8.5%), neutrophil count decreased (7.4%), and anemia (2.8%)
- Chemo: neutropenia (11.9%), neutrophil count decreased (10.8%), anemia, febrile neutropenia (3.4% each), and white blood cell count decreased (2.8%)

Table 52: Adverse Events by Worst CTC Grade Reported in ≥ 10% of All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

System Organ Class (%) / Preferred Term (%)	Arm A: Nivo + Ipi N = 111			Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	97 (87.4)	22 (19.8)	1 (0.9)	163 (92.6)	72 (40.9)	0	171 (97.2)	77 (43.8)	0
GI disorders	32 (28.8)	3 (2.7)	0	102 (58.0)	4 (2.3)	0	124 (70.5)	9 (5.1)	0
Nausea	12 (10.8)	0	0	67 (38.1)	1 (0.6)	0	79 (44.9)	2 (1.1)	0
Constipation	10 (9.0)	0	0	59 (33.5)	0	0	57 (32.4)	2 (1.1)	0
Vomiting	4 (3.6)	1 (0.9)	0	19 (10.8)	2 (1.1)	0	22 (12.5)	1 (0.6)	0
Diarrhoea	15 (13.5)	3 (2.7)	0	16 (9.1)	1 (0.6)	0	24 (13.6)	4 (2.3)	0
General disorders and administration site conditions	47 (42.3)	0	1 (0.9)	85 (48.3)	5 (2.8)	0	78 (44.3)	4 (2.3)	0
Fatigue	19 (17.1)	0	0	29 (16.5)	2 (1.1)	0	22 (12.5)	1 (0.6)	0
Malaise	2 (1.8)	0	0	26 (14.8)	1 (0.6)	0	25 (14.2)	1 (0.6)	0
Asthenia	7 (6.3)	0	0	16 (9.1)	2 (1.1)	0	19 (10.8)	1 (0.6)	0
Pyrexia	14 (12.6)	0	0	12 (6.8)	0	0	14 (8.0)	0	0
Blood and lymphatic system disorders	4 (3.6)	0	0	76 (43.2)	26 (14.8)	0	74 (42.0)	36 (20.5)	0
Anaemia	4 (3.6)	0	0	51 (29.0)	7 (4.0)	0	47 (26.7)	9 (5.1)	0
Neutropenia	0	0	0	29 (16.5)	16 (9.1)	0	31 (17.6)	21 (11.9)	0
Investigations	17 (15.3)	5 (4.5)	0	66 (37.5)	22 (12.5)	0	77 (43.8)	25 (14.2)	0
Neutrophil count decreased	0	0	0	26 (14.8)	13 (7.4)	0	37 (21.0)	19 (10.8)	0
WBC count decreased	0	0	0	13 (7.4)	3 (1.7)	0	19 (10.8)	6 (3.4)	0
Metabolism and nutrition disorders	15 (13.5)	2 (1.8)	0	63 (35.8)	9 (5.1)	0	64 (36.4)	10 (5.7)	0
Decreased appetite	7 (6.3)	1 (0.9)	0	36 (20.5)	2 (1.1)	0	41 (23.3)	4 (2.3)	0
Skin and subcutaneous tissue disorders	49 (44.1)	3 (2.7)	0	58 (33.0)	4 (2.3)	0	47 (26.7)	1 (0.6)	0
Rash	16 (14.4)	0	0	24 (13.6)	1 (0.6)	0	5 (2.8)	0	0
Alopecia	1 (0.9)	0	0	19 (10.8)	0	0	26 (14.8)	0	0
Pruritus	16 (14.4)	0	0	9 (5.1)	0	0	4 (2.3)	0	0
Respiratory, thoracic and mediastinal disorders	33 (29.7)	4 (3.6)	0	54 (30.7)	1 (0.6)	0	51 (29.0)	2 (1.1)	0
Hiccups	1 (0.9)	0	0	18 (10.2)	0	0	26 (14.8)	0	0

MedDRA Version: 24.0; CTC Version: 4.0; Includes events reported between first dose and 30 days after last dose of neoadjuvant study therapy.

Table 53: Drug-Related AEs by Worst CTC Grade Reported in ≥ 10% of All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

System Organ Class (%)	Arm A: Nivo + Ipi N = 111	Arm C: Nivo + Chemo N = 176	Arm B: Chemo (Concurrent) N = 176

Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	72 (64.9)	15 (13.5)	0	145 (82.4)	59 (33.5)	0	156 (88.6)	65 (36.9)	0
Gastrointestinal disorders	15 (13.5)	3 (2.7)	0	80 (45.5)	4 (2.3)	0	103 (58.5)	7 (4.0)	0
Nausea	7 (6.3)	0	0	58 (33.0)	1 (0.6)	0	73 (41.5)	1 (0.6)	0
Constipation	0	0	0	37 (21.0)	0	0	36 (20.5)	2 (1.1)	0
Vomiting	2 (1.8)	1 (0.9)	0	15 (8.5)	2 (1.1)	0	19 (10.8)	1 (0.6)	0
Diarrhoea	8 (7.2)	3 (2.7)	0	10 (5.7)	1 (0.6)	0	20 (11.4)	4 (2.3)	0
Blood and lymphatic system disorders	2 (1.8)	0	0	68 (38.6)	24 (13.6)	0	66 (37.5)	34 (19.3)	0
Anaemia	2 (1.8)	0	0	42 (23.9)	5 (2.8)	0	40 (22.7)	6 (3.4)	0
Neutropenia	0	0	0	28 (15.9)	15 (8.5)	0	29 (16.5)	21 (11.9)	0
General disorders and administration site conditions	34 (30.6)	0	0	67 (38.1)	4 (2.3)	0	61 (34.7)	3 (1.7)	0
Malaise	2 (1.8)	0	0	24 (13.6)	1 (0.6)	0	22 (12.5)	1 (0.6)	0
Fatigue	15 (13.5)	0	0	22 (12.5)	1 (0.6)	0	15 (8.5)	0	0
Investigations	12 (10.8)	4 (3.6)	0	54 (30.7)	16 (9.1)	0	65 (36.9)	23 (13.1)	0
Neutrophil count decreased	0	0	0	26 (14.8)	13 (7.4)	0	37 (21.0)	19 (10.8)	0
Skin and subcutaneous tissue disorders	39 (35.1)	3 (2.7)	0	52 (29.5)	4 (2.3)	0	37 (21.0)	0	0
Rash	14 (12.6)	0	0	23 (13.1)	1 (0.6)	0	5 (2.8)	0	0
Alopecia	0	0	0	17 (9.7)	0	0	25 (14.2)	0	0
Metabolism and nutrition disorders	6 (5.4)	0	0	45 (25.6)	8 (4.5)	0	51 (29.0)	7 (4.0)	0
Decreased appetite	4 (3.6)	0	0	29 (16.5)	2 (1.1)	0	38 (21.6)	4 (2.3)	0
Respiratory, thoracic and mediastinal disorders	9 (8.1)	3 (2.7)	0	22 (12.5)	0	0	34 (19.3)	0	0
Hiccups	0	0	0	12 (6.8)	0	0	24 (13.6)	0	0

MedDRA Version: 24.0; CTC Version: 4.0

Includes events reported between first dose and 30 days after last dose of neoadjuvant study therapy.

Serious adverse event/deaths/other significant events

Serious adverse events

Among treated subjects concurrently randomized to the nivo+chemo and chemo arms, the types and frequencies of all-causality and drug-related SAEs were similar between the nivo+chemo and chemo arms.

Any-grade SAEs (regardless of causality) were reported in 30 (17.0%) and 24 (13.6%) subjects in the concurrently randomized nivo+chemo and chemo arms, respectively. Grade 3-4 SAEs were reported in 19 (10.8%) subjects in the nivo+chemo arm and 17 (9.7%) subjects in the chemo arm. The most commonly reported any-grade SAEs (all-causality) were:

- Nivo+chemo: vomiting and pneumonia (2.3% each), embolism and febrile neutropenia (1.1% each)
- Chemo: febrile neutropenia (2.8%), pneumonia (1.7%), neutropenia and diarrhea (1.1% each)

Any-grade drug-related SAEs were reported in 21 (11.9%) and 18 (10.2%) subjects in the concurrently randomized nivo+chemo and chemo arms, respectively. Grade 3-4 drug-related SAEs were reported in 15 (8.5%) subjects in the nivo+chemo arm and 14 (8.0%) subjects in the chemo arm. The most commonly reported any-grade drug-related SAEs were:

- Nivo+chemo: vomiting (2.3%) and febrile neutropenia (1.1%)
- Chemo: febrile neutropenia (2.8%), and pneumonia, neutropenia, and diarrhea (1.1% each)

Table 54: Serious Adverse Events by Worst CTC Grade Reported in ≥1% of All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

System Organ Class (%) / Preferred Term (%)	Arm A: Nivo + Ipi N = 111			Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	15 (13.5)	11 (9.9)	1 (0.9)	30 (17.0)	19 (10.8)	0	24 (13.6)	17 (9.7)	0
Infections and infestations	3 (2.7)	2 (1.8)	0	7 (4.0)	3 (1.7)	0	8 (4.5)	5 (2.8)	0
Pneumonia	2 (1.8)	1 (0.9)	0	4 (2.3)	1 (0.6)	0	3 (1.7)	2 (1.1)	0
Vascular disorders	0	0	0	6 (3.4)	4 (2.3)	0	2 (1.1)	0	0
Embolism	0	0	0	2 (1.1)	1 (0.6)	0	0	0	0
Blood and lymphatic system disorders	0	0	0	5 (2.8)	4 (2.3)	0	9 (5.1)	9 (5.1)	0
Febrile neutropenia	0	0	0	2 (1.1)	2 (1.1)	0	5 (2.8)	5 (2.8)	0
Neutropenia	0	0	0	0	0	0	2 (1.1)	2 (1.1)	0
Gastrointestinal disorders	1 (0.9)	1 (0.9)	0	5 (2.8)	3 (1.7)	0	7 (4.0)	4 (2.3)	0
Vomiting	0	0	0	4 (2.3)	2 (1.1)	0	0	0	0
Diarrhoea	1 (0.9)	1 (0.9)	0	0	0	0	2 (1.1)	2 (1.1)	0
Respiratory, thoracic and mediastinal disorders	4 (3.6)	2 (1.8)	0	2 (1.1)	0	0	1 (0.6)	0	0
Pneumonitis	3 (2.7)	1 (0.9)	0	1 (0.6)	0	0	0	0	0

MedDRA Version: 24.0; CTC Version: 4.0
Includes events reported between first dose and 30 days after last dose of neoadjuvant study therapy.

Table 55: Drug-Related Serious Adverse Events by Worst CTC Grade Reported in ≥ 1% of All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

System Organ Class (%) / Preferred Term (%)	Arm A: Nivo + Ipi N = 111			Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	10 (9.0)	6 (5.4)	0	21 (11.9)	15 (8.5)	0	18 (10.2)	14 (8.0)	0
Blood and lymphatic system disorders	0	0	0	5 (2.8)	4 (2.3)	0	9 (5.1)	9 (5.1)	0
Febrile neutropenia	0	0	0	2 (1.1)	2 (1.1)	0	5 (2.8)	5 (2.8)	0
Neutropenia	0	0	0	0	0	0	2 (1.1)	2 (1.1)	0
Gastrointestinal disorders	1 (0.9)	1 (0.9)	0	4 (2.3)	3 (1.7)	0	5 (2.8)	3 (1.7)	0
Vomiting	0	0	0	4 (2.3)	2 (1.1)	0	0	0	0
Diarrhoea	1 (0.9)	1 (0.9)	0	0	0	0	2 (1.1)	2 (1.1)	0
Infections and infestations	1 (0.9)	0	0	3 (1.7)	2 (1.1)	0	4 (2.3)	3 (1.7)	0
Pneumonia	1 (0.9)	0	0	0	0	0	2 (1.1)	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	4 (3.6)	2 (1.8)	0	2 (1.1)	0	0	0	0	0
Pneumonitis	3 (2.7)	1 (0.9)	0	1 (0.6)	0	0	0	0	0

MedDRA Version: 24.0; CTC Version: 4.0

Includes events reported between first dose and 30 days after last dose of neoadjuvant study therapy.

Deaths

As of the 20-Oct-2021 database lock, 35 (19.9%) and 59 (33.5%) treated subjects who were concurrently randomized in the nivo+chemo and chemo arms died. Disease progression was the most common cause of death in both arms.

Only AEs that led to death within 24 hours were documented as Grade 5. Events leading to death >24 hours after onset are reported with the worst grade before death.

Table 56: Death Summary - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

	Arm C: Nivo + Chemo N = 176	Arm B: Chemo (Concurrent) N = 176
NUMBER OF SUBJECTS WHO DIED (%)	35 (19.9)	59 (33.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	24 (13.6)	45 (25.6)
STUDY DRUG TOXICITY	0	3 (1.7)
UNKNOWN	2 (1.1)	5 (2.8)
OTHER (a)	9 (5.1)	6 (3.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST NEOADJUVANT DOSE (%)	0	0
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER (a)	0	0
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST NEOADJUVANT DOSE (%)	9 (5.1)	4 (2.3)
PRIMARY REASON FOR DEATH (%)		
DISEASE	3 (1.7)	1 (0.6)
STUDY DRUG TOXICITY	0	3 (1.7)
UNKNOWN	0	0
OTHER (a)	6 (3.4)	0

[a] See Section 2.1.2.3 for more information on deaths due to other reasons

Table 57: Death After Surgery Summary - All Treated Subjects with Surgery in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

	Arm C: Nivo + Chemo N = 149	Arm B: Chemo (Concurrent) N = 135
NUMBER OF SUBJECTS WHO DIED (%)	23 (15.4)	36 (26.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	15 (10.1)	27 (20.0)
STUDY DRUG TOXICITY	0	1 (0.7)
UNKNOWN	0	2 (1.5)
OTHER	8 (5.4)	6 (4.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF SURGERY (%)	4 (2.7)	1 (0.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	1 (0.7)
UNKNOWN	0	0
OTHER	4 (2.7)	0
NUMBER OF SUBJECTS WHO DIED WITHIN 90 DAYS OF SURGERY (%)	5 (3.4)	2 (1.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	1 (0.7)
UNKNOWN	0	0
OTHER	5 (3.4)	1 (0.7)

Table 58: Deaths Within 90 Days of Surgery - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

Subject ID (Age/Gender/Race)	Randomization Date/ First Dose Date	Date of Surgery	Death Date/ Days Since Surgery	CRF Source	Cause of Death	Specify

Arm C: Nivolumab 360 mg + Chemotherapy						
CA209816-2-478 (72/M/B)	18MAR2019/ 19MAR2019	25JUN2019	27JUN2019/ 3	DEATH	OTHER	COMPLICATIONS DURING SURGERY MASSIVE HEMORRHAGE
				AE/SAE	INTRAOPERATIVE HEMORRHAGE	Procedural haemorrhage* (GR 4; SAE; not related)
CA209816-13-253 (69/M/C)	17SEP2018/ 19SEP2018	14DEC2018	07FEB2019/ 56	DEATH	OTHER	ESOPHOGEAL PERFORATION
				AE/SAE	SURGICAL COMPLICATIONS	Oesophageal perforation* (GR 4; SAE; not related)
CA209816-51-311 (74/M/C)	14NOV2018/ 14NOV2018	20MAR2019	05APR2019/ 17	DEATH	OTHER	PNEUMONIA
				AE/SAE	RESPIRATORY FAILURE	Pneumonia* (GR 4; SAE; not related)
CA209816-122-722 (57/M/C)	30SEP2019/ 02OCT2019	12DEC2019	19DEC2019/ 8	DEATH	OTHER	CARDIOPULMONARY ARREST DUE TO PULMONARY EMBOLISM
				AE/SAE	PULMONARY EMBOLISM	Pulmonary embolism* (GR 5; SAE; not related
CA209816-138-738 (68/M/C)	11OCT2019/ 16OCT2019	14JAN2020	14JAN2020/ 1	DEATH	OTHER	SURGICAL COMPLICATION: AORTIC RUPTURE
				AE/SAE	AORTIC RUPTURE WITH MYOCARDIAL INFARCTION	Aortic rupture* (GR 5; SAE; not related)

Subject ID (Age/Gender/Race)	Randomization Date/ First Dose Date	Last Dose Date	Death Date/ Days Since Surgery	CRF Source	Cause of Death	Specify
Arm B: Chemotherapy (Concurrent)						
CA209816-28-453 (72/M/C)	22FEB2019/ 22FEB2019	24MAY2019	01AUG2019/ 70	DEATH	OTHER	PNEUMONIA
				AE/SAE	PNEUMONIA	Pneumonia (GR 4; SAE; not related)
CA209816-161-381 AS (56/M/A)	22DEC2018 24DEC2018	11MAR2019	10APR2019/ 31	DEATH	STUDY DRUG TOXICITY	LUNG INFECTION WAS ASSESSED LIKELY TO BE ASSOCIATED WITH CHEMOTHERAPY
				AE/SAE	DRUG TOXICITY	Pneumonia* (GR 4; SAE; drug-related

* Events were identified as surgical complications per investigator on the AE CRF page; Deaths may be captured on death, adverse event, ECOG performance status, and follow-up case report form pages.
The primary source of Death date is the death case report form. If the date is missing, the death date reported on the adverse event case report form is reported.
A=Asian; B=Black/African American; C=White; GR=grade; I=American Indian/Alaska Native; O=Other; P=Native Hawaiian/Other Pacific Islander; SAE=serious adverse event.

Table 59: Verbatim Terms for Deaths Attributed to "Other"- All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

Nivo+Chemo	Chemo
Intraoperative hemorrhage	COVID-19 and acute hypoxemic respiratory failure
Respiratory failure	Pneumonia
Esophageal perforation	Natural death
Pneumonia (3 subjects)	Hemoptysis
Cardiopulmonary arrest due to pulmonary embolism	Radiation pneumonitis
Surgical complication: aortic rupture	Cough up phlegm suffocation
Chronic congestive heart failure, lung cancer, non-obstructive artery disease	

Other significant events

Select Adverse Events

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms, the majority of select AEs were Grade 1 - 2 and most were considered drug-related by the investigator.

- The most frequently reported drug-related select AE categories (any-grade) were as follows:

– Nivo+chemo: skin (22.2%), and hepatic and renal (7.4% each)

– Chemo: gastrointestinal (11.9%), hepatic (10.8%), and renal (10.2%)

with nivo+chemo, there were only 2 subjects (1.1%) experiencing select pulmonary events; these AEs were both Grade 1-2 and resolved.

- The most frequently reported drug-related select AEs by PT (any-grade) were as follows:

– Nivo+chemo: rash (13.1%), blood creatinine increased (6.8%), and diarrhea (5.7%)

– Chemo: diarrhea (11.4%), alanine aminotransferase (ALT) increased (8.0%), and blood creatinine increased (6.3%)

- Drug-related serious select AEs in the concurrently randomized nivo+chemo and chemo arms were infrequent, with all PTs reported in single subjects except for diarrhea (2 subjects; 1.1%) in the chemo arm.
- Across the select AE categories, the majority of drug-related select AEs in the nivo+chemo arm were manageable using the established algorithms, with resolution occurring when immune-modulating medications (systemic or topical corticosteroids) were administered.
- Across the select AE categories, the majority of drug-related select AEs resolved (ranging from 70% to 100% across categories) at the time of DBL. In the nivo+chemo arm, only 9 subjects with drug-related select AEs in the endocrine, renal, and skin categories (3 subjects each) were not considered to be resolved at time of DBL.

Table 60: Onset, Management, and Resolution of Drug-Related Select AEs - All Treated Subjects in Concurrently Randomized Arm C (Nivo+Chemo) (N = 176) - Study CA209816

Category	N (%) Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE (range), wks[c,d,e]	% Subj. with Drug-related Select AE that Resolved[d,e,]
Endocrine	10 (5.7) / 0	6.07 (3.1 - 10.7)	0	0 / 0	10.50 (0.9 - 169.1+)	70.0
Gastrointestinal	10 (5.7) / 1 (0.6)	1.00 (0.3 - 4.9)	0	0 / 0	0.71 (0.1 - 1.3)	100.0
Hepatic	13 (7.4) / 0	1.29 (1.0 - 6.9)	0	0 / 0	2.43 (0.7 - 21.1)	100.0
Pulmonary	2 (1.1) / 0	10.43 (10.3 - 10.6)	0	100.0 / 50.0	16.14 (5.7 - 26.6)	100.0
Renal	13 (7.4) / 1 (0.6)	1.29 (0.9 - 9.1)	1.1	0 / 0	2.86 (0.7 - 140.7+)	76.9
Skin	39 (22.2) / 4 (2.3)	1.29 (0.1 - 6.3)	1.1	38.5 / 7.7	3.00 (0.3 - 142.7+)	92.3
Hypersensitivity / Infusion Reaction	11 (6.3) / 4 (2.3)	2.00 (0.1 - 6.1)	1.7	27.3 / 9.1	0.14 (0.1 - 16.0)	100.0

[a]Denominator is based on the number of subjects who experienced the event
[b]From Kaplan-Meier estimation.
[c]Symbol + indicates a censored value.

[d]Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.
[e]Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.
Includes events reported between first dose and 30 days after last dose of study therapy. MedDRA Version 24.0; CTC Version 4.0 Source: Refer to Table 8.7-1 of the CA209816 Primary CSR3

Immune-mediated AEs

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms:

- The majority of IMAEs were Grade 1-2, and the most frequently reported IMAEs (any-grade, by category) were as follows:
- Nivo+chemo: rash (8.5%), hyperthyroidism (4.0%), and hypothyroidism/ thyroiditis (2.3%)
- Chemo: pneumonitis and rash (0.6% each)
- Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when IMMs (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. Across all IMAE categories, only 4 subjects had IMAEs that were not known to be resolved at time of DBL.

Other Events of Special Interest

Among all treated subjects concurrently randomized to the nivo+chemo and chemo arms, no OESIs (all-causality or IMM treatment) with extended follow-up were reported.

Surgical complications

Table 61: All-Causality AEs Identified as Surgical Complications by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) in ≥2% of All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

System Organ Class (%) Preferred Term (%)	Arm C: Nivo + Chemo N = 149			Arm B: Chemo (Concurrent) N = 135		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	62 (41.6)	17 (11.4)	2 (1.3)	63 (46.7)	20 (14.8)	0
Injury, poisoning and procedural complications	27 (18.1)	4 (2.7)	0	20 (14.8)	1 (0.7)	0
Wound complication	11 (7.4)	1 (0.7)	0	8 (5.9)	0	0
Procedural pain	9 (6.0)	0	0	6 (4.4)	0	0
Post procedural complication	3 (2.0)	1 (0.7)	0	1 (0.7)	0	0
Incision site pain	1 (0.7)	0	0	2 (1.5)	0	0
Cardiac function disturbance postoperative	0	0	0	0	0	0
Postoperative delirium	0	0	0	0	0	0
Postoperative respiratory failure	0	0	0	0	0	0
Blood and lymphatic system disorders	20 (13.4)	3 (2.0)	0	17 (12.6)	3 (2.2)	0
Anaemia	18 (12.1)	3 (2.0)	0	17 (12.6)	3 (2.2)	0
Respiratory, thoracic and mediastinal disorders	20 (13.4)	5 (3.4)	1 (0.7)	24 (17.8)	8 (5.9)	0
Pneumothorax	5 (3.4)	1 (0.7)	0	2 (1.5)	0	0
Cough	3 (2.0)	0	0	6 (4.4)	0	0

Pleural effusion	3 (2.0)	0	0	4 (3.0)	0	0
Dyspnoea	2 (1.3)	0	0	6 (4.4)	0	0
Pulmonary fistula	2 (1.3)	0	0	4 (3.0)	4 (3.0)	0
General disorders and administration site conditions	15 (10.1)	1 (0.7)	0	29 (21.5)	0	0
Pain	11 (7.4)	1 (0.7)	0	21 (15.6)	0	0
Pyrexia	7 (4.7)	0	0	3 (2.2)	0	0
Non-cardiac chest pain	1 (0.7)	0	0	4 (3.0)	0	0
Asthenia	0	0	0	1 (0.7)	0	0

System Organ Class (%) Preferred Term (%)	Arm C: Nivo + Chemo N = 149			Arm B: Chemo (Concurrent) N = 135		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Infections and infestations	10 (6.7)	4 (2.7)	0	14 (10.4)	7 (5.2)	0
Pneumonia	8 (5.4)	3 (2.0)	0	8 (5.9)	4 (3.0)	0
Investigations	10 (6.7)	1 (0.7)	0	5 (3.7)	0	0
C-reactive protein increased	4 (2.7)	0	0	1 (0.7)	0	0
White blood cell count increased	3 (2.0)	0	0	0	0	0
Cardiac disorders	6 (4.0)	1 (0.7)	0	5 (3.7)	2 (1.5)	0
Atrial fibrillation	4 (2.7)	1 (0.7)	0	4 (3.0)	0	0
Skin and subcutaneous tissue disorders	6 (4.0)	0	0	3 (2.2)	0	0
Subcutaneous emphysema	5 (3.4)	0	0	3 (2.2)	0	0
Metabolism and nutrition disorders	5 (3.4)	0	0	7 (5.2)	1 (0.7)	0
Hypoalbuminaemia	3 (2.0)	0	0	2 (1.5)	0	0
Decreased appetite	0	0	0	3 (2.2)	0	0
Gastrointestinal disorders	4 (2.7)	1 (0.7)	0	5 (3.7)	0	0
Nausea	2 (1.3)	0	0	4 (3.0)	0	0
Constipation	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (2.0)	0	0	2 (1.5)	0	0
Musculoskeletal chest pain	1 (0.7)	0	0	2 (1.5)	0	0

MedDRA Version 24.0
CTC Version 4.0
Includes events reported up to 90 days after definitive surgery.

Adverse Events leading to delay or cancellation of surgery

Table 62: All-Causality AEs Leading to Delay of Surgery by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

System Organ Class (%) Preferred Term (%)	Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	6 (3.4)	2 (1.1)	0	9 (5.1)	4 (2.3)	0
Infections and infestations	2 (1.1)	1 (0.6)	0	1 (0.6)	0	0
Bronchitis	1 (0.6)	0	0	0	0	0
Pneumonia	1 (0.6)	1 (0.6)	0	0	0	0
Herpes zoster	0	0	0	1 (0.6)	0	0

Investigations	1 (0.6)	0	0	2 (1.1)	0	0
Lipase increased	1 (0.6)	0	0	0	0	0
Lung diffusion test decreased	0	0	0	1 (0.6)	0	0
Neutrophil count decreased	0	0	0	1 (0.6)	0	0
White blood cell count decreased	0	0	0	1 (0.6)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	2 (1.1)	1 (0.6)	0
Pneumonitis	1 (0.6)	0	0	0	0	0
Pulmonary embolism	0	0	0	2 (1.1)	1 (0.6)	0
Skin and subcutaneous tissue disorders	1 (0.6)	0	0	0	0	0
Rash maculo-papular	1 (0.6)	0	0	0	0	0
Vascular disorders	1 (0.6)	1 (0.6)	0	1 (0.6)	0	0
Embolism	1 (0.6)	1 (0.6)	0	0	0	0
Deep vein thrombosis	0	0	0	1 (0.6)	0	0

System Organ Class (%)	Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Cardiac disorders	0	0	0	2 (1.1)	2 (1.1)	0
Cardiac ventricular thrombosis	0	0	0	1 (0.6)	1 (0.6)	0
Myocardial infarction	0	0	0	1 (0.6)	1 (0.6)	0
Stress cardiomyopathy	0	0	0	1 (0.6)	1 (0.6)	0
Gastrointestinal disorders	0	0	0	1 (0.6)	1 (0.6)	0
Colitis	0	0	0	1 (0.6)	1 (0.6)	0
Nausea	0	0	0	0	0	0
Nervous system disorders	0	0	0	1 (0.6)	0	0
Ataxia	0	0	0	1 (0.6)	0	0
Myasthenia gravis	0	0	0	0	0	0

MedDRA Version 24.0
CTC Version 4.0

Table 63: **All causality Adverse Events Leading to Cancellation of Surgery by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816**

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Ipi N = 111			Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (2.7)	2 (1.8)	0	2 (1.1)	0	0	1 (0.6)	0	0
Infections and infestations	0	0	0	1 (0.6)	0	0	0	0	0
Tuberculosis	0	0	0	1 (0.6)	0	0	0	0	0
Nervous system disorders	0	0	0	1 (0.6)	0	0	0	0	0
Ischaemic stroke	0	0	0	1 (0.6)	0	0	0	0	0
Gastrointestinal disorders	1 (0.9)	1 (0.9)	0	0	0	0	0	0	0
Diarrhoea	1 (0.9)	1 (0.9)	0	0	0	0	0	0	0
Investigations	0	0	0	0	0	0	1 (0.6)	0	0
Blood creatinine increased	0	0	0	0	0	0	1 (0.6)	0	0
Respiratory, thoracic and mediastinal disorders	2 (1.8)	1 (0.9)	0	0	0	0	0	0	0
Pneumonitis	1 (0.9)	0	0	0	0	0	0	0	0
Pulmonary embolism	1 (0.9)	1 (0.9)	0	0	0	0	0	0	0

MedDRA Version: 24.0
CTC Version: 4.0

Adverse drug reactions

Pooled safety data from CA209816, CA209648 and CA209649 were used to summarize the safety profile of nivo+chemo for Section 4.8 of SmPC, ie, the tabulated summary of adverse reactions (nivo+chemo column) as well as the description of select irARs.

Adverse Reactions in Section 4.8 of the SmPC

Based on the EU guidance document "A guideline on summary of product characteristics (SmPC) September 2009" and EMA guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5), the following methodology was used to generate the adverse reactions with nivolumab + chemotherapy for section 4.8 of the SmPC:

1. Pool all-causality AE data from CA209816 (neoadjuvant resectable NSCLC), CA209649 (GC/GEJC/OAC), and CA209648 (OSCC) for the nivo+chemo regimen.
2. Programmatically remap MedDRA PTs representing the same or similar clinical conditions and generate summary tables using the MedDRA version for the most recent study.
3. Identify clinically relevant events based on BMS medical review of the all-causality re-mapped AE summary table.
4. Present resulting clinically relevant re-mapped events by SOC and all-causality frequency in the final adverse drug reaction (ADR) table.
5. To calculate the frequencies of laboratory ADR, BMS used the laboratory abnormality change from baseline tables for CA209816 pooled with CA209649 and CA209648.

For the proposed Opdivo SmPC, selection of specific adverse reactions in section 4.8 of the SmPC was based on clinical relevance as determined by the BMS medical reviewer.

The frequencies of selected irARs are based on all drug-related selected irARs (ie, drug-related select AEs, as reported by investigators) in the pooled nivo+chemo dataset (CA209816 [updated data] + CA209649 + CA209648) as irARs are characterized by their immune-mediated nature and relationship to the immuno-modulatory mechanism of action of nivolumab.

Table 64: Summary of Most Frequent (≥ 10%) Any Adverse Events (Re-mapped Terms) by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 30 days Follow-up - All Nivolumab + Chemotherapy Treated Subjects in CA209816 (14-Oct-2022 Database Lock), CA209648 (04-Oct-2021 Database Lock) + CA209649 (10-Jul-2020 Database Lock), and Pooled Studies

	Pooled Nivolumab + Chemotherapy Including CA209816 N = 1268		
System Organ Class (%) ---------- Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
Gastrointestinal disorders	1030 (81.2)	286 (22.6)	3 (0.2)
Nausea	643 (50.7)	39 (3.1)	0
Diarrhoea	416 (32.8)	51 (4.0)	0
Constipation	389 (30.7)	8 (0.6)	0
Vomiting	337 (26.6)	42 (3.3)	0
Stomatitis	278 (21.9)	42 (3.3)	0
Abdominal pain	263 (20.7)	28 (2.2)	0
Dysphagia	113 (8.9)	39 (3.1)	0
Blood and lymphatic system disorders	867 (68.4)	459 (36.2)	2 (0.2)
Anaemia	519 (40.9)	150 (11.8)	0
Neutropenia	518 (40.9)	294 (23.2)	0
Thrombocytopenia	386 (30.4)	53 (4.2)	1 (<0.1)
Leukopenia	97 (7.6)	9 (0.7)	0
General disorders and administration site conditions	795 (62.7)	99 (7.8)	6 (0.5)
Fatigue	489 (38.6)	72 (5.7)	0
Pyrexia	219 (17.3)	9 (0.7)	0
Oedema	155 (12.2)	4 (0.3)	0
Malaise	122 (9.6)	3 (0.2)	0
Metabolism and nutrition disorders	728 (57.4)	195 (15.4)	0
Decreased appetite	420 (33.1)	51 (4.0)	0
Hypoalbuminaemia	144 (11.4)	4 (0.3)	0
Hypokalaemia	141 (11.1)	41 (3.2)	0
Hyponatraemia	127 (10.0)	50 (3.9)	0
Nervous system disorders	674 (53.2)	108 (8.5)	1 (<0.1)
Neuropathy peripheral	491 (38.7)	58 (4.6)	0
Headache	119 (9.4)	6 (0.5)	0
Investigations	646 (50.9)	181 (14.3)	0
Transaminases increased	230 (18.1)	27 (2.1)	0
White blood cell count decreased	181 (14.3)	43 (3.4)	0
Weight decreased	178 (14.0)	12 (0.9)	0
Blood alkaline phosphatase increased	121 (9.5)	12 (0.9)	0
Lipase increased	116 (9.1)	61 (4.8)	0
Skin and subcutaneous tissue disorders	496 (39.1)	38 (3.0)	0
Rash	223 (17.6)	19 (1.5)	0
Alopecia	76 (6.0)	0	0
Respiratory, thoracic and mediastinal disorders	465 (36.7)	66 (5.2)	2 (0.2)
Cough	162 (12.8)	2 (0.2)	0
Hiccups	98 (7.7)	0	0
Musculoskeletal and connective tissue disorders	312 (24.6)	22 (1.7)	0
Musculoskeletal pain	199 (15.7)	12 (0.9)	0
Neoplasms benign malignant and unspecified (incl cysts and polyps)	192 (15.1)	89 (7.0)	63 (5.0)
Malignant neoplasm progression	149 (11.8)	78 (6.2)	63 (5.0)

MedDRA Version: 25.0; CTC Version 4.0; Includes events reported between first dose and last dose of therapy + 30 days. Some preferred terms are re-mapped based on BMS medical review. Nivo+Chemo Pooled groups consists of nivo+chemo treatment group from studies CA209648, CA209649 and CA209816.

Description of selected irADRs from the pooled nivo+chemo dataset (1268 patients):

The incidence of pneumonitis including interstitial lung disease was 4.8% (61/1268). Grade 2, Grade 3, and Grade 4 cases were reported in 2.4% (31/1268), 1.0% (13/1268), and 0.2% (3/1268), of patients, respectively. Two patients (0.2%) had a fatal outcome. Median time to onset was 24.1 weeks (range: 1.6-96.9). Resolution occurred in 42 patients (68.9%) with a median time to resolution of 10.4 weeks (range: 0.3+-121.3+).

The incidence of diarrhoea or colitis was 26.4% (335/1268). Grade 2, Grade 3, and Grade 4 cases were reported in 8.2% (104/1268), 3.5% (45/1268), and 0.5% (6/1268) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 4.3 weeks (range: 0.1-93.6). Resolution occurred in 293 patients (88.0%) with a median time to resolution of 1.4 weeks (range: 0.1-117.6+).

The incidence of liver function test abnormalities was 20.0% (253/1268). Grade 2, Grade 3 and Grade 4 cases were reported in 6.2% (78/1268), 2.9% (37/1268) and < 0.1% (1/1268) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-84.1). Resolution occurred in 202 patients (81.1%) with a median time to resolution of 7.4 weeks (range: 0.4-150.6+).

The incidence of nephritis or renal dysfunction was 8.8% (112/1268). Grade 2, Grade 3, and Grade 4 cases were reported in 3.3% (42/1268), 1.0% (13/1268), and 0.2% (2/1268) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 9.6 weeks (range: 0.7-60.7). Resolution occurred in 72 patients (64.3%) with a median time to resolution of 11.1 weeks (range: 0.1-191.1+).

The incidence of thyroid disorders was 10.8% (137/1268). Grade 2 thyroid disorder was reported in 4.8% (61/1268) patients. Grade 3 hypophysitis occurred in < 0.1% (1/1268) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (3/1268) and 0.2% (3/1268) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.6% (8/1268), 0.2% (2/1268) and <0.1% (1/1268) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus and fulminant Type 1 diabetes mellitus (2 Grade 2, 2 Grade 3 and 1 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. Median time to onset of these endocrinopathies was 13.0 weeks (range: 2.0-124.3). Resolution occurred in 63 patients (40.9%). Time to resolution ranged from 0.4 to 221.6+ weeks.

The incidence of rash was 24.1% (306/1268). Grade 2 and Grade 3 cases were reported in 6.4% (81/1268), and 2.4% (31/1268) of patients, respectively. Median time to onset was 6.6 weeks (range: 0.1-97.4). Resolution occurred in 205 patients (67.0%) with a median time to resolution of 13.6 weeks (range: 0.1-188.1+).

The incidence of hypersensitivity/infusion reactions was 9.8% (124/1268). Grade 2, Grade 3, and Grade 4 cases were reported in 5.7% (72/1268), 1.4% (18/1268) and 0.2% (3/1268) of patients, respectively.

Laboratory findings

Laboratory abnormalities (haematology, liver tests, kidney function tests, and electrolytes) were primarily Grade 1-2 in severity.

Table 65: Summary of On-Treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters that Worsened Relative to Baseline within 30 Days Follow-up (SI Units) - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

	Number of Subjects (%)					
	Arm C: Nivo + Chemo			Arm B: Chemo (Concurrent)		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	170	107 (62.9)	6 (3.5)	170	119 (70.0)	10 (5.9)
PLATELET COUNT	170	41 (24.1)	5 (2.9)	169	37 (21.9)	5 (3.0)
LEUKOCYTES	171	91 (53.2)	9 (5.3)	169	86 (50.9)	18 (10.7)
LYMPHOCYTES (ABSOLUTE)	170	65 (38.2)	8 (4.7)	169	53 (31.4)	3 (1.8)
ABSOLUTE NEUTROPHIL COUNT	170	99 (58.2)	37 (21.8)	169	98 (58.0)	45 (26.6)
ASPARTATE AMINOTRANSFERASE	171	19 (11.1)	0	171	28 (16.4)	1 (0.6)
ALANINE AMINOTRANSFERASE	171	39 (22.8)	0	171	34 (19.9)	2 (1.2)
BILIRUBIN, TOTAL	171	1 (0.6)	0	171	7 (4.1)	2 (1.2)
CREATININE	170	29 (17.1)	0	171	35 (20.5)	0
AMYLASE, TOTAL	167	39 (23.4)	6 (3.6)	164	21 (12.8)	3 (1.8)
LIPASE, TOTAL	170	31 (18.2)	11 (6.5)	167	23 (13.8)	6 (3.6)
HYPERNATREMIA	170	3 (1.8)	0	170	2 (1.2)	0
HYPONATREMIA	170	42 (24.7)	4 (2.4)	170	48 (28.2)	3 (1.8)
HYPERKALEMIA	170	32 (18.8)	2 (1.2)	170	16 (9.4)	3 (1.8)
HYPOKALEMIA	170	9 (5.3)	1 (0.6)	170	14 (8.2)	0
HYPERCALCEMIA	169	5 (3.0)	0	170	7 (4.1)	0
HYPOCALCEMIA	169	29 (17.2)	1 (0.6)	170	27 (15.9)	0
HYPERMAGNESEMIA	168	3 (1.8)	0	168	8 (4.8)	2 (1.2)
HYPOMAGNESEMIA	168	43 (25.6)	3 (1.8)	168	52 (31.0)	2 (1.2)

	Number of Subjects (%)					
	Arm C: Nivo + Chemo			Arm B: Chemo (Concurrent)		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HYPERGLYCEMIA	73	27 (37.0)	4 (5.5)	68	24 (35.3)	2 (2.9)
HYPOGLYCEMIA	73	2 (2.7)	0	68	0	0

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

Source: Appendix L.7.USPI.6.2

Hematology

Among all treated subjects in the concurrently randomized nivo+chemo (Arm C) and chemo (Arm B) arms:

- Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2.
- Hematologic parameters that worsened to Grade 3-4 from baseline (≥ 5% of subjects) were as follows:
  - Nivo+chemo: decreased absolute neutrophil count (21.8%) and decreased leukocytes (5.3%)
  - Chemo: decreased absolute neutrophil count (26.6%), decreased leukocytes (10.7%), and decreased haemoglobin (5.9%)

Serum Chemistry

Liver Function Tests

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms:

- Abnormalities in hepatic parameters (all increases) were primarily Grade 1-2.
- Hepatic abnormalities that worsened to Grade 3-4 relative to baseline were as follows:
  - Nivo+chemo: none
  - Chemo: increased ALT and increased bilirubin (1.2% each), and increased AST (0.6%)
- Only 1 subject in the chemo arm had concurrent ALT or AST > 3 x ULN with total bilirubin 2 x ULN within 1 day and within 30 days of last dose of study therapy.

Table 66: On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

Abnormality (%)	Arm C: Nivo + Chemo N = 176	Arm B: Chemo (Concurrent) N = 176
	N = 175	N = 171
ALT OR AST > 3XULN	3 (1.7)	7 (4.1)
ALT OR AST > 5XULN	0	2 (1.2)
ALT OR AST > 10XULN	0	1 (0.6)
ALT OR AST > 20XULN	0	0
	N = 175	N = 171
TOTAL BILIRUBIN > 2XULN	0	2 (1.2)
	N = 175	N = 167
ALP > 1.5XULN	7 (4.0)	9 (5.4)
	N = 175	N = 171
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	0	1 (0.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	0	1 (0.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	0	1 (0.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	0	1 (0.6)

Includes laboratory results reported after the first dose and within 30 days of last dose of neoadjuvant study therapy.
Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Source: Refer to Table 8.12.2.1-1 of the CA209816 Primary CSR

Kidney Function Tests

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms:

- Most subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period.
- All abnormalities in creatinine (increases) were Grade 1 or 2.

Thyroid Function Tests

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms:

- Thyroid-stimulating hormone (TSH) increases (>ULN) from baseline (≤ ULN) were reported in 5/166 (3.0%) subjects and 0/35 (0%) subjects, respectively.
- Decreases (< lower limit of normal [LLN]) from baseline (≥ LLN) were reported in 19 (11.4%) subjects and 1 (2.9%) subject, respectively.

Table 67: On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) with at Least One On-Treatment TSH Measurement - Study CA209816

Abnormality (%)	Arm C: Nivo + Chemo N = 166	Arm B: Chemo (Concurrent) N = 35 (A)
TSH > ULN	9 (5.4)	0
TSH > ULN		
WITH TSH <= ULN AT BASELINE	5 (3.0)	0
TSH > ULN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (B)	3 (1.8)	0
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (B)	5 (3.0)	0
WITH FT3/FT4 TEST MISSING (B) (C)	1 (0.6)	0
TSH < LLN	26 (15.7)	1 (2.9)
TSH < LLN		
WITH TSH >= LLN AT BASELINE	19 (11.4)	1 (2.9)
TSH < LLN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (B)	9 (5.4)	0
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (B)	8 (4.8)	1 (2.9)
WITH FT3/FT4 TEST MISSING (B) (C)	9 (5.4)	0

Includes laboratory results reported after the first dose and within 30 days of last dose of neoadjuvant study therapy.
(A) Per protocol, chemo treated subjects were not required to have thyroid function tests performed.
(B) Within a 2-week window after the abnormal TSH test date.
(C) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.
Source: Refer to Table 8.12.2.3-1 of the CA209816 Primary CSR

Pancreas Function Tests

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms:

- Most subjects had normal amylase and lipase levels during the treatment period; abnormalities in amylase and lipase during treatment were primarily Grade 1-2.
- Grade 3-4 abnormalities (increases) in amylase and lipase that worsened from baseline were as follows:
  - Nivo+chemo: increased lipase (6.5%) and increased amylase (3.6%)
  - Chemo: increased lipase (3.6%) and increased amylase (1.8%)

Electrolytes

Among all treated subjects in the concurrently randomized nivo+chemo and chemo arms:

- Most subjects had normal electrolyte levels during the treatment period; abnormalities in electrolytes during treatment were primarily Grade 1-2.
- The following electrolyte abnormalities worsened to Grade 3-4 relative to baseline in ≥ 1% of subjects:
  - Nivo+chemo: hyponatremia (2.4%), hypomagnesemia (1.8%), and hyperkalemia (1.2%)
  - Chemo: hyponatremia and hyperkalemia (1.8% each), hypomagnesemia and hypermagnesemia (1.2% each)

Glucose

- Among treated subjects in the concurrently randomized nivo+chemo and chemo arms with available glucose values:
- Most subjects had normal glucose levels during the treatment period; abnormalities in glucose during treatment were primarily Grade 1-2.

- 5.5% of nivo+chemo subjects and 2.9% of chemo subjects had Grade 3-4 increases in glucose (ie, hyperglycemia) that worsened from baseline.

In the pooled nivo+chemo dataset (1268 patients), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 14.5% for anaemia, 5.4% for thrombocytopaenia, 10.7% leukopaenia, 14.0% for lymphopaenia, 25.7% neutropaenia, 2.4% for increased alkaline phosphatase, 3.6% for increased AST, 2.7% for increased ALT, 1.9% for increased bilirubin, 1.2% for increased creatinine, 4.6% for increased amylase, 5.6% for increased lipase, 0.5% for hypernatraemia, 7.8% for hyponatraemia, 1.6% for hyperkalaemia, 6.4% for hypokalaemia, 0.9% for hypercalcaemia, 1.8% for hypocalcaemia, 1.7% for hypomagnesaemia, 3.4% for hyperglycaemia, and 0.6% for hypoglycaemia.

Safety in special populations

Intrinsic Factors and Extrinsic Factors

Table 68: All-Causality AEs Classified by the Worst CTC Grade and by Age, Sex, Race, and Region - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

	All-Causality AEs (n [%])							
	Nivo + Chemo (Arm C)				Chemo (Arm B)			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	176	163 (92.6)	72 (40.9)	0	176	171 (97.2)	77 (43.8)	0
By Age								
< 65 yrs	91	84 (92.3)	33 (36.3)	0	82	82 (100.0)	29 (35.4)	0
≥ 65 and < 75 yrs	75	72 (96.0)	33 (44.0)	0	81	76 (93.8)	43 (53.1)	0
≥ 75 and < 85 yrs	10	7 (70.0)	6 (60.0)	0	13	13 (100.0)	5 (38.5)	0
≥ 75 yrs	10	7 (70.0)	6 (60.0)	0	13	13 (100.0)	5 (38.5)	0
≥ 65 yrs	85	79 (92.9)	39 (45.9)	0	94	89 (94.7)	48 (51.1)	0
By Sex								
Male	127	116 (91.3)	54 (42.5)	0	126	121 (96.0)	60 (47.6)	0
Female	49	47 (95.9)	18 (36.7)	0	50	50 (100.0)	17 (34.0)	0
By Race								
White	88	79 (89.8)	32 (36.4)	0	77	77 (100.0)	34 (44.2)	0
Black or African American	4	4 (100.0)	3 (75.0)	0	3	3 (100.0)	1 (33.3)	0
Asian	84	80 (95.2)	37 (44.0)	0	93	88 (94.6)	39 (41.9)	0
Other	0	0	0	0	3	3 (100.0)	3 (100.0)	0
By Region								
North America	41	40 (97.6)	16 (39.0)	0	47	47 (100.0)	18 (38.3)	0
Europe	40	35 (87.5)	16 (40.0)	0	25	25 (100.0)	16 (64.0)	0
Asia	83	79 (95.2)	37 (44.6)	0	92	87 (94.6)	38 (41.3)	0
Rest of the World	12	9 (75.0)	3 (25.0)	0	12	12 (100.0)	5 (41.7)	0

MedDRA version 24.0; CTC version 4.0;
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.6-1 of the CA209816 Primary CSR

Table 69: Drug-related AEs Classified by the Worst CTC Grade and by Age, Sex, Race, and Region - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

	Drug-Related AEs (n [%])							
	Nivo + Chemo (Arm C)				Chemo (Arm B)			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	176	145 (82.4)	59 (33.5)	0	176	156 (88.6)	65 (36.9)	0
By Age								
< 65 yrs	91	73 (80.2)	27 (29.7)	0	82	75 (91.5)	26 (31.7)	0
≥ 65 and < 75 yrs	75	65 (86.7)	27 (36.0)	0	81	68 (84.0)	35 (43.2)	0
≥ 75 and < 85 yrs	10	7 (70.0)	5 (50.0)	0	13	13 (100.0)	4 (30.8)	0
≥ 75 yrs	10	7 (70.0)	5 (50.0)	0	13	13 (100.0)	4 (30.8)	0
≥ 65 yrs	85	72 (84.7)	32 (37.6)	0	94	81 (86.2)	39 (41.5)	0
By Sex								
Male	127	103 (81.1)	45 (35.4)	0	126	110 (87.3)	52 (41.3)	0
Female	49	42 (85.7)	14 (28.6)	0	50	46 (92.0)	13 (26.0)	0
By Race								
White	88	67 (76.1)	24 (27.3)	0	77	68 (88.3)	27 (35.1)	0
Black or African American	4	4 (100.0)	1 (25.0)	0	3	2 (66.7)	0	0
Asian	84	74 (88.1)	34 (40.5)	0	93	83 (89.2)	37 (39.8)	0
Other	0	0	0	0	3	3 (100.0)	1 (33.3)	0
By Region								
North America	41	36 (87.8)	10 (24.4)	0	47	38 (80.9)	8 (17.0)	0
Europe	40	28 (70.0)	13 (32.5)	0	25	24 (96.0)	16 (64.0)	0
Asia	83	73 (88.0)	34 (41.0)	0	92	82 (89.1)	36 (39.1)	0
Rest of the World	12	8 (66.7)	2 (16.7)	0	12	12 (100.0)	5 (41.7)	0

MedDRA version 24.0; CTC version 4.0;
Includes events reported between first dose and 30 days after last dose of study therapy.

Age groups

Table 70: Summary of On-treatment Adverse Events by Age Group-All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) – Study CA209816

	Age Group (Years)				
	< 65	65-74	75-84	>= 85	
Total MedDRA Terms (%)	N = 91	N = 75	N = 10	N = 0	N = 176
Treatment Group: Arm C: Nivo + Chemo N = 176					
TOTAL SUBJECTS WITH AN EVENT	84 (92.3)	72 (96.0)	7 (70.0)	0	163 (92.6)
SERIOUS AE - TOTAL	16 (17.6)	13 (17.3)	1 (10.0)	0	30 (17.0)
FATAL (DEATH)	0	0	0	0	0
HOSPITALIZATION/PROLONGATION	13 (14.3)	12 (16.0)	0	0	25 (14.2)
LIFE THREATENING	1 (1.1)	0	0	0	1 (0.6)
CANCER	1 (1.1)	0	0	0	1 (0.6)

DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	1 (1.1)	2 (2.7)	1 (10.0)	0	4 (2.3)
AE LEADING TO DISCONTINUATION	7 (7.7)	9 (12.0)	2 (20.0)	0	18 (10.2)
PSYCHIATRIC DISORDERS	11 (12.1)	8 (10.7)	0	0	19 (10.8)
NERVOUS SYSTEM DISORDERS	20 (22.0)	14 (18.7)	5 (50.0)	0	39 (22.2)
ACCIDENT AND INJURIES	0	7 (9.3)	0	0	7 (4.0)
CARDIAC DISORDERS	4 (4.4)	2 (2.7)	0	0	6 (3.4)
VASCULAR DISORDERS	6 (6.6)	9 (12.0)	3 (30.0)	0	18 (10.2)
CEREBROVASCULAR DISORDERS	1 (1.1)	1 (1.3)	0	0	2 (1.1)
INFECTIONS AND INFESTATIONS	14 (15.4)	15 (20.0)	2 (20.0)	0	31 (17.6)
ANTICHOLINERGIC SYNDROME	12 (13.2)	8 (10.7)	3 (30.0)	0	23 (13.1)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	1 (1.1)	8 (10.7)	3 (30.0)	0	12 (6.8)

	Age Group (Years)				
	< 65	65-74	75-84	>= 85	
Total MedDRA Terms (%)	N = 82	N = 81	N = 13	N = 0	N = 176
Treatment Group: Arm B: Chemo (Concurrent) N = 176					
TOTAL SUBJECTS WITH AN EVENT	82 (100.0)	76 (93.8)	13 (100.0)	0	171 (97.2)
SERIOUS AE - TOTAL	10 (12.2)	14 (17.3)	0	0	24 (13.6)
FATAL (DEATH)	2 (2.4)	1 (1.2)	0	0	3 (1.7)
HOSPITALIZATION/PROLONGATION	10 (12.2)	11 (13.6)	0	0	21 (11.9)
LIFE THREATENING	0	2 (2.5)	0	0	2 (1.1)
CANCER	0	0	0	0	0
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	0	2 (2.5)	0	0	2 (1.1)
AE LEADING TO DISCONTINUATION	6 (7.3)	11 (13.6)	3 (23.1)	0	20 (11.4)
PSYCHIATRIC DISORDERS	11 (13.4)	9 (11.1)	1 (7.7)	0	21 (11.9)
NERVOUS SYSTEM DISORDERS	19 (23.2)	20 (24.7)	3 (23.1)	0	42 (23.9)
ACCIDENT AND INJURIES	2 (2.4)	0	0	0	2 (1.1)
CARDIAC DISORDERS	4 (4.9)	7 (8.6)	0	0	11 (6.3)
VASCULAR DISORDERS	8 (9.8)	7 (8.6)	0	0	15 (8.5)
CEREBROVASCULAR DISORDERS	0	0	0	0	0
INFECTIONS AND INFESTATIONS	14 (17.1)	12 (14.8)	1 (7.7)	0	27 (15.3)
ANTICHOLINERGIC SYNDROME	13 (15.9)	10 (12.3)	1 (7.7)	0	24 (13.6)

QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	3 (3.7)	3 (3.7)	0	0	6 (3.4)

MedDRA ver 24.0; CTC ver 4.0; Includes events reported between first dose and 30 days after last dose of study therapy. Source: Appendix L.425-EUSCS

Type of Platinum Chemotherapy (Cisplatin or Carboplatin)

Table 71: Summary of Safety by Type of Platinum Chemotherapy - All Treated Subjects in Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo) - Study CA209816

	No. of Subjects n (%)[a]											
	Cisplatin				Carboplatin				Switched from Cisplatin to Carboplatin[b]			
	Nivo + Cisplatin (N = 124)		Cisplatin (N = 134)		Nivo + Carboplatin (N = 39)		Carboplatin (N = 33)		Nivo+ Cis→Carbo (N = 12)		Cis→Carbo (N = 9)	
Safety Parameters	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality AEs	114 (91.9)	46 (37.1)	130 (97.0)	49 (36.6)	37 (94.9)	19 (48.7)	32 (97.0)	22 (66.7)	11 (91.7)	6 (50.0)	9 (100.0)	6 (66.7)
Drug-Related AEs	99 (79.8)	37 (29.8)	119 (88.8)	41 (30.6)	34 (87.2)	16 (41.0)	29 (87.9)	18 (54.5)	11 (91.7)	5 (41.7)	8 (88.9)	6 (66.7)

[a] In 1 subject in the nivo+chemo arm, the type of platinum chemotherapy administered was not reported, as the subject never received platinum chemotherapy and the subject had a hypersensitivity reaction to paclitaxel leading to study drug discontinuation at Cycle 1 (refer to Appendix 4.1 [dosing listing] and Appendix 6.1.2.1 [AEs leading to DC listing] of the CA209816 Primary CSR).

[b] Per protocol, any cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockroft Gault formula) requires discontinuation of cisplatin. The other chemotherapeutic agent could be continued, and the platinum agent could be switched to carboplatin

MedDRA v24.0; CTC v4.0. All events are within 30 days of the last dose of neoadjuvant study therapy.
Abbreviations: AEs - adverse events, carbo - carboplatin; cis - cisplatin; CTC - Common Toxicity Criteria, MedDRA - Medical Dictionary for Regulatory Activities

Safety related to drug-drug interactions and other interactions

No new data has been provided by the MAH regarding drug-drug interactions or other interactions.

Immunogenicity

Immunogenicity has not been evaluated in Study CA209816. A descriptive summary of nivo ADA assessment has been presented side-by-side for subjects with 1L NSCLC who were treated with nivolumab monotherapy (3 mg/kg Q2W or 240mg Q2W, CA209026, and CA209227 Part 1 Arm A), and nivo+chemo (nivo 360 mg Q3W+chemo, CA209227 Part 1 Arm G and CA209227 Part 2 Arm H).

Of 552 subjects with NSCLC who were treated with nivolumab 3 mg/kg or 240 mg Q2W and evaluable for the presence of ADA, 98 subjects (17.8%) tested positive for treatment-emergent ADA. Of those who were ADA positive, 3 subjects (0.5%) were persistent positive and neutralizing antibodies were detected in 5 subjects (0.9%).

Of 449 subjects with NSCLC who were treated with first line nivolumab 360 mg Q3W in combination with 4 cycles of platinum-doublet chemotherapy and evaluable for the presence of ADA, 60 subjects (13.4%) tested positive for treatment-emergent ADA. Of those who were ADA positive, 2 subjects (0.4%) were persistent positive and neutralizing antibodies were detected in 15 subjects (3.3%). The frequency of nivolumab ADA with nivo+chemo was consistent with that observed with nivolumab monotherapy (13.4% vs 17.8%, respectively).

Discontinuation due to adverse events

AEs leading to discontinuation included events where 1 or more drugs of a multi-drug regimen were discontinued, even if the subject remained on treatment. Among treated subjects concurrently randomized to the nivo+chemo and chemo arms, the types and frequencies of all-causality and drug-related AEs leading to discontinuation of at least 1 study drug were similar between the arms.

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 18 (10.2%) and 20 (11.4%) subjects in the concurrently randomized nivo+chemo and chemo arms, respectively. Grade 3-4 AEs leading to discontinuation of at least 1 study drug were reported in 10 (5.7%) subjects in the nivo+chemo arm and 7 (4.0%) subjects in the chemo arm.

The most frequently reported any-grade AEs leading to discontinuation (all-causality) were:

- Nivo+chemo: anaphylactic reaction (1.7%) and neutrophil count decreased and fatigue (1.1% each)
- Chemo: neutropenia (2.3%), and neutrophil count decreased, blood creatinine increased, and pneumonia (1.1% each)

Drug-related AEs leading to discontinuation were reported in 18 (10.2%) and 17 (9.7%) subjects in the concurrently randomized nivo+chemo and chemo arms. Grade 3-4 AEs leading to discontinuation were reported in 10 (5.7%) subjects in the nivo+chemo arm and 6 (3.4%) subjects in the chemo arm.

The most frequently reported any-grade drug-related AE leading to discontinuation were:

- Nivo+chemo: anaphylactic reaction (1.7%), fatigue and neutrophil count decreased (1.1% each)
- Chemo: neutropenia (2.3%), neutrophil count decreased, and blood creatinine increased (1.1% each)

Table 72: Adverse Events Leading to Discontinuation by Worst CTC Grade Reported in ≥2 Subjects - All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

System Organ Class (%)	Arm A: Nivo + Ipi N = 111			Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	6 (5.4)	5 (4.5)	0	18 (10.2)	10 (5.7)	0	20 (11.4)	7 (4.0)	0
Investigations	0	0	0	6 (3.4)	2 (1.1)	0	4 (2.3)	0	0
Neutrophil count decreased	0	0	0	2 (1.1)	2 (1.1)	0	2 (1.1)	0	0
Blood creatinine increased	0	0	0	1 (0.6)	0	0	2 (1.1)	0	0
Immune system disorders	0	0	0	3 (1.7)	3 (1.7)	0	0	0	0
Anaphylactic reaction	0	0	0	3 (1.7)	3 (1.7)	0	0	0	0
Blood and lymphatic system disorders	0	0	0	2 (1.1)	1 (0.6)	0	4 (2.3)	3 (1.7)	0
Neutropenia	0	0	0	1 (0.6)	0	0	4 (2.3)	3 (1.7)	0
General disorders and administration site conditions	0	0	0	2 (1.1)	1 (0.6)	0	1 (0.6)	0	0
Fatigue	0	0	0	2 (1.1)	1 (0.6)	0	0	0	0
Infections and infestations	0	0	0	1 (0.6)	1 (0.6)	0	5 (2.8)	2 (1.1)	0
Pneumonia	0	0	0	0	0	0	2 (1.1)	1 (0.6)	0
Gastrointestinal disorders	2 (1.8)	2 (1.8)	0	0	0	0	1 (0.6)	1 (0.6)	0
Diarrhoea	2 (1.8)	2 (1.8)	0	0	0	0	0	0	0

Respiratory, thoracic and mediastinal disorders	2 (1.8)	1 (0.9)	0	0	0	0	0	0	0
Pneumonitis	2 (1.8)	1 (0.9)	0	0	0	0	0	0	0

---MedDRA Version: 24.0; CTC Version: 4.0

Includes events reported between first dose and 30 days after last dose of neoadjuvant study therapy. This captures discontinuation of at least 1 study drug. Source: Table S.6.4.2.1

Table 73: Drug-Related Adverse Events Leading to Discontinuation by Worst CTC Grade Reported in ≥2 Subjects - All Treated Subjects in Arm A (Nivo+Ipi) and Concurrently Randomized Arms C (Nivo+Chemo) and B (Chemo)

	Arm A: Nivo + Ipi N = 111			Arm C: Nivo + Chemo N = 176			Arm B: Chemo (Concurrent) N = 176		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	6 (5.4)	5 (4.5)	0	18 (10.2)	10 (5.7)	0	17 (9.7)	6 (3.4)	0
Investigations	0	0	0	6 (3.4)	2 (1.1)	0	4 (2.3)	0	0
Neutrophil count decreased	0	0	0	2 (1.1)	2 (1.1)	0	2 (1.1)	0	0
Blood creatinine increased	0	0	0	1 (0.6)	0	0	2 (1.1)	0	0
Immune system disorders	0	0	0	3 (1.7)	3 (1.7)	0	0	0	0
Anaphylactic reaction	0	0	0	3 (1.7)	3 (1.7)	0	0	0	0
Blood and lymphatic system disorders	0	0	0	2 (1.1)	1 (0.6)	0	4 (2.3)	3 (1.7)	0
Neutropenia	0	0	0	1 (0.6)	0	0	4 (2.3)	3 (1.7)	0
General disorders and administration site conditions	0	0	0	2 (1.1)	1 (0.6)	0	1 (0.6)	0	0
Fatigue	0	0	0	2 (1.1)	1 (0.6)	0	0	0	0
Gastrointestinal disorders	2 (1.8)	2 (1.8)	0	0	0	0	1 (0.6)	1 (0.6)	0
Diarrhoea	2 (1.8)	2 (1.8)	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (1.8)	1 (0.9)	0	0	0	0	0	0	0
Pneumonitis	2 (1.8)	1 (0.9)	0	0	0	0	0	0	0

MedDRA Version: 24.0; CTC Version: 4.0

Includes events reported between first dose and 30 days after last dose of neoadjuvant study therapy. This captures discontinuation of at least 1 study drug.

The table below presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment in the pooled nivo+chemo dataset (1268 patients).

Additionally, for patients who experienced an event, the table presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents).

Table 74: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab in combination with chemotherapy)

	Nivolumab in combination with chemotherapy %
Immune-related adverse reaction leading to permanent discontinuation	
Pneumonitis	2.1
Colitis	2.1
Hepatitis	1.0
Nephritis and renal dysfunction	3.0
Endocrinopathies	0.5
Skin	1.1
Hypersensitivity/Infusion reaction	2.3
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]	
Pneumonitis	59
Colitis	8
Hepatitis	8
Nephritis and renal dysfunction	9
Endocrinopathies	5
Skin	6
Hypersensitivity/Infusion reaction	23

[a] at least 40 mg daily prednisone equivalents
[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Post marketing experience

Postmarketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities. The review of the latest Periodic Benefit-Risk Evaluation Report (PBRER) Number 11 (04-Jul-2020 to 03-Jul-2021) concluded on 24 February 2022.

As of 03-Jul-2021, the global, cumulative patient exposure to nivolumab as monotherapy or combination therapy is estimated to be 767,256 subjects/patients. This is composed of patients in BMS- and ONO-sponsored clinical trials (42,580 subjects), early patient access programs (21,925 patients), and post-marketing experience (702,751 patients). The cumulative nivolumab treatment duration to nivolumab is estimated to be 3,966,714 patient-months. Further to the review of the latest PBRER, the benefit-risk balance remains unchanged. No new safety concerns or change in benefits have been identified.

2.5.1. Discussion on clinical safety

Safety assessment for the indication of neoadjuvant treatment of patients with Stage IB-IIIA resectable non-small cell lung cancer (NSCLC) is based on safety data from all 352 treated subjects receiving at least one dose of study drug who were concurrently randomized to nivo+chemo (N=176; Arm C) and chemo (N=176; Arm B) in the pivotal study, CA209816. These data are from the 20-Oct-2021 database lock (DBL) of the CA209816 Primary CSR.

Patient exposure - Minimum follow-up was 21.0 months and median follow-up was 29.5 months. Considering that nivolumab is intended for neoadjuvant treatment and that patients were to receive

only 3 doses of treatment, these minimum and median follow-up are considered acceptable for an initial safety assessment. At the time of the DBL all treated subjects had discontinued neoadjuvant treatment for >18 months. This duration is also considered to be sufficient to characterize the safety profile of nivolumab in this setting. Most subjects had completed the course of neoadjuvant therapy (93.8% in the nivo+chemo arm, and 84.7% in the chemo arm). Reasons for not continuing neoadjuvant treatment were similar between both arms.

The number of doses of nivolumab received in the nivo+chemo arm was 3 in 93.2% of patients, whereas for carboplatin and cisplatin was 3 in 70.6% and 84.6% of patients, respectively. This suggests that the addition of nivolumab did not have a negative impact on the number of doses received by patients and most patients could complete the neoadjuvant treatment course.

Definitive surgery was conducted in a higher percentage of patients in the nivo+chemo arm than in the chemo arm (83.2% vs. 75.4%), and definitive cancellations were also reported in a lower percentage of patients in the nivo+chemo arm (15.6% vs. 20.7%). This suggests that the addition of nivolumab does not adversely affect the feasibility of the surgery and this is an important and reassuring point to take into account in the neoadjuvant setting. The reasons for cancellation were similar among arms, most of them due to disease progression or to "other" reasons, and only 2 patients (7.1%) in the nivo+chemo arm and 1 patient (2.7%) in the chemo arm cancelled due to adverse events. In both arms the most commonly reported "other" causes for surgery cancellation were subject's refusal and tumour deemed unresectable by medical team. Regarding delayed surgeries, the percentage of patients in the nivo+chemo arm was slightly higher than in the chemo arm (20.8% vs. 17.8%), although most of the delays were due to administrative reasons or "other" reasons. The percentage of patients who underwent a surgery delay due to AEs was significantly lower in the nivo+chemo arm than in the chemo arm (19.4% vs. 37.5%).

Per protocol, following definitive surgery, subjects could receive up to 4 cycles of adjuvant chemotherapy and/or radiation at the discretion of the investigator, following local recommendations. Considering only adjuvant systemic therapy, 14.8% of subjects from the nivo+chemo arm and 25% from the chemo arm received adjuvant chemotherapy. Most patients received between 1 and 4 cycles of platinum doublet chemotherapy. Since patients with adjuvant therapy received more doses of chemotherapy, some imbalance on the long-term safety (in detriment of patients having received neoadjuvant + adjuvant therapy) cannot be discarded, although this may reflect current clinical practice. It should be noted that with the currently available evidence, it does not seem that patients who received adjuvant therapy had an unacceptable worse toxicity than patients who did not receive it. Regarding the percentage of subjects who received PORT/adjuvant radiotherapy, it does not seem either that the evidence so far available suggests an unacceptable toxicity of PORT/adjuvant radiotherapy on patients who have previously received nivolumab as neoadjuvant therapy.

Regarding dose delays, dose reductions, dose infusion interruptions, infusion rate reductions and dose omissions, no relevant differences have been identified between both treatment arms or between the subgroups of patients who received different allowed chemotherapy schemes.

No apparent differences were observed between arms regarding the length of delay, duration of surgery or length of hospital stay.

Adverse events – Almost all patients reported an AE during study treatment: 92.6% of subjects in the nivo+chemo arm and 97.2% of subjects in the chemo arm. These percentages are similar, and even slightly lower in the nivo+chemo arm, which suggests that the addition of nivolumab does not significantly worsen the toxicity profile. Overall, the incidence of AEs in the nivo+chemo arm was similar or slightly lower in the nivo+chemo arm in comparison with the chemo arm, except for "fatigue", which was reported in 16.5% of patients in the nivo+chemo arm vs. 12.5% in the chemo

arm; and "rash", which was reported in 13.6% in the nivo+chemo arm vs. 2.8% in the chemo arm. No significant differences were observed between the incidences or nature of AEs (regardless of causality) and drug-related AEs.

SAE – Any-grade SAEs were reported in a higher percentage of patients in the nivo+chemo arm than in the chemo arm (17.0% vs. 13.6%), although G3-4 SAEs were reported with a similar frequency (10.8% vs. 9.7%). Overall the nature of the SAEs most frequently reported was similar in both arms, except for the frequency of SAEs belonging to "vascular disorders", which was higher in the nivo+chemo arm than in the chemo arm (3.4% vs. 1.1%). Additionally, 2 patients (1.1%) from the nivo+chemo arm reported an embolism, whereas in the chemo arm there were no cases of embolism. In terms of drug-related SAEs, the incidences of both any-grade AEs and G3-4 SAEs were similar in both arms (11.9% vs. 10.2% for any-grade SAEs, and 8.5% vs. 8.0% for G3-4 SAEs). Although the incidence of all-causality any-grade SAEs was higher in the nivo+chemo arm than in the chemo arm, this increase is considered acceptable, taking into account that adding nivolumab to the backbone chemotherapy inevitably adds toxicity. Besides, G3-4 SAEs were reported with a similar frequency; and when the causality is established, the differences between arms are less marked than in the all-causality any-grade SAEs.

Deaths – Overall, fewer patients died in the nivo+chemo arm than in the chemo arm: 19.9% vs. 33.5%. Of note, the number of patients who died within 100 days of last neoadjuvant dose was higher in the nivo+chemo arm than in the chemo arm: 5.1% vs. 2.3%.

In line with the number of subjects who died in each arm, the incidence of subjects who died after surgery was lower in the nivo+chemo arm than in the chemo arm (15.4% vs. 26.7%). However, both the rate of deaths within 30 days of surgery and within 90 days of surgery was higher in the nivo+chemo arm than in the chemo arm: 2.7% (4 deaths, all attributed to "other") vs. 0.7% (1 death, due to study drug toxicity) for deaths within 30 days; and 3.4% (5 deaths, all attributed to "other") vs. 1.5% (2 deaths, 1 due to study drug toxicity and 1 attributed to "other") for deaths within 90 days. These rates are also in line with the number of subjects who died within 100 days of last neoadjuvant dose.

As mentioned, the cause of death of 9 subjects in the nivo+chemo arm was attributed to "other". The verbatim terms for those deaths were provided and could be considered as expected taking into account the population under study and the complications associated with major thoracic surgery.

The cause of death of 2 subjects in the nivo+chemo arm was considered as "unknown". These deaths occurred 379 and 193 days since last neoadjuvant dose, respectively, and therefore the implication of nivolumab on those deaths can be considered unlikely.

More patients died in the chemo arm than in the nivo+chemo arm (35 (19.9%) patients in the nivo+chemo arm vs. 59 (33.5%) in the chemo arm). However, both the number of patients who died within 30 and within 100 days of last neoadjuvant dose was higher in the nivo+chemo arm than in the chemo arm. It was confirmed that the higher rate of deaths reported in the chemo arm was mainly due to the contribution of deaths in the chemo arm after these 100 days after the last neoadjuvant dose, and due to disease progression.

Other significant events – The most frequently reported drug-related select AE categories in the nivo+chemo arm was "skin" (22.2%; "rash" accounting for 13.1%), followed by "hepatic" and "renal" (7.4% each). It should be noted that "rash" and other skin disorders are well-known AEs of nivolumab. In the chemo arm "gastrointestinal" was reported in 11.9% ("diarrhoea" accounting for 11.4%), followed by "hepatic" (10.8%) and "renal" (10.2%). The majority of drug-related select AEs had resolved at time of DBL. However, some drug-related select AEs in the "endocrine", "renal" and "skin" categories were still considered as unresolved at the time of DBL. It is well-known that patients with

endocrine AEs take long time to recover (median time to resolution: 10.50 weeks, according to the data submitted by the MAH) or even need supplementary treatment in the long-term, therefore it is not surprising that patients suffering from AEs of this category had not recovered by DBL.

Regarding immune-mediated AEs, in the nivo+chemo arm "rash" was the most frequently reported IMAE (8.5%), followed by "hyperthyroidism" (4.0%) and "hypothyroidism/thyroiditis" (2.3%). As expected, IMAEs were reported with a significantly lower frequency in the chemo arm than in the nivo+chemo arm. It should be noted that all "rash" cases were considered as resolved by time of DBL. On the contrary, only 50% of patients reporting "hypothyroidism/thyroiditis" and "diabetes mellitus" were considered as recovered by time of DBL, and the MAH states that 4 patients across all categories had IMAEs that were not resolved by DBL. With the information available so far, which includes an update from the MAH (DBL 14-Oct-2022), there is no evidence suggesting a worse trend regarding the recovery from these events in this indication than in the approved ones. Besides, the percentage of patients not yet recovered is considered as acceptable in this therapeutic context. Considering the nature of the events that were not considered as recovered at the moment of this update (notably endocrine events), it is expected that most of these patients will not recover soon.

Concerning surgical complications, 41.6% of patients in the nivo+chemo arm reported an event of any grade identified as a surgical complication vs. 46.7% in the chemo arm; and 11.4% reported a G3-4 event in the nivo+chemo arm vs. 14.8% in the chemo arm. Overall these percentages are similar, and even slightly lower in the nivo+chemo arm. Of note, in the nivo+chemo arm there were 2 G5 events ("pulmonary embolism" and "aortic rupture") but they were not considered as related to the treatment by the investigator. AEs belonging to "Injury, poisoning and procedural complications" SOC were reported with a higher frequency in the nivo+chemo arm (18.1% for any-grade AEs; 2.7% for G3-4 AEs) than in the chemo arm (14.8% for any-grade AEs; 0.7% for G3-4 AEs). On the other hand, any-grade AEs belonging to "General disorders and administration site conditions" were reported with a significant lower frequency in the nivo+chemo arm than in the chemo arm: 10.1% vs. 21.5%.

Overall, fewer patients had an AE leading to delay of surgery in the nivo+chemo arm than in the chemo arm: 3.4% vs. 5.1% for the any-grade AEs, and 1.1% vs. 2.3% for the G3-4 AEs. No G5 AEs were reported in any arm, and no particular trend is observed across the nature of AEs which led to delay of surgery. 2 patients (1.1%) in the nivo+chemo arm reported an AE leading to cancellation of surgery vs. 1 patient (0.6%) in the chemo arm. The PTs for these AEs were "tuberculosis" and "ischaemic stroke" in the nivo+chemo arm, and "blood creatinine increased" in the chemo arm. Both the percentages of AEs leading to delay of surgery and AEs leading to cancellation of surgery are considered low and somehow expected due to the nature of the underlying disease.

Discontinuation due to adverse events – Any-grade AEs leading to discontinuation were reported with a similar frequency in both arms: 10.2% in the nivo+chemo arm vs. 11.4% in the chemo arm. G3-4 AEs leading to discontinuation were also reported with a similar frequency, although it was slightly higher in the nivo+chemo arm: 5.7% vs. 4.0%. The most common AE leading to discontinuation in the nivo+chemo arm was anaphylactic reaction (1.7%) and in the chemo arm it was neutropenia (2.3%). These rates remained similar after establishing the causality, although also slightly higher in the nivo+chemo arm: drug-related AEs leading to discontinuation were reported in 10.2% in the nivo+chemo arm vs. 9.7% in the chemo arm. Drug-related G3-4 AEs leading to discontinuation were reported in 5.7% of patients in the nivo+chemo arm, vs. in 3.4% in the chemo arm. The nature of the drug-related AEs did not differ from the nature of AEs regardless of causality. Although these rates are slightly higher in the nivo+chemo arm they are considered acceptable, taking into account that the addition of nivolumab to the chemotherapy backbone inevitably adds toxicity, and the observed increase remains within acceptable limits.

Laboratory findings – Laboratory abnormalities were mainly G1-2 in severity in both arms, with "haemoglobin" the parameter for which most alterations were reported followed by "absolute neutrophil count" and by "leukocytes". The incidences in both arms were overall similar and no particular differences were observed in terms of frequencies. G3-4 events were overall reported with a low frequency, except for "absolute neutrophil count", which was reported in 21.8% of subjects in the nivo+chemo arm vs. 26.6% in the chemo arm. In the nivo+chemo arm, no patients had concurrent ALT or AST > 3 x ULN with total bilirubin 2 x ULN within 1 day and within 30 days of last dose of study therapy, whereas in the chemo arm this was reported in 1 patient. As expected, considering the already known safety profile of nivolumab, thyroid function alterations were most frequently reported in the nivo+chemo arm than in the chemo arm: 3.0% patients reported TSH increases (> ULN) from baseline (≤ ULN) in the nivo+chemo arm, vs. no patients in the chemo arm. Decreases (< lower limit of normal [LLN]) from baseline (≥ LLN) were reported in 19 (11.4%) subjects in the nivo+chemo arm and 1 (2.9%) subject in the chemo arm. Regarding pancreas alterations, G3-4 events of increased lipase and increased amylase were reported with a higher incidence in the nivo+chemo arm (6.5% and 3.6%) vs. the chemo arm (3.6% and 1.8%). Lipase and amylase increases were also reported in the phase 2 study NADIM, where increased lipase was among the most common treatment-related Grade 3 events (7%) and both are included in section 4.8 of Opdivo SmPC. However, no cases of pancreatitis were observed. G3-4 increases in glucose were also higher in the nivo+chemo arm than in the chemo arm: 5.5% vs. 2.9%.

Vital signs observations performed prior to each treatment dose were not recorded in the clinical database. Vital signs observed as part of the physical examination within 72 hours prior to each dose were reported in the CRF and any clinically relevant safety event related to those observations was reported as an AE. AEs that could be related to vital signs alterations have been reviewed: all included AEs were mild and only some cases of Grade 3 febrile neutropenia, hypertension and dyspnea were reported. The most common AE was pyrexia in both arms.

Safety in special populations - The MAH presented data by age, sex, race and region, but overall, no significant findings were identified in these analyses.

Regarding safety by type of platinum chemotherapy (cisplatin or carboplatin), in both arms the incidence of G3-4 AEs was higher with carboplatin than with cisplatin. It does not seem that the addition of nivolumab impacts on the incidence of all-causality or drug-related AEs. In addition, the MAH has provided safety data by randomization period and no apparent differences have been identified.

The MAH has provided subgroup analysis by PD-L1 expression and by disease stage. Overall, it does not seem that there are relevant safety differences among subgroups. Nevertheless, it is difficult to draw any firm conclusion due to the small size of the database.

Immunogenicity has not been evaluated in Study CA209816. According to the MAH, the nivolumab ADA incidence rate is expected to be low in this setting and similar to monotherapy in 1L metastatic NSCLC. In addition, the fact that patients will only receive 3 treatment cycles reduces the risk. However, the *Guideline on Immunogenicity assessment of therapeutic proteins* (EMEA/CHMP/BMWP/14327/2006 Rev 1) states that testing of immunogenicity should be included in all pivotal clinical pharmacokinetic, pharmacodynamics, safety, and efficacy trials of a biological medicinal product targeting patient populations that have not been exposed to the product previously. Since IMG samples were not collected in study CA209816, an immunogenicity assessment is not possible. The MAH is recommended to perform an immunogenicity evaluation based on IMG samples from studies CA20977T and CA20973L, two ongoing trials that include patients with early-stage NSCLC.

Regarding the safety information included in section 4.8 of the SmPC, the MAH has pooled the results from study CA209816 with the already included results from studies CA209648 and CA209649. Although it is acknowledged that populations differ and some incidences have been decreased as a result of the pooling strategy, this approach is considered acceptable. The nivolumab in combination with chemotherapy for NSCLC neoadjuvant treatment safety profile is considered to be adequately represented by the proposed pool and the identified differences are not enough relevant to grant a separated subsection in 4.8 of the SmPC.

As noted in section 2.3.1 above, a **GCP deviation** in two China sites was identified by the MAH. Multiple potential adverse events (AEs, all non-serious) and concomitant medications documented in medical notes across all study arms were not entered into the Electronic Data Capture (EDC) system. Following complete source data review, sites entered the missing data into the EDC and preliminary assessment of the newly entered safety information was performed in July 2022. Overall, the newly entered AEs were consistent with the known safety profiles observed with nivo+chemo and chemo in the study, and are distributed evenly across those arms. There were no new serious adverse events (SAEs) or AEs leading to dose modification. A CSR addendum containing updated safety data, which includes also these additional AEs from China subjects, was submitted as part of the responses to the second RSI.

Updated safety data – Addendum 01 to the Primary CSR (14-Oct-2022 Database Lock)

Updated safety data provided by the MAH in Addendum 01 to the Primary CSR (DCO 14-Oct-2022) was consistent with the safety data provided in the DCO-1 (20-Oct-2021) (data not shown). Of note, all subjects had completed treatment at least 2 years before the IA2 database lock.

There continued to be no deaths due to study drug toxicity in the nivo+chemo arm. Some additional deaths were reported in both arms, but most of them were due to the disease and were reported with a similar frequency in both arms.

There were not any new SAEs reported, nor any new AE leading to discontinuation. No new AEs leading to delay or cancellation of surgery were reported either.

Regarding AEs, there were slight differences between both DCOs: any grade AEs were reported in the nivo+chemo arm in 92.6% of patients in the DCO-1, vs. in 93.8% of patients in the DCO-2. Regarding G3-4 AEs in the nivo+chemo arm, 40.9% of patients reported any G3-4 events in the DCO-1, vs. 43.2% in the DCO-2. The differences between both DCOs in terms of PTs were only 1 new AE in most cases, except for "neutropenia", for which the difference was 2 new AEs in the nivo+chemo arm for the any-grade AEs (15.9% in the DCO-1 vs. 17.0% in the DCO-2) and 4 new AEs in the nivo+chemo arm for the G3-4 events (8.5% in the DCO-1 vs. 10.8% in the DCO-2).

All-causality select AEs were reported with a very similar frequency in both DCOs. There was only a slight increase (1 additional select AE) in the hepatic select AEs and the renal select AEs. Regarding drug-related select AEs there was only a slight increase (1 additional select AE) in the hepatic category and in the hypersensitivity/infusion reaction category.

All-causality IMAEs within 100 days of last dose remained also pretty similar between both DCOs. Indeed, the IMAEs belonging to the "hypersensitivity/infusion reactions" reported in DCO-2 were lower than in DCO-1: 2 IMAEs (1.1%) in DCO-1 vs. 1 IMAE (0.6%) in DCO-2. Regarding all-causality endocrine IMAEs within 100 days of last dose, the percentages between both DCOs remained the same except for the case of "hypothyroidism/thyroiditis", for which 1 additional IMAE was reported (4 (2.3%) in DCO-1 vs. 5 (2.8%) in DCO-2).

The MAH review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the post-marketing setting supports the

favourable benefit-risk profile of nivolumab established during clinical trials.

2.5.2. Conclusions on clinical safety

The addition of nivolumab to the chemotherapy in the context of this neoadjuvant setting does not seem to translate into a significantly worse toxicity profile. Indeed, the number of AEs, SAEs and AEs leading to discontinuation remain overall similar between treatment arms and no major differences have been identified. Importantly, the addition of nivolumab did not lead to an increase in the number of surgery delays, surgery cancellations or surgical complications.

The nature of AEs is reflective of the known safety profile of nivolumab and chemotherapy and no new safety issues were identified. As expected, slight increases in the immune-mediated AEs in the nivo+chemo arm were observed, but severe IMAEs occurred with a very low frequency.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 27.4 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 27.4 with the following content:

Safety concerns

Table 75: **Summary of Safety Concerns**

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs) Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Complications of allogeneic HSCT following nivolumab therapy in cHL Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Table 76: **Ongoing and Planned Additional Pharmacovigilance Activities**

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/ effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related ARs (including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other irARs [uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH]), and severe infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06-2019 4Q2022

Risk minimisation measures

Table 77: **Summary of Risk Minimization Measures**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: Patient Alert Card	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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 MAH and has been found acceptable for the following reasons:

The extension of indication does not result in a relevant impact on the PL that would require performing a full user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria).

3.1.2. Available therapies and unmet medical need

Treatment options for patients with newly-diagnosed non-metastatic NSCLC depend on tumour resectability and patient operability. Key considerations include tumour characteristics and location, extent of nodal involvement, lung function, patient age and comorbidities.

Treatment guidelines (ESMO, NCCN, ASCO) state that patients with resected stage II-IIIA tumours should receive adjuvant chemotherapy. The role of adjuvant chemotherapy in stage IB tumours is not clear and should be decided on individual basis and depending on the size of the tumour among other factors. For stage III tumours that are considered resectable but not operable at first, neoadjuvant chemotherapy is recommended. Between 2 and 4 cycles of platinum-doublet chemotherapy are the standard course of treatment in those cases. Cisplatin combined with vinorelbine (non-squamous) or gemcitabine (squamous histology) are the most commonly used chemotherapy regimens in this setting. There are no other agents approved for NSCLC neoadjuvant treatment.

3.1.3. Main clinical studies

The current application is based on the results from the first interim analysis of Study CA209816. This is a phase 3, randomized, open-label study of nivolumab combined with different platinum-based chemotherapy regimens for the treatment of stage IB-IIIA NSCLC in the neoadjuvant setting. A total of 773 patients were enrolled in the study, of whom 505 were randomized to receive either nivo+ipi (n=113), chemo (n=213) or nivo+chemo (n=179). The primary population for the efficacy analyses (n=358) is comprised by all subjects concurrently randomized to the nivo+chemo and chemo arm (n=179 each) who received three cycles of either nivolumab + platinum-based chemotherapy or platinum-based chemotherapy before definitive surgery.

3.2. Favourable effects

The combination therapy of nivolumab+chemotherapy for the neoadjuvant treatment of stage IB-IIIA (AJCC 7th edition) NSCLC showed an improvement in event free survival (EFS) by BICR compared to chemotherapy [HR=0.63 (97.38% CI: 0.43, 0.91), p=0.0052, median EFS 31.57 vs. 20.80 months] in a prespecified first interim analysis. Nivo+chemo also demonstrated a statistically significant improvement in pCR rate per BIPR compared with chemo: 24.0% (43/179; 95% CI: 18.0, 31.0) vs. 2.2% (4/179; 95% CI: 0.6, 5.6). Results from the EFS subgroup analyses by stratification factors were generally consistent with the main analysis and also favoured the nivo+chemo arm. In patients with stage II-IIIA disease and PD-L1 expression ≥1%, reported EFS per BICR (DBL 14-Oct-2022) showed a HR point estimate of 0.44 (95% CI: 0.26, 0.76), with a median EFS not reached (95% CI: 44.42, NA)

in the nivo+chemo group and 26.71 (95% CI: 13.40, NA) months in the chemo treatment group. Several sensitivity analyses for EFS also confirmed the reported main results.

Regarding secondary endpoints, TTDM and MPR also favoured the nivo+chemo arm. EFS2 was also analysed as an exploratory endpoint and the results favoured the combination.

Updated exploratory efficacy analyses were provided for the main endpoints which confirmed the previous findings.

A first interim analysis of OS was performed (50.8% information fraction). A positive trend in OS has been observed: HR=0.57 (99.67% CI: 0.30, 1.07); stratified log-rank test p-value = 0.0079 (p <0.0033 needed for statistical significance). A second pre-planned OS IA was performed (60.0% information fraction) which also showed a positive trend but, again, it did not cross the prespecified boundary for statistical significance (p <0-0066). An OS HR point estimate of 0.62 (99.34% CI: 0.36, 1.05; 95% CI: 0.42, 0.90); stratified log-rank test p-value = 0.0124, was reported. In patients with stage II-IIIA disease and PD-L1 expression ≥1%, an OS HR of 0.43 (95% CI: 0.22, 0.83) (DBL 14-Oct-2022) was reported.

3.3. Uncertainties and limitations about favourable effects

Study CA209816 was originally designed to compare the combination of nivolumab+ipilimumab vs. chemotherapy and was subject to multiple amendments where a third arm of nivolumab+chemotherapy was added, randomization to the nivo+ipi arm was later closed and the efficacy analyses in terms of endpoints, population of analysis and statistical plan were also changed.

Available OS results come from two pre-planned interim analyses. Even if data do not show evidence of a detriment, the reported results are considered still immature, and the MAH is requested to submit the final OS analysis of study CA209816 (see Annex II).

3.4. Unfavourable effects

In Study CA209816, with a minimum follow-up of 21 months and a median follow-up of 29.5 months, 92.6% of subjects in the nivo+chemo arm and 97.2% of subjects in the chemo arm reported any AEs during the study. The most frequently reported AEs, by SOC, belonged to "GI disorders" in both arms: 58.0% vs. 70.5%. By PT, the most frequently reported events were the same in both arms: "nausea" (38.1% vs. 44.9%), "constipation" (33.5% vs. 32.4%) and "anaemia" (29.0% vs. 26.7%).

Regarding G3-4 AEs, 40.9% of patients reported a G3-4 AE in the nivo+chemo arm vs. 43.8% in the chemo arm, being "neutropenia" the most commonly reported.

Any-grade SAEs were reported in a higher percentage of patients in the nivo+chemo arm than in the chemo arm (17.0% vs. 13.6%). Overall the nature of the SAEs most frequently reported was similar in both arms, except for the frequency of SAEs belonging to "vascular disorders", which was higher in the nivo+chemo arm than in the chemo arm (3.4% vs. 1.1%).

For immune-mediated AEs, in the nivo+chemo arm "rash" was the most frequently reported IMAE (8.5%), followed by "hyperthyroidism" (4.0%) and "hypothyroidism/thyroiditis" (2.3%).

Updated safety results with longer follow up confirmed the above findings (data not show).

3.5. Uncertainties and limitations about unfavourable effects

Although the safety profile of nivo+chemo in the neoadjuvant setting does not seem too worrying, this could be related to the fact that subjects only received 3 treatment cycles.

Immunogenicity has not been evaluated in Study CA209816 and the MAH will perform additional investigations to address this uncertainty (REC).

3.6. Effects Table

Table 78: **Effects Table for Opdivo (nivolumab) in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable Stage IBstage II-IIIA and PD-L1 expression ⩾1% NSCLC (data cut-off: 20-Oct-2021)**

Effect	Short description	Unit	Treatment n=81	Control n=86	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoints (concurrently randomized n=167)						
pCR (BIPR) (DCO: 16-Sept-2020)	Pathologic complete response: number of randomized subjects with an absence of residual tumour in lung resected tissue and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each treatment arm	N responders (%) (95% CI)	26 (32.1) (22.2, 43.4)	2 (2.3) (0.3, 8.1)	Difference (95% CI), % 29.8 (19.0, 40.7)	CSR
EFS (BICR) (DCO: 20-Oct-2021)	Event free survival: the length of time from randomization to any of the following events: a) any progression of disease precluding surgery, b) progression or recurrence of disease (based on BICR assessment per Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) after surgery, or c) death due to any cause	Median, months (95%CI)	Not reached (NA, NA)	21.06 (11.47, NA)	HR = 0.44 (0.26, 0.76)	CSR
Secondary endpoints (concurrently randomized n=167)						
TTDM (BICR) (DBL 14-Oct-2022)	Time to death or distant metastases: time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis	Median, months (95%CI)	Not reached (44.42, NA)	Not reached (18.83, NA)	HR = 0.40 (0.22, 0.72)	CSR
OS IA2 (DBL 14-Oct-2022)	Overall survival: time between the date of randomization and the date of death due to any cause	Median, months (95%CI)	Not reached (NA, NA)	Not reached (NA, NA)	HR = 0.43 (95% CI: 0.22, 0.83)	CSR
Unfavourable Effects						

Effect	Short description	Unit	Treatment n=81	Control n=86	Uncertainties / Strength of evidence	References
Grade 3-4 AEs	All causality (drug-related)	%	40.9% (33.5%)	43.8% (36.9%)		Primary CSR
SAEs	All causality (drug-related)	%	17% (11.9%)	13.6% (10.2%)		
AE leading to DC	All causality (drug-related)	%	10.2% (10.2%)	11.4% (9.7%)		

Abbreviations: AE: adverse event; BICR: blinded independent central review; CSR: clinical study report; HR: hazard ratio; OR: estimate of odds ratio; RECIST 1.1: Response Evaluation Criteria In Solid Tumours version 1.1; SAE: serious adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study CA209816, administration of 3 cycles of nivolumab in combination with platinum-based chemotherapy for neoadjuvant treatment of NSCLC showed a statistically significant improvement in both pCR and EFS compared to chemotherapy in all concomitantly randomized patients. Secondary endpoints also favoured the combination arm. OS data are still immature but a positive trend has been observed for nivolumab + chemotherapy. Subjects with stage IB to IIIA tumours (by AJCC TNM staging 7th edition) irrespective of PD-L1 tumour expression were included in the study. According to the provided results, patients with stage IIIA tumours seem to derive more benefit from the proposed treatment intervention. Further, with regards to PD-L1 expression the reported positive results in the overall patient population are mainly driven by the subgroup of patients with PD-L1 tumour expression ≥1% questioning whether the proposed neoadjuvant treatment with nivolumab would lead to long term benefit in the PD-L1 <1% population.

With regards to safety, the addition of nivolumab to platinum-based chemotherapy resulted in an increased toxicity although the limited number of treatment cycles administered in this setting decreases the toxicity burden of the addition of nivolumab.

3.7.2. Balance of benefits and risks

The MAH is applying for a broad indication (i.e. regardless of tumour cell PD-L1 expression) of nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of patients with resectable NSCLC at risk of recurrence (stage IB-IIIA; AJCC 7th edition) but the role of neoadjuvant treatment in stage IB and II is not fully established. Stage IB and II tumours have better prognosis than stage IIIA so there is a high heterogeneity in the population included in this study. A greater benefit seems apparent in patients with stage IIIA tumours while the stage IB population included in the study is so limited (n=18) that treatment efficacy cannot be inferred from the obtained results. This fact, combined with the added toxicity that nivolumab treatment may expose patients to, justify the exclusion of stage IB (per the AJCC-TNM 7th edition) tumours from the therapeutic indication. Further, the positive results reported with the combination are mainly driven by the subgroup of patients with PD-L1 tumour expression ≥1%, questioning whether the proposed neoadjuvant treatment with nivolumab would lead to long term benefit in the PD-L1 <1% population. Considering this, an unrestricted indication is not justified and the benefit-risk is considered positive for patients with disease stage II-IIIA (7th TNM edition) and PD-L1 tumour expression ≥1%.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Opdivo in combination with platinum-based chemotherapy is considered positive for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include OPDIVO in combination with platinum-based chemotherapy for neoadjuvant treatment of adult patients with resectable Stage IB-IIIA non-small cell lung cancer (NSCLC), based on results from study CA209816; a randomised, open-label, phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 27.4 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

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

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

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

Description	Due date

Post authorisation efficacy study (PAES): In order to further characterize the efficacy of nivolumab as neoadjuvant treatment of adults with non-small cell lung cancer, the MAH should submit the OS data from the final OS analysis of the Phase 3 study CA209816.	By 30th June 2025

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0117'